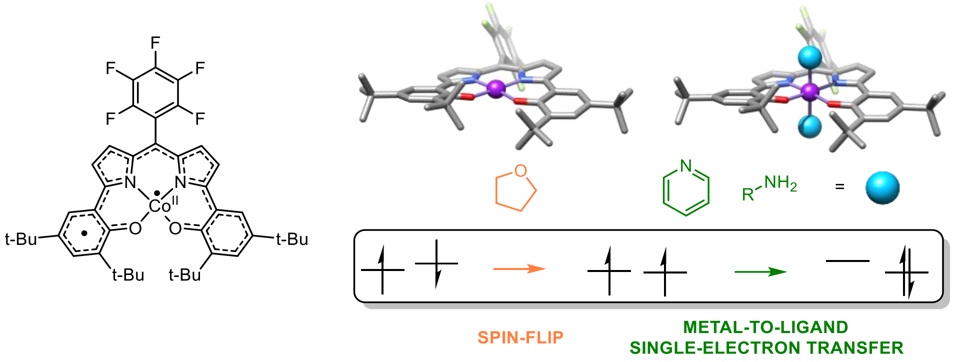
Summary

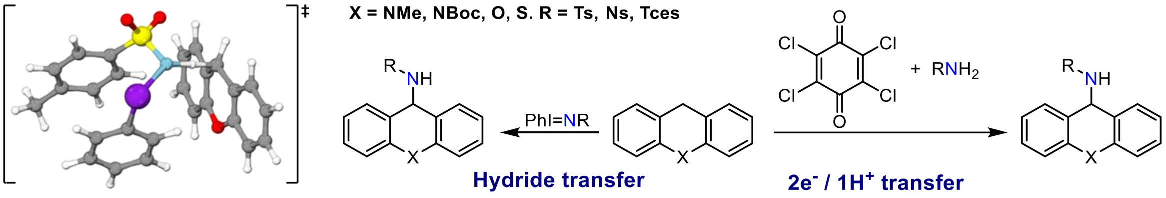
Homogeneous transition metal catalysis has been instrumental for the development of new and selective chemical transformations. Traditionally, the judicious choice of a second or third row transition metal bearing a specific (spectator or redox-innocent) ligand has led to great advances in terms of catalyst selectivity, activity and stability. In addition, the Nature-inspired use of base metals and redox-active ligands to gain control over radical (one-electron) reactivity has seen tremendous advances in recent decades. Moreover, atom and group transfer reactions are ubiquitous in Nature and attractive from a synthetic point of view, as they allow for the direct functionalization of (unactivated) substrates and thereby open new routes to access desirable target molecules. Within group transfer reactions, nitrene transfer is particularly interesting as this allows for the direct installment of an *N*-group, which is present in a plethora of e.g. bioactive molecules and polymers. Especially nitrene transfer reactions that operate via radical-type mechanisms offer opportunities to take advantage of the associated (often) low-energy demanding one-electron pathways. A challenge, however, is to control these radicals and perform the reactions in a selective manner. In **Chapter 1** an introduction to homogeneous catalysis and the tools to control the radical-type reactivity is provided, with special attention to the use of redox-active ligands and the implications for, and advances in, nitrene radical transfer reactions. The following Chapters of this dissertation contain our contributions to the fields of redox-active ligands on cobalt, nitrene radical formation and nitrene transfer reactions.

We first set out to investigate the role of redox-active ligands on the spin state of a metal complex. In **Chapter 2** we therefore synthesized a new variant of the redox-active DPP^{2-} ligand (DPP = dipyrrin-bis-(*o*,*p*-di-*tert*-butylphenolato)) that bears a pentafluorophenyl moiety on the *meso*-position (Scheme 1). Coordination of this ligand to cobalt afforded the square planar [Co^{II}(DPP$^{\bullet 2-}$)] complex and provided a platform to study the influence of the redox-active ligand on spin state changes. [Co^{II}(DPP$^{\bullet 2-}$)] was characterized as an open-shell singlet due to antiferromagnetic coupling between low-spin (S = ½) cobalt(II) and a ligand centered radical. Bis-coordination of THF on the axial positions changes the orbital overlap between the DPP$^{\bullet 2-}$ ligand radical π-orbitals and the cobalt(II) metalloradical *d*-orbitals, resulting in a spin-flip to the triplet state. Bis-coordination of the stronger donors pyridine, *t*BuNH$_2$ or AdNH$_2$ (Ad = 1-adamantyl) destabilizes the d_{z^2} orbital to the extent that metal-to-ligand single-electron transfer occurs. This results in the formation of low-spin (S = 0) cobalt(III)-complexes [Co^{III}(DPP^{3-})(L)$_2$] containing a fully reduced DPP^{3-} ligand and consequently closed-shell singlet electronic ground states.



