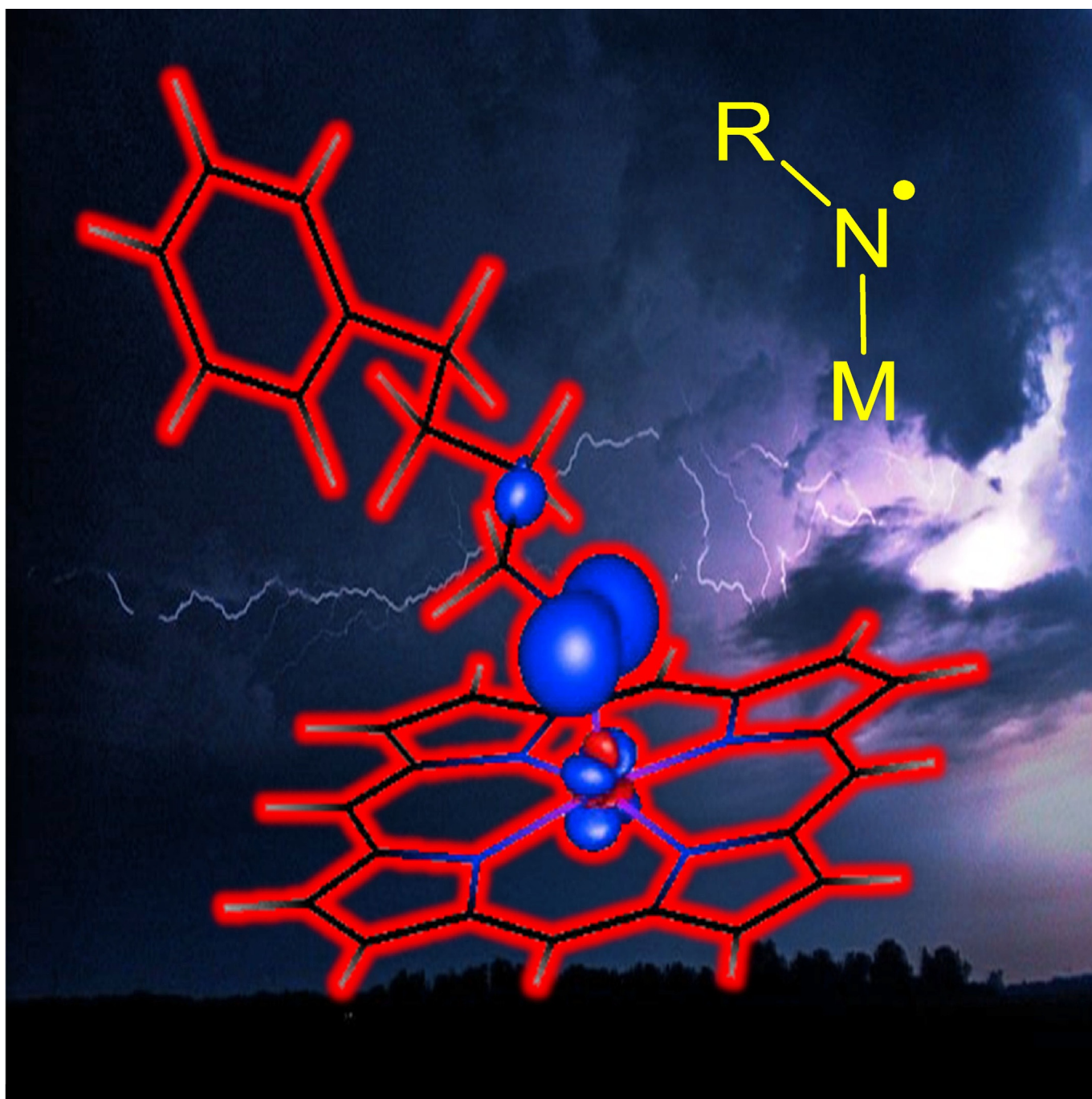


■ Metalloradical Catalysis

Nitrene Radical Intermediates in Catalytic Synthesis

Petrus F. Kuijpers,^[a] Jarl Ivar van der Vlugt,^[a] Sven Schneider,^[b] and Bas de Bruin^{*[a]}

Abstract: Nitrene radical complexes are reactive intermediates with discrete spin density at the nitrogen-atom of the nitrene moiety. These species have become important intermediates for organic synthesis, being invoked in a broad range of C–H functionalization and aziridination reactions. Nitrene radical complexes have intriguing electronic structures, and are best described as one-electron reduced Fischer type nitrenes. They can be generated by intramolecular single electron transfer to the “redox non-innocent” nitrene moiety at the metal. Nitrene radicals generated at open-shell cobalt(II) have thus far received most attention in terms of spectroscopic characterization, reactivity screening, catalytic nitrene-transfer reactions and (computational and experimental) mechanistic studies, but some interesting iron and precious metal catalysts have also been employed in related reactions involving nitrene radicals. In some cases, redox-active ligands are used to facilitate intramolecular single electron transfer from the complex to the nitrene moiety. Organic azides are among the most attractive nitrene precursors in this field, typically requiring pre-activated organic azides (e.g. RSO_2N_3 , $(\text{RO})_2\text{P}(=\text{O})\text{N}_3$, $\text{ROC}(=\text{O})\text{N}_3$ and alike) to achieve efficient and selective catalysis. Challenging, non-activated aliphatic organic azides were recently added to the palette of reagents useful in synthetically relevant reactions proceeding via nitrene radical intermediates. This concept article describes the electronic structure of nitrene radical complexes, emphasizes on their usefulness in the catalytic synthesis of various organic products, and highlights the important developments in the field.

Introduction

The use of nitrogen-centered radicals in synthesis, although initially perhaps not recognized as such, dates back to the late 19th century Hofmann–Löffler–Freitag reaction for the synthesis of pyrrolidines.^[1] The free organic radicals involved in these

reactions are often associated with low selectivities.^[2] Free organic radicals indeed often lead to radical disproportionation and other side reactions, generating insoluble materials. Nevertheless, many selective reactions based on free N-centered radicals have since been achieved, taking advantage of kinetic control (desired reactions outcompeting undesired ones).^[3] Better control can be achieved in the coordination sphere of a metal, and transition metal bound N-centered radicals are increasingly recognized as important intermediates to enable controlled radical type C–N bond formation reactions.^[4] Transition metal-bound N-centered radicals can be catalytically generated, in low and controlled amounts, thereby giving rise to much higher selectivities than typically achieved with free organic radicals.

Ligands surrounding the metal are used to fine-tune the reactivity of these intermediates, both sterically and electronically.^[5] Transition metal-bound nitrene/imido-based nitrogen-centered radicals $\text{M–N}\cdot\text{R}$ (i.e. nitrene- and imidyl radical complexes; see Figure 1 and Figure 2), have received quite some attention, as they enable a variety of useful nitrene-insertion and nitrene-transfer reactions. Such reactions are typically more selective than those involving free N-centered radicals or free nitrenes.

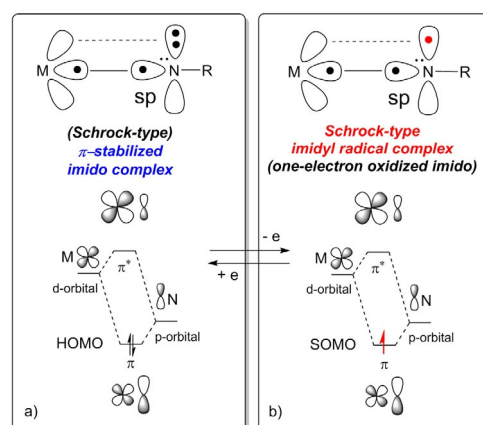


Figure 1. Simplified frontier molecular orbital diagrams of: a) Schrock type imido complex (metal–nitrogen π -interactions stabilizing in two directions, nitrogen sp-hybridization and linear coordination modes favored). b) Schrock type imidyl radical complex (one-electron oxidized Schrock type imido).

