

Summary

The development of new, efficient and sustainable approaches towards functionalised molecules is the driving force for the discovery of new synthetic pathways for the future. Ease of use, and environmental and cost issues are important factors that justify the search for new synthesis routes, which holds for a wide range of synthetic applications ranging from the synthesis of low-molecular weight compounds (drug discovery) to the production of new polymeric materials (i.e. functionalised polymers) that broaden the scope of current technologies or introduce new ones. In this perspective, the typical hypervalent reactivity of ‘carbenes’ and ‘nitrenes’ offers interesting opportunities to develop new synthesis routes to introduce functionalities in low-molecular weight compounds and polymers.

Transition metal-bound carbenoids and nitrenoids display an often controlled, but still high reactivity that provides powerful synthetic approaches towards substrate functionalisation. In the aforementioned perspective, the primary objective of the investigations described in this thesis was to elucidate the mechanistic features of transition metal mediated hypervalent group transfer reactions in detail, with the ultimate goal to use these new insights in the rational design and development of new and improved catalytic systems.

Synthetic applications of (metal) carbenes have meanwhile been developed to a quite high level, but related developments in (metal) nitrene chemistry currently lag behind. The same holds for mechanistic insight in nitrene chemistry. The existence, (electronic) structure and exact nature of the proposed key nitrene intermediates in nitrene-transfer reactions have remained under debate for the past decades. Remarkably, only recently the redox activity of

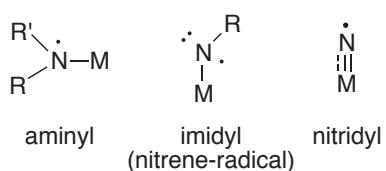


Figure 1. Nitrogen centred radicals as ligands for metal complexes.

In most of the examples, these nitrogen-centred ligand radicals reveal selective reactions despite their radical nature. In fact, the use of nitrogen-centred ligand radicals proves to be an effective new tool for the (catalytic) synthesis of a variety of nitrogen-containing organic

nitrene/imido ligands has been discovered, and meanwhile it is becoming clear that nitrogen centred radicals play a key role in several nitrene-transfer reactions. In **chapter 1**, an overview of the reported well-defined, characterised and isolated nitrogen-centred radical complexes is presented. This includes the aminyl-radical complexes ($[M(\bullet NR_2)]$), nitrene/imido-radical complexes ($[M(\bullet NR)]$) and nitridyl-radical complexes ($[M(\bullet N)]$) reported in the past decade (Figure 1).

molecules (e.g. aziridines, pyrazoles, amines, amides, and ammonia). A classification system of nitrogen-centered ligand radical complexes is introduced on the basis of their electronic structure, leading to a description as either one-electron-reduced Fischer-type systems, one electron oxidised Schrock-type systems or systems with a (nearly) covalent M–N π-bond. The information and classification of the examples reviewed in this chapter should contribute to a better understanding of the (catalytic) reactivity of nitrogen-centered ligand radicals and the role they play in tuning the reactivity of coordination compounds.

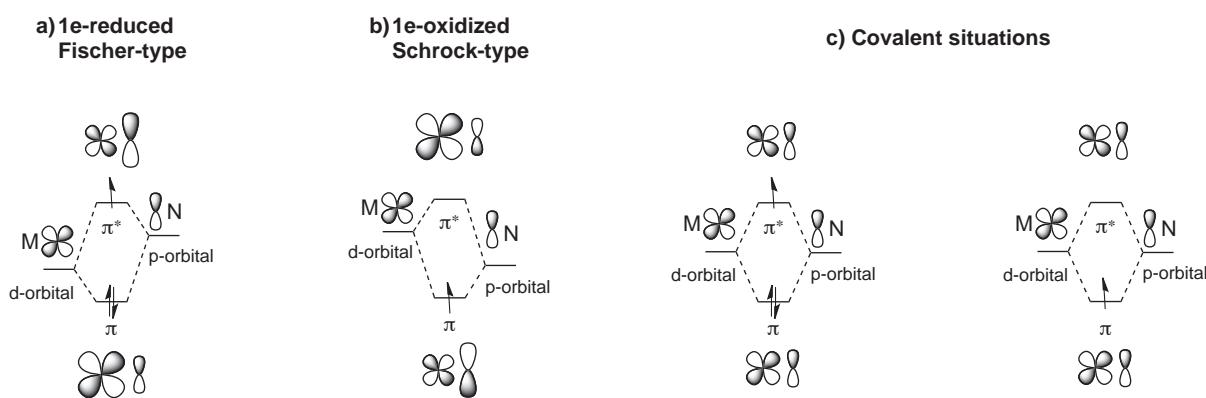


Figure 2. MO diagrams of open-shell nitrogen-centered ligand radicals: a) 1e-reduced Fischer-type, b) 1e-oxidised Schrock-type, c) covalent complexes.

