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Controlling Radical-Type Single-Electron Elementary Steps in Catalysis with Redox-Active Ligands and Substrates
Nicolaas P. van Leest, Felix J. de Zwart, Minghui Zhou, and Bas de Bruin*

ABSTRACT: Advances in (spectroscopic) characterization of the unusual electronic structures of open-shell cobalt complexes bearing redox-active ligands, combined with detailed mapping of their reactivity, have uncovered several new catalytic radical-type protocols that make efficient use of the synergistic properties of redox-active ligands, redox-active substrates, and the metal to which they coordinate. In this perspective, we discuss the tools available to study, induce, and control catalytic radical-type reactions with redox-active ligands and/or substrates, contemplating recent developments in the field, including some noteworthy tools, methods, and reactions developed in our own group. The main topics covered are (i) tools to characterize redox-active ligands; (ii) novel synthetic applications of catalytic reactions that make use of redox-active carbene and nitrene substrates at open-shell cobalt−porphyrins; (iii) development of catalytic reactions that take advantage of purely ligand- and substrate-based redox processes, coupled to cobalt-centered spin-changing events in a synergistic manner; and (iv) utilization of redox-active ligands to influence the spin state of the metal. Redox-active ligands have emerged as useful tools to generate and control reactive metal-coordinated radicals, which give access to new synthetic methodologies and intricate (electronic) structures, some of which are yet to be exposed.

KEYWORDS: redox-active ligands and substrates, radical-type reactivity, catalysis, (electronic) structure, spin state

INTRODUCTION

The development and mechanistic understanding of homogeneous catalysts is of pivotal importance for the synthesis of new (fine) chemicals and bioactive compounds. Typically, the reactivity of a transition-metal-based homogeneous catalyst is primarily determined by the redox reactions taking place at the metal center, which is indirectly influenced by the redox-innocent (redox-inactive) spectator ligands that control the steric and electronic properties of the metal. However, while still less common, many catalytic reactions have also been disclosed over the past years in which the ligand plays a much more active role, which includes both cooperative and redox-active ligands. In particular, studies regarding the influence of reactive redox-active ligands on the reactivity of transition metals have gained momentum and have led to significant advances in challenging homogeneously catalyzed reactions, such as CO2 reduction, water oxidation, and methanol dehydrogenation for H2 production.

Redox-active ligands typically have filled bonding π-orbitals of relatively high energy or empty antibonding π-orbitals of relatively low energy and, therefore, oxidation or reduction potentials close to or lower/higher than those of the metal center to which they coordinate. Consequently, a redox stimulus easily triggers a ligand-centered redox event, with the metal retaining its original oxidation state (Scheme 1A). Redox non-innocent ligands belong to the exact same subclass as redox-active ones, but whereas for complexes with redox-active ligands discrete assignment of physical oxidation states is usually clear and measurable, this is difficult or ambiguous for complexes with redox non-innocent ligands.

Ligand-centered redox processes are also observed in several enzymatic processes that operate via radical-type mechanisms, wherein redox-active protein residues play a key role in some of the most impressive metabolic processes such as photosynthesis and methane oxidation. Nature has served as an inspiration for many researchers to use redox-active ligands to control radical-type reactions with synthetic catalysts, which has proven to be a successful strategy. The ability of redox-active ligands to stabilize ligand-centered radicals has given access to a broad range of novel radical-type reactions, wherein redox-active ligands play different roles (Scheme 1B). They
can (i) change the Lewis acidity or basicity of the metal center, (ii) act as electron reservoirs, (iii) generate reactive ligand-centered radicals, and (iv) directly activate substrates via radical-type reactions such as SET (single-electron transfer) or HAT (hydrogen atom transfer).4−6 Also metal-bound substrates can act as redox-active moieties in one or more intermediates during catalytic turnover.15,16 In this manner, redox-active substrates can be involved in single-electron (transfer) processes, thus generating discrete substrate-centered radicals that trigger or undergo radical-type elementary steps. Specifically, redox-active carbene and nitrene substrates were recently proven to undergo one-electron reduction upon coordination to cobalt(II), 17,18 iron(II), nickel(I), and copper(I)19 complexes, which are subsequently involved in low-barrier radical-type pathways. This makes them particularly suitable for group transfer to otherwise relatively unreactive substrates.

In addition to inducing radical-type reactivity, accessing different spin states is also inherently connected to open-shell systems. Moreover, changing the absolute amount and relative coupling of unpaired electrons is known to have a tremendous influence on the observed reactivity.

Accessing more than one spin state during catalysis (multistate reactivity) can result in lower reaction barriers than reactions that are restricted to a single spin surface.20−22 This is a well-understood paradigm in bioinorganic chemistry, and enzymes selectively oxidize substrates depending on the spin surface accessed during a reaction (spin-selective reactivity),23 and these concepts have successfully been implemented in catalysis using biomimetic metal complexes.24−26 However, the concepts and design rules that afford control over the spin state of a complex bearing a redox-active ligand are still a topic of investigation, and further research is directed toward expanding the currently known applications of redox-active ligands by controlling the spin state of a complex or catalyst.