The scientific literature is highly inconsistent about the electronic structure description and nature of M–NR species in general, and frequently confusing descriptions are presented that are based on formal oxidation state counting arguments. As such, the NR ligand is most typically considered as an imido fragment (R–N^{2-}), and frequently even as a redox inactive moiety. This description fails to reflect the electrophilic and radical-type reactivity observed for many late transition metal M–NR species.^[6] The metal–nitrogen π -interactions of a genuine imido complex are stabilizing in case of early transition metals (electropositive, relatively high-energy empty d_{π} -type orbitals; see Figure 1 a), in which case the imido moiety should have a tendency to bind in a linear manner due to the presence of

[a] Dr. P. F. Kuijpers, Dr. Ir. J. I. van der Vlugt, Prof. Dr. B. de Bruin
Van 't Hoff Institute for Molecular Sciences (HIMS)
University of Amsterdam (UvA)
Science Park 904, 1098 XH Amsterdam
(The Netherlands)
E-mail: b.debruin@uva.nl

[b] Prof. S. Schneider
Institut für Anorganische Chemie
Universität Göttingen, Tammannstr. 4
37077 Göttingen (Germany)

The ORCID identification number(s) for the author(s) of this article can be found under <https://doi.org/10.1002/chem.201702537>.

© 2017 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of Creative Commons Attribution NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

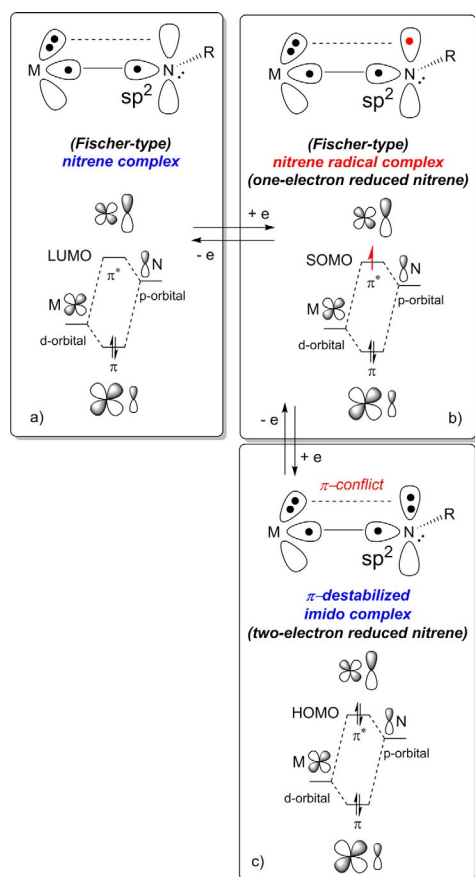


Figure 2. Simplified frontier molecular orbital diagrams of: a) Fischer type nitrene complex (nitrogen sp^2 hybridization and bent coordination modes favored for late transition metal complexes); b) Nitrene radical complex (one-electron reduced Fischer type nitrene); c) π -destabilized imido complex.

two stabilizing π -interactions between the electropositive metal and the sp -hybridized imido nitrogen atom. In analogy with the Fischer/Schrock terminology used to explain the reactivity of transition-metal carbene complexes, such species are best described as Schrock type nitrene or π -stabilized imido complexes (Figure 1 a). The corresponding π -interactions in a genuine imido complex involving a late transition metal (electronegative, relatively low-energy and filled d_{π} -type orbitals) are destabilizing, thus favoring a bent coordination mode. Such complexes are perhaps best characterized as π -destabilized imido complexes or two-electron reduced Fischer type nitrene complexes (Figure 2). In both cases, the imido fragments are expected to be relatively nucleophilic at nitrogen.^[5] However, many of the catalytically relevant late transition metal M–NR species are in fact electrophilic at nitrogen, and hence are better described as Fischer type nitrene complexes rather than imido species. They have a π -stabilized empty p -orbital on nitrogen being the LUMO of the complex (Figure 2), thus explaining their electrophilic nature. For late transition metal Fischer type nitrene complexes the bent coordination mode is favored, in order to avoid unfavorable π -conflicts between the filled metal d_{π} -type orbitals and the remaining lone pair at the sp^2 hybridized nitrogen atom (Figure 2).

Obviously, the simplified Fischer and Schrock type MO diagrams in Figures 1 and 2 are merely extremes of a continuum of intermediate cases, and these simplified and generalized pictures get severely blurred, with increasing covalency, in particular for second and third row transition metals where relativistic effects further complicate the electronic structure via spin-orbit coupling. However, for most first row transition metals the diagrams should be quite useful to understand their reactivity, including the redox activity of the imido/nitrene moiety.

With the frontier orbitals shown in Figure 1 and Figure 2 in mind, it should be clear that both Schrock type imido complexes (HOMO dominated by the nitrogen p -orbital) and Fischer type nitrene complexes (LUMO dominated by the nitrogen p -orbital) are potentially redox-active at the nitrogen atom, and hence they can easily form M–NR radicals. Two distinct electronic structures are possible for such species: (1) Schrock type imidyl radicals (Figure 1 b), formed by 1e-oxidation of (Schrock type) π -stabilized imido species, or (2) Fischer type nitrene radical complexes (Figure 2 b). The latter can be formed either by 1e-reduction of (Fischer type) nitrene radical species (Figure 2 a to 2b), or by 1e-oxidation of a π -destabilized imido complex (Figure 2 c to 2b). Schrock type imidyl radical species are distinctly different from Fischer type nitrene radicals. In the first case the singly occupied molecular orbital (SOMO) is a half-filled metal–nitrogen π -bonding orbital, while in the second it is a half-filled metal–nitrogen π -antibonding orbital. Few examples of Schrock type imidyl radicals formed in stoichiometric reactions exist,^[7] but they are very scarce and, to our best knowledge, no unequivocal examples of such species involved in catalytic reactions have been reported to date. This is perhaps not very surprising, as the strong M–N bonding interactions and the linear coordination mode of these species are likely to hamper nitrene-transfer reactivity (Figure 1 b). The situation is quite different for Fischer type nitrene radical complexes, which have weaker metal–nitrogen bonds and for which several catalytically relevant examples have already been reported. Nitrene radical complexes can be considered as the nitrogen analogues of carbene radical complexes.^[8] This Concept paper provides an overview of their spectroscopic properties, electronic structure and catalytic reactivity. The paper primarily focusses on reactions and complexes for which clear indications for the involvement of nitrene radicals in catalytic reactions are reported.

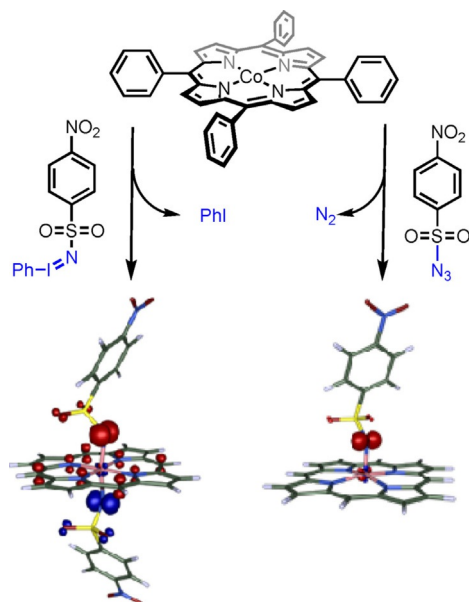
Typically used nitrene-precursor reagents

Nitrene radical complexes can in principle be generated in several ways, but in most catalytic examples a reaction between a low-valent transition-metal complex and an oxidizing nitrene-transfer reagent is the method of choice. These reagents typically contain good leaving groups, and have a strong driving force for nitrene transfer to the metal. Bromamine-T and iminodanones were frequently used as nitrene source in early studies, but these reagents suffer from waste formation, over-oxidation and other selectivity issues. Organic azides have been used as the nitrene precursor of choice in most of the recently reported catalytic reactions proceeding via nitrene radi-

cal intermediates. Azides are quite attractive nitrene precursors, not only because they produce only dinitrogen as a side product, but also because of their ease of synthesis and long bench stability at room temperature. Furthermore, with a variety of available azides it is easier to introduce versatility of the nitrogen substituents in the products.