Despite the existence of different nitrene sources, these species are generally difficult to generate. Organic azides are among the most promising and environmentally friendly alternatives, for which a large substrate scope is already available. Only recently, organic azides were introduced as nitrene-precursor substrates in catalytic olefin aziridination and C–H amination reactions, and Co^{II}(Por) complexes have demonstrated to be one of the most outstanding catalysts. In **chapter 2**, we describe our studies to shine more light on the mechanistic features of cobalt mediated olefin aziridination reactions. The studies focus in particular on understanding the important factors that play a role under the catalytic conditions.

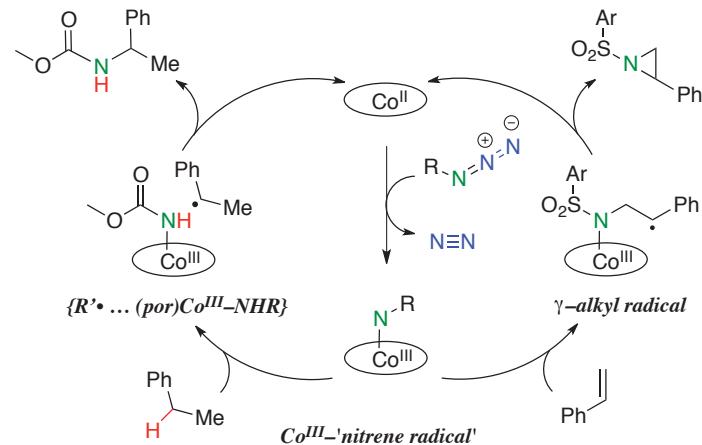


Figure 3. Catalytic cycle of Co(por)-based C–H amination (left) or aziridination (right) with organic azides.

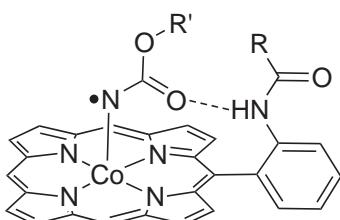
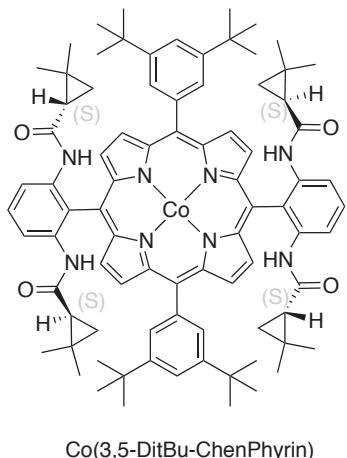


Figure 4. $\text{Co}^{\text{II}}(3,5\text{-Di}^{\prime}\text{Bu-IbuPhyrin})$ and H-bond donors stabilizing the nitrene radical

‘nitrene radical’ intermediate plays a key role. The radical nature of this intermediate facilitates the addition of the olefin, yielding a γ -alkyl radical intermediate that readily collapses in ring closure to form the aziridines ring (Figure 3).

Experimentally, the most successful catalyst reported by Zhang and co-workers is the $\text{Co}(3,5\text{-Di}'\text{Bu-IbuPhyrin})$ (for enantioselective reactions) and $\text{Co}^{\text{II}}(3,5\text{-Di}^{\prime}\text{Bu-Chen-Phyrin})$ for aziridination reactions; both complexes contain carboxamido functionalities as H-donors (Figure 4). The ability of the H-donors to arrange the sulfonazide substrate is reflected in the increased activity of the modified porphyrin cobalt complexes. According to our computational studies, this hydrogen bonding in fact lowers the energy barriers for formation of the nitrene intermediate, as well as the olefin addition, thus explaining the improved performance of these catalysts. The computed radical-type mechanism (Figure 3) thus agrees well with all available mechanistic and kinetic information, and readily explains the excellent performance of the H-bond donor appended $\text{Co}^{\text{II}}(\text{por})$ systems developed in the group of Zhang.