In this perspective, we discuss the tools available to study, induce, and control catalytic radical-type reactions with redox-active ligands and/or substrates, contemplating recent developments in the field, including some noteworthy tools, methods, and reactions developed in our own group. The main topics covered in this perspective are (i) tools to characterize redox-active ligands; (ii) novel synthetic applications of catalytic reactions that make use of redox-active carbene and nitrene substrates at open-shell cobalt−porphyrins; (iii) development of catalytic reactions that take advantage of purely ligand- and substrate-based redox processes, coupled to cobalt-centered spin changing events in a synergistic manner; and (iv) utilization of redox-active ligands to influence the spin state of the metal. We will conclude by placing these findings in a broader perspective, by providing an outlook for new developments and synthetic opportunities offered by these fascinating ligand scaffolds.

### CHARACTERIZATION OF REDOX-ACTIVE LIGANDS

The characterization of complexes bearing redox-active ligands, as well as measuring changes in the oxidation state of the ligand upon a (redox) reaction, is an endeavor that typically requires combined information from various techniques. Closed-shell complexes can be investigated routinely by nuclear magnetic resonance (NMR), wherein especially the degree of ligand (de)aromatization is easily recognized in 13C and 1H NMR and can be used as an identifier of the ligand oxidation state. Unpaired electron density can be probed with electron paramagnetic resonance (EPR) techniques, and further information about the oxidation state and coordination...
geometry of the metal center can be obtained by X-ray absorption spectroscopy (XAS).\textsuperscript{31,32} Noteworthy, the latter can also be applied to donor atoms in the ligand, although this is often accompanied with poor data quality. UV–vis/NIR spectroscopy can be used to probe metal-to-ligand (or ligand-to-metal) charge transfer and intraligand excitation processes, which are both sensitive to perturbation of the ligand bond lengths (IR) and $\pi$-conjugation (UV–vis) by a redox stimulus.\textsuperscript{33}

Especially when coupled to electrochemical techniques such as cyclic voltammetry (CV) or differential pulse voltammetry (DPV) in spectro-electrochemical (SEC) studies, this can afford useful information about the redox potentials and locus of the redox events (i.e., metal- or ligand-centered).\textsuperscript{34,35}

Magnetic susceptibility data and information about the spin state of a complex can be obtained in solution by virtue of Evans’ method or in the solid state by a superconducting quantum interference device (SQUID) that probes the temperature dependence of the magnetization.\textsuperscript{36,37}

For electronic doublet ($S = 1/2$) systems, EPR spectroscopy is a particularly useful technique to locate the spin density in paramagnetic complexes, thereby elucidating the electronic structure of open-shell complexes containing redox-active ligands.\textsuperscript{28} In continuous wave EPR, the magnetic field is swept under a constant wavelength of microwave irradiation, detecting signals at different strengths of the magnetic field. The magnetic field at which a signal is detected can be converted to a $g$ value, which provides information on the local environment of an unpaired electron. Generally speaking, if the unpaired electron is primarily located on a light atom (e.g., carbon, nitrogen, or oxygen), the $g$ value is close to that of a free electron ($2.05 > g_e = 2.0032 > 1.95$), whereas for unpaired electrons located on heavier atoms (i.e., metal centers), spin–orbit coupling interactions in the molecule typically cause deviations from $g = 2.0032$. The $g$ value is therefore very useful to study the location of the unpaired electron, i.e., metal- or ligand-centered (Scheme 2A,B). The presence and magnitude of coupling of a certain nuclear spin to the unpaired electron, the hyperfine coupling interactions, provides even more information about the location of the unpaired electron, especially when combined with (density functional theory, DFT) EPR property calculations. At low temperatures (i.e., in absence of molecular rotation during measurement), both the $g$ values and hyperfine interactions can be split into their $x$, $y$, and $z$ components, providing information regarding the electronic symmetry of the paramagnetic compound.

These techniques are often used in combination with computational studies to obtain additional insight into the electronic structure of the complex bearing a redox-active ligand. Whereas (time-dependent) single-reference DFT\textsuperscript{38–41} calculations are relatively cheap (computationally inexpensive), adequate, and well-established, also the use of multi-reference post-Hartree–Fock methods such as complete active space self-consistent field (CASSCF) is sometimes warranted for computational analysis of complexes bearing redox-active ligands. The possible involvement of multi-reference states can often be investigated routinely by an inexpensive fractional occupation density analysis, clearly indicating whether additional (computationally expensive and elaborate) multi-reference calculations are necessary.\textsuperscript{43}

Ligand bond distortions upon oxidation or reduction are characteristic of ligand-centered redox activity (Scheme 2C) and can be readily measured by SC-XRD (single crystal X-ray
diffraction), which is therefore a useful tool to study redox events taking place at redox-active ligands. Accompanied by technological advances, crystal structure determination has changed from a vocational to a routine measurement. Consequently, SC-XRD-derived structures were pivotal in solving many early redox noninnocence issues, such as in the description of metal–dithiolene complexes. After a crystal structure is acquired and solved, the oxidation state of the ligand can be reliably deduced through comparison of the observed bond metrics to similar complexes in the literature. With the aid of structural databases (i.e., the Cambridge Structural database (CSD) and the Protein Databank (PDB)), the possibility arose to use a set of crystal structures for more subtle ligand distortion effects. This approach was used in 2000 by Wieghardt et al. to describe the redox noninnocence of the pyridine-2,6-diimine (PDI) ligand framework, for which the reduced forms had not been described up until that point. A larger literature study in 2019 on the same PDI ligand framework described the use of a single structural parameter (Δ) to study oxidation-state-dependent distortions. In addition to oxidation-state-dependent ligand bond distortions, it was reported that π-backdonation from second- and third-row transition metals to the PDI ligand also influences the ligand bond lengths.