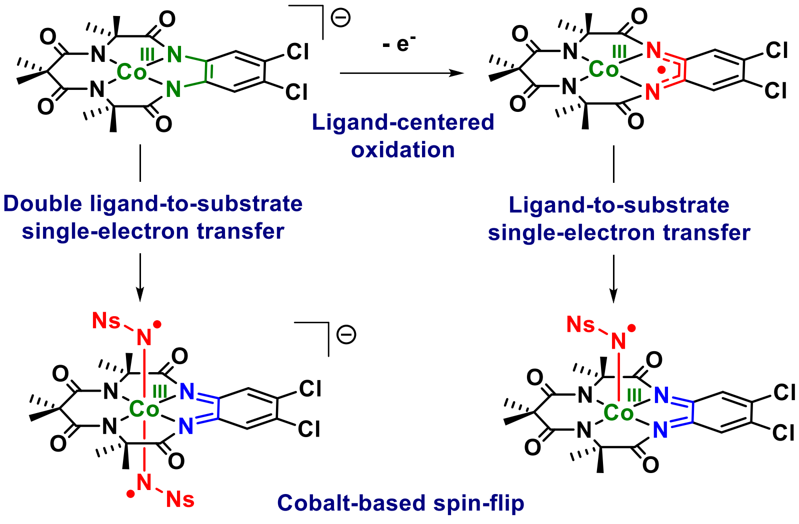
Scheme 1. Changes in the spin state of a Co-DPP complex upon coordination of axial donors (Chapter 2).

Hereafter, we initially set out to study double hydrogen atom transfer reactions on amines coordinated to cobalt complexes to afford the corresponding nitrene species. However, we found an interesting C–H amination approach based on proton and electron transfer that does not require a metal catalyst at all. In **Chapter 3** we describe the details of this new one-step oxidative C–H amination of xanthene and thioxanthene with sulfonamides and a benzoquinone (Scheme 2). In addition, we also disclose the previously unknown and uncatalyzed reaction between iminoiodinanes and xanthene, thioxanthene and dihydroacridines. The reactions are initiated by formal hydride (or two-electron and one-proton) transfer from the dihydroheteroanthracene to the iminoiodinane or benzoquinone. Subsequent conjugate addition of the sulfonamido intermediate or sulfonamide, respectively, to the oxidized heteroaromatic compound affords the C–H aminated products. Besides being an interesting new approach by itself, this work is particularly relevant for the study of metal-catalyzed nitrene insertion reactions. Xanthene is often employed as a substrate for mechanistic studies in these reactions due to its low C–H bond dissociation energy. However, these substrates clearly undergo non-catalyzed (proton-coupled) C–H amination, thus providing alternative (or background) pathways that might compete with the widely assumed metal-catalyzed mechanisms.



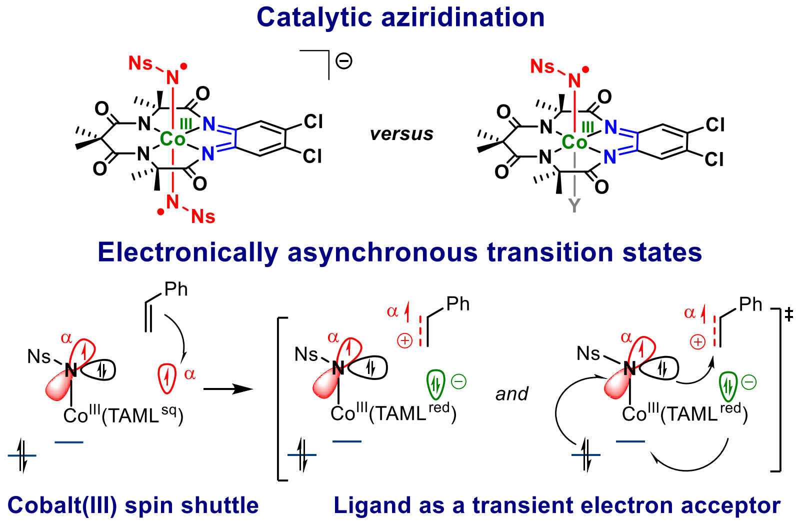
Scheme 2. The direct oxidative C–H amination of dihydroheteroanthracenes with iminoiodinanes or sulfonamides and a benzoquinone (Chapter 3).

