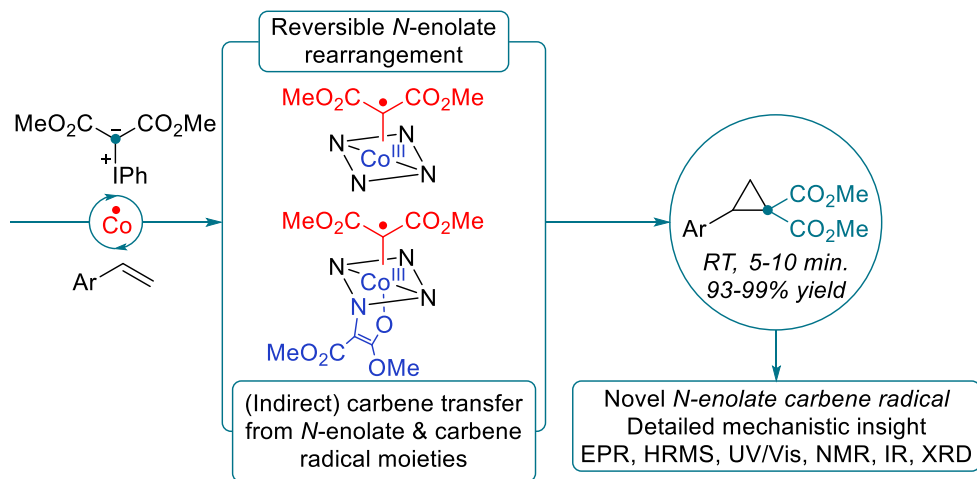


Summary

Catalysis plays a key role in modern society due to the ever-growing demand for bulk- and fine chemicals, materials and fuels. Although highly efficient, contemporary catalysts often feature scarce 2nd and 3rd-row transition metals and researchers have therefore focused more attention to the far cheaper, abundant and generally less toxic 1st-row transition metals or base metals. Whereas the 2nd and 3rd-row transition metals operate via established two-electron, concerted mechanisms, base metals often react via stepwise, one-electron radical pathways, thus offering new routes to valuable chemicals. Often erroneously touted as “too reactive to be selective”, synthetic methodologies using such radical reactivity have seen an explosive growth in literature in the past few decades. A prime example is the transfer of a carbene synthon via use of transition metal catalysts, which is a highly popular field as carbon is the backbone of almost any synthetic methodology. Consequently, base metal catalysts have been used to impart radical reactivity upon these metal carbenes to allow for alternate, stepwise reactivity. This thesis is focused on understanding and application of Co and Fe catalysis for radical-type carbene transfer.

Chapter 1 gives a brief introduction on homogeneous catalysis, the lessons learned from how Nature controls radical reactions and the application of this toolbox using redox-active ligands. A particular focus on carbenes as redox non-innocent reagents is given with a comprehensive overview of the unique mechanisms involved for these radical species and their catalytic application. Of note is the dominance of cobalt-based systems and diazo-based precursors in carbene radical transfer. The work in this thesis aims to expand upon this successful, rich chemistry by exploring iodonium ylides as alternative precursors and iron as a more biocompatible replacement for cobalt.

Chapter 2 demonstrates the effective use of acceptor-acceptor iodonium ylides in place of their diazo analogues using the established cobalt(II)-tetraphenylporphyrin ([Co(TPP)]) catalyst. Here we show that via use of these hypervalent iodine reagents, we can access *bis*-carbenoid intermediates where one carbene rearranges to form the active *N*-enolate carbene radical species (Scheme 1). These relatively stable species allowed for extensive spectroscopic characterization of cobalt(III)-carbene radicals, which is more difficult for the contemporary *mono*-substituted cobalt(III)-carbene radicals.