In related work, Brown described an empirical model to calculate a metrical oxidation state of amidophenoxide and catecholate ligands, which is based on correlations between bond lengths and the ligand oxidation state. The model is based on crystallographic information from the CSD and through input of the intraligand bond distances the model provides a single numerical value which reflects the ligand oxidation state. By comparing various molybdenum and vanadium complexes, the π-donation capability of various amidophenoxide and catecholate ligands was investigated. Whereas intermediate bond distances in redox-active ligands are typically interpreted in terms of partial electron transfer from/to the ligand, this work showed that a π-bonding model can also provide a satisfactory description of redox-active ligands that seem to have a geometry between two integer ligand oxidation states. As such, caution is required in assigning oxidation states to ligands in cases where strong π-bonding effects may be important.

A metrical oxidation state model was recently also established for α-diimine, or diazabutadiene (DAD) ligands, where it was shown that the intraligand bond distances for the DAD ligand framework depend on the ligand oxidation state and coordination mode. In the fully reduced form, coordination of the C=C backbone allows for a η2-N2-DAD–DAD bonding mode that enhances the Lewis acidity of the metal and Bronsted basicity of the ligand (Scheme 2E). This was also observed previously to play a key role in catalytic cycles, by allowing for either ligand-centered protonation or metal-centered radical addition. By analysis of a large data set of structures available in the CSD, this coordination fluxionality was described in a way that would not be possible by analysis of just a select few DAD complexes, contributing to a better understanding of the DAD coordination modes and their influence on the metal- or ligand-centered reactivity. Furthermore, these studies underline the general value of comparing intraligand bond metrics of newly acquired structures to those available in large data sets of known complexes with redox-active ligands, which can help tremendously in assigning (ligand) oxidation states.

### TAMING REDOX-ACTIVE CARBENES

In addition to redox-active ligands, redox-active substrates are currently under active investigation, and cobalt(III)–porphyrin carbene radical species are one of the remarkable examples in this field. Some applications of these useful intermediates are still undisclosed, but current protocols have already shown
tremendous potential in the synthesis of several challenging structures, including a plethora of ring-closed products. The reactive character of the key cobalt(III)−carbene radical intermediates is induced by square-planar cobalt−porphyrin complexes (e.g., [Co II(TPP)], TPP = meso-tetraphenylporphyrin), which have a well-defined open-shell doublet \( S = \frac{1}{2} \) low-spin \( d^7 \)-electronic configuration. Upon reaction with a carbene precursor (e.g., diazo compound), these systems generate reactive cobalt(III)−carbene radical intermediates by a process that is best described as an intramolecular metal-to-substrate single-electron transfer process from cobalt(II) to the carbene carbon atom, concomitant with \( \text{N}_2 \) extrusion from the diazo compound. The resulting cobalt(III)−carbene radical intermediates are involved in a variety of useful radical-type cyclization reactions \((\text{vide infra})\). Moreover, the presence of spin density on the carbene moiety reduces its electrophilicity compared to that of the traditional Fischer-type carbene complexes, thereby inhibiting dimerization via reaction with another diazo compound, which thus retards unwanted side reactions and hence makes these system better suitable for the desired reactivity.15,16,52,53

The cobalt(III)−carbene radical intermediates can also be generated from \( \text{N} \)-tosylhydrazones, which are converted \( \text{in situ} \) to the corresponding carbene precursor diazo compound upon treatment with base, thereby preventing the direct use of diazo compounds. Since diazo compounds can be cumbersome to prepare and are often explosive and poisonous, the \( \text{N} \)-tosylhydrazone route provides access to a variety of different substrates enhancing the generality of the applied method.54−57 The formed cobalt−carbene radical intermediate can engage in stepwise controlled radical addition or HAT and then transform to various interesting structures in a mild and efficient manner. The redox-active carbene substrates thereby give access to the \([\text{Co}^{\text{III}}(\text{TPP})]\)-catalyzed formation of (among others) cyclopropanes,58−63 chromenes,54,65 furans,66 indenes,67 indolines,68,69 ketenes,70,71 butadienes,72 dihydronaphthalenes,72 piperidines,73 pyrrolidines,74 dibenzocyclooctatetraenes,75,76 and monobenzocyclooctadienes.76 Based on previous work, and driven by a continuing need for development of new, efficient protocols for the synthesis of \( \text{N} \)-heterocycles, a method was recently developed to construct medicinally relevant piperidines in high yields via these cobalt−carbene radical intermediates.73 Starting from Boc-protected \( \text{N} \)-tosylhydrazones, a range of piperidines was efficiently obtained under mild reaction conditions using \([\text{Co}^{\text{III}}(\text{TPP})]\) as the catalyst.