In **chapter 3**, the mechanistic studies are extended to Co^{II} porphyrin-catalysed benzylic C–H bond amination of ethylbenzene, toluene and 1,2,3,4-tetrahydronaphthalene (tetralin) with a series of different organic azides ($\text{N}_3\text{C}(\text{O})\text{OMe}$, $\text{N}_3\text{SO}_2\text{Ph}$, $\text{N}_3\text{C}(\text{O})\text{Ph}$ and $\text{N}_3\text{P}(\text{O})(\text{OMe})_2$) as nitrene sources. Also in these reactions Co^{III} -nitrene radicals were demonstrated to be key intermediates in the overall C–H bond activation process (Figure 3). These reactions proceed readily via a hydrogen atom abstraction process from the benzylic positions of the organic substrates by the Co^{III} -nitrene radicals. The thus formed close-contact radical pairs $\{\text{R}'\cdot \dots (\text{por})\text{Co}^{\text{III}}-\text{NHR}\}$ readily collapse in a virtually barrierless fashion to produce the Co^{II} -amine adduct. Product dissociation completes the cycle, and affords the final amine products

We found, on the basis of DFT calculations, that a radical pathway for the $\text{Co}^{\text{II}}(\text{por})$ -catalysed aziridination of styrene is operative. The reaction mechanism proceeds via a two-step radical addition-substitution pathway, in which the redox non-innocent behaviour of the Co^{III} -

NHRR'. This study further includes mechanistic studies to understand the catalyst deactivation pathways, and explains formation of side-products observed experimentally.

The formation of Co^{III}-'nitrene radical' species, predicted to be exothermic by DFT calculations, was confirmed experimentally by EPR spectroscopic studies. Signals with *g*-values characteristic for ligand radical complexes were obtained from (por)Co complexes in the presence of an excess of the organic azides in benzene, and thus provided the first experimental evidence of these key intermediates in nitrene transfer reactions mediated by metallo-radical cobalt(II)-porphyrins.

Some Fe^{III}-porphyrin systems have been used to mimic catalytic nitrene transfer reactions mediated by cytochrome P450. In these studies, $[(\text{por}^\bullet)\text{Fe}^{\text{IV}}=\text{NR}]^+$ species (isoelectronic to high-valent $[(\text{por}^\bullet)\text{Fe}^{\text{IV}}=\text{O}]$, known as O-Cpd I) have been proposed as possible intermediates in analogy with the well-known oxygen-transfer mechanism of this enzyme and its model systems. However, the existence of such high oxidation state $[(\text{por}^\bullet)\text{Fe}^{\text{IV}}=\text{NR}]^+$ species has not been proven. In **chapter 4**, we describe our investigations aimed at experimental detection of the putative nitrene intermediates and understanding their electronic structure. In this chapter, combined computational and spectro-electrochemical studies show that neutral Fe-nitrene/imido intermediates of the type $[(\text{por}^{2-})\text{Fe}^{\text{IV}}=\text{NR}]$ (containing a non-oxidised porphyrin-ring) are readily formed from the ferrous complex $[(\text{por}^{2-})\text{Fe}^{\text{II}}]$ and organic azides with accessible energy barriers ($\Delta G^\ddagger = +20 \text{ kcal mol}^{-1}$) at room temperature. Formation of the previously proposed azo-ferryl porphyrin cation radical species $[(\text{por}^\bullet)\text{Fe}^{\text{IV}}=\text{NR}]^+$ (analogous to O-Cpd I) from ferric species $[(\text{por})\text{Fe}^{\text{III}}]$ could not be confirmed experimentally and also in our computational studies the ferric pathway leading to $[(\text{por}^\bullet)\text{Fe}^{\text{IV}}=\text{NR}]^+$ species is associated with much higher energy barriers than the corresponding ferrous pathway leading to $[(\text{por}^{2-})\text{Fe}^{\text{IV}}=\text{NR}]$ species (Figure 5).

According to DFT calculations, and supported by the small shift of the Soret band in the experimental UV-Vis spectra, these species are best described being in between the Fe^{II}-nitrene and an Fe^{IV}-imido formalisms involving the following resonance structures: $[(\text{por})\text{Fe}^{\text{IV}}\{\text{NR}^{2-}\}] \leftrightarrow [(\text{por})\text{Fe}^{\text{III}}\{\text{N}\bullet\text{R}^-\}] \leftrightarrow [(\text{por})\text{Fe}^{\text{II}}\{\text{NR}^0\}]$. These iron imido/nitrene species are more reasonably proposed as key-intermediates in catalytic nitrene-transfer reactions.