Characterization of nitrene radical complexes

Distinguishing various types of nitrene radical complexes can be quite challenging, and most often the combination of different spectroscopic and analytical techniques is needed to properly establish their identity. Electron paramagnetic resonance (EPR) and X-ray absorption spectroscopy (XAS) are frequently used to determine the locus of the unpaired electron and the oxidation state of the metal, respectively. For iron complexes, Mössbauer spectroscopy has also proven highly useful. In addition, computational tools such as those based on density functional theory (DFT) are frequently used to determine the nature of the short-lived reactive nitrene radical intermediates in synthetic reactions. In particular, spectroscopic property calculations have proven highly useful in this field. Such detailed spectroscopic and computational studies were recently performed by de Bruin and co-workers to characterize a series of catalytically relevant cobalt porphyrin nitrene radical species.^[8,10] EPR spectroscopy proved particularly useful to characterize these species. Upon mixing of a cobalt-porphyrin complex and an azide (Scheme 1, right) the characteristic signals of the cobalt porphyrin gradually decrease to form a nitrene radical species, as is clear from the EPR spectra (Figure 3).



Scheme 1. Formation of bis-nitrene radical species upon reaction of cobalt(II) porphyrins with iminoiodanes as nitrene precursor (left), in contrast to formation of mono-nitrene radical complexes when using organic azide substrates (right).

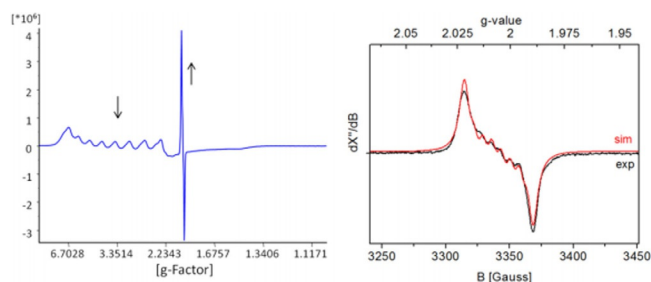


Figure 3. Changes in the X-band EPR spectra for a mixture of cobalt porphyrin and an azide over time (left) and zoom of the nitrene radical complex (right).^[9,10]

A clear EPR signal around a *g*-value of 2.0 revealing small but detectable cobalt and nitrogen hyperfine coupling indicates a nitrogen-centered radical rather than a metal-centered radical upon reaction with the azide (Figure 3, right). All other spectroscopic and analytical data (XANES, IR, ESI-MS) data are in agreement with this assignment.^[10] DFT calculated spectroscopic properties match well with the experimental data, showing that the computed electronic structure (Figure 4) closely matches the experimentally derived configuration. The data show that the nitrene ligand formed at cobalt(II) undergoes one-electron reduction by the cobalt(II) center to produce a cobalt(III)–nitrene radical complex. The unpaired electron resides in a Co–N antibonding π -bond (Figure 4, right), reminiscent of a Fischer type nitrene radical complex (Figure 2b). As a result, the spin density of the complexes is almost exclusively nitrogen-centered (Figure 4, left).

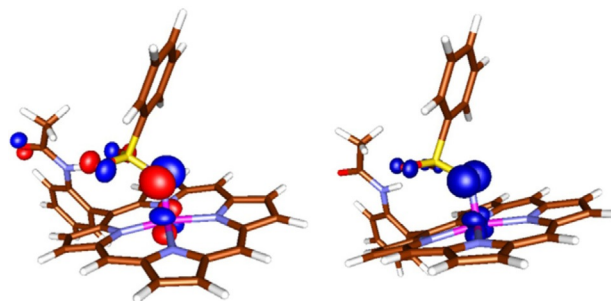
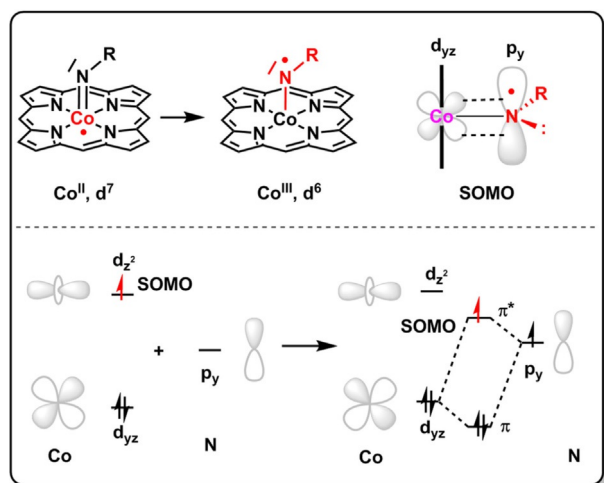


Figure 4. SOMO (left) and spin density (right) plots of a cobalt(III) porphyrin nitrene radical complex [(por)Co(NR)] ($R = -SO_2Ph$).^[9,10]

Interestingly, formation of the key cobalt(III) nitrene radical intermediate is the result of an intramolecular electron transfer process from cobalt(II) to the redox-active (redox-noninnocent) nitrene moiety, once generated at the metal (Scheme 2). This gives direct access to controlled and catalytic radical-type reactions taking place in the coordination sphere of cobalt.

Surprisingly, nitrene radical species formed in the reaction of cobalt porphyrins with iminoiodanes yielded entirely different EPR spectra, which could be assigned to bis-nitrene radical species (Scheme 1, left). In this case the second nitrene ligand formed at the cobalt center is reduced by the porphyrin ligand ring to yield a complex containing three unpaired electrons; one on each nitrene radical moiety, and one delocalized over the π -system of the porphyrin ring (antiferromagnetically cou-



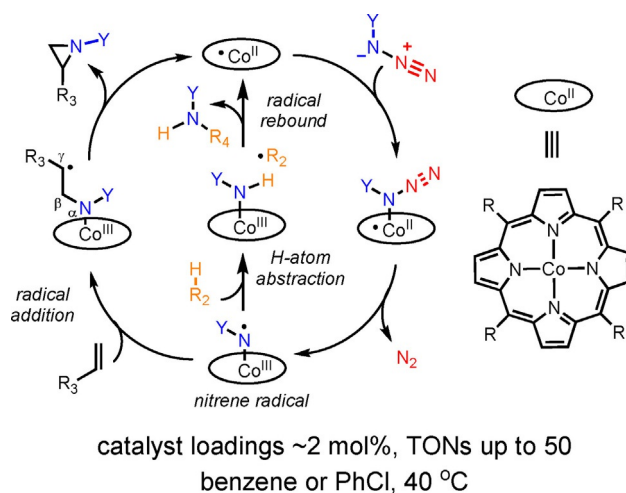
Scheme 2. Intramolecular single-electron transfer from the cobalt(II) metal-loradical to the redox-active nitrene moiety generated upon azide activation at the metal, thus producing a cobalt(III)-nitrene radical complex (one-electron-reduced Fischer type nitrene).

pled to one of the nitrene radicals). While these bis-nitrene radical species have an intriguing electronic structure, they are less useful for catalysis, because these over-oxidized complexes easily decompose, resulting in rapid, unwanted and nonselective catalyst deactivation. The bis-nitrene radicals decompose much more rapidly than the mono-nitrene analogues, clearly showing the additional advantage of using (activated) organic azides as the nitrene precursor, as these generate only the mono-nitrene radical species.^[10] These results emphasize the importance of the nitrene transfer reagent choice.

Catalytic reactions via nitrene radical species produced from activated nitrene precursors

Cobalt porphyrins have been used in a variety of nitrene-transfer and nitrene-insertion reactions, including aziridination,^[11] C–H amination^[12] and C–H amidation.^[13] Cobalt(III) nitrene radical complexes, similar to those described above, are proposed as the key-reactive intermediates (Scheme 3). They are typically generated in reactions between cobalt(II)-porphyrin complexes with nitrene precursors, such as iminoiodanes or activated organic azides. Cobalt(III) nitrene radical intermediates react via discrete radical-type mechanisms. Radical addition to C=C double bonds or hydrogen atom transfer (HAT) from (activated benzylic or allylic) C–H bonds (Scheme 3) leads to a variety of desirable N-containing organic products such as amides,^[13] linear and cyclic amines,^[12] aziridines,^[11] dihydrobenzoxazine, and azabenzenes^[14] (Figure 5).