DFT studies revealed that the \( \text{N} \)-tosylhydrazone precursor is first activated \( \text{in situ} \) to the corresponding diazo compound, which is subsequently trapped by the cobalt(II) catalyst to produce the key cobalt(III)−carbene radical intermediate (Scheme 3). The generated carbene radical is involved in a subsequent intramolecular 1,6-HAT process (TS2) to produce a benzylic radical. A radical rebound step (TS3) then leads to formation of the desired product and regenerates the cobalt(II) catalyst.

Another application we like to highlight is the activation of a series of \( \text{o} \)-styril-\( \text{N} \)-tosylhydrazones as carbene precursors, leading to selective formation of a series of unexpected, but useful, reaction products. Depending on the specific substitution pattern of the substrates, dihydronaphthalenes,72 (\( \text{E} \))-aryl dienes,72 dibenzocyclooctatetraenes,75,76 and monobenzocyclooctadienes76 could be generated in high yields using \([\text{Co}^{\text{III}}(\text{TPP})]\) as the catalyst. Each of these reactions has a
broad substrate scope and shows excellent functional group tolerance. The initial steps of the reaction are quite similar, as described for the generation of piperidines (vide supra), and according to DFT calculations, the formation of the cobalt(III)—carbene radical intermediate is again followed by an intramolecular HAT process. However, the resulting allyl radicals are in direct conjugation with the weak cobalt—carbon bond of these intermediates, leading to easy dissociation of o-quinodimethane intermediates from the catalyst. The fate of these reactive compounds largely depends on the substituents of the allylic position in the substrate (R² in Scheme 4), which direct the pathways of subsequent (uncatalyzed) follow-up reactions. Selective formation of 2H-chromenes in intramolecular reactions between salicyl radicals are in direct conjugation with the weak cobalt according to DFT calculations, the formation of the cobalt—pharmaceutically relevant spiro compounds.

Very recently, the group of Betley reported a noteworthy study involving intramolecular C—H alkoxylation of α-diazo-β-ketoesters, catalyzed by Fe(acac)₃ (Scheme 5). As observed for cobalt(II) in the above examples, activation of the diazo compound by the iron(II) catalyst triggers one-electron reduction and formation of a carbon-centered radical upon N₂ loss from the substrate. However, in this reaction, an iron(III) vinyl radical intermediate is generated from the diazo compound instead of a carbene radical because the substrate binds via the β-ketoester moieties in a chelating manner. The chelating vinyl radical undergoes 1,5-hydrogen atom transfer to generate an allyl radical that recombines with the iron-bound keto-oxygen to furnish a five-membered oxacycle. The high chemoselectivity toward THF-like O-heterocyclic motifs seems to be entropy-driven. The authors displayed an impressive scope of fused bis- and tricyclic motifs, which highlights the applicability of this methodology for the synthesis of pharmaceutically relevant spiro compounds.

**NITRENE RADICAL TRANSFER FROM ALIPHATIC AZIDES**

Similar to the above-described reactivity of carbene radicals, activation of organic azides at open-shell transition metal complexes such as cobalt(II)—porphyrins leads to formation of nitrone radical (or nitridyl) complexes. These species bear discrete spin density at the reactive nitrogen atom, which enables valuable nitrone transfer reactions that proceed via base-metal-catalyzed radical-type reactions. Most (older) reports describe (enantioselective) radical-type nitrone transfer from reactive “preactivated” azides such as aryl azides, sulfonylazides (e.g., TsN₃), and carbonazidates (e.g., TroCN₃). Recently, the Zhang and Chang groups reported cobalt-catalyzed intramolecular enantioconvergent amination of C(sp³)−H bonds with sulfonylazides and intermolecular C(sp³)−H amination of unactivated alkanes with TroCN₉, respectively.

Also noteworthy in the context of previous work on activated nitrone precursors are the copper and silver catalysts bearing hydrotris(pyrazolyl)borate ligands, which form nitrone radicals upon reaction with iminodiodanes. These nitrone radicals react with alkenes to afford aziridines via concerted (silver) or stepwise (copper) mechanisms, therefore affording the products with retention or partial loss of stereochemistry, respectively. Interestingly, spin state changes on the nitrone radical complexes dictate the exact mechanism, and minimum energy crossing points connect the triplet to closed-shell singlet (silver) and triplet to open-shell singlet (copper) surfaces. Control over the spin state of (transient) intermediates is thus highly important and will be further discussed in the “Synergistic Redox Activity at the Ligand and Substrate” and “Changing Spin States” sections.

While the development of various nitrone radical transfer catalysts provides important tools for direct functionalization of C−H and C≡C bonds, most of these systems fail to activate nonactivated aliphatic azides. That is unfortunate because aliphatic azides provide a substantially broader substrate scope, thus expanding the synthetic toolbox of nitrone transfer reactions to prepare bioactive compounds such as N-heterocycles.