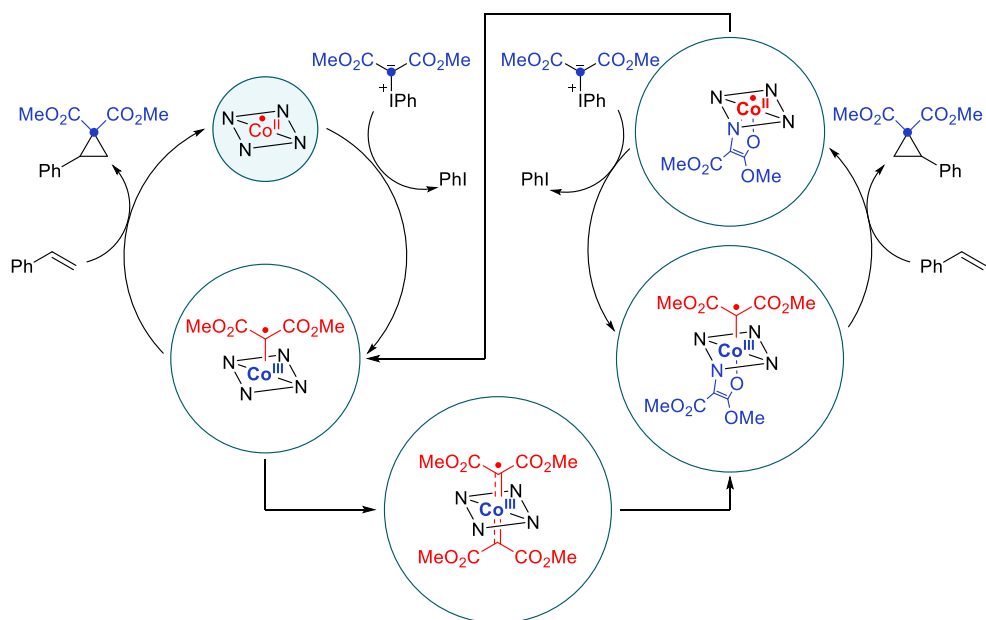


Scheme 1. Rapid carbene transfer at ambient conditions via *N*-enolate carbene radical species (Chapter 2).

Catalytic application of iodonium ylides in [Co(TPP)]-catalysed styrene cyclopropanation revealed a complex mechanism with two active intermediates. One is a *mono*-terminal carbene radical and the other the unprecedented *bis*-carbenoid *N*-enolate carbene radical. Notably, *N*-enolate formation is not a deactivation pathway but a reversible process, enabling transfer of two carbene moieties from a single *N*-enolate carbene radical intermediate. Catalyst deactivation involves hydrogen atom transfer (HAT) from the solvent or trace impurities to the carbene radical moieties of these intermediates. Further application of the newfound methodology revealed that the reaction works excellently for *mono*-substituted styrenes and well for electron poor and 1,1-substituted styrenes. The system is highly susceptible to steric hindrance on the β -vinylic position and internal alkenes revealed poor conversion if any at all.

Chapter 3 further supports the experimental findings of **Chapter 2** via use of density functional theory (DFT) calculations that show the overall reaction proceeds via two interconnected catalytic cycles (Scheme 2). Here, one cycle consists of the *mono*-terminal carbene radical at its center and a second cycle that involves the *N*-enolate carbene radical. These are interconnected by the reversible rearrangement of the *N*-enolate moiety to a terminal carbene radical moiety dictated by the $\text{Co}^{\text{II/III}}$ redox-cycle. The overall reaction takes place entirely on the doublet spin surface. Additional multireference N-electron valence perturbed complete active space self-consistent field (NEVPT2-CASSCF) calculations

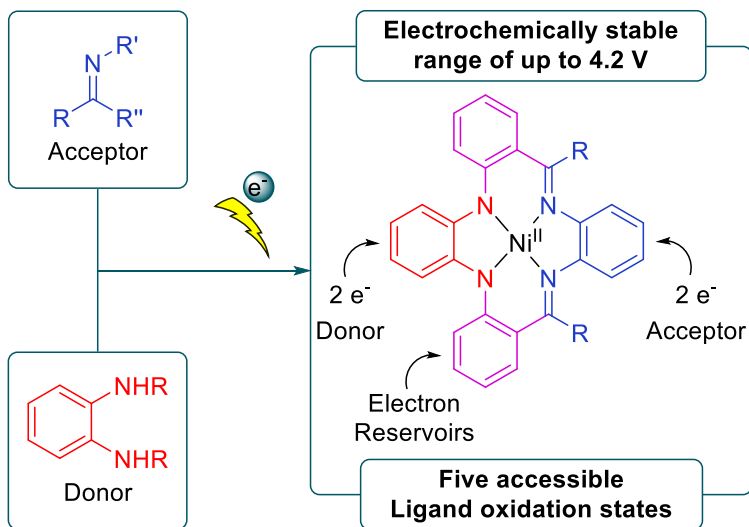
support these findings and show that higher spin states are well separated from the ground doublet state of the active intermediates. Comparison of the activation barrier for addition of styrene or iodonium ylide to the *mono*-terminal carbene is almost equal and thereby competitive. This is in line with the experimentally observed dependence on addition order. Deactivation via bridged carbene/*N*-enolate formation was not thermodynamically feasible and the active *N*-enolate carbene radical was found to be the most stable species. The *N*-enolate moiety also has a “protective” effect by slowing down HAT-deactivation as it has the highest barrier out of all types of carbene radical species. A comparison study of the analogous diazo reagent revealed that a combination of increased leaving group capability, greater carbanion character on the carbene atom and thermodynamic driving force explains the superiority of iodonium ylides over diazo compounds in acceptor-acceptor carbene formation.