The first cobalt-porphyrin-catalyzed aziridination was described by Zhang and co-workers in 2005, in which the authors used Bromamine-T as the nitrene precursor.^[15] Interestingly, a few years earlier (2000) the group of Cenini and co-workers has shown that organic azides are also suitable nitrene transfer agents in cobalt(II)-porphyrin-catalyzed C–H bond amination reactions.^[16] These, when compared to Bromamine-T, are easier to work with, more sustainable, and have a broader synthetic



Scheme 3. Generalized nitrene radical reactivity and mechanisms of cobalt(II)-porphyrin metalloradical-catalyzed nitrene-transfer reactions.

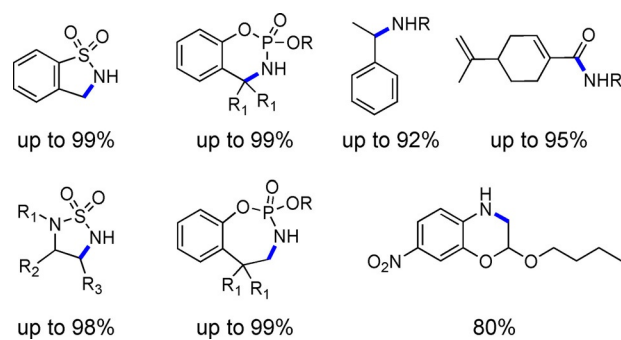
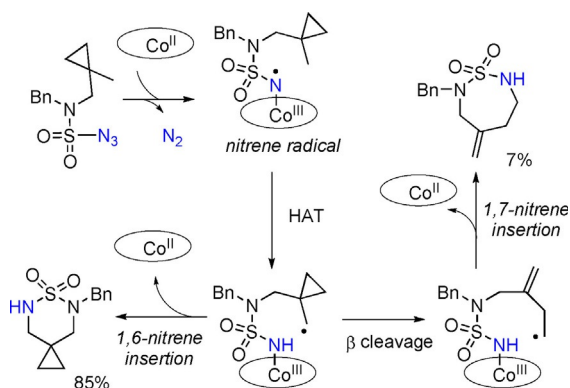


Figure 5. Selection of the various products that can be synthesized by cobalt(II) porphyrin catalyzed nitrene insertion protocols involving nitrene radicals.

scope. As a result, in most subsequent studies involving nitrene-transfer or nitrene-insertion reactions mediated by cobalt(II) porphyrins, organic azides were chosen as the preferred nitrene precursors (including most aziridination and C–H bond amination studies reported by the Zhang group after 2005; vide infra). The mechanism of the aziridination reaction was investigated in our group (de Bruin and co-workers) in 2010 using DFT methods, confirming formation of nitrene radical intermediates as the key reactive species in the catalytic cycle (Scheme 3).^[17]

Initial reports of C–H amination with cobalt porphyrins using aromatic azides suggested that a cobalt(II)-azide adduct is formed, which reacts directly with the hydrocarbon in the rate limiting step without forming a detectable intermediate.^[12c,16] However, subsequent studies of C–H amination reactions with cobalt(II) porphyrins and non-aromatic azides have clearly shown these reactions to proceed via discrete nitrene radical intermediates.^[9,12e] Experimentally, the presence of the nitrene radical intermediate was verified using EPR spectroscopy (see above),^[9,10] and by the use of a radical clock substrate. The latter reaction reveals partial radical-type ring-opening of the cyclopropane-ring probe after HAT (Scheme 4).^[12f,g] DFT



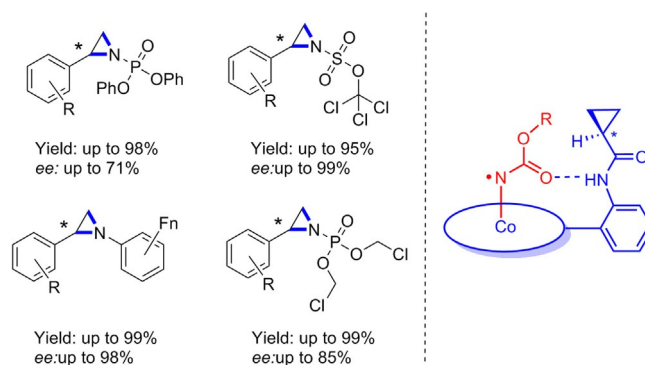
Scheme 4. Radical probe experiment confirming the radical-type mechanism.

computational studies of the C–H amination mechanism reveal a pathway involving cobalt(III) nitrene radical formation, HAT from the hydrocarbon to the nitrogen-centered radical, followed by a “radical-substitution” reaction with the free carbon radical attacking the antibonding orbital of the weak Co–N bond, thus leading to simultaneous C–N bond formation and Co–N bond homolysis to liberate the product and regenerate the catalyst in the cobalt(II) oxidation state (Scheme 3).^[9] For reasons of similarity with mechanisms proposed for (enzymatic) C–H bond functionalization reactions mediated by other metallo-porphyrins, the last step of this mechanism is conveniently referred to as a “radical rebound” step.

One of the important advantages of using nitrene radical complexes instead of free N-centered radicals or free nitrenes in organic synthesis is the ability to perform reactions in an enantioselective manner. Chiral information can be efficiently transferred from chiral porphyrin ligands to the nitrene radical substrates, as was elegantly demonstrated by the group of Zhang.^[10] By changing the substituents on the porphyrin ligand, highly enantioselective synthesis of a wide range of chiral aziridines proved possible (Scheme 4, left).

A cooperative, chiral H-bond donor motif in the second coordination sphere (amide functionality of the porphyrin ligand) enhances the activity of the catalyst,^[17] and enables efficient chirality transfer (Scheme 5, right).^[12] The enantioselective reactions as reported by the Zhang group were thus far all based on the use of activated organic azides (e.g. RSO_2N_3 , $(\text{RO})_2\text{P}(=\text{O})\text{N}_3$, $\text{ROC}(=\text{O})\text{CN}_3$ and so forth) as the nitrene precursors, which are activated by the chiral cobalt(II) catalysts at rather mild reaction temperatures (40 °C).

In 2013, the group of Pérez proposed on the basis of DFT calculations that tris-pyrazolylborate copper nitrene complexes react on the triplet surface, involving nitrene radical reactivity of the key copper nitrenoid intermediate, while the corresponding silver complexes react on the singlet surface leading to closed-shell electrophilic nitrene reactivity.^[18a,b] Similarly, the groups of Manca and Gallo proposed on the basis of DFT calculations that nitrene transfer catalysis via the mono- and bis-imido intermediates $[\text{Ru}(\text{TPP})(\text{NR})(\text{CO})]$ and $[\text{Ru}(\text{TPP})(\text{NR})_2]$ involves the triplet spin state of these species, again leading to nitrene radical reactivity also for these Ru catalysts.^[18c] Also the

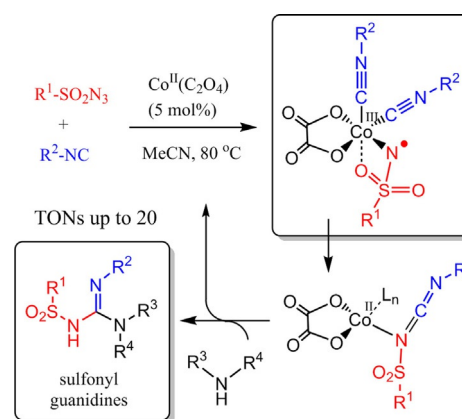


Scheme 5. Left: Chiral aziridines obtained in cobalt(II)-porphyrin catalyzed aziridination reactions. Right: Cooperative H-bonding interactions between the nitrene radical substrate and amide functionalities of the ligand in the second coordination sphere enhance the rate of the reaction and mediate efficient chirality transfer.

aziridination and C–H bond amination reactions reported by J.-L. Zhang and co-workers, catalyzed by iron(III) complexes with fluorinated porpholactone ligands and using TsN_3 as the nitrene precursor, proceed most likely via nitrene radical intermediates.^[18d] Another interesting precursor leading to controlled metal-bound nitrogen-centered radical reactivity is *N*-fluorobenzenesulfonamide (NSFI), which has been used in some interesting copper catalyzed amination reactions to give a wide range of difunctionalized products in moderate to excellent yield (up to 91 %).^[18e–g] However, while showing interesting related chemistry, the “aminyl-radical” intermediates formed in the latter reactions do not belong to the class of nitrene radicals and are therefore not discussed in any further detail.