The first reported catalyst capable of activating aliphatic azides for direct nitrone insertion to synthetize N-heterocyclic ring structures was reported by Betley in 2013 (Scheme 6, left). This pioneering study has triggered several follow-up studies that attempted to address some of the limitations of the original report: requirement of quite high catalyst loadings, high reaction temperatures, unwanted production of non-cyclized amine, and nitrile side products and a requirement for in situ protection of the secondary amine products to prevent product inhibition. Hence, different catalysts have been developed since, in part by our own group. Among those, metalloradical cobalt(II) catalysts are particularly noteworthy, as noncylcized amine and nitrile side-product formation is largely suppressed by these systems (Scheme 6, right). However, each of these catalysts still requires heating and in situ protection of the product to minimize product inhibition effects.

The first example of enantioselective catalytic pyrrolidine synthesis from azides was recently reported by our own group (Scheme 6, right). However, the enantioselectivities were low at the high temperatures needed to activate the azides (Scheme 6). Recently, Meggers described an interesting chiral-at-Ru complex capable of highly enantioselective cyclization of aliphatic amines to pyrrolidines. Unfortunately, this system is based on a nonabundant second-row transition metal, requires phosphines to preactivate the azides, seems to be restricted to five-membered ring formation, and generates significant amounts of undesired noncyclized side products (~15–20%).
Traditional Cu and Rh \textsubscript{1} nitrogen-group transfer catalysts\textsuperscript{1} cannot activate aliphatic azides, to our best knowledge. Hence, significant improvements are needed to advance this field, which include enhancing catalytic activity, increasing functional group tolerance, enhancing enantioselectivity, development of methods that allow synthesis of larger ring structures, and gaining a better mechanistic understanding of how different electronic structures give rise to different catalytic capabilities.\textsuperscript{90,99} The Betley group recently reported a particularly noteworthy development, in which the authors disclosed unique nickel(I)-catalyzed ring-closing amination reactions of aliphatic azides (Scheme 7).\textsuperscript{100} The low-valent, low-coordinate [Ni\textsubscript{I}(dipyrrin)] complex (Scheme 7) described in their work is particularly active. It operates at room temperature, is highly functional group tolerant, and does not require in situ Boc protection of the N-heterocyclic amine products. However, the system does require strict protection of the \(\beta\)-CH\(_2\) positions to prevent (otherwise quantitative) formation of noncyclized nitrile side products, which currently limits the synthetic applicability (Scheme 7). Furthermore, the catalyst is nonchiral, and also this system seems to be restricted to formation of five-membered rings. Yet, this report shows that room temperature activation of aliphatic azides is possible, thus opening up several opportunities for development of new enantioselective protocols.\textsuperscript{101}

\begin{center}
\textbf{SYNERGISTIC REDOX ACTIVITY AT THE LIGAND AND SUBSTRATE}
\end{center}

Following up on the above-described mechanistic and catalytic studies employing cobalt–porphyrins, our group became interested in the use of a TAML (tetra-amido macrocyclic ligand\textsuperscript{102}) to promote ligand-mediated nitrene radical formation on a cobalt(III) platform. While the redox noninnocence of TAMLs on cobalt has been suspected, it was debated over the past two decades. Therefore, we first investigated this matter to conclude that the TAML is indeed redox-active on cobalt(III), whereafter its influence on spin states, nitrene radical formation, and transfer was investigated.

Via a combination of spectroscopic techniques (EPR, magnetic moment measurements, SC-XRD, XANES (X-ray absorption near-edge structure), UV−vis, and SEC), supported by DFT and N-electron valence state perturbation theory (NEVPT2) corrected CASSCF calculations, it was demonstrated that oxidation of \([\text{Co}\textsubscript{III}(\text{TAML}\text{red})]^−\) takes place at the ligand to afford \([\text{Co}\textsubscript{III}(\text{TAML}\text{sq})]^−\) (Scheme 8).\textsuperscript{103} \([\text{Co}\textsubscript{III}(\text{TAML}\text{red})]^−\) has a triplet (\(S = 1\)) spin state, with both unpaired electrons residing on the intermediate spin cobalt(III) center. One of the most exciting aspects of this work is the ability to tune the catalytic properties of the complex by oxidizing the ligand, which allows for the development of new enantioselective protocols.

\begin{center}
\begin{table}
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\begin{tabular}{|c|c|}
\hline
Entry & Reaction Conditions & TON & ee \\
\hline
1 & 100 °C, 33% yield & 8 & 29% \\
2 & 80 °C, 22% yield & 6 & 46% \\
\hline
\end{tabular}
\caption{Enantioselective Catalytic Amination of Aliphatic Azides}
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nosyl)-selectively afforded the anionic bisnitrrene radical complex $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{N}^\bullet\text{Ns})_2]^{-}$ and neutral mononitrrene complex $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\bullet\text{Ns})]^{-}$ respectively (Scheme 8). Cobalt retains the $+\text{III}$ oxidation state during these reactions but adopts a low-spin state, and the ligand resides in the fully oxidized dianionic state ($\text{TAML}^{\text{sq}}$), affording the nitrrene radicals in a triplet ($[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})(\text{N}^\bullet\text{Ns})_2]^{-}$) or doublet ($[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\bullet\text{Ns})]^{-}$) spin state. This means that the metal does not change its oxidation state in these reactions, and the nitrrene radicals are formed via ligand-to-substrate single-electron transfer on a cobalt(III) center. The oxidation state of the TAML dictates the formation of the neutral mono- or anionic bisnitrrene radical complexes.