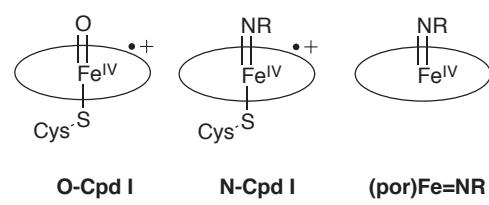


Figure 5. Iron-oxo intermediate O-Cpd I, the putative isoelectronic iron-nitrene/imido analogue N-Cpd I, and the experimentally detected $[(\text{por})\text{Fe}=\text{NR}]$ species.

The Fe^{III} precursors must first get reduced to the active Fe^{II} species to activate the organic azide.

In **chapter 5**, we present our comparative mechanistic studies, based on experimental screening and computational studies, using Co^{II}- and Fe^{II}- porphyrins on the catalytic activation of organic azides and subsequent nitrene-transfer to styrenes. We focussed in particular on the competition between 3-membered ring (aziridine) and 5-membered ring (tetrahydropyrrol) formation, the influence of the olefinic substrates and the influence of the type of metallo-porphyrin and metallo-porpholactone used as catalyst. We found that Co and Fe have very similar mechanisms for nitrene formation and transfer to the olefin, albeit with interesting subtle differences in their electronic structures. While Co forms a discrete nitrene radical intermediate $[(\text{por})\text{Co}^{\text{III}}\{\text{N}\bullet\text{R}^-\}]$ upon activation of the azide, Fe produces a nitrene intermediate with a much more covalent $\text{Fe}=\text{NR}$ π -bond having each of its two π^* Fe–N antibonding SOMOs half-filled. This covalency complicates the assignment of metal and ligand oxidation states (resonance structures: $[(\text{por})\text{Fe}^{\text{IV}}\{\text{NR}^2\}] \leftrightarrow [(\text{por})\text{Fe}^{\text{III}}\{\text{N}\bullet\text{R}^-\}] \leftrightarrow [(\text{por})\text{Fe}^{\text{II}}\{\text{NR}^0\}]$). The species does contain a significant amount of spin density at the nitrene/imido nitrogen, allowing the description of its reactivity with styrene to proceed via the $[(\text{por})\text{Fe}^{\text{III}}\{\text{N}\bullet\text{R}^-\}]$ resonance form. Radical addition of $[(\text{por})\text{Fe}^{\text{III}}\{\text{N}\bullet\text{R}^-\}]$ to styrene produces a genuine Fe^{III} γ -alkyl radical, comparable to the Co^{III} γ -alkyl radical intermediate obtained by radical addition of $[(\text{por})\text{Co}^{\text{III}}\{\text{N}\bullet\text{R}^-\}]$ to styrene (Figure 6). These results highlight the importance of having discrete spin density located at the nitrene nitrogen in $(\text{por})\text{M}^{\text{III}}\{\text{N}\bullet\text{R}^-\}$ species prior to olefin attack ($\text{M} = \text{Co, Fe}$), which explains the reactivity displayed by these catalysts.

Selectivity for formation of the aziridines (3-membered ring) vs. tetrahydropyrrol (5-membered ring) arises, from the competition between ring-closure and addition of the second styrene moiety. For all catalyst, we found almost barrierless ring-closure of the γ -alkyl radical species. Only for

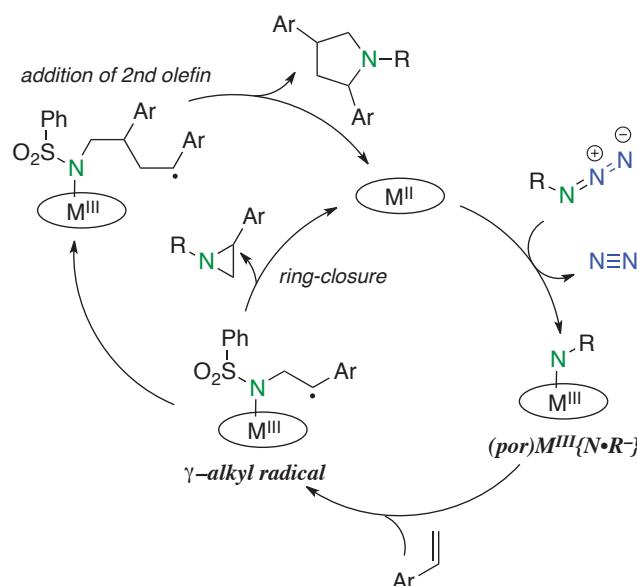


Figure 6. Catalytic cycle of $\text{M}(\text{por})$ ($\text{M} = \text{Co, Fe}$) aziridination (3-membered ring) and tetrahydropyrrols (5-membered ring) with organic azides.