Scheme 2. Simplified representation of the cyclopropanation reaction mechanism calculated with DFT (Chapter 3).

Chapter 4 focuses on the development of a new redox-active ligand platform, the tetraphenyltetraaza[14]annulene ligand (PhenTAA). Here we have combined existing elements of redox-active moieties, a *o*-phenylenediamine donor group and a diimine group linked by two flanking phenylene substituents (Scheme 3). This resulted in the new, highly

conjugated PhenTAA macrocycle. Using nickel(II) as a redox-innocent square-planar metal, the oxidation chemistry of various $[\text{Ni}(\text{R}_2\text{PhenTAA})]$ complexes was investigated with the imine position substituted ($\text{R} = \text{H}, \text{Me}$ or Ph). The unsubstituted ($\text{R} = \text{H}$) complex exhibited two electrochemically reversible ligand-based oxidation states, but further investigation revealed the reduction resulted in dimerization of the α -iminocarbon radical. The substituted versions ($\text{R} = \text{Me/Ph}$) did not dimerize and even exhibited electrochemically detectable doubly reduced ligand-based oxidation states, resulting in five different oxidation states for the overall macrocycle. Supported by computational investigations, the overall electronic structure exhibited a clear donor \rightarrow acceptor dual nature, consisting of four main ligand-based orbitals that dominate the redox- and photophysical properties of the $[\text{Ni}(\text{R}_2\text{PhenTAA})]$ complexes.

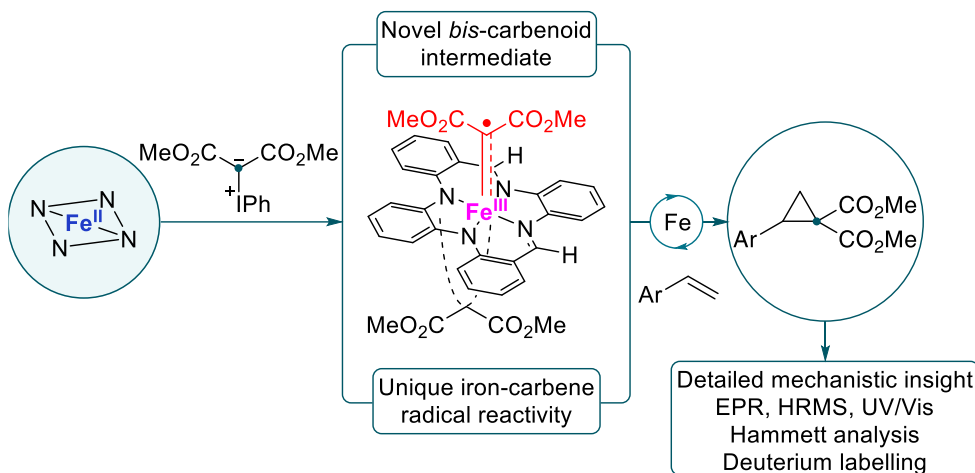


Scheme 3. Combination of redox-active donor and acceptor moieties leads to the unique PhenTAA macrocycle that exhibits high electrochemical stability and five different ligand oxidation states (Chapter 4).

Chapter 5 combines and applies the knowledge obtained in **Chapters 2–4** to achieve catalytic iron-carbene radical transfer. The combination of the electron-rich nature of the PhenTAA macrocycle with the highly reactive iodonium ylides led to distinct carbene radical reactivity in styrene cyclopropanation (Scheme 4). Similar to the reactivity observed for $[\text{Co}(\text{TPP})]$ in **Chapter 2–3**, the system is predominantly deactivated by hydrogen atom

transfer and leads to the formation of Fe(III)-alkyl species. Here too, one reactive carbene moiety is observed with one rearranged carbene moiety.