Intrigued by the influence of the redox-active TAML on the selective formation of nitrrene radicals at cobalt(III), the catalytic applicability and mechanisms of the neutral and anionic complexes in nitrene radical transfer to alkenes and thioethers was investigated. These reactions are typically sensitive to oxygen and water, as this often leads to decomposition of the catalytically active nitrrene radical intermediates. However, it was found that the anionic $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^{-}$ complex catalyzes nitrene radical transfer to alkenes and thioethers under ambient conditions (e.g., in the presence of $\text{O}_2$ and $\text{H}_2\text{O}$), and that the redox-active TAML has a key role in the mechanism and efficiency of these reactions.

Free energies ($\Delta G^\circ_{298K}$ in kcal mol$^{-1}$) calculated with DFT (BP86/def2-TZVP/disp3) at the triplet ($S = 1$) spin surface.

Scheme 8. Ligand-Centered Oxidation of $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^{-}$ to $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})]^{-}$ and Formation of $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\bullet\text{Ns})_2]^{-}$ and $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\bullet\text{Ns})]^{-}$ via Ligand-to-Substrate Single-Electron Transfer

Scheme 9. Proposed Mechanism for the $[\text{Co}^{\text{III}}(\text{TAML}^{\text{red}})]^{-}$-Catalyzed Aziridination of Styrene (Left) and Sulfinidation of Thioanisole (Right) via the Anionic Mononitrrene $[\text{Co}^{\text{III}}(\text{TAML}^{\text{sq}})(\text{N}^\bullet\text{Ns})]^{-}$
With a variety of techniques (quantitative EPR, EXAFS (extended X-ray absorption fine structure), UV–vis titrations, and high-resolution mass spectrometry), three reactive intermediates for nitrene radical transfer to alkenes were identified: [CoIII(TAMLq)(N^Ns)]^−, [CoIII(TAMLsq)(N^Ns)]^−, and [CoIII(TAMLq)(N^Ns)]^2^−. Notably, under catalytic conditions, also the anionic mononitrene radical complex ([CoIII(TAMLsq)(N^Ns)]^−) is formed via ligand-to-substrate single-electron transfer to afford the nitrene radical complex in the triplet spin state on a low-spin cobalt center, with the two unpaired electrons localized on the TAML and nitrene. We herein highlight the mechanistic aspects of the TAML-assisted nitrene radical transfer reactions catalyzed by the anionic mononitrene radical complex ([CoIII(TAMLsq)(N^Ns)]^−), but it is worth noting that the reactions and mechanisms of the neutral mononitrene and anionic bisnitrene radical complexes are very similar.

Employing PPh4[CoIII(TAMLred)] as the catalyst, a variety of styrene derivatives, 1-hexene, and cyclohexene can be converted under aerobic conditions to the corresponding substrate radical cation. These observations do not match the commonly observed radical-type addition pathway, for which much smaller |ρ^α/ρ^β| ratios are observed. Moreover, the trapping and detection of styrene radicals in the aziridination reactions support the formation of substrate radicals during the reactions.

Computational (NEVPT2-CASSCF and DFT) studies are consistent with the data obtained from the Hammett analysis and were used to further study the role of the redox-active ligand and substrates during catalysis. The calculated mechanisms for aziridination via [CoIII(TAMLsq)(N^Ns)]^− (B) are depicted in Scheme 9. Nitrene radical formation via ligand-to-substrate single-electron transfer is exergonic and is followed by C–N (aziridination, left) or S–N (sulfimidation, right) bond formation via electronically asynchronous transition states TS1 and TS3 (vide infra). Notably, these transition states were calculated using single-reference DFT calculations, as the size of these complex—substrate adducts precluded the use of much more expensive post-Hartree–Fock NEVPT2-CASSCF calculations. However, fortunately, these DFT calculations did not show major spin contamination, and consistency with the experimental data justified the use of DFT calculations for description of the transition states.

With an electronic spin transition from a nitrene radical to the corresponding substrate, single-turnover experiments were used to further study the role of the redox-active ligand and substrates during catalysis. These observations do not match the commonly observed radical-type addition pathway, for which much smaller |ρ^α/ρ^β| ratios are observed. Moreover, the trapping and detection of styrene radicals in the aziridination reactions support the formation of substrate radicals during the reactions.