metallo-porpholactones, the barrier for the addition of the second unit becomes comparable to the ring formation barrier, and thus energetically competitive. Experimentally, tetrahydropyrrol formation is only observed when using metallo-porpholactones as catalysts and *p*-MeO-styrene as a substrate. In good agreement, also in the computational studies the use of *p*-MeO-styrene further lowers the activation barrier for addition of the second styrene moiety, and in case of the Fe-porpholactone catalysts this path is nearly barrierless.

In **chapter 6**, we describe our efforts to extend the scope of ‘Rh-catalysed C1 (co)polymerisation’ reactions. These reactions proceed via a migratory ‘carbene’ insertion pathway, and represent a new way to synthesise stereoregular polymers. We first focussed on understanding the influence of the diene ligand on the activity of Rh catalysts for carbene polymerisation, and then designed and synthesised bulky di-substituted 1,5-Ar-cod-type diene ligands and applied them in Rh-mediated C1 polymerisation reactions. These new Rh^I(diene) catalysts enabled us to demonstrate, for the first time, that sulfur ylides are interesting carbene monomer precursors for applications in carbene polymerisation reactions (Figure 7). Furthermore, we show that it is possible to generate unique diblock copolymers from sulfoxonium ylides and diazoesters as the respective carbene monomer precursors. This constitutes an entirely new approach to the synthesis of functional copolymers. The new technique proved to be tuneable for the content of the polar and non-polar groups, hence opening new doors for variation of polarities of different materials since the copolymer properties are highly dependent on the functional group content. These copolymers can be used as single materials with benefits from both blocks, but also as blending agents (compatibilisers) to mix polyethylene (PE) or polymethylene (PM) with poly(ethyl 2-ylidene-acetate) (PEA). Additionally, we presented our findings in model studies that explained the influence of the catalyst structure on the obtained polymer yields. These studies then provide insights into the catalyst activation and deactivation and hence valuable information on the design of the catalyst.

The mechanistic information described in this thesis is of important value for further developments in the field of controlled reactions by

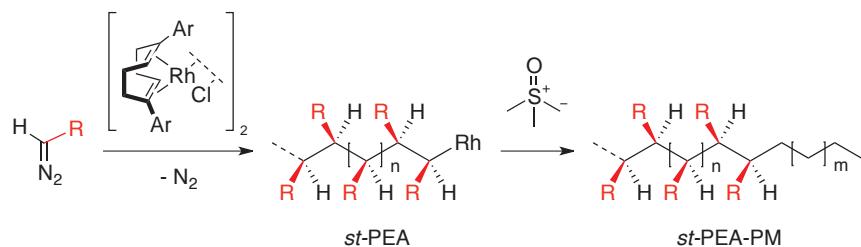


Figure 7. Copolymerisation of functionalised (from diazo-compounds) and non-functionalised (sulfoxonium ylides) carbenes as alternative to olefin polymerisation.

hypo-valent reagents such as carbenes and nitrenes. Controlling these reagents with transition metals allows the synthesis of new (functionalised) small molecules as well as macromolecules.

These reagents display a wide variety of chemical reactivity patterns. The formation of nitrene radical intermediates in catalysis offers interesting new avenues in controlled radical-type ring-closure and C–H bond activation reactions, and carbene intermediates offer fascinating opportunities to prepare new polymeric materials via Rh-mediated C1 polymerisation. There are still many unexplored possibilities in this field that require future attention. We think, in particular, that the involvement of radical intermediates in nitrene transfer (activation) is crucial to achieve highly controlled reactions. In this perspective, looking at the very similar chemical reactivity that nitrene and carbene chemistry display, we can speculate on expanding the scope of metal-nitrene chemistry, such as catalytic synthesis of isocyanates (useful in polymer synthesis), and enantioselective nitrene transfer and insertion reactions.