Very recently, the groups of Ji, Bao, and Wang reported on the interesting cobalt(II)-catalyzed formation of sulfonyl guanidines in a series of tri-component reactions between sulfonylazides, isonitriles and secondary amines (Scheme 6). Computational and EPR studies suggest the reactions proceed via cobalt(III)-nitrene radical intermediate.^[19]

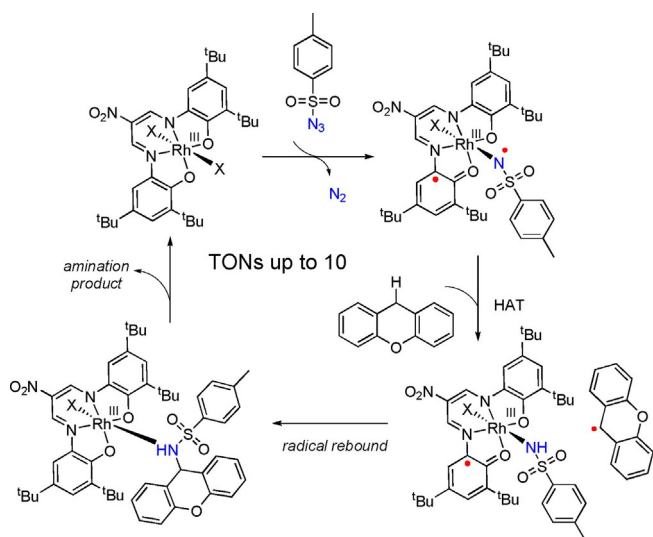
While these intermediates are quite similar to the ones described above for the Co(por) systems, the availability of *cis*-



Scheme 6. Cobalt(II)-catalyzed tri-component coupling of sulfonylazides, isonitriles and secondary amines, proceeding via a chelating nitrene radical intermediate.

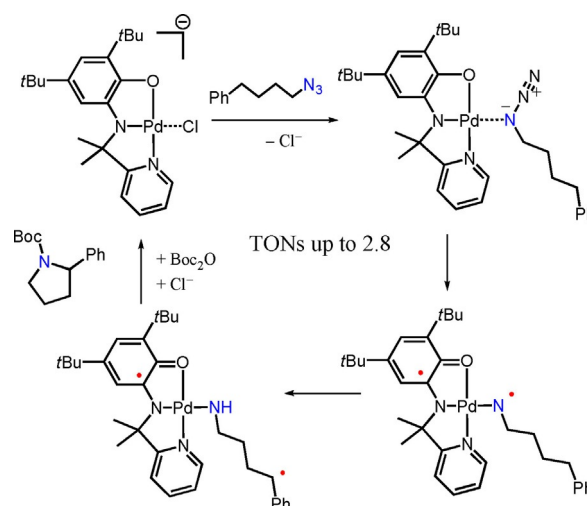
vacant sites in the catalyst used in the reactions described by Li lead to a chelating coordination mode of the sulfonyl-based nitrene radical moiety. For the same reason, coupling of this nitrene radical moiety to the isocyanide substrate occurs via internal attack of a *cis*-coordinated isocyanide, producing a cobalt-coordinated carbodimide intermediate. The latter subsequently reacts with the secondary amine substrate to produce the sulfonyl guanidine product in excellent yield (up to 96%).

In addition to the cobalt-catalyzed reactions described above, the groups of Yoshizawa and Itoh recently reported an interesting catalytic approach to generate nitrene radicals at a diamagnetic Rh^{III} complex precursor by making use of a redox-active ligand. The latter is involved in the required intramolecular single-electron transfer from the complex to the nitrene moiety generated at rhodium (Scheme 7).^[20] The complex showed efficient intermolecular C–H amination from an activated tosyl azide (73% amination product was obtained under optimized conditions). The nitrene radical complex is formed by one-electron transfer from the redox-active ligand to the rhodium(III)-bound nitrene moiety, and the metal stays in the Rh^{III} oxidation state throughout the entire catalytic cycle. As a result, the key-intermediate has two unpaired electrons: One at the 1e-reduced Fischer type nitrene moiety, and one at the 1e-oxidized redox-active ligand.



Scheme 7. Proposed mechanism for nitrene radical C–H amination with a rhodium(III) complex containing a “redox non-innocent” ONNO-ligand.

The approach of Itoh and Yoshizawa (Scheme 8) is quite similar to the redox-active ligand approach used a bit earlier by van der Vlugt and co-workers to generate nitrene radicals at a diamagnetic palladium(II) complex.^[21] The palladium(II) complex used contains a redox-active (non-innocent) NNO ligand, capable of electron transfer to the nitrene moiety generated at palladium. Interestingly, this system is capable of activating the aliphatic azide 4-(azidobutyl)benzene (Scheme 8). The nitrene radical intermediate undergoes ring-closure via HAT and radical rebound steps, and in the presence of Boc₂O more or less stoichiometric



Scheme 8. Activation of an aliphatic azide at palladium(II) to a nitrene radical intermediate made possible by the presence of a redox-active NNO-ligand.

amounts of the saturated N-heterocyclic ring products could be isolated.^[21a]

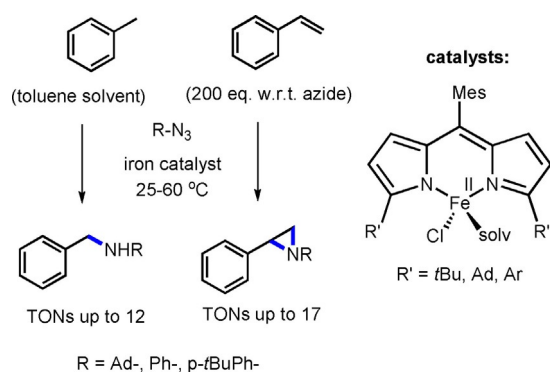
The palladium center remains in the Pd^{II} oxidation state throughout the process. Using an isotopically labeled substrate analogue, an intramolecular kinetic isotope effect (KIE) of 3.35 was experimentally observed and computationally reproduced. Careful removal of CHCl₃ from the crystal lattice of the Pd-catalyst enabled catalytic turnover, but unfortunately only very low turnover numbers (TON_{max} = 2.8, 28% yield) could be achieved with this system.^[21b] Other examples of catalyst systems capable of activating aliphatic azides, producing aminated products via nitrene radical intermediates with higher turnover numbers, are described in the next section.

Catalytic reactions via nitrene radical species produced from aliphatic nitrene precursors

Most of the catalytic reactions described above require aromatic or pre-activated organic azides (e.g. RSO₂N₃, (RO)₂P(=O)N₃, ROC(=O)CN₃ and alike) to achieve efficient and selective turnover. These azides are typically easier to activate than aliphatic azides, and hence more efficient reactions proceeding at lower temperatures are possible using these pre-activated reagents. Similar reactions with aliphatic azides are more cumbersome, and generally require more reactive catalysts and higher reaction temperatures. The use of aliphatic azides, however, substantially broadens the scope of these reactions, leading to a broad range of interesting N-containing (cyclic) products. Hence, efforts in developing new protocols to activate aliphatic azides are desirable. Recent developments in the field indeed show that it is possible to convert (less reactive) aliphatic azides in catalytic reactions, which are all processes that involve the intermediacy of nitrene radical complexes.