Computational (NEVPT2-CASSCF and DFT) studies are consistent with the data obtained from the Hammett analysis and were used to further study the role of the redox-active ligand and substrates during catalysis. The calculated mechanisms for aziridination via [CoIII(TAMLsq)(N^Ns)]^− (B) are depicted in Scheme 9. Nitrene radical formation via ligand-to-substrate single-electron transfer is exergonic and is followed by C–N (aziridination, left) or S–N (sulfimidation, right) bond formation via electronically asynchronous transition states TS1 and TS3 (vide infra). Notably, these transition states were calculated using single-reference DFT calculations, as the size of these complex—substrate adducts precluded the use of much more expensive post-Hartree–Fock NEVPT2-CASSCF calculations. However, fortunately, these DFT calculations did not show major spin contamination, and consistency with the experimental data justified the use of DFT calculations for description of the transition states.
In the aziridination reaction, the formed benzylic radical (C) collapses via a low-lying transition state TS2 to the aziridine, concomitant with single-electron reduction of the TAML. OFF-cycle isomerization of the cis-aziridine then affords the more stable trans isomer as the reaction product and regenerates the starting cobalt catalyst with the ligand in the fully reduced state (TAML\textsuperscript{red}). In the sulfoxidation reactions, the zwiterionic sulfur ylide coordinated to cobalt is immediately obtained after TS3, with the ligand already residing in the fully reduced state. Decoordination of the sulfimide product then liberates the starting catalyst and completes the catalytic cycle.

While these nitrene transfer reactions often proceed via concerted or stepwise processes\textsuperscript{17,18}, the electronically asynchronous transition states follow a novel pathway wherein the redox noninnocence of the ligand and substrates is pivotal.\textsuperscript{104,105} Although the overall pathways can still be described as stepwise (aziridination) or concerted (sulfoxidation), the initial step of these reactions involves an electronically asynchronous transition state, which we define as a process wherein a (partial) electron transfer event precedes bond formation in a single process, without forming discrete redox intermediates. The electron transfer processes for TS1 and TS3 are depicted in Scheme 10 and are both initiated by partial substrate-to-ligand single-electron transfer to afford a transition state with a transient and partial substrate radical cation character and the ligand approaching the fully reduced (TAML\textsuperscript{red}) state on the anionic mononitrene radical complex. For the aziridination reaction, this process is coupled to simultaneous TAML-to-cobalt and cobalt-to-nitrene single-electron transfer, wherein cobalt effectively adopts an intermediate spin state and thus acts as a spin shuttle. Remarkably, C–N bond formation does not occur via the unpaired electron on the nitrrene but rather involves nucleophilic attack of the doubly filled nitrrene lone pair onto the formed styrene radical cation. For the sulfoxidation reaction, TAML-to-cobalt single-electron transfer essentially triggers spin exchange between cobalt and the sulfide radical cation, with the formation of an intermediate spin cobalt center being the intrinsic driving force for this process. Again, S–N bond formation occurs via attack of the doubly filled nitrrene lone pair, followed by intramolecular S-to-N single-electron transfer to afford the zwiterionic sulfur ylide.

During these electronically asynchronous transition states, cobalt retains the +III oxidation state throughout and only acts as a spin shuttle. Remarkably, the TAML, alkene or sulfide, and the nitrrene all behave as redox-active (substrate) ligands and thereby facilitate efficient product formation. While the generality of these electronically asynchronous transition states is currently not explored to the fullest, we expect that judicious tuning of substrate, ligand, and metal oxidation and spin states might give access to other reactions proceeding via similar pathways that are triggered by substrate-to-ligand single-electron transfer and synergistic cooperation between the ligand, metal, and substrate. Synergetic use of spectroscopic and experimental data, in conjunction with DFT and where possible multireference calculations, can lead to insights into other reactions that might proceed via electronically asynchronous transition states.

## Changing Spin States

Tuning or changing the spin state on a complex can have tremendous influence on chemical reaction pathways and rates\textsuperscript{10,106} and plays a pivotal role in biochemistry\textsuperscript{107}, spintronics,\textsuperscript{108} and molecular magnets.\textsuperscript{109} We foresee that further control over spin states using redox-active ligands opens the door towards novel spin-controlled reactions. Therefore, it is important to understand the roles redox-active ligands play in accessing multiple spin surfaces. Control over the spin state in metal complexes bearing redox-innocent ligands is well-understood in terms of the ligand-field splitting parameter (Δ), which describes the energetic difference between (partly) filled and empty d-orbitals.\textsuperscript{110} If, however, a redox-active ligand is coordinated to the metal center, additional (open-shell) electronic configurations are possible, therefore complicating the parameters that contribute to the spin ground state.\textsuperscript{111}
To obtain more insight into the factors controlling the spin state in complexes bearing redox-active ligands, a cobalt complex bearing a functionalized dipyrin–bisphenol (DPP) ligand was studied to elucidate the respective roles of the metal and redox-active ligand in the ground state wave function and spin state changes upon axial coordination of redox-innocent donor ligands. The square-planar complex [CoII(DPP3−)] was characterized by SC-XRD, NMR, SQUID, magnetic moment determination, and supporting DFT and NEVPT2-CASSCF calculations as an open-shell singlet, containing a ligand centered radical (DPP3−) of α spin, located in a L2+xΔL−L− orbital. The electron is antiferromagnetically coupled to a low-spin (S = 1/2) cobalt(II) center with the unpaired β-spin electron residing in the d2− orbital (Figure 1). The small contribution of the d2− orbital to the ligand-centered singly occupied molecular orbital causes significant spin–spin repulsion in the d2− manifold, thus leading to preference of the open-shell singlet over the triplet spin state.