We next became interested in Co-TAML (Tetra-Amido Macrocyclic Ligand) complexes as potential candidates for nitrene transfer reactions on a cobalt(III) platform. In **Chapter 4** we first investigated the literature-debated redox non-innocence of the TAML scaffold in cobalt-TAML complexes (Scheme 3). We found that the TAML is indeed redox-active on cobalt and that one-electron oxidation of $[\mathrm{Co^{III}(TAML^{red})}]^-$ affords $[\mathrm{Co^{III}(TAML^{sq})}]$ via ligand-centered oxidation. Cobalt retains the +III oxidation state and has an intermediate-spin (S = 1) ground state in both starting complexes. However, ligand-centered oxidation triggers a transition from a triplet spin state ($[\mathrm{Co^{III}(TAML^{red})}]^-$) to a net doublet spin state ($[\mathrm{Co^{III}(TAML^{sq})}]$) due to antiferromagnetic coupling between cobalt- and ligand-centered unpaired electrons in the oxidized complex. The redox-active TAML was found to control the selective formation of mono- or bis-nitrene radical complexes via ligand-to-substrate single-electron transfer. Specifically, reaction of $[\mathrm{Co^{III}(TAML^{red})}]^-$ with PhINNs cleanly afforded the anionic bis-nitrene radical complex $[\mathrm{Co^{III}(TAML^{q})(N^{\bullet}Ns)_2}]^-$ via two-electron oxidation of the ligand and a transition to a low-spin (S = 0) cobalt(III) center. Reaction of PhINNs with the neutral analogue $[\mathrm{Co^{III}(TAML^{sq})}]$ selectively afforded the mono-nitrene radical complex $[\mathrm{Co^{III}(TAML^{q})(N^{\bullet}Ns)}]$, again with a low-spin (S = 0) cobalt(III) center. In both cases the ligand-to-nitrene single-electron transfer events give rise to the formation of one-electron reduced Fischer-type nitrene radical complexes.



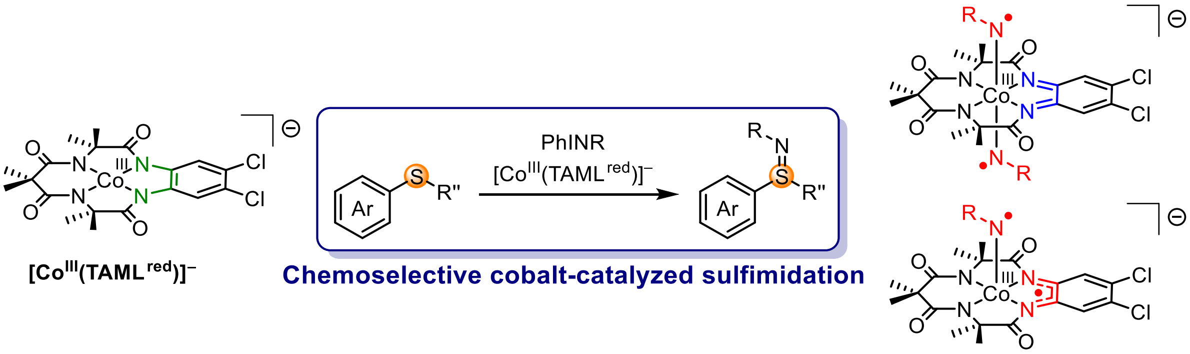
Scheme 3. TAML as a redox-active ligand on cobalt(III) enables the selective formation of an anionic bis-nitrene radical or a neutral mono-nitrene radical complex (Chapter 4).