The first reports on the activation of aliphatic azides were published quite recently by the group of Betley, who used iron-catalysts based on “half-porphyrin” dipyrromethene ligands. The Fe^{II} complexes proved active in both intermolecu-

lar^[22] and intramolecular^[23] C–H bond amination reactions. The initial paper published in 2011 reports on intermolecular C–H bond amination with aromatic and bulky aliphatic azides (Scheme 9).^[22a] The nitrene intermediate has a rather complicated electronic structure, with one of the five unpaired electrons at the (high spin) Fe^{III} center being antiferromagnetic coupled to the nitrene radical moiety, leading to an *S* = 2 ground state. As a result, it is not so clear if this intermediate

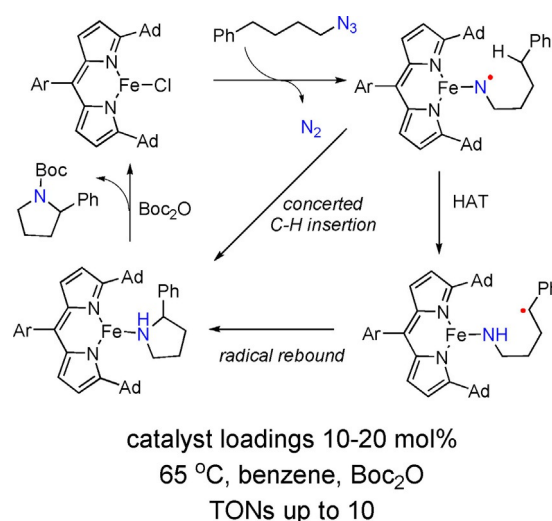


Scheme 9. Nitrene-transfer/insertion reactivity (left) of the high-spin iron(II) catalyst (right) developed by Betley and co-workers.

should be regarded as a Fischer type nitrene radical (Figure 2), or rather as a Schrock type imidyl radical complex (Figure 1). In any case, the intermediate exhibits discrete nitrogen-centered spin density and seems to react as an N-radical. The mechanisms proposed for these reactions are very similar to those described for most other catalysts discussed above: HAT from the hydrocarbon by the metal-bound N-radical, followed by a radical rebound step to produce the aminated organic product, which is in line with the high chemoselectivity for allylic C–H insertion over aziridination.^[22b] The nitrene radical character can also lead to undesired side-reactions with aromatic azides as nitrene sources. Spin-delocalization into the phenyl ring of the transient phenylnitrene catalyst species results in bimolecular coupling of two nitrene fragments inhibiting catalysis.^[22]

Although the turnover numbers (TONs) reported thus far for intermolecular nitrene transfer are modest (TONs up to 12 for the C–H amination of toluene, and TONs up to 17 for aziridination of styrene) the reactivity can likely be expanded by variation of the catalyst and the azides used.

Later studies reported by the same group showed that similar catalysts have a quite broad synthetic scope in intramolecular ring-closing C–H amination reactions of (unactivated) aliphatic azides (Scheme 10). A large substrate scope was explored to produce a wide variety of N-heterocyclic organic ring compounds.^[23] For most of these reactions the TONs are still rather low, but catalyst screening using different ligands is expected to improve the catalytic efficiency. An additional point of attention is the selectivity of these catalysts. The key-reactive N-radical intermediate does not seem to be very discriminative, as it reacts with several C–H bonds within a quite broad range of different bond dissociation enthalpies (BDEs),



Scheme 10. Proposed mechanisms for intramolecular C–H bond amination leading to N-heterocycles. After formation of the Fe-bound N-radical intermediate, formal nitrene insertion can proceed via a stepwise HAT-radical rebound mechanism as well as in a concerted manner.

resulting in chemoselectivity issues. The Fe^{II}-catalysts also produce significant amounts of unwanted linear (Boc-protected) amine side-products in some of the reported reactions, which is probably a related issue.

As proposed for the intermolecular reaction, the authors suggest the involvement of Fe-bound N-radical intermediates in the intramolecular ring-closing amination reactions (Scheme 10). In order to explain the reactivity towards several different C–H bonds, the authors suggest that the Fe-bound N-radical intermediate not only reacts via a stepwise HAT-radical rebound mechanism, but also react in a concerted (electrophilic) manner with C–H bonds.

Recent studies performed by van der Vlugt, de Bruin and co-workers focused on improving the stability of an Fe-based catalyst and increasing the TONs of these type of reactions. Inspired by the positive effects of using redox-active ligands observed in catalytic reactions with Pd and Rh (vide supra), an air- and moisture-stable Fe^{III}-based catalyst with a redox-active NNO ligand was synthesized and used in the intramolecular C–H bond amination ring-closure reactions of aliphatic azides to N-heterocycles.^[24] The respective iron complex (Figure 6) proved remarkably stable, and the catalyst can be efficiently recycled after the reactions. Furthermore, the catalyst gives rise to quite high catalytic turnover numbers (TONs up to 620). Some selectivity issues still arise from the non-discriminating

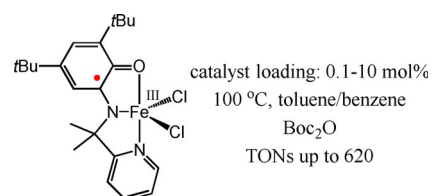
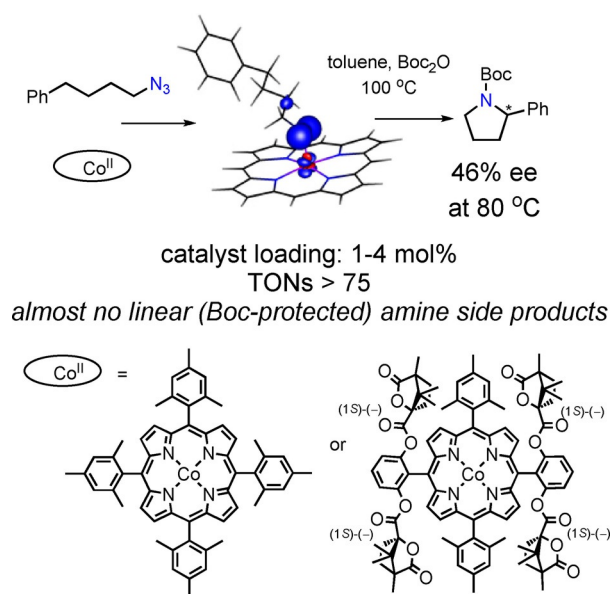


Figure 6. Stable, recyclable Fe-catalyst for intramolecular C–H amination.

reactivity of the Fe-nitrenoid intermediate reacting with different C–H bonds in a comparable range of BDEs, as observed in the Fe-catalysed reactions reported by Betley. In particular, formation of substantial amounts of linear (Boc-protected) amine side products is currently a disadvantage of this system.

Interestingly, kinetic studies reveal the reaction to be first order in [Fe], zero order in [azide] and first order in [Boc₂O]. This unusual and unexpected kinetic behavior is suggestive of (rate-limiting) catalyst activation by the Boc₂O reagent for this system. The exact mechanism remains rather unclear at present. The underlying chemistry of the kinetic effect of Boc₂O is not understood and the precise nitrene-transfer mechanism and electronic structure of the key intermediates remain unresolved, due to the complex electronic structure of these type of Fe(NNO) complexes (several spin-state possibilities of the exchange-coupled system, potentially involving Fe and the redox-active ligand and substrate). However, while the mechanism is currently still under investigation, most likely also these reactions proceed via (Fischer type) nitrene-radical species or (Schrock type) imidyl radical intermediates.

Most recently, de Bruin and co-workers investigated the activity of cobalt(II) porphyrins in ring-closing C–H amination of aliphatic azides (Scheme 11).^[25] These catalysts are also air and moisture stable. In addition, almost no unwanted linear (Boc-protected) amine side products are formed.



Scheme 11. Nitrene radical intermediate for enantioselective C–H amination.