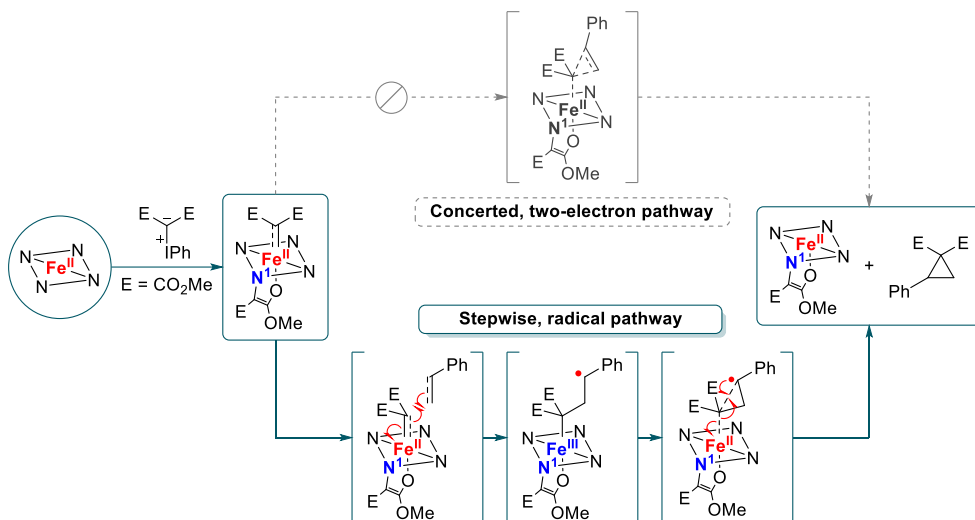
Interestingly, Hammett analysis revealed that these iron carbenes react as pure radical species as opposed to the nucleophilic *and* radical cobalt-carbene radical species observed for [Co(TPP)]. Deuterium labelling studies further corroborate the radical, stepwise nature of the overall reaction.



Scheme 4. [Fe(H₂PhenTAA)]-catalyzed styrene cyclopropanation via iodonium ylides leading to unique iron-carbene radical reactivity (Chapter 5).

Chapter 6 dives into the mechanism behind the observed reactivity of **Chapter 5** using a combination of DFT and multireference NEVPT2-CASSCF calculations (Scheme 5). The reaction is quite similar to the mechanism shown in **Chapter 2–3**, with two interconnected cycles with a “*mono*-carbene” and a “*bis*-carbene” cycle. The nature of the rearranged carbene was investigated and a *N*-enolate moiety on the negatively charged amide position was found to be the most kinetically accessible and thermodynamically viable route. In contrast to the [Co(TPP)] system, styrene addition to the *N*-enolate carbene moiety is the highest overall barrier with *N*-enolate rearrangement being much lower and more accessible. The radical character of the reaction is not as clear cut as for the cobalt-based system. DFT calculations point towards an entirely closed-shell structure for both the *mono*-terminal and *N*-enolate carbene species, but no concerted transition state could be found and all attempts

led to a stepwise mechanism. Multireference NEVPT2-CASSCF calculations show that both carbene species have significant, but relatively small carbene π^* -antibonding character. Additional multireference calculations on the transition state of styrene addition to the carbene intermediate reveal an increase of π^* -antibonding character and buildup of radical character on the benzylic styrene position. This is in line with the observed experimental radical reactivity.



Scheme 5. Acceptor-acceptor [Fe(H₂PhenTAA)]-carbenes react via distinct stepwise, radical pathways as shown by both single- and multireference computational methods (Chapter 6).

This dissertation contributes to the overall carbene radical field and the wider redox-active ligand literature. Here we have shown that by switching to alternative, more reactive hypervalent iodine precursors, new modes of reactivity and alternative pathways can be unlocked. We have demonstrated here that a combined approach of extensive experimental and spectroscopic work as well as computational findings can establish a strong fundamental basis upon which to expand into further work. This has allowed us to combine different aspects of radical and redox chemistry to translate the well-established cobalt-carbene radical chemistry to iron. We envision that these findings can help solve existing challenges within the field of cobalt- and iron-carbene transfer, and at the same time they provide a starting point for the application of iodonium ylides in carbene radical transfer.

For one, cobalt-catalysed intermolecular C–H transfer is still a significant challenge. Insight into failed attempts to do so for acceptor-acceptor carbene radicals and related deactivation studies show that the problem is most likely radical escape from the solvent cage. Supramolecular approaches to bind the hydrogen-atom donor could facilitate the radical rebound step towards the C–H insertion product.

The iron carbenes discussed in **Chapters 5–6** are electronically not so different from the established *mono*-substituted iron-porphyrin carbenes, yet display stepwise, radical reactivity as opposed to the concerted, two-electron reactivity seen for the iron-porphyrin carbenes. This is likely due to the difference between acceptor-acceptor carbenes and *mono*-substituted acceptor carbenes, something also seen by White et al. in intramolecular C–H insertion. Therefore, such radical reactivity is likely not limited to the [Fe(H₂PhenTAA)] catalyst and could be applied to other iron carbene transfer catalysts as well.

The work in this thesis shows the first, yet highly successful application of iodonium ylides for the established [Co(TPP)] catalyst. This reactivity shows promising potential to be expanded for the synthesis of various carbo- and heterocycles, giving both access to disubstituted frameworks as well as using acidic methylenes (CH₂ groups bearing two acceptor moieties) as an alternative synthetic starting point. The acquired fundamental insights illustrated here provide new synthetic access points for metal carbene radical species and offer a platform to develop novel types of reactivity.