We were eager to explore the competence of the nitrene radical complexes in nitrene transfer reactions. We therefore studied the reactivity and nitrene transfer mechanisms of these nitrene radical complexes in catalytic aziridination in **Chapter 5** (Scheme 4). We found that both $[Co^{III}(TAML^{red})]^-$ and $[Co^{III}(TAML^{sq})]$ catalyze the aziridination of styrene derivatives, 1-hexene and cyclohexene under mild and even aerobic (for $[Co^{III}(TAML^{red})]^-$) conditions with iminoiodinanes as the nitrene precursors. The reactions proceed in a chemo- and diastereoselective manner and we identified $[Co^{III}(TAML^{q})(N^{\bullet}Ns)(Y)]$, $[Co^{III}(TAML^{q})(N^{\bullet}Ns)_2]^-$ and $[Co^{III}(TAML^{sq})(N^{\bullet}Ns)]^-$ as key electrophilic intermediates in the aziridination reactions. Interestingly, the nitrene radical complexes did not react via the commonly assumed stepwise radical-type addition and recombination pathways, but rather via unusual electronically asynchronous transition states. In these transition states the actual C–N bond formation is preceded by (partial) substrate-to-ligand single-electron transfer, coupled to TAML-to-cobalt and cobalt-to-nitrene single-electron transfer via a transition to an intermediate-spin ($S = 1$) cobalt center. These processes induce nucleophilic attack of the nitrene (radical) lone pair to the (partially) oxidized substrate to afford C–N bond formation. Such a mechanism was hitherto unknown for cobalt catalyzed hypovalent group transfer, and more in general for transition metal catalyzed nitrene transfer to alkenes, but is now shown to complement the established concerted and stepwise mechanisms for *N*-group transfer. Moreover, new roles were found for the ligand, metal and nitrene radical: the TAML moiety can be regarded as a transient electron acceptor, while the cobalt-center behaves as a spin shuttle and the nitrene radical acts as a nucleophile.



Scheme 4. Co-TAML catalyzed aziridination occurs through electronically asynchronous transition states on the nitrene radical complexes (Chapter 5).

Triggered by the finding that substrate-to-ligand single-electron transfer and electronically asynchronous transition states are operative in the aziridination reaction, we reasoned that the oxidation potential of functional groups might be used as a tool to control chemoselectivity in related nitrene transfer reactions catalyzed by [Co^{III}(TAML^{red})]$^{-}$. Indeed, in **Chapter 6** we demonstrate that PPh$_4$[Co^{III}(TAML^{red})] is a competent and stable catalyst for the sulfimidation of various (aryl)(alkyl)-substituted sulfides with iminoiodinanes under mild and aerobic conditions, with turnover numbers up to 900 and turnover frequencies up to 640 min^{-1} (Scheme 5). The sulfimidation proceeds in a highly chemoselective manner that is controlled by the electrophilicity of the nitrene radical intermediate and the oxidation potential of the substrate. Sulfimidation is preferred over nitrene transfer to alkenes or weak C–H bonds, as supported by inter- and intramolecular competition experiments. Mechanistic studies suggest that the actual nitrene transfer to the sulfide proceeds via electrophilic nitrene radical intermediates that afford the sulfimide products via electronically asynchronous transition states, in which single-electron transfer from the sulfide to the nitrene radical complex precedes N–S bond formation in a single concerted process.



Scheme 5. Chemoselective sulfimidation catalyzed by PPh$_4$[Co^{III}(TAML^{red})] via electronically asynchronous transition states (Chapter 6).

With this dissertation we have contributed to the expansion of the applications of redox-active ligands on cobalt to stabilize (unconventional) electronic structures and enable new mechanisms for nitrene radical formation and transfer reactions. Moreover, we have shown that a synergistic synthetic, spectroscopic and theoretical approach to study a chemical problem or question can lead to a fundamental understanding of the systems, which would not be obtained in a single research perspective. We foresee that the studied cobalt-TAML complexes will also be useful systems for other hypovalent groups transfer reactions (e.g. oxo and carbene transfer) under mild conditions. In addition, electronic asynchronous transition states could turn out to be more important for related nitrene transfer reactions than is currently assumed and the potential generality of this mechanism should be investigated. Investigations towards further fine-tuning of (relative) redox potentials of the (TAML) ligand and substrate can aid further substrate-to-ligand single-electron transfer reactions to generate reactive (substrate centered) radicals in a selective manner.