A thorough experimental kinetic study combined with supporting computational investigations confirmed the reaction mechanism to proceed through a nitrene radical intermediate. In this case the reaction is first order in [Co], first order in [azide] and zero order in [Boc₂O]. Kinetic isotope measurements reveal a clear intramolecular kinetic isotope effect (KIE = 7), but no kinetic isotope effect (KIE = 1) in intermolecular competition experiments. Hence, Boc₂O is not involved in the rate

determining step, and the C–H bond activation step is thus not rate limiting. All the available data point to azide activation being the slowest step. Experimentally determined Eyring and Arrhenius activation parameters are reproduced well by supporting DFT calculations.

Remarkably, in reactions with a chiral porphyrin catalyst enantiomerically enriched N-heterocycles are obtained (ee up to 46% at 80 °C), representing the first example of enantioselective radical-type ring-closure of aliphatic azides using metal-radical catalysis (Scheme 11). Furthermore, this observation has mechanistic implications, strongly suggesting that the ring-closing steps occur in the coordination sphere of cobalt (see Scheme 3). Formation of free nitrenes, as observed for some Fe and Ru systems,^[26] seems rather unlikely for these Co(por) systems.

The ability of the Fe and Co catalysts, as well as the Pd and Rh systems described in this section to activate aliphatic azides is a major advancement, both from fundamental inorganic and catalytic understanding as well as from an organic chemistry viewpoint, as it provides straightforward synthetic routes to the synthesis of a wide variety of N-heterocycles in moderate to excellent yields (27–96%) (Figure 7).

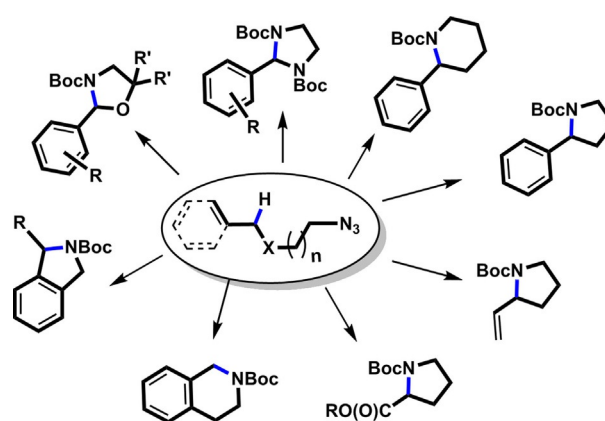


Figure 7. Variety of N-heterocyclic organic products synthesized by the radical-type nitrene radical C–H amination protocols described in this section.

Furthermore, the prospects of performing these reactions in an enantioselective manner bodes well for future studies aimed at developing new synthetically useful protocols to chiral N-heterocycles based on metalloradical catalysis.

Summary and Future Prospects

The use of nitrene radical complexes in synthesis has rapidly expanded over the last decade. This development is accompanied by a much better understanding of the nature of the nitrene radical species. Detailed computational and experimental studies have revealed that most metal-bound nitrene/imido-based nitrogen-centered M–N–R radical species applicable in catalytic synthesis are best described as one-electron-reduced Fischer type nitrene radical complexes. Besides their intriguing electronic structures, such nitrene radical complexes are of syn-

thetic interest due to their selective catalytic radical-type reactivity. They are key intermediates in a variety of radical-type nitrene-transfer and nitrene-insertion reactions, including aziridination, C–H amination and C–H amidation. Organic azides are among the most attractive nitrene precursors in this field, although typically pre-activated derivatives (e.g. RSO_2N_3 , $(\text{RO})_2\text{P}(=\text{O})\text{N}_3$, $\text{ROC}(=\text{O})\text{N}_3$ and alike) are used to achieve efficient and selective catalysis. More recently, challenging, non-activated aliphatic organic azides were added to the palette of reagents useful in synthetically relevant reactions proceeding via nitrene radical intermediates.

Some obvious but important challenges that still need to be addressed in this field are: (1) Increasing the turnover numbers for many of the substrate–catalyst combinations, in particular with the aliphatic azide substrates; (2) addressing selectivity issues arising from the non-discriminating reactivity of some of the metal–nitrenoid intermediates reacting with different C–H bonds in a comparable range of BDEs (in particular in case of activation of aliphatic azides with Fe); (3) Enhancing the enantioselectivities of the metalloradical C–H bond amination protocols; (4) Application of the C–H amination protocols in synthesis of complex organic molecules with many different functional groups, simultaneously addressing several regio- and chemoselectivity issues.

A thorough understanding of the mechanisms of these reactions, in particular those of the iron-based systems would certainly help in addressing some of the abovementioned challenges. More and detailed mechanistic studies are thus important, and such obtained insights are quite likely to advance further developments leading to synthetic applications of nitrene radical complexes in common synthetic methodologies. A final additional important aspect to address in this field is to critically (re)evaluate the sustainability of the nitrene precursors used in these reactions. Clearly, Bromamine-T and iminoiodanes are polluting, waste-generating reagents. However, while more sustainable, also organic azides are not ideal. They eliminate only harmless N_2 as a waste product upon formation of the metal–nitrenoid species, but they are still high-energy “pre-oxidized” reagents requiring energy-demanding synthetic procedures. As such, new developments aimed at more sustainable generation of the key high-energy nitrene radical intermediates are required. One of the most appealing strategies to access more sustainable nitrene-radical intermediates is perhaps to use simple amines as the nitrene source via deprotonation and electrochemical oxidation. Initial reports show that these routes are indeed accessible with Group 9 transition metals.^[27,28] However, significant additional work is required to obtain catalytic turnovers for these reactions. Future developments will therefore be required before nitrene radicals can become a standard strategy in chemical synthesis.

Acknowledgements

Financial support from NWO-CW (VICI project 016.122.613) and the University of Amsterdam (RPA Sustainable Chemistry) is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: C–H amination · electronic structure–reactivity correlations · metalloradical catalysis · noninnocent ligands · radicals

- [1] L. Stella, *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 337–350; *Angew. Chem.* **1983**, *95*, 368–380.
- [2] a) A. Studer, D. P. Curran, *Angew. Chem. Int. Ed.* **2016**, *55*, 58–102; *Angew. Chem.* **2016**, *128*, 58–106; b) K. U. Ingold, *Pure Appl. Chem.* **1997**, *69*, 241–243.
- [3] S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603–1618.
- [4] T. Xiong, Q. Zhang, *Chem. Soc. Rev.* **2016**, *45*, 3069–3087.
- [5] While the electron-pulling effect of the empty π -accepting metal d-orbitals in linear bound Schrock type imido complexes (Figure 1a) can induce some electrophilic behaviour, this rarely leads to discrete nitrene transfer/insertion for these type of complexes, due to the stabilising M–N π -interactions: R. A. Eikey, M. M. Abu-Omar, *Coord. Chem. Rev.* **2003**, *243*, 83–124.
- [6] Late transition metal catalyzed nitrene insertion reactions into C–H bonds typically proceed via concerted pathways involving electrophilic nitrene intermediates: a) A. Varela-Álvarez, T. Yang, H. Jennings, K. P. Kornecki, S. N. Macmillan, K. M. Lancaster, J. B. C. Mack, J. Du Bois, J. F. Berry, D. G. Musaev, *J. Am. Chem. Soc.* **2016**, *138*, 2327–2341; b) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247–9301.
- [7] A. I. Olivos Suarez, V. Lyaskovskyy, J. N. H. Reek, J. I. van der Vlugt, B. de Bruin, *Angew. Chem. Int. Ed.* **2013**, *52*, 12510–12529; *Angew. Chem.* **2013**, *125*, 12740–12760.
- [8] W. I. Dzik, X. P. Zhang, B. de Bruin, *Inorg. Chem.* **2011**, *50*, 9896–9903.
- [9] V. Lyaskovskyy, A. I. Olivos Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2011**, *133*, 12264–12273.
- [10] a) M. Goswami, V. Lyaskovskyy, S. R. Domingos, W. J. Buma, S. Woutersen, O. Troeppner, I. Ivanovic-Burmazovic, H. Lu, X. Cui, X. P. Zhang, E. J. Reijerse, S. DeBeer, M. M. van Schooneveld, F. F. Pfaff, K. Ray, B. de Bruin, *J. Am. Chem. Soc.* **2015**, *137*, 5468–5479; b) similar cobalt nitrene radical species were recently detected by the groups of Piers and Maron, undergoing a set of interesting stoichiometric reactions: L. Nurdin, D. M. Spasyuk, W. E. Piers, L. Maron, *Inorg. Chem.* **2017**, *56*, 4157–4168.
- [11] a) G.-Y. Gao, J. E. Jones, R. Vyas, J. D. Harden, X. P. Zhang, *J. Org. Chem.* **2006**, *71*, 6655–6658; b) J. E. Jones, J. V. Ruppel, G.-Y. Gao, T. M. Moore, X. P. Zhang, *J. Org. Chem.* **2008**, *73*, 7260–7265; c) V. Subbarayan, J. V. Ruppel, S. Zhu, J. A. Perman, X. P. Zhang, *Chem. Commun.* **2009**, 4266–4268; d) L.-M. Jin, X. Xu, H. Lu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 5309–5313; *Angew. Chem.* **2013**, *125*, 5417–5421; e) J. Tao, L.-M. Jin, X. P. Zhang, *Beilstein J. Org. Chem.* **2014**, *10*, 1282–1289.
- [12] a) J. V. Ruppel, R. M. Kamble, X. P. Zhang, *Org. Lett.* **2007**, *9*, 4889–4892; b) H. J. Lu, J. R. Tao, J. E. Jones, L. Wojtas, X. P. Zhang, *Org. Lett.* **2010**, *12*, 1248–1251; c) J. D. Harden, J. V. Ruppel, G. Y. Gao, X. P. Zhang, *Chem. Commun.* **2007**, 4644–4646; d) H. J. Lu, V. Subbarayan, J. R. Tao, X. P. Zhang, *Organometallics* **2010**, *29*, 389–393; e) H. Lu, Y. Hu, H. Jiang, L. Wojtas, X. P. Zhang, *Org. Lett.* **2012**, *14*, 5158–5161; f) H. Lu, H. Jiang, Y. Hu, L. Wojtas, X. P. Zhang, *Chem. Sci.* **2011**, *2*, 2361–2366; g) H. Lu, H. Jiang, L. Wojtas, X. P. Zhang, *Angew. Chem. Int. Ed.* **2010**, *49*, 10192–10196; *Angew. Chem.* **2010**, *122*, 10390–10394.
- [13] L.-M. Jin, H. Lu, Y. Cui, C. L. Lizardi, T. N. Arzua, L. Wojtas, X. Cui, X. P. Zhang, *Chem. Sci.* **2014**, *5*, 2422–2427.
- [14] M. Goswami, C. Rebreyend, B. de Bruin, *Molecules* **2016**, *21*, 242.
- [15] G.-Y. Gao, J. D. Harden, X. P. Zhang, *Org. Lett.* **2005**, *7*, 3191–3193.
- [16] a) S. Cenini, E. Gallo, A. Penoni, F. Ragaini, S. Tollari, *Chem. Commun.* **2000**, 2265–2266; b) F. Ragaini, A. Penoni, E. Gallo, S. Tollari, C. L. Gotti, M. Lapadula, E. Mangioni, S. Cenini, *Chem. Eur. J.* **2003**, *9*, 249–259.
- [17] A. I. Olivos Suarez, H. Jiang, X. P. Zhang, B. de Bruin, *Dalton Trans.* **2011**, *40*, 5697–5705.
- [18] a) L. Maestre, W. M. C. Sameera, M. M. Díaz-Requejo, F. Maseras, P. J. Pérez, *J. Am. Chem. Soc.* **2013**, *135*, 1338–1348; b) M. Besora, A. A. C.

- Braga, W. M. C. Sameera, J. Urbano, M. R. Fructos, P. J. Pérez, F. Maseras, *J. Organomet. Chem.* **2015**, *784*, 2–12; c) G. Manca, E. Gallo, D. Intriери, C. Mealli, *ACS Catal.* **2014**, *4*, 823–832; d) L. Liang, H. Lv, Y. Yu, P. Wang, J.-L. Zhang, *Dalton Trans.* **2012**, *41*, 1457–1460; e) H. Zhang, W. Pu, T. Xiong, Y. Li, X. Zhou, K. Sun, Q. Liu, Q. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 2529–2533; *Angew. Chem.* **2013**, *125*, 2589–2593; f) K. Kaneko, T. Yoshino, S. Matsunaga, M. Kanai, *Org. Lett.* **2013**, *15*, 2502–2505; g) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1790–1793.
- [19] Z.-Y. Gu, Y. Liu, F. Wang, X. Bao, S.-Y. Wang, S.-J. Ji, *ACS Catal.* **2017**, *7*, 3893–3899.
- [20] D. Fujita, H. Sugimoto, Y. Shiota, Y. Morimoto, K. Yoshizawa, S. Itoh, *Chem. Commun.* **2017**, *53*, 4849–4852.
- [21] a) D. L. J. Broere, B. de Bruin, J. N. H. Reek, M. Lutz, S. Dechert, J. I. van der Vlugt, *J. Am. Chem. Soc.* **2014**, *136*, 11574–11577; b) D. L. J. Broere, N. P. van Leest, B. de Bruin, M. A. Siegler, J. I. van der Vlugt, *Inorg. Chem.* **2016**, *55*, 8603–8611. See also: W. Zhou, B. O. Patrick, K. M. Smith, *Chem. Commun.* **2014**, *50*, 9958–9960.
- [22] a) E. R. King, E. T. Hennessy, T. A. Betley, *J. Am. Chem. Soc.* **2011**, *133*, 4917–4923; b) E. T. Hennessy, R. Y. Liu, D. A. Iovan, R. A. Duncan, T. A. Betley, *Chem. Sci.* **2014**, *5*, 1526–1532; c) D. A. Iovan, T. A. Betley, *J. Am. Chem. Soc.* **2016**, *138*, 1983–1993.
- [23] a) E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591–595; b) similar iron nitrene radical species were reported by the groups of Piers, Neidig and Maron, undergoing a set of interesting stoichiometric reactions: D. M. Spasyuk, S. H. Carpenter, C. E. Kefalidis, W. E. Piers, M. L. Neidig, L. Maron, *Chem. Sci.* **2016**, *7*, 5939–5944.
- [24] B. Bagh, D. L. J. Broere, V. Sinha, P. F. Kuijpers, N. P. van Leest, B. de Bruin, S. Demeshko, M. A. Siegler, J. I. van der Vlugt, *J. Am. Chem. Soc.* **2017**, *139*, 5117–5124.
- [25] P. F. Kuijpers, M. J. Tiekink, W. B. Breukelaar, D. L. J. Broere, N. P. van Leest, J. I. van der Vlugt, J. N. H. Reek, B. de Bruin, *Chem. Eur. J.* **2017**, *23*, 7945–7952.
- [26] a) N. P. Mankad, P. Müller, J. C. Peters, *J. Am. Chem. Soc.* **2010**, *132*, 4083–4085; b) A. Takaoka, M.-E. Moret, J. C. Peters, *J. Am. Chem. Soc.* **2012**, *134*, 6695–6706.
- [27] K. P. Kornecki, J. F. Berry, *Chem. Eur. J.* **2011**, *17*, 5827–5832.
- [28] a) M. G. Scheibel, J. Abbenseth, M. Kinauer, F. W. Heinemann, C. Würtele, B. de Bruin, S. Schneider, *Inorg. Chem.* **2015**, *54*, 9290–9302; b) M. Kinauer, S. Demeshko, M. Diefenbach, E. J. Reijerse, C. Volkmann, M. C. Holthausen, B. de Bruin, S. Schneider, *submitted*.

Manuscript received: June 2, 2017

Accepted manuscript online: July 4, 2017

Version of record online: September 14, 2017