Activation of N–O σ Bonds with Transition Metals: a Versatile Platform for Organic Synthesis and C–N Bonds Formation

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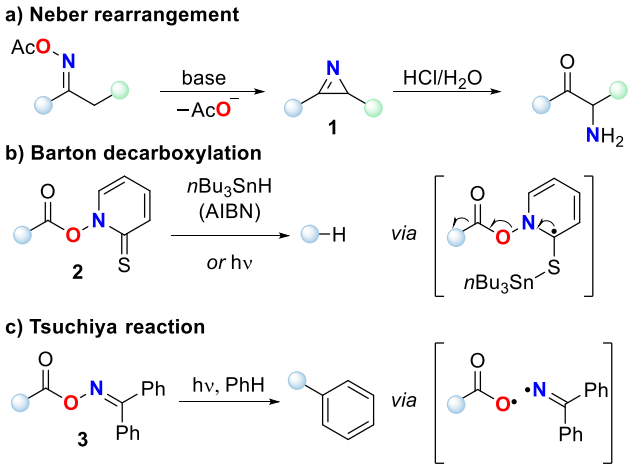
Abstract: N–O σ bonds containing compounds are versatile substrates for organic synthesis in presence of transition metal catalysis. Their ability to react through both ionic (oxidative addition, formation of metallanitrene, nucleophilic substitution) and radical pathways (single electron transfer, homolytic bond scission) have triggered the development of a large scope of synthetic methodologies, in particular towards the synthesis of nitrogen containing compounds. In this review, we discuss the different mode of activation of N–O bonds in presence of transition metal catalysts, emphasizing the experimental and computational mechanistic proofs in the literature to help designing new synthetic pathways towards the synthesis of C–N bonds..

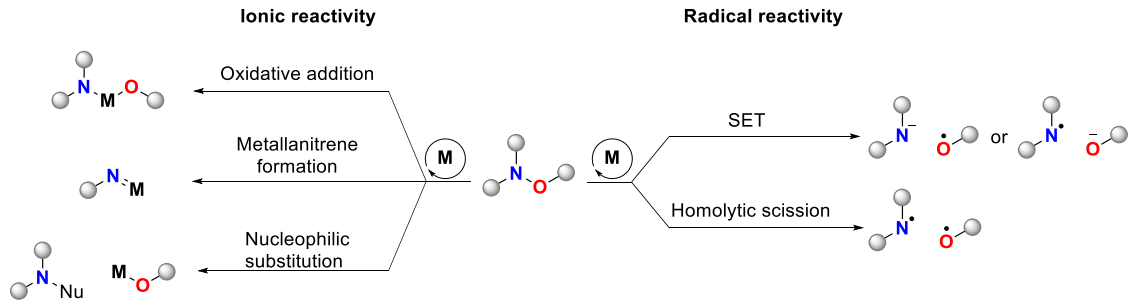
The formation of C–N bonds is central in fine chemistry and is estimated to represent 35% of all reactions in pharmaceutical industries. Traditional methods rely on nucleophilic sources of nitrogen and include *N*-alkylation of alkyl halides, the reductive amination of carbonyl derivatives, and the cross-coupling of aryl halides with amines.[1] In line with the renaissance of radical chemistry, the active development of photoredox pathways, and the emergence of electrophilic aminations, the reactivity of N–O σ bonds (hydroxylamine derivatives, substituted oximes…) has triggered an increased interest for the elaboration of complex *N*-containing molecules. Their high reactivity relies on the electrophilic character of the nitrogen atom, a weak bond, and their high propensity to be reduced.

As soon as in the 1920s, Neber and Friedolsheim made use of the electrophilic character of tosylated ketoximes.[2] The resulting Neber rearrangement of *O*-acylated ketoximes corresponds to their base-induced rearrangement into α-amino ketones through an aziridine intermediate **1**. There, the release of the carboxylate is presumably occurring *via* a concerted anionic or nitrene pathway (Scheme 1a). The electrophilic character at the nitrogen atom has been thereafter extensively used, e.g. in electrophilic aminations.[3] Note that the electrophilic character is in most cases bore by the nitrogen atom, except in very specific substrates such as *N*-substituted oxaziridines, where the oxygen atom represents the electrophilic center.[4] These substrates are nevertheless out of the scope of the present review.

Resulting from the repulsion of the lone electron pairs on the nitrogen and oxygen atoms, the low bond dissociation energy (BDE) of N–O σ bonds also imparts hydroxylamine derivatives a similar reactivity compared to chloramines (BDE≈63.0 kcal/mol^{-1} for the parent hydroxylamine H_2N–OH vs. 60.5 kcal.mol^{-1} for chloramine H_2N-Cl),[5] while at the same time being less toxic, and in most cases more stable. The resulting high reactivity of N–O σ bonds compared to other N–Y bonds (e.g. H_2N–CH_3 BDE= 85.1 ± 0.5 kcal/mol)[5] thus allows to design orthogonal reaction



Scheme 1. Seminal reactions involving N–O σ bonds containing substrates: a) Neber rearrangement with acyl oximes; b) Barton decarboxylation through thiohydroxamate esters; c) Tsuchiya reaction of benzophenone oxime ester.



Scheme 2. Versatile reactivity of hydroxylamine derivatives in presence of transition-metal catalysts M. Nu = nucleophile; SET = single electron transfer.

processes leading to high selectivity in complex molecules. Homolytic fragmentation of an N–O σ bond is for example key to the Barton decarboxylation (also referred to as Barton-Motherwell decarboxylation), where a thiohydroxamate ester **2** is reduced under thermal or photoactivation (Scheme 1b).[6] The same strategy was employed by Tsuchiya with benzophenone oxime esters **3**, where the homolytic cleavage of the N–O bond occurred through photolysis, followed by the decarboxylation of the carboxyl radical. The resulting carbon-centered radical is then trapped by benzene, creating thus a C–C bond (Scheme 1c).[7]

These seminal examples showcase the high reactivity and high versatility of the N–O σ bond, which can be activated via both ionic and radical pathways. In presence of transition metals, hydroxylamine derivatives display the same duality. Ionic pathways can formally lead to the oxidative addition product, metal nitrenoid-like intermediates, or follow S_N2-type reactivity, whereas radical pathways lead to the generation of nitrogen and/or oxygen radicals *via* single electron transfer (SET) or homolytic scission (Scheme 2). The main drawback of the high reactivity lies in the difficulty to predict which pathway will be followed – hence the outcome of the reaction – and the frontiers between them are often delicate to define. Only a deep understanding of how the fine-tuning of both the substrate and the reaction conditions will trigger one or the other pathway could allow foreseeing the outcome, and few examples of direct proofs are reported in the literature

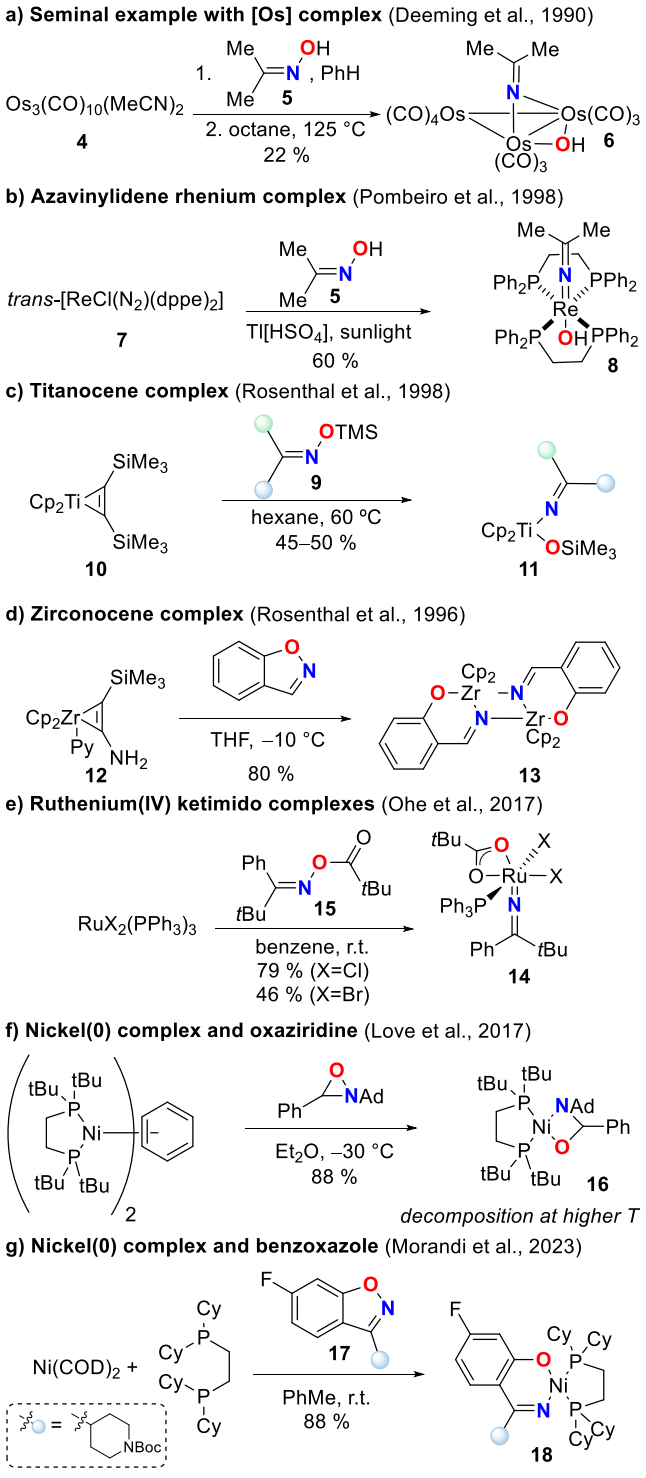
This review does not intend to list exhaustively the abundant literature using hydroxylamine derivatives' activation with transition metals but aim at emphasizing the different features guiding the reactivity of these versatile compounds, especially in their use towards the elaboration of C–N bonds. In particular, we will pinpoint the mechanistic proofs, both experimental and computational, hinting at one or another mechanistic pathway.

1. Transition metals oxidative addition in the N–O σ bond

The oxidative addition pathway corresponds to the addition of the N–O bond to a low-valent metal center [M] to form two new bonds [M]–N and [M]–O, with an increase of +2 in the redox state of the metal center. Initially described in the 1960s with halide derivatives,[8] the first experimental proof for an oxidative addition of a N–O bond to a metal complex was described by Deeming et al. in 1990. The trinuclear osmium cluster $[Os_3(CO)_{10}(MeCN)_2]$ **4** reacted with acetone oxime (**5**), initially providing an oxidative addition in the O–H bond and leading to the hydrido complex $[Os_3(\mu\text{-}H)(\mu\text{-}Me_2C{=}NO)(CO)_{10}]$ in 46% yield. Upon reflux in octane for 2 h, the osmium cluster isomerized into the non-hydrido cluster $[Os_3(\mu\text{-}OH)(\mu\text{-}Me_2C{=}N)(CO)_{10}]$ (**6**), obtained in 48% yield (overall yield of 22% over 2 steps), and which structure has been confirmed by X-Ray crystallography. The authors suggested that the hydroxy compound **6** resulting from an oxidative addition of the N–O bond was thus the thermodynamic product (Scheme 3a).[9]

A direct oxidative addition of an N–O bond was as well reported between acetone oxime (**5**) and *trans*-$[ReCl(N_2)(dppe)_2]$ (**7**) (dppe=1,2-bis(diphenylphosphino) ethane) in presence of $Tl[HSO_4]$ as chlorine abstractor. The resulting *trans*-$[Re(OH)(N{=}CMe_2)(dppe)_2]$ (**8**) was characterized by X-ray crystallography. The preferential oxidative addition into the N–O versus O–H bond was explained by the high electron richness of the rhenium metal center together with its high π-donor character. The latter, combined with the steric hindrance induced by the bulky diphosphine ligands, helped stabilizing the final complex, bearing a π-acceptor linear ligand $N{=}CMe_2$. The π-backbonding promoted the formation of a significant double-bond character, i.e. an azavinylidene complex, between the rhenium core and the nitrogen atom, proved by a short bond distance between these two atoms in the X-ray structure (1.901 Å, shorter than the Re–N average value of 2.107 Å, Scheme 3b).[10]

Rosenthal's group disclosed in the late 90's examples of group IV metal complexes oxidative addition in N–O bonds. To avoid the competitive oxidative addition in the O–H bond of oximes, silylated oximes **9** were reacted with titanocene $[Cp_2Ti(Me_3SiC_2SiMe_3)]$ (**10**). An intermediate coordination of both the nitrogen and oxygen atoms to the metal core was assumed to trigger the N–O bond scission, leading to the titanocene complex $[Cp_2Ti(N{=}CR_2)(OSiMe_3]$ (**11**), as confirmed by X-ray analysis. In this case, the Ti–N bond length showed a clear single bond character (1.903 Å, Scheme 3c).[11] The same group also showed that the zirconocene complex $[Cp_2Zr(Pyr)(Me_3SiC_2SiMe_3)]$ (Pyr = pyridine, **12**) led in presence of 1,2-benzisoxazole to the dimer **13**, where a Zr–O and a Zr–N bonds were formed upon opening of the 5-membered ring, as demonstrated by X-ray crystallography (Scheme 3d).[12]



Scheme 3. Selected examples of complexes obtained by oxidative addition in N–O bonds whose structures were confirmed by X-Ray analysis. Cp = cyclopentadienyl; dppe = 1,2-bis(diphenylphosphino)ethane; Cy = cyclohexyl; COD = 1,5-cyclooctadiene.

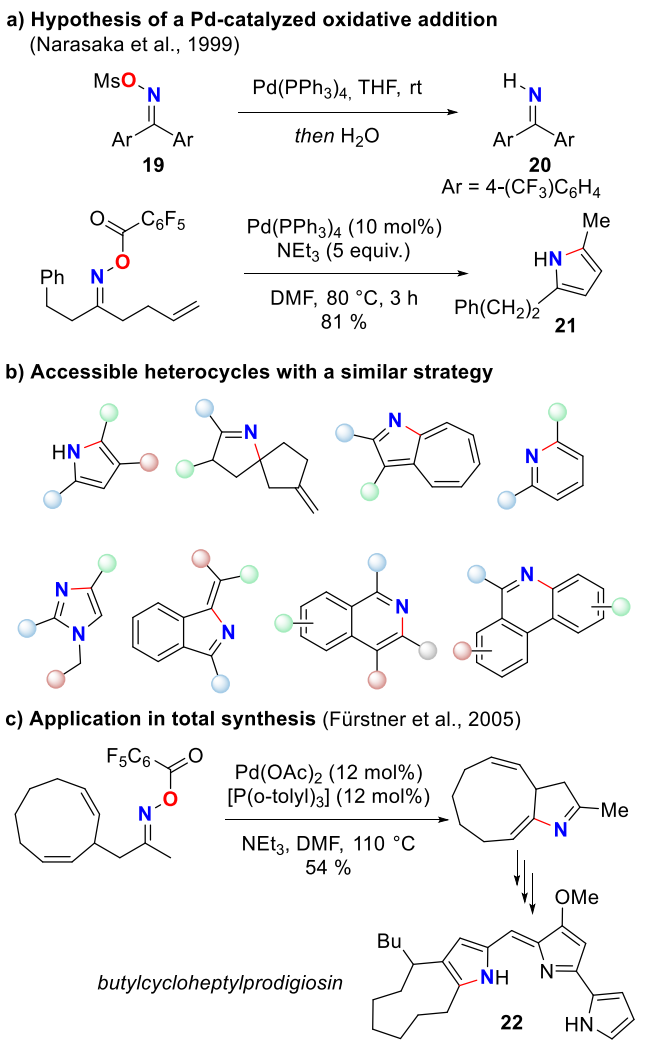
More recently the same reactivity has been showcased with late transition metals. Ohe and coworkers were able to synthesize ruthenium(IV) ketimido complexes **14** resulting from the oxidative addition of oxime ester **15** to [$RuX_2(PPh_3)_3$] (X=Cl or Br). As in the case of Pombeiro's rhenium complex **8**,[10] the short bond distance (1.790 Å) claimed for a significant double bond character, which was supported by natural bond orbital (NBO) analysis (Scheme 3e).[13] The group of Love isolated the Ni(II) complex **16** resulting from the oxidative addition of [(dtbpe)Ni(0)] complex (dtbpe = 1,2-bis(di-tert-butylphosphino)ethane) into the N–O bond of *N*-adamantyl oxaziridine. This complex proved to be stable enough at –30 °C to grow crystals (Scheme 3f), but decomposed at higher temperatures.[14] A very recent example by the Morandi's group also showcased the propensity of the nickel(0) complex [(dcype)Ni] (dcype = 1,2-bis(dicyclohexylphosphino)ethane) to insert in the N–O bond of benzoxazole **17**. The structure of the resulting Ni(II) complex **18** was confirmed by X-ray, NMR and HRMS analysis (Scheme 3g).[15]

These selected examples showcase the propensity of transition metals to activate N–O bonds via oxidative addition. However, X-Ray structures are not giving any information on the mechanistic pathway followed, and more investigations are required to distinguish between pure oxidative addition and single electron pathways. This duality will be discussed later on in this review.
Based on these seminal examples, the ability of transition metal to undergo oxidative addition in N–O bonds was utilized to develop metal-catalyzed C–N bonds formation, essentially with late transition metals such as palladium or copper.

1.1 Pd-catalyzed reactions

In the late 90's, the group of Narasaka made an interesting observation in the reaction of *O*-sulfonyloxime derivative **19** with $Pd(PPh_3)_4$. After hydrolysis, the derived imine **20** was observed, hinting at an oxidative addition of the Pd(0) into the N–O bond and a putative Pd(II) intermediate. Making use of this hypothesis, Pd-catalyzed aza-Heck reactions of *O*-acyloximes bearing a pendant alkene group were developed, furnishing pyrroles such as compound **21** (Scheme 4a). The authors found out that using a pentafluorobenzoyl group as *O*-substituent completely suppressed the side-product formation resulting from the Beckmann rearrangement of the oxime.[16] This strategy allowed to develop Pd-catalyzed syntheses of *N*-heterocycles[17] such as pyrroles, spiro imines,[18] 1-azaazulenes,[19] pyridines,[20] imidazoles,[21] isoindoles,[22] isoquinolines,[20,23] or phenanthridines (Scheme 4b).[23] Involvement of a similar oxidative addition was claimed in the cyclobutanone *O*-benzoyloxime Pd-catalyzed ring cleavage.[24] The applicability of this methodology was finally demonstrated by Fürstner and his group in the total synthesis of butylcycloheptylprodigiosin (**22**) (Scheme 4c).[25]

The possibility of an oxidative addition of the N–O bond to a Pd(0) species was only proven in 2010 when Hartwig and his group isolated the Pd(II)-complex intermediate **23**, resulting from the oxidative addition of [$Pd(PCy_3)_2$] in the *O*-pentafluorobenzoyl oxime **24**. The authors thereafter confirmed that the isolated Pd(II)-complex **23** was leading to the same product as their

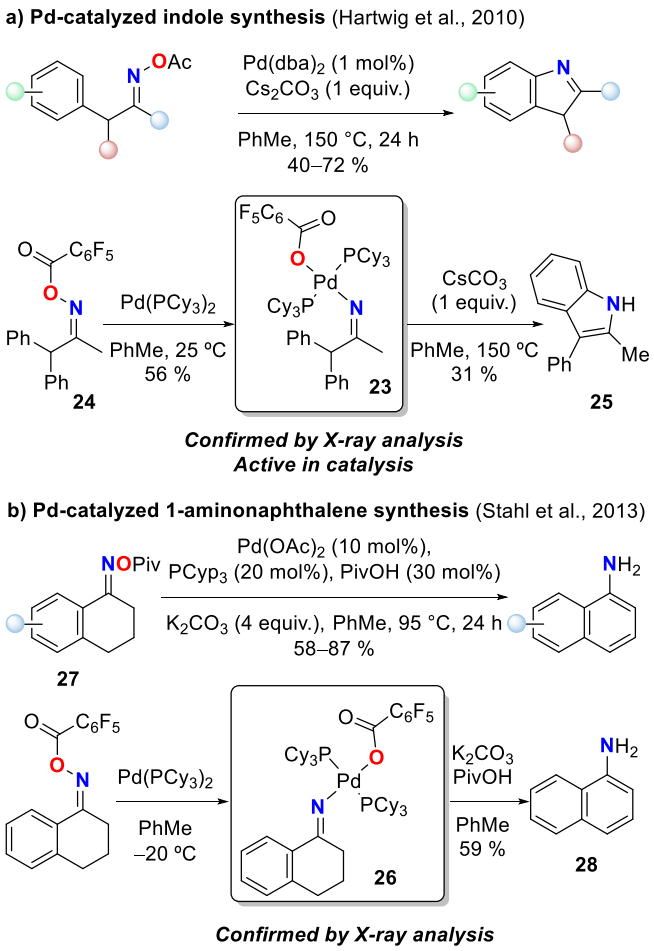


Scheme 4. Reactions based on a possible oxidative addition of N–O bond to a [Pd] species: a) Preliminary results of Narasaka et al.; b) Accessible *N*-heterocycles via the same mechanistic rational; c) Application to the synthesis of butylcycloheptylprodigiosin (**22**) by the group of Fürstner.

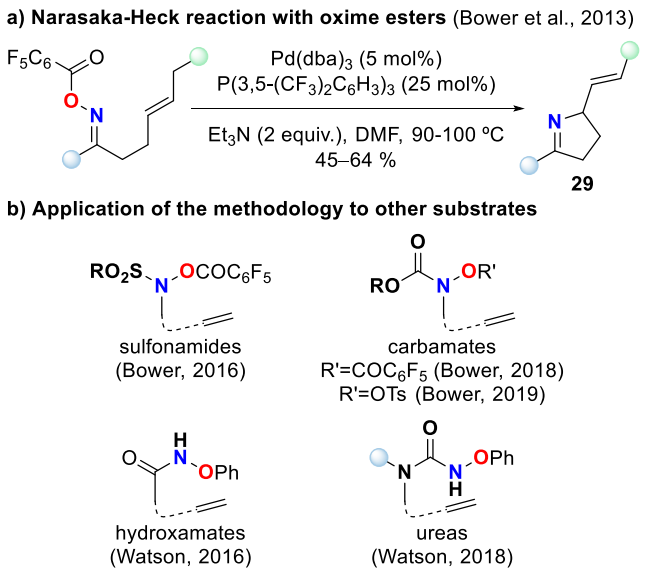
catalytic methodology, namely the indole product **25**, and was active in catalysis (Scheme 5a). The same strategy was employed later on by Stahl who isolated Pd(II)-complex **26**, when developing a Pd-catalyzed 1-aminonaphthalene synthesis from the corresponding tetralone pivaloyl oximes **27**. The authors confirmed as well that complex **26** was leading to the corresponding 1-aminonaphthalene **28** (Scheme 5b). In both cases, no information was given on the mechanistic pathway. In all likelihood, since electron-rich phosphine ligands PCy_3 are used, Pd(II)-complexes **23** and **26** should result from a two-steps pathway, involving a single electron transfer as demonstrated later by the group of Bower.[26] This pathway will be discussed in a following section (*vide infra*).

Inspired by Narasaka's pioneering work,[27] Bower et al. developed 5-*exo*-iminopalladation reactions, leading to the intramolecular elaboration of N–C(sp^3) bond, the N–O bond acting here as an internal oxidant.[28] With an extended alkyl chain, the authors showed that the 3,4-dihydro-2*H*-pyrrole **29** with an exocyclic alkene could be selectively obtained (Scheme 6a), instead of the pyrrole as in Narasaka's system (see product **21**, Scheme 4). This difference arose from a precise ligand-control regioselectivity of the β-hydride elimination. Moreover, introduction of a chiral TADDOL-derived phosphoramidite ligand allowed controlling the stereochemistry of the C(sp^3).[28a-d] Some aspects are important in these modifications. The electron deficient phosphine ligand $P(3,5\text{-}(F_3C)_2C_6H_3)_3$ is believed to enhance the σ-donation from the imine ligand to the metal after oxidative addition, which will increase the N–Pd bond strength and decrease the basicity of the nitrogen lone pair, suppressing the competitive protodepalladation to the NH imine. In addition, lowering the electron density on the Pd(II) species could accelerate the alkene migratory insertion, and have a strong influence on the outcome of the reaction. Indeed, the authors showed that an electron neutral phosphine like PPh_3 led to more protodepalladation, while an electron-rich phosphine such as $P(t\text{Bu})_3$ promoted the formation of an iminyl radical via N–O bond homolysis (see section 3.3 for more details).[26] The bulky ligand was finally believed to be crucial for the regioselectivity of the β-hydride elimination, resulting from steric effects.[28c]

Bower also explained the key effect of the *O*-pentafluorobenzoyl substituent already observed by the group of Narasaka.[16] After oxidative addition, the decoordination of the benzoate ligand, forming a cationic $Pd(II)^+$ intermediate, promotes an efficient migratory insertion of the alkene. Using the electron-poor pentafluorobenzoate facilitates the decoordination, and its



Scheme 5. Experimental proofs for an oxidative addition of N–O bonds to Pd(0) complexes. Synthesis of indoles by Hartwig et al. (a), of 1-aminonaphthalene derivatives by Stahl et al. (b), and corresponding isolated complexes.



Scheme 6. a) Narasaka-Heck reaction developed by the group of Bower on oxime derivatives; b) Substrates reacting under similar reaction conditions *via* a supposed similar pathway.

subsequent spontaneous protodecarboxylation under the reaction conditions (90 °C, NEt_3 2 equiv. in DMF) prevents its coordination back.[28d]

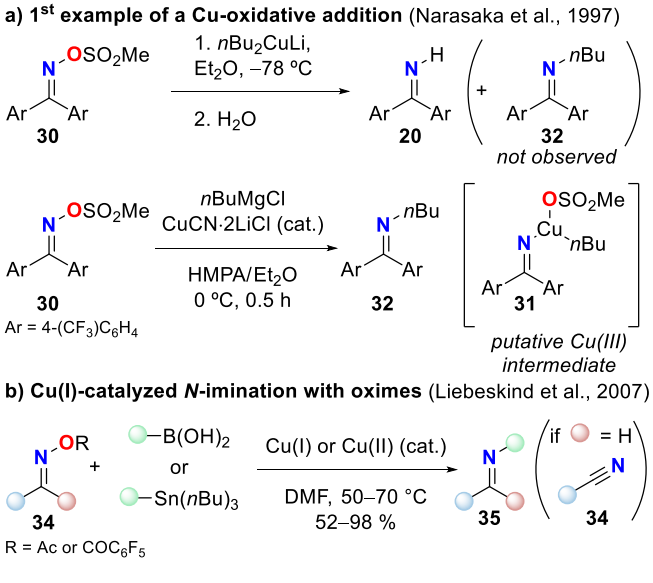
Beyond the Narasaka-Heck reaction, other vicinal imino-functionalizations (-acylation,[28d] -carboxylation,[28d] -arylation,[28d,29] -vinylation,[28d] -alkynylation,[28d] -halogenation[30]) have been developed, making use of the migratory insertion of an alkene in the imminopalladium(II) intermediate. Interestingly, aza-Heck reactions were also developed with other hydroxylamine derivatives (sulfonamides,[31] carbamates,[32] hydroxamates,[33] ureas[34]) in presence of Pd-catalysts, using the same strategy (Scheme 6b). Albeit no direct proof for an oxidative addition of the metal catalyst in the N–O bond exists, indirect results such as the inactivity of the corresponding N–H compounds or the decarboxylation of the pentafluorobenzoate ligand hinted at the implication of a similar mechanistic pathway.

1.2 Cu-catalyzed oxidative additions: ambiguous results

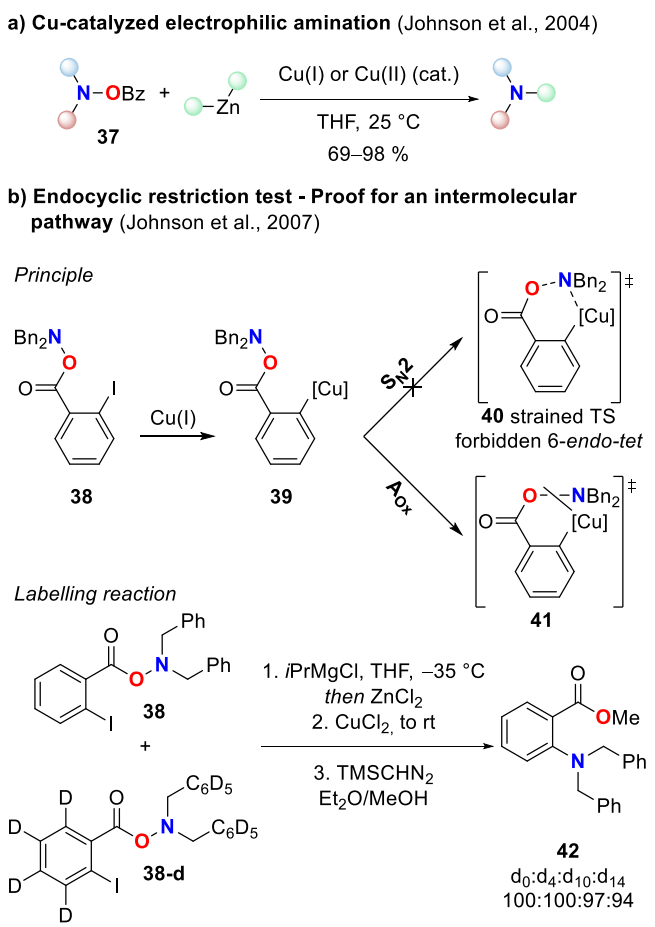
The use of copper for N–O bond scission was initially reported by Narasaka and his group in 1997. When reacting Gilman reagent nBu$_2$CuLi with *O*-methylsulfonyloxime **30**, they observed the formation, upon hydrolysis, of the corresponding NH-imine **20**. This observation led to the hypothesis that the Cu(I) species was able to perform an oxidative addition in the N–O bond, similar to Pd(0), giving a putative Cu(III) intermediate **31**. The latter, however, was unable to undergo reductive elimination to the desired *N*-butyl imine **32** under these conditions. Employing a HMPA/Et$_2$O (HMPA = Hexamethylphosphoramide) mixture as solvent finally allowed the authors to develop a Cu(I)-catalyzed addition of Grignard reagents to *O*-sulfonyloxime **30** (Scheme 7a). Ten years later, Liebeskind and coworkers made a similar observation in the Cu-catalyzed *N*-imination of boronic acids or organostannanes with *O*-acyl ketoximes **33**. A 1:1 mixture of the catalyst and the starting ketoxime **33** led, upon work-up, to the corresponding NH-imine, hinting at an oxidative addition in the N–O bond. The observation of nitrile derivatives **34** instead of imine **35** from the corresponding aldoximes under the reaction conditions stood as an additional indirect proof for an oxidative addition into the N–O bond (Scheme 7b). Indeed, nitrile **34** could arise from a β-hydride elimination of the putative Cu(III)-intermediate. Based on these observations, a Cu(I)-mediated cross-coupling of boronic acids and organostannanes with *O*-acetyl hydroxamic acids **36** was reported by the same group (Scheme 7c). In this case, a stoichiometric amount of copper was required, certainly due to the higher stability of the possible Cu-amido intermediate. Again, the mechanism is supposed to go through an oxidative addition of the Cu(I) species in the N–O bond, since in the absence of nucleophile and after hydrolysis, the primary amide PhCONH$_2$ was obtained. Nevertheless, radical pathways cannot be completely ruled out and will be discuss in a next section (*vide infra*).

In 2004, Johnson and coworkers reported the Cu-catalyzed electrophilic amination of organozinc reagents with *O*-benzoyl hydroxylamine derivatives **37** (Scheme 8a).[35] In a follow-up publication, the group postulated that three different pathways could be involved in this reaction: an oxidative addition pathway as hypothesized by Narasaka and coworkers, a S_N2-type mechanism, and a radical pathway (see Scheme 2).

The retention of configuration observed alongside the reaction first ruled out a radical mechanism. To distinguish between a S_N2 and an oxidative addition mechanism, the so-called endocyclic restriction test was performed. In this test, *O*-(2-iodobenzoyl)hydroxylamine **38** is supposed to furnish a Cu(I)-intermediate **39**. With this particular substrate, an intramolecular S_N2 reaction is forbidden because of the strained transition state **40**, whereas an intramolecular oxidative addition through transition state **41** is allowed. Hence if the reaction was following



Scheme 7. Examples of Cu-mediated reactions of oxime (a,b) and hydroxamate derivatives (c) supposed to happen through Cu(I)-oxidative addition to the N–O bond. HMPA = hexamethylphosphoramide.



Scheme 8. a) Cu-catalyzed electrophilic amination with diorganozinc reagents; b) Principle and reaction outcome of the endocyclic restriction test performed by Johnson and coworkers.

only an intramolecular pathway, it would validate the hypothesis of an oxidative addition mechanism. In the competition reaction between substrate **38** and its D-labelled version **38-d**, the authors observed both non-crossover (**42-d₀** and **42-d₁₄**) and crossover products (**42-d₄** and **42-d₁₀**) in similar amounts (d_0:d_4:d_{10}:d_{14} 100:100:97:94). This outcome could only arise *via* an intermolecular pathway, hence a S_N2 mechanism and not an oxidative addition (Scheme 8b).[36]

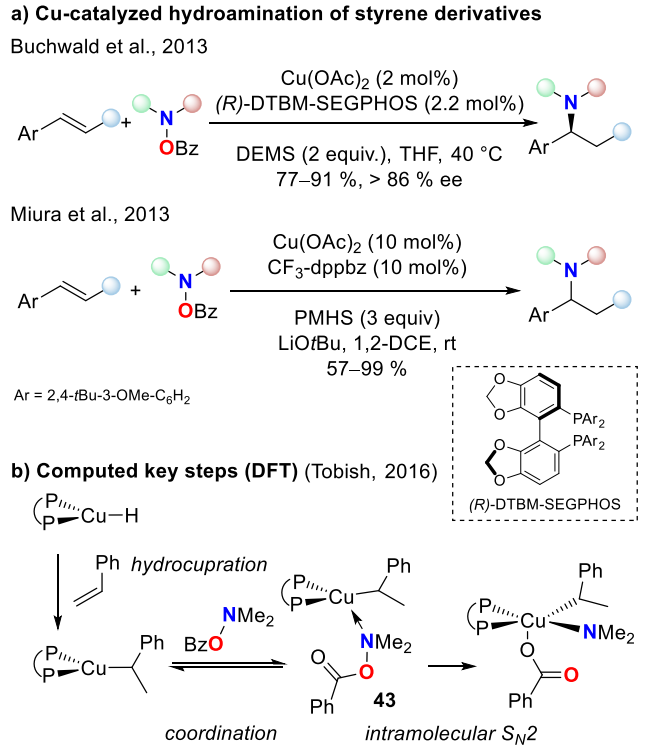
Tobisch confirmed these findings in 2016 by DFT calculations on a similar electrophilic hydroamination of alkenes[37] concomitantly developed by the groups of Miura[38] and Buchwald[39] in 2013 (Scheme 9a). The reaction involved a copper catalyst which is supposed to react *via* initial alkene hydrocupration, producing an alkyl copper(I), as later validated by Tobish's study.[37] Initially, Buchwald and coworkers proposed that the copper(I) intermediate was undergoing an oxidative addition in the N–O bond. The subsequent reductive elimination from the Cu(III) intermediate would finally promote the formation of the desired hydroaminated product. Actually, according to computational studies, a pre-coordination of the benzoate on the metallic center occurs prior to N–O bond scission, forming intermediate **43**. Among the possible oxidative addition pathways, DFT calculations suggested a favorable S_N2-reminiscent reactivity on the N core through the nucleophilic attack of the copper center and benzoate dissociation ($\Delta G^{\ddagger}$=16.3 kcal.mol^{-1} from **43**, Scheme 9b). The alternative classical three center oxidative addition into the N–O bond showed a more energetically demanding pathway ($\Delta G^{\ddagger}$=27.6 kcal.mol^{-1} from **43**) and therefore, a less accessible route.

A similar mechanism was proposed based on experimental and computational results for Rh(III)-catalyzed reaction of hydroxamate derivatives with alkynes.[40]

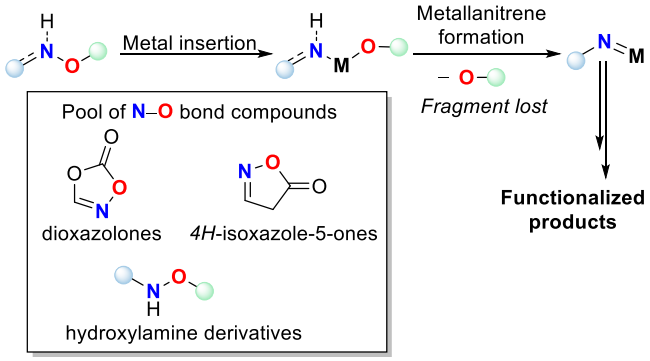
These last examples show the drastic influence of the nature of the *N*-oxide derivative. Whereas in the case of oxime derivatives, the oxidative addition pathway seems to be favored in presence of copper(I) catalysts, *O*-acylated hydroxylamines are more prone to reacting *via* S_N2 mechanisms under similar reaction conditions. Surprisingly, mechanistic proofs for a catalytic pathway going through an oxidative addition of *N*-oxide derivatives to metallic species are rather rare. Yet, the large variety of isolated metal-complexes resulting from oxidative addition with Os-, Re-, Zr-, Ti-, Ru-, Ni-, or Pd-complexes (see Scheme 3 and Scheme 5) demonstrates the high reactivity of N–O bond containing compounds towards transition metal complexes and should allow to design new catalytic reactions.

2. Metallanitrenes formation from N–O σ bonds

As discussed in the first part, various metals can oxidatively insert into the N–O bond. Under certain conditions, the oxygenated ligand is lost, and it is possible to afford intermediate metallanitrene species which can then engage into further reactivity (Scheme 10). This nitrene pathway is favored when the



Scheme 9. a) Reductive Cu-catalyzed hydroamination of styrene derivatives with *O*-benzoylhydroxylamines described concomitantly by Buchwald et al. and Miura et al.; b) Key steps according to computational results by Tobish. DEMS = diethoxymethylsilane; PMHS = polymethylhydrosiloxane; dppbz = 1,2-([3,5-$(CF_3)_2C_6H_3$]P)C_6H_4; 1,2-DCE = 1,2-dichloroethane.



Scheme 10. Metallanitrenes generation from N–O bond containing compounds.

oxygenated part can undergo decarboxylation (i.e. with *4H*-isoxazole-5-ones or with dioxazolones[41]) and/or is a poor ligand (i.e. because of steric bulkiness). In the later case, the remaining oxygen-containing part of the molecule might even be incorporated in the final product (i.e. in an amino-oxygenation process).

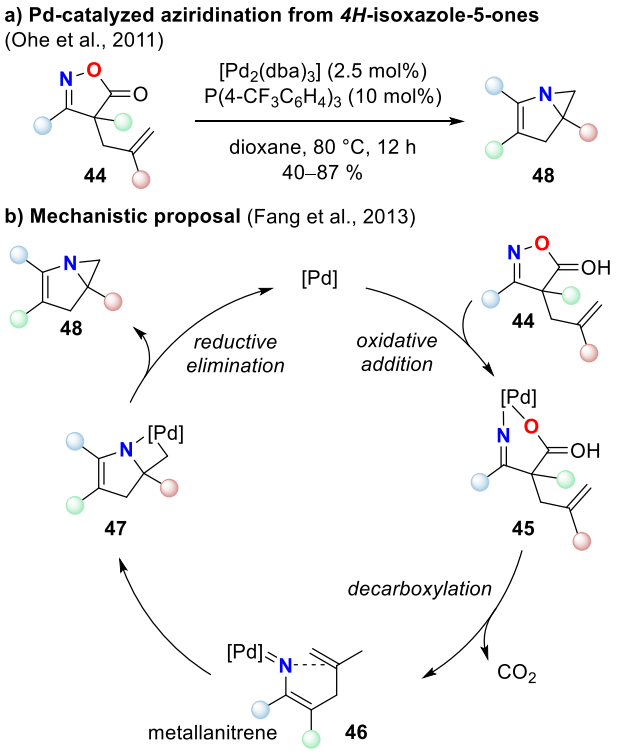
Nitrenes are highly reactive species, which can be thought of as nitrogen analogues of carbenes.[42] However, due to their extreme reactivity, they are only formed and observed as intermediates.[43] Classically, nitrenes can be prepared as transient intermediates from azides, *via* release of dinitrogen. The fact that a non-stabilized nitrene is able to insert into a C–H bond to perform an amination reaction speaks of the synthetic utility of this intermediate.[44] However, owing to this extreme reactivity, a need for better selectivity and reaction control arises. Although it is possible to stabilize nitrenes by using silylenes,[45] a widely employed strategy is to utilize a reducing transition metal, which can even be achieved in a catalytic manner. It should be noted that the description of metallanitrene species is somewhat inconsistent throughout literature, as one can imagine that both Schrock- and Fischer-type species could explain the observed reactivity, the latter especially in the case of nitrenes which are electrophilic at nitrogen atom. Besides, these complexes are most of the time redox active at the nitrogen atom and their reactivities can often be explained by radical pathways. Therefore, it is important to be aware of the nature of this species, which is highly dependent on the involved metal, ligands, and *N*-derivatives.[46] This approach paves the way towards reactivity tuning, as by choosing the metal center and coordinated ligands, one can influence the nature and the reactivity of the resulting stabilized nitrene.[47]

2.1 Decarboxylative transformations

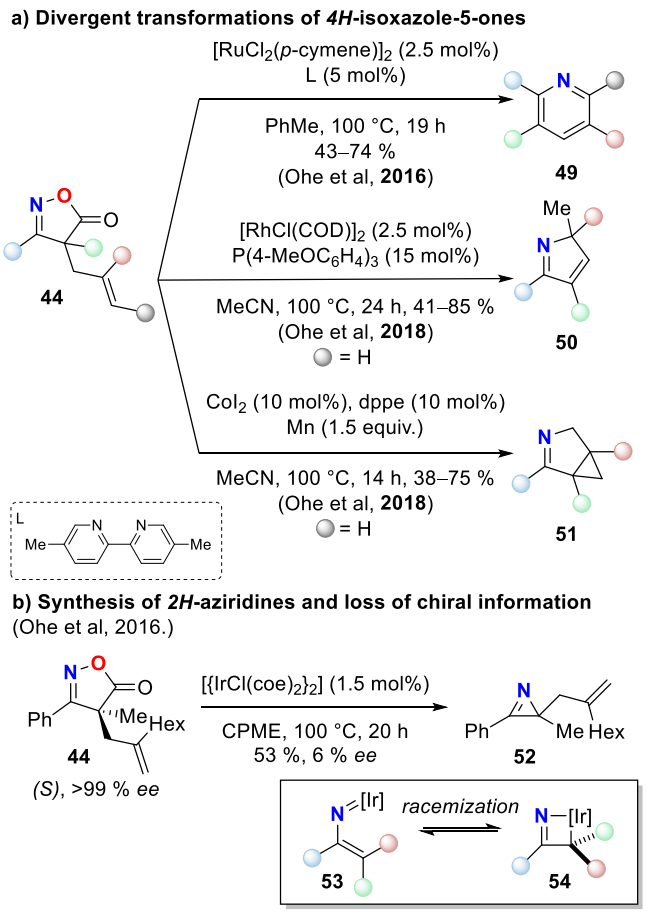
Various classes of heterocycles, such as differently substituted isoxazole derivatives and dioxazolones, containing the N–O bond can afford nitrene species upon decarboxylation of the substrate (Scheme 10). This unlocks synthetic access points to heterocyclic structures which can't be otherwise easily prepared, and/or enable interesting ring rearrangements.

One example from Ohe and coworkers, showed that it is possible to convert *4H*-isoxazol-5-ones, easily obtained from the corresponding β-ketoester, into 1-azabicyclo[3.1.0]hex-2-enes in the case of substrates bearing a pendant alkene such as compound **44** (Scheme 11a).[48] The reaction mechanism was thereafter investigated by Fang and coworkers by utilizing DFT calculations and their work revealed close to initial assumption by Ohe's research team.[49] The main mechanistic steps include the formation of the oxidative adduct **45**, which undergoes decarboxylation to afford the palladium-stabilized vinyl nitrene **46**. It is interesting to note, and based on computational calculations, that the formed metallanitrene is further stabilized by the distant olefin coordination. This could explain why up-to-date no intermolecular version of the reaction was reported. Then, olefin insertion takes place to afford the palladacycle **47**. This step is followed by reductive elimination to regenerate the Pd(0)-catalyst, furnishing the bicyclic system **48** (Scheme 11b).

Careful choice of the metal/ligand system coupled with different substituents on the substrate can vastly influence the outcome of such transformations. The same research group was indeed able to further streamline this idea and use the same class of substrates to access highly subsituted pyridines **49**,[50] and the authors also suggested that a Ru-ketimido complex was a possible intermediate species (Scheme 12a), as in the case of oxime esters (Scheme 3e).[13] Further confirming the exploitability of this fact, Ohe and coworkers were able to utilize Rh and Co catalysts to access *2H*-pyrroles **50** and azabicyclic cyclopropanes **51**, respectively (Scheme 12a).[51] It is very intriguing how these different catalytic conditions can greatly influence the reaction outcome. To gain further insight into this fact, Li and coworkers have done an in-depth DFT analysis of both reaction pathways. Here, we will not describe the reaction mechanism in detail, but only mention that it was found the main influence in selectivity comes from the respectively different geometries of Rh(I) and Co(II) key catalytic species, which is in line with the usually



Scheme 11. a) Decarboxylative aziridination of *4H*-isoxazol-5-ones; b) Mechanistic proposal based on DFT calculations (only the main intermediates are drawn).



Scheme 12. Divergent reactivity of *4H*-isoxazol-5-ones under various catalysis: a) Synthesis of highly substituted pyridines under Ru(II)-catalysis, *2H*-pyrroles synthesized under Rh-catalysis, and Co-catalyzed formation of azabicyclic cyclopropanes; b) *2H*-Aziridines obtained under Ir(I)-catalysis and racemization rational. COD = 1,5-cyclooctadiene; dppe = 1,2-bis(diphenylphosphino)ethane; coe = cyclooctene; CPME = cyclopentyl methyl ether.

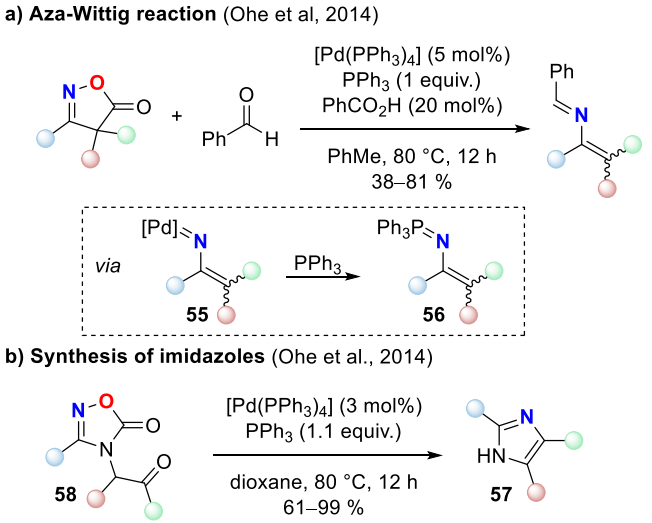
favored geometries of the respective systems. This is a very interesting case study, as it has also revealed that the insertion of the olefin precedes decarboxylation, as opposed to what was initially expected by the authors. These findings could also explain why no intermolecular version of these reactions is up-to-date reported.[52]

Under decarboxylative reaction conditions with the aid of an Ir(I) catalyst, it is also possible to synthesize ring-contraction products, *2H*-azirines **52**.[53] In this latter case, the chiral information is not transferred to the product. This is highly suggestive of a metallanitrene intermediate, as the equilibrium between the vinyl nitrene **53** and iridacycle **54** can account for the racemization of the substrate (Scheme 12b).

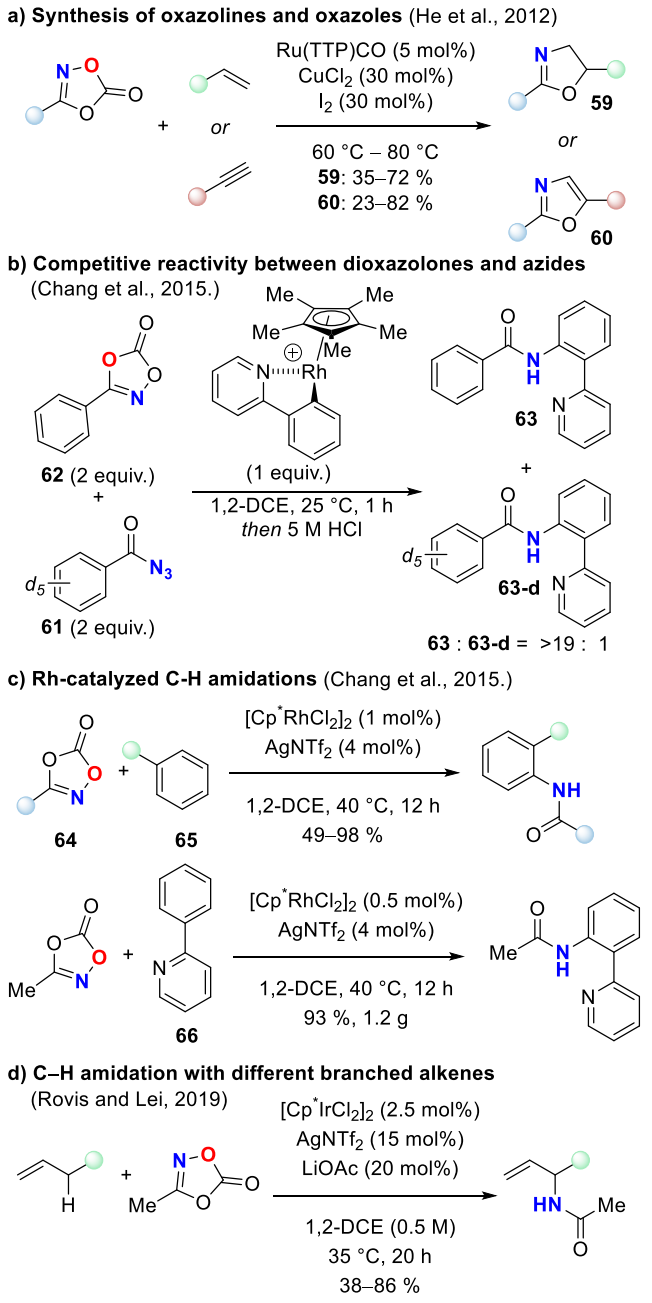
Interestingly, putative Pd(II)-nitrenoid intermediates can also engage in aza-Wittig-type reactions. This method is orthogonal to the Staudinger reduction, and thus opens another pathway towards iminophosphoranes. Here, the generated nitrenoid **55** is supposed to perform a nitrene transfer to the phosphine or alternatively directly engage in the aza-Wittig reaction (not shown). This method has a benefit that no explosive azides are used, in contrast to the traditional generation of iminophosphoranes in the Staudinger reaction. Note the use of catalytic amounts of benzoic acid, required to activate the aldehyde. The need for a stoichiometric amount of triphenyl phosphine confirmed that the transformation indeed proceeds *via* an iminophosphorane of type **56**. A full equivalent is necessary, as it is consumed by an oxidation event during the aza-Wittig reaction (Scheme 13a).[54] This transformation is not limited to the aldehyde, as well as to the heterocyclic partner. The group of Ohe has also reported a synthesis of imidazoles **57** in an equivalent manner, by using appropriate diazoles **58** (Scheme 13b).[55] Therefore, it should be noted that this chemistry has a potential to be further developed and expanded to different classes of iminophosphoranes.

Along with isoxazolones, dioxazolones, easily obtained from the corresponding carboxylic acids, are known since the 60's as readily accessible nitrene precursors.[41] However, their use as metallanitrene precursors date back to the beginning of the 2010's when He and colleagues demonstrated that both oxazolines **59** and oxazoles **60** can be readily synthesized from dioxazolones in presence of a Ru-based catalyst by employing alkynes or alkenes, respectively (Scheme 14a). Even if the involvement of a metallanitrene was highly probable, no experimental proof was given in this seminal example.[56]

Remarkably, dioxazole derivatives seems to more readily lead to nitrenes compared to the classically used azides. Chang, Kim, and colleagues have demonstrated the difference in reactivity by subjecting a mixture of these two classes of compounds to a stoichiometric amount of a cationic Rh(III)-complex to perform a C–H amidation. In a competition reaction, when only the phenyl moiety of the azide partner **61** was labelled with deuterium, contrary to the substituted 1,4,2-dioxazole-5-one **62**, it was noted that the non-labelled product **63** forms in a significant excess (**63**:**63-d**>19:1, Scheme 14b). To explain this reactivity, the authors have performed DFT calculations, which showed that the formation of the intermediate metallanitrene was more favorable in the case of the carbon dioxide expulsion, i.e., in the case of dioxazole derivatives **62** – as compared to the azides **61** ($\Delta\Delta G^{\ddagger}$=12.7 kcal.mol^{-1}). The authors also demonstrated that a



Scheme 13. Synthesis via an iminophosphorane intermediate in presence of a phosphine and under Pd-catalysis: a) Aza-Wittig type reaction starting from *4H*-isoxazol-5-ones; b) synthesis of imidazoles from diazoles.

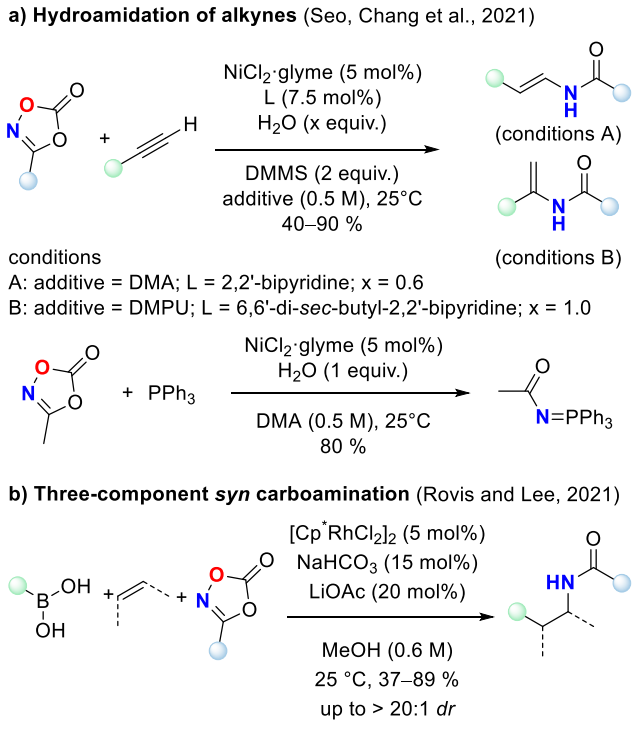


Scheme 14. a) Ru-catalyzed synthesis of oxazolines and oxazoles from dioxazolones via amino-oxygenation of alkenes and alkynes; b) Competition reaction between azides and dioxazoles under Rh-catalysis; c) Rh-catalyzed C–H amidation reactions with dioxazoles as metallanitrene precursors; d) Ir-catalyzed C–H amidation of branched alkenes. TPP = 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine; 1,2-DCE = 1,2-dichloroethane

variety of differently substituted dioxazoles **64** and arenes **65** can be successfully reacted to achieve a C–H amidation, conditions which are catalytic in the rhodium complex. A particularly interesting example from this publication is a gram-scale amidation of arene **66** – note that a pyridyl directing group allows for a selective C–H amidation in the *ortho* position (Scheme 14c).[57] The same mechanistic rational was used by the group of Baik and Chang to develop an Ir-catalyzed intramolecular C–H amidation towards the synthesis of γ-lactams. Although no direct proof for an Ir-nitrene intermediate was given, the outcome of the reaction is consistent with such a pathway. The authors performed DFT calculations to confirm that an Ir(V)-nitrene intermediate was indeed energetically accessible under the reaction conditions ($\Delta G^{\ddagger}$=14.7 kcal.mol^{-1} from the Ir(III)-dioxazolone complex).[44c]

Over the past decades, dioxazolones have proven their versatility as a novel class of C–H amidating reagents through a metallanitrene intermediate. Directing groups are most of the time required and a large variety of them have been utilized in this transformation, such as: thioamides[58], fused azoles,[59] oxazolinyl- moiety,[60] and anilides.[61] Interestingly, Rovis and Lei have developed the branch-selective allylic C–H amidation which proceeds via Ir(III) catalysis without making use of a directing group. Here an allyl-Ir(III) intermediate further participates in the oxidative amidation to afford an amide at the branched position of a terminal alkene (Scheme 14d).[62] Bolm and Hermann have shown that it's even possible to perform a ball-milling Rh(III)-catalyzed amidation of arenes under solvent-free conditions.[63] Bolm and coworkers have also reported the amidation of sulfides using [Ru(TPP)CO] as catalyst under light irradiation with a high-pressure mercury vapor lamp, where the product could be oxidized *in situ* to *N*-acyl sulfimides.[64]

The metallanitrenes generated from dioxazolones can even be engaged in cascade reactions, for instance for the hydroamidation of alkynes in presence of a Ni-catalyst as described by the group of Seo and Chang. Note the fine control of the regioselectivity towards either the anti-Markovnikov or the Markovnikov product, allowed by a fine-tuning of the reaction conditions. In this work, evidence for a Ni(III)-nitrene intermediate was given by its capture with PPh_3 as an imidophosphorane and supported by DFT computations (Scheme 15a).[65] Rovis and Lee have also developed a three component Rh(III)-catalyzed *syn*-carboamination of alkenes, by employing the same class of



Scheme 15. Selected examples of the reactivity of oxazolone-derived nitrene species engaged in cascade reactions: a) Hydroamidation of alkynes b) Three-component carboamination of olefins. DMMS = dimethoxymethylsilane; DMA = *N*,*N*-dimethylacetamide; DMPU = *N*,*N*'-dimethylpropyleneurea.

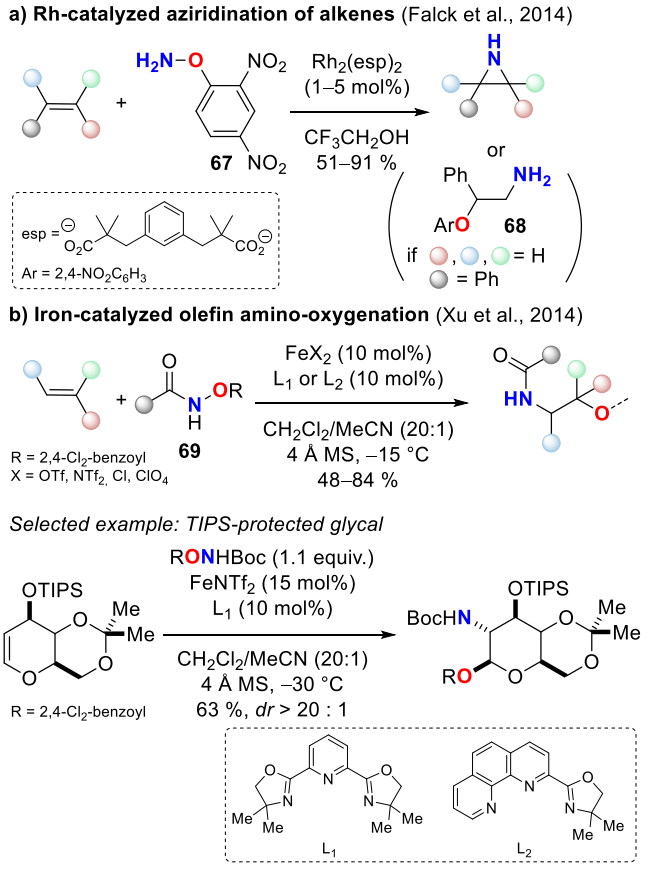
a nitrene source and arylboronic acids (Scheme 15b). This method is highly valuable in the context of opening another access point towards unnatural alpha-amino acids.[66]

The variety of described conditions further solidify the potential of isoxazoles and dioxazolones, as by controlling the reactivity one can effectively construct a C–N bond in a selective manner.

2.2. Non-decarboxylative transformation leading to nitrene intermediates

Other classes of compounds containing an N–O bond can be downstreamed into synthetically highly appealing products via metallanitrene intermediates.

The research team of Falck has first reported a Rh-catalyzed synthesis of aziridines from alkyl substituted alkenes starting with *O*-(2,4-dinitrophenyl)hydroxylamine (**67**) as aminating reagent. Involvment of a metallanitrene intermediate was suggested by DFT computations. Interestingly, the authors showed that in the case of styrenyl derivatives, even the oxygen-containing part of the hydroxylamine can be incorporated in the molecule, leading to a 1,2-amino-alcohol derivative **68**. This presumably arose from the ring opening of an aziridine intermediate.[67]



Scheme 16. Reaction involving a putative nitrenoid intermediate generated from hydroxylamine derivatives. a) Rh-catalyzed aziridination of alkenes; b) Iron-catalyzed olefin amino-oxygenation and application to a TIPS-protected glycal.

Olefin difunctionalization is a synthetically economic process. Classically, enantioselective olefin amino-oxygenations are performed via Sharpless epoxidation. This reaction implies the use of non-precious metals in presence of a strong oxidant (typically peroxides such as *t*BuOOH), which means a disadvantage that nitrene species generated from N–O bonds can overcome, the hydroxylamine derivative acting as both an internal oxidant and a source of amine and alcohol.

Xu and coworkers had reported an intramolecular Fe(II)-catalyzed amino-oxygenation of olefins with *N*-protected hydroxylamines **69**. In this example, the authors showcased the possibility to diastereoselectively amino-oxygenate a protected glycal to afford an amino-sugar. The use of a tridentate ligand (**L_1** or **L_2**) is crucial for a successful transformation. The exact mechanism of this transformation remains unknown. However radical clock probing experiments furnished a positive result, the authors thus suggested a stepwise transformation which goes through a radical amination step (Scheme 16b).[68]. This is in line with the expected behavior of the iron-stabilized nitrene: the radical pathway is more likely in this case.[69] In any case, one can highly suspect that an intermediate nitrene species gets involved in the process.

Morandi and Legnani have reported the utilization of the bench-stable nitrogen source $PivONH_3OTf$ (**70**) for direct access to unprotected primary amines, in combination with a Fe(II)-phthalocyanine(Pc) catalyst in presence of *O*-nucleophiles (MeOH, higher order alcohols, or water) as oxygen source. This approach provides a novel access to multiple active molecules, as for example the natural antibacterial product **71**, obtained in two steps (amino-oxygenation followed by acylation) as a racemic mixture (Scheme 17a).[70] This concept was further applied to amino-chlorination,[71] amino-azidation,[72] and to the synthesis of sulfur containing compounds.[73]

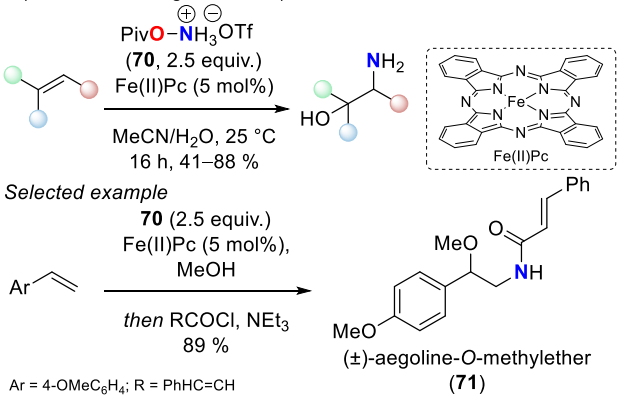
From a mechanistic point of view, the involvement of a carbon centered radical intermediate in those reactions was suggested by the absence of alkyl shift in the reaction with camphene[71a] or 3,3-dimethyl-1-butene.[72] Different radical clock experiments further proved that this carbon centered radical must be short-living.[70-71,72] Indeed, fast radical-clock **72** ($k=7.10^{10}$ s^{-1}) underwent ring-opening, whereas the slower **73** ($k=4.10^{5}$ s^{-1}) did not.[70-71,72] Note that the yields dropped in presence of radical scavengers (TEMPO, BHT) but no adduct could be obtained.[71a,72] These specific examples showcase the major influence of kinetics in trapping radical intermediates, in particular when they are short-living. The absence of ring-opened product could be sometimes misleading, since it does not mean that no radical intermediates are involved. At that stage, two mechanistic pathways were proposed, involving either a nitrenoid Fe(IV) complex **74** or an aminyl complex of Fe(III) **75** as intermediate. In both cases addition to the olefin will lead to a carbon centered radical intermediate **76** (Scheme 17b).

The exact mechanism is still controversial but recent advanced spectroscopic and computational mechanistic studies show a dramatic effect of the ligand on the reaction pathway. Indeed both N–O bond homolysis and heterolysis have been proposed with $[Fe(acac)_2(H_2O)_2]$[74] and [Fe(II)Pc][75] as catalysts, respectively. Whereas in the first case a high-spin iminyl radical species Fe(III)-$NH^{\bullet}$ **77** is assumed to be directly formed from **70**, a cationic iron-amido complex Fe(III)-NH_2^+ **78** is presumed to be the catalytic intermediate in the latter, allowing the use of the acetate derivative (Scheme 17c). Both studies however ruled out the involvement of a true nitrenoid intermediate of type **74** and confirmed the

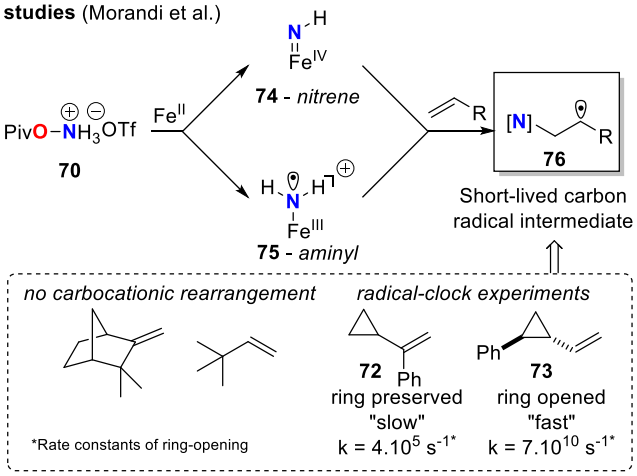
involvement of a carbon-radical intermediate as a result of their reaction with styrene.

Using different metals to stabilize highly reactive nitrenes has thus shown as a very interesting approach to the N–O bond activation, as reactivity can be diversified and controlled with a careful choice of all configuring parameters.

a) Fe(II)-phthalocyanine catalyzed synthesis of amino alcohols (Morandi and Legnani, 2016)

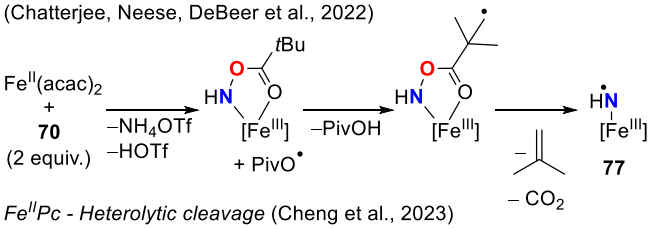


b) Proposed mechanism based on preliminary mechanistic studies (Morandi et al.)

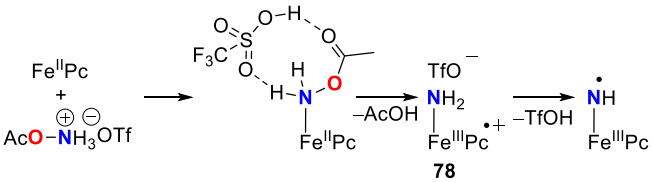


c) Proposed mechanisms for the N–O bond cleavage based on advanced mechanistic studies (spectroscopic & computational)

Fe^II(acac)2 - Homolytic cleavage (Chatterjee, Neese, DeBeer et al., 2022)



Fe^IIPc - Heterolytic cleavage (Cheng et al., 2023)



Scheme 17. a) Iron(II)-catalyzed synthesis of amino alcohols and application to the synthesis of a natural antibacterial natural product; b) Preliminary mechanistic studies and initial mechanism proposed; c) Mechanisms proposals based on advanced mechanistic studies.

3. Nitrogen-centered radicals generation

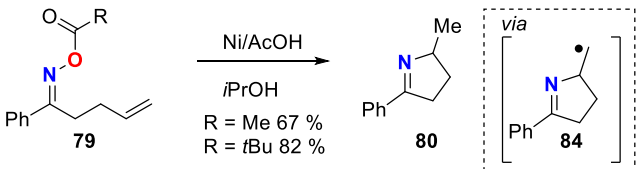
Along with the renaissance of radical chemistry in the last decades, an increased number of publications employing hydroxylamine derivatives have arisen, making use of the low BDE of the N–O bond. Such a reactivity was originally key to the Barton and Tsuchiya reactions developed in the 80's (Scheme 1).[6-7] Most of these reactions rely on the use of specific nitrogen substituents acting as electrophores, in particular oxime esters[76] and the so-called "redox active esters"[77] inspired by the works of Barton (thiohydroxamate esters)[6] and Okada (*N*-hydroxyphthalimides derivatives).[78] Thermal,[79] photochemical,[80] and electrochemical activations[81] have been employed to break the N–O bond, either homolytically or heterolytically (generating either nitrogen or oxygen radicals). Recently, the groups of Cho and Glorius independently showed that oxime esters could as well undergo energy transfer from a photoexcited catalyst and generate both nitrogen and oxygen radicals.[82]

Among the developed methodologies, single electron transfer (SET) from an (organo)metallic compound has grown quickly, since it allows generating nitrogen radicals[83] and/or carbon radicals after decarboxylation,[77] depending on the substrate used. This third part will focus on the generation and use of nitrogen radicals generated through single electron transfer from a metallic species, highlighting the experimental proofs for a radical mechanism.

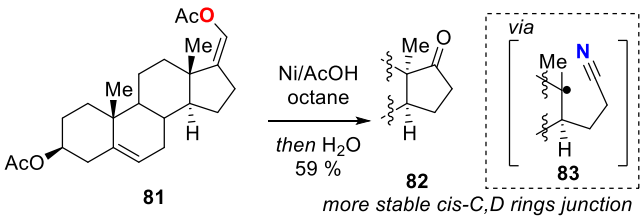
3.1 Stoichiometric reactivity

Zard and coworkers reported the seminal examples of SET to a N–O bond from a metallic species.[84] They showed that oxime esters **79** could be singly reduced with a stoichiometric amount of Ni powder in presence of acetic acid using isopropanol as solvent. Other plain metals proved less efficient, as the second reduction to the imine anion is much faster. In contrast, with Ni(0), after scission of the N–O bond, the resulting nitrogen radical is long-lived enough to undergo intramolecular 5-exo cyclization with a pendant alkene, forming dihydropyrroles such as compound **80**. Both acetate and pivalate derivatives **79** were tested, with the latter determined as more robust towards premature hydrolysis of the oxime ester (82% yield vs. 67% with acetate) (Scheme 18a).

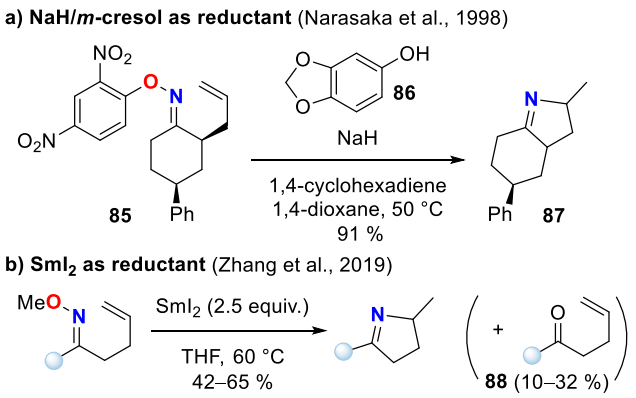
a) Ni as stoichiometric reductant (Zard et al., 1992)



b) Experimental hint for a radical mechanism



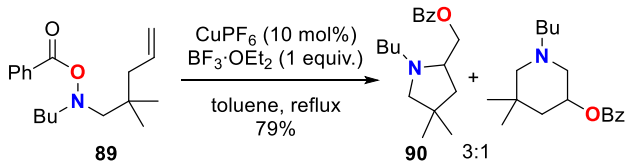
Scheme 18. a) Reduction of oxime esters with stoichiometric Ni(0) towards the synthesis of dihydropyrroles; b) Epimerization of a ketosteroid derivative as radical mechanistic proof.



Scheme 19. a) Synthesis of dihydropyroles from *O*-2,4-dinitrophenyloximes via reduction with a phenol and NaH; b) Reduction of methoxy oxime ethers with stoichiometric SmI_2

From a mechanistic point of view, the reduction could have also led to a carboxylic radical RCOO•, which would then undergo a fast decarboxylation but no side-products could be detected. The epimerization of 17-ketosteroid oxime derivative **81** via D ring opening/closing represents a mechanistic proof for the formation of an iminyl radical intermediate. Indeed, the more stable 13-epi-17-ketosteroid **82**, where the C-D rings junction is cis, was detected as the major product of the reaction after hydrolysis. This resulted from a ring opening of the 17-iminyl radical intermediate to form the tertiary radical **83**, which upon closing furnished steroid **82** (Scheme 18b). The authors explained that isopropanol was thus serving as hydrogen donor in the reaction. They also demonstrated that the resulting carbon centered radical **84** could react with other radical traps as hydrogen donors such as diphenyl diselenide or an allyl tolyl sulfone.

In the meantime, Narasaka and coworkers disclosed the reaction of *O*-2,4-dinitrophenyloximes **85** in presence of phenol **86** and NaH. The reaction was believed to go through single electron transfer into the dinitrophenyl substituent, playing the role of an electrophore, and subsequent formation of an iminyl radical intermediate via homolytic scission of the N–O bond. According to the authors, the favored 5-exo cyclization with a pendant olefin, over the 6-endo cyclization, leading to dihydropyrroles **87** would first confirm the radical character of the intermediate (Scheme 19a).[79b] More recently, the group of Zhang showed that 2.5 equivalents of SmI_2 could also trigger the formation of an iminyl radical from methoxy oxime ethers. However, the formation of a doubly reduced imine anion resulting from the reduction of the iminyl radical with SmI_2, could not be completely suppressed under the described conditions and led to the formation of the ketone **88** in significant amount (Scheme 18b).[85]

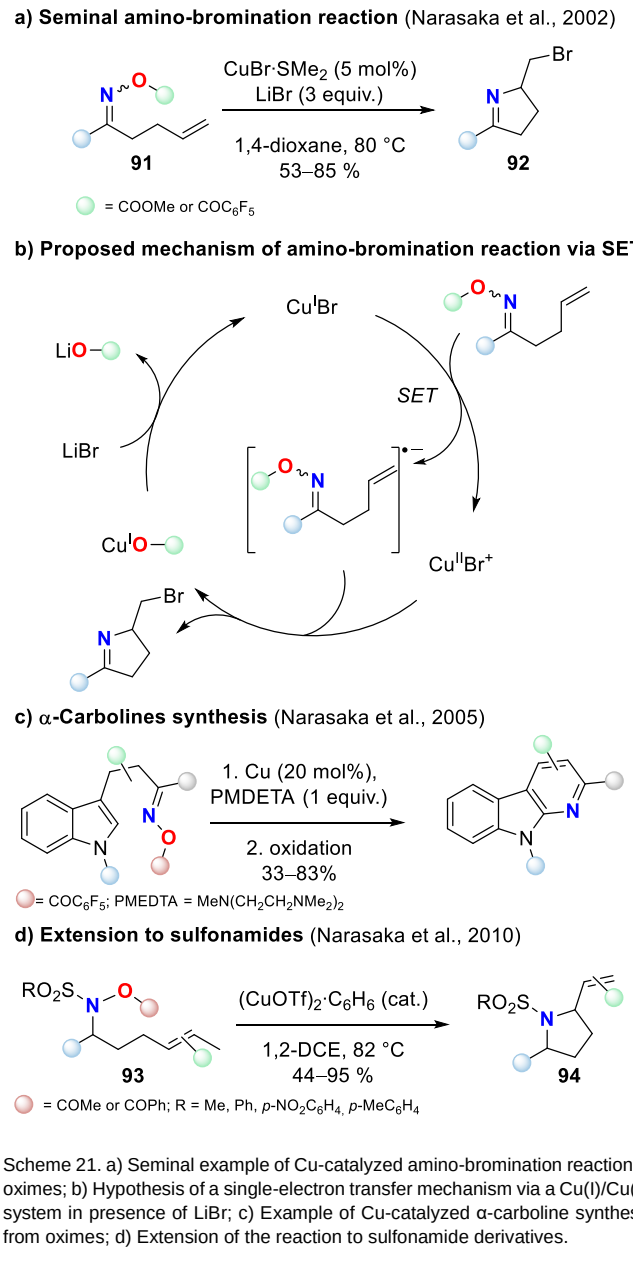


Scheme 20. Pyrrolidine synthesis via intramolecular aminohydroxylation reactions under Cu(I)-catalyzed conditions described by Göttlich et al.

3.2. Cu-catalyzed reactions

Avoiding the use of stoichiometric metallic species, Göttlich and coworkers disclosed a Cu-catalyzed pyrrolidine synthesis in 2002. The reaction corresponded to an aminohydroxylation starting from the corresponding *O*-benzylated hydroxylamines with a pendant alkene group such as compound **89**. A stoichiometric amount of $BF_3{\cdot}OEt_2$ drastically improved the yield of the reaction, certainly by coordinating the benzoyl group and thus destabilizing the N–O bond. Interestingly here, both the amino and the benzoyl parts were transferred in the final molecule, leading to an amino-oxygenation of the alkene. Although no direct proof for a radical mechanism was given, the major formation of the 5-membered ring **90** supported the hypothesis of a Cu(I)/Cu(II) mechanism, according to the authors (Scheme 20).[86]

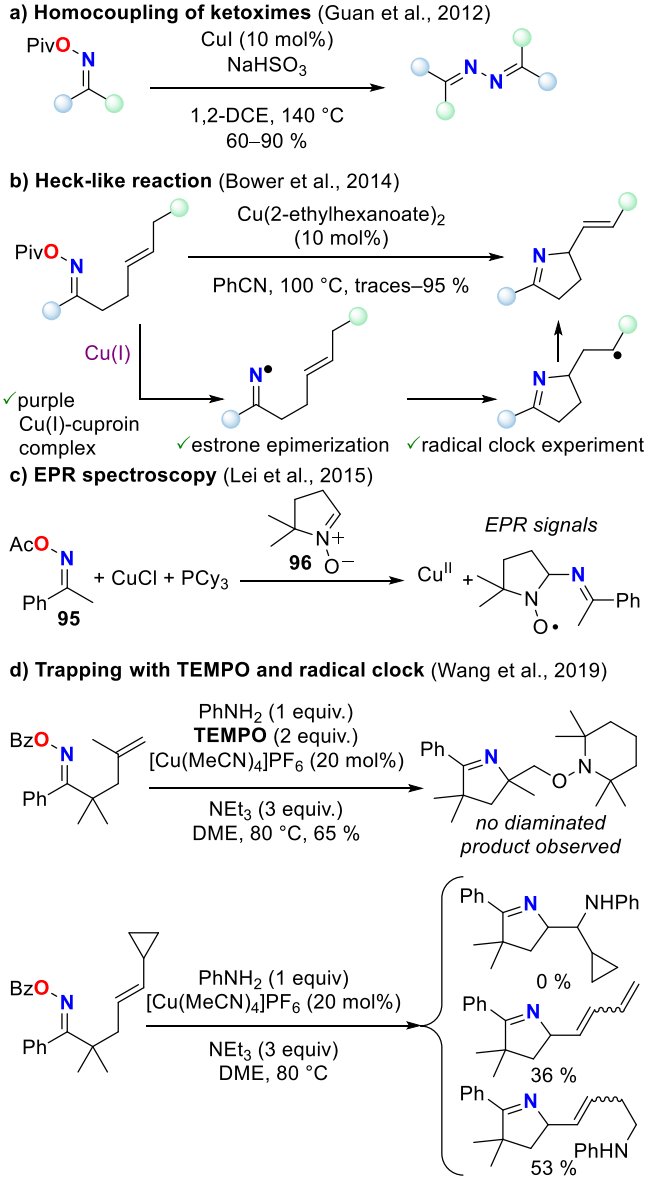
The same year, Narasaka and coworkers reported that the copper(I) salt $CuBr{\cdot}SMe_2$ could also catalyze the cyclization reaction of oxime esters. *O*-methoxycarbonyl- and *O*-pentafluoro-



Scheme 21. a) Seminal example of Cu-catalyzed amino-bromination reaction of oximes; b) Hypothesis of a single-electron transfer mechanism via a Cu(I)/Cu(II) system in presence of LiBr; c) Example of Cu-catalyzed α-carboline synthesis from oximes; d) Extension of the reaction to sulfonamide derivatives.

benzoyloximes **91** both underwent efficient cyclization. They showed that the addition of LiBr improved the reaction efficiency and furnished brominated dihydropyrroles **92** (Scheme 21a). Although a putative radical pathway was proposed, no direct proof was given (Scheme 21b).[87] The strategy was applied to the synthesis of cyclic imines as well as α-carbolines derivatives (Scheme 21c).[88] The group expanded further the reaction to *N*-alkenyl and alkynyl *N*-benzoylsulfonamides **93** towards the synthesis of pyrrolidines **94** where $(CuOTf)_2C_6H_6$ proved the most efficient (Scheme 21d). Here again, a radical mechanism was proposed since the 5-membered ring was obtained as the major product if not the only one.[89]

Further experimental proofs for the radical pathway in the reaction of copper(I) salts and oxime esters have only been disclosed recently. Ten years after the seminal communications, the



Scheme 22. Experimental proofs for the generation of iminyl radicals with Cu(I) catalysts from oxime esters by homocoupling (a),[90] by estrone epimerization and radical clock experiment (b),[91] by EPR spectroscopy (c),[92] by trapping, and radical clock experiments (d).[94] TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; DME = dimethylether.

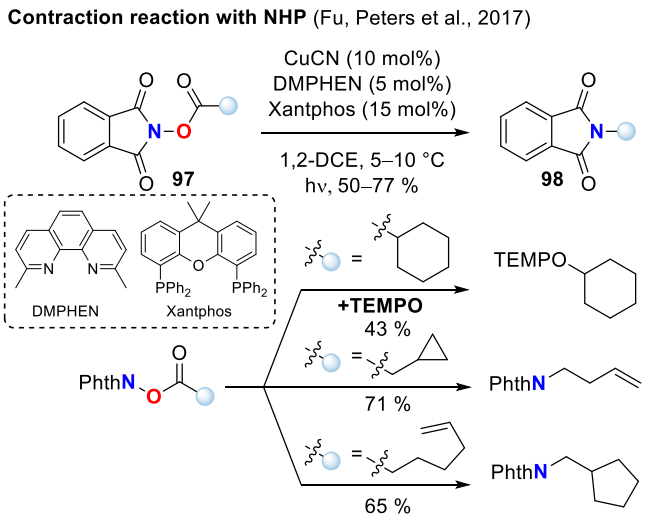
reported homocoupling of oxime esters under Cu(I)-catalysis brought another argument for the involvement of radical events under such conditions (Scheme 22a).[90] In 2014, Bower et al. reported a Cu-catalyzed intramolecular Heck-like reaction starting from pivaloyl and acetyl oxime esters. Their mechanistic investigations revealed that the alkene did not react *via* migratory insertion in the Cu–N bond but most likely *via* the addition of an iminyl radical intermediate. The latter was formed either by SET from Cu(I) to the oxime ester or through the homolytic scission of a Cu(III)–N bond. Evidence of a copper(I) species was given by the formation of a characteristic deep-purple Cu(I)-cuproin complex when cuproin was added under the reaction conditions (Scheme 22b). The involvement of iminyl and alkyl radical intermediates was confirmed by the estrone epimerization and radical clock experiments, respectively.[91]

One year later, the group of Lei demonstrated the presence of copper(II) salts when reacting *O*-acetyl oxime **95** and CuCl by EPR spectroscopy. In presence of a radical trap, 5,5-dimethyl-1-pyrroline *N*-oxide (**96**, DMPO), the experimental spectrum suggested that an iminyl radical was generated in the process (Scheme 22c).[92] Wang and coworkers furnished other experimental proofs by trapping the carbon centered radical intermediate with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and using a radical clock experiment, when investigating the mechanistic features of a diamination reaction (Scheme 22d).

An interesting example was disclosed by Fu and Peters in 2017. Employing *N*-hydroxyphthalimide (NHP) esters **97** under light irradiation in presence of CuCN (10 mol%) with neocuproine (DMPHEN, 5 mol%), and Xantphos (15 mol%), their groups observed the decarboxylation of the starting material, followed by recombination of both parts of the molecule leading to protected amine **98**. This contraction reaction is believed to result, upon excitation of a copper(I) species, from single electron-transfer to the NHP ester, forming a phthalimidate ligand and a carboxyl radical, which undergoes fast decarboxylation. The radical character of the intermediate was proven by a trapping with TEMPO and radical clock experiments. Remarkably, the reaction worked more efficiently with primary carboxylic acid derivatives than with secondary or tertiary one (Scheme 23).[93]

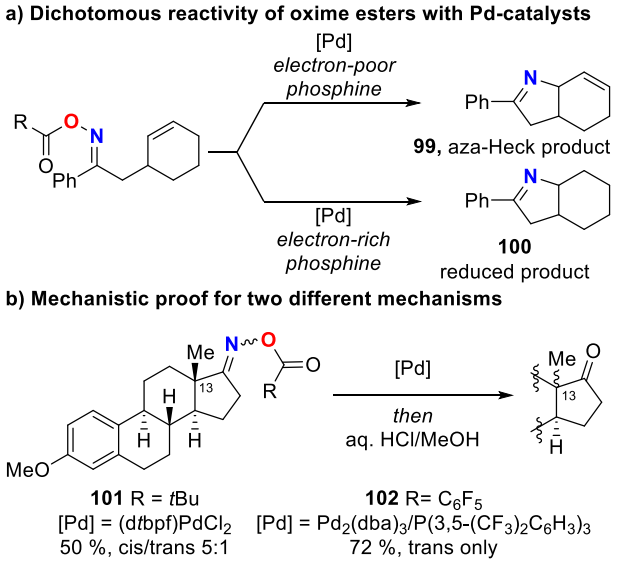
3.3. Pd dichotomous reactivity

In the course of their study on Pd-catalyzed Narasaka-Heck cyclization, Bower and coworkers serendipitously found a dichotomous reactivity of [Pd] catalysts, depending on the nature of the phosphine ligands. Whereas electron-poor phosphines favored the typical oxidative addition and the aza-Heck product **99** (see before), electron-rich phosphines (typically SPhos , $P(tBu)_3$, $P(Cy)_3$) and PEPPSI-IPr as ligands led to the reduced product **100** (Scheme 24a). The authors then hypothesized that a radical pathway was involved. Introducing sacrificial hydrogen donors such as 1,4-cyclohexadiene and δ-terpinene improved the reaction efficiency, whereas proton donors such as formic acid did not change the reaction outcome, suggesting a radical intermediate. The radical clock opening and a trapping reaction with TEMPO further hinted at the radical pathway. Inspired by the work of Zard (Scheme 18),[84] a final experiment using oxime



Scheme 23. Contraction reaction as described by the groups of Fu and Peters with experimental proofs of a radical mechanism. 1,2-DCE = 1,2-dichloroethane; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

estrones **101** and **102** was performed. When the electron-rich phosphine ligand 1,10-bis(di-*tert*-butylphosphino)ferrocene (d*t*bpf) was used, epimerization of the carbon 13 was observed, demonstrating a radical pathway. In contrast, with the electron-poor phosphine ligand $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, no epimerization could be detected (Scheme 24b). Interestingly, this result shed light on the mechanistic pathway of the oxidative addition towards the synthesis of Hartwig's and Stahl's complexes **23** and **26** bearing electron-rich phosphine ligands (PCy_3, Scheme 5). According to Bower's findings, their formations certainly went via a single electron transfer from Pd(0) to the oxime ester, followed by recombination of the iminyl radical and the Pd(I), instead of a 2-electrons pathway.