Solvation of this complex in the weak sp3-hybrid donor THF quantitatively affords the octahedral complex [CoII(DPP3−)-(THF)]2+, which has a triplet spin and again a low-spin cobalt(II) center and ligand-centered radical (Figure 1).112 The ligand-centered α-spin electron mainly resides in the strongly correlated antibonding combinations of the d2− orbital with the ligand pyrrole π-framework (d2−−πL) and the complete ligand π-system (L2−−d2−). The latter is more delocalized over the ligand and bears the major amount of spin density to prevent electron–electron repulsion and thereby enhance radical stabilization. With the d2− orbital being isolated, both unpaired electrons adopt an α spin to maximize the total spin, in accordance with Hund’s rule.115

Axial coordination of the stronger donors (L) pyridine (ζ-donor, weak ζ-acceptor), tBuNH2, or AdNH2 (ζ-donors, Ad = 1-adamantyl) affords the octahedral complexes [CoIII(DPP3−)]. (L)3, which all reside in the closed-shell singlet state (Figure 1).116 The major destabilization of the cobalt-centered d2− orbital due to coordination of these strong donors raises the energy of this orbital to such an extent that intramolecular metal-to-ligand single-electron transfer occurs. Consequently, cobalt adopts a low-spin +III oxidation state, and the ligand is reduced to the closed-shell trianionic state.

Combined, this work provides a detailed understanding of the factors that determine spin states and spin state changes for complexes bearing redox-active ligands: (i) radical stabilization, (ii) relative orbital overlap and energy, (iii) spin–spin interactions, and (iv) intramolecular electron transfer. The influence of these factors on the reactivity of these complexes remains an interesting topic to be explored in future studies.

WHAT’S NEXT?
The ability of redox-active ligands to change properties of the metal (i.e., Lewis acidity/basicity), engage in radical-type reactivity, and favor the stabilization of certain spin states, opens the door to several new reactions and novel mechanisms. The assistance of redox-active ligands in spin changing events during catalysis has already been shown to have enormous effects on product selectivity, reaction feasibility, and rates.20,106,114 With further expanding knowledge about redox-active ligands, their characterization, and application, we foresee a focus on the use of these fascinating ligands as tools to control reactivity. Furthermore, (transient) spin states and spin state changes might lead to rational design of spin-controlled reactions. This could give access to formally spin-forbidden reactions, multistate reactivity, and catalysis that can be tuned by switching of spin states and spin location. Moreover, the ability of redox-active (substrate) ligands to induce challenging transformations under mild (and ambient) conditions by taking advantage of the (often) low-barrier radical-type reactivity gives several opportunities for future research focusing on novel enantioselective reactions and broadly applicable late-stage transformations. Formation of medium-sized ring compounds is another topic of particular relevance, in particular, for the synthesis of new bioactive compounds.

TAKE-HOME MESSAGE
The overarching lessons that can be learned from this perspective are as follows:

- Assignment of (ligand) oxidation states in complexes bearing redox-active ligands is a cumbersome task, typically requiring combined information from several techniques. Among those, EPR spectroscopy and SC-XRD database analysis have proven particularly useful as tools to assign ligand oxidation states.
- Specific redox-active carbene and nitrene substrates are particularly useful reagents to functionalize heteroatoms, C=C=H, and C==C bonds and give access to a plethora of valuable products, which are otherwise difficult to obtain. Tuning the activity and selectivity and expanding the substrate scope of these reactions remains an important topic for future research, and redox-active ligands provide useful additional tools to gain control over the reactivity of these redox-active substrates.
- In a broader sense, protocols using redox-active substrates are on the verge of making a large impact in organic synthesis and natural product total synthesis, in particular, because they provide easy access to a variety of (hetero)cyclic compounds of different ring sizes that are otherwise difficult to access.
- Redox-active ligands can be used to tune selectivity, reaction mechanisms, and spin states, leading to catalytic protocols under mild conditions and new tools to control electronic structures.

In conclusion, redox-active ligands and substrates are actively studied to uncover their potential as tools to control radical-type reactivity. Although spectroscopic, theoretical, and synthetic studies have resulted in a wide variety of applications and in-depth knowledge on their properties, this rapidly growing field is far from saturated. Much has yet to be discovered, among others in terms of (enantio)selectivity, ring-size control, late-stage functionalization, expanded substrate scope, and multistate transformations that are unfeasible with innocent ligands. We look forward to a bright future of redox-active ligands in catalysis research.

AUTHOR INFORMATION

Corresponding Author

Bas de Bruin — Homogeneous, Supramolecular and Biomimetic Catalysis Group, van ’t Hoff Institute for Molecular Sciences (HIMS), University of Amsterdam, 1098 XH Amsterdam, The Netherlands; orcid.org/0000-0002-3482-7669; Email: b.debruin@uva.nl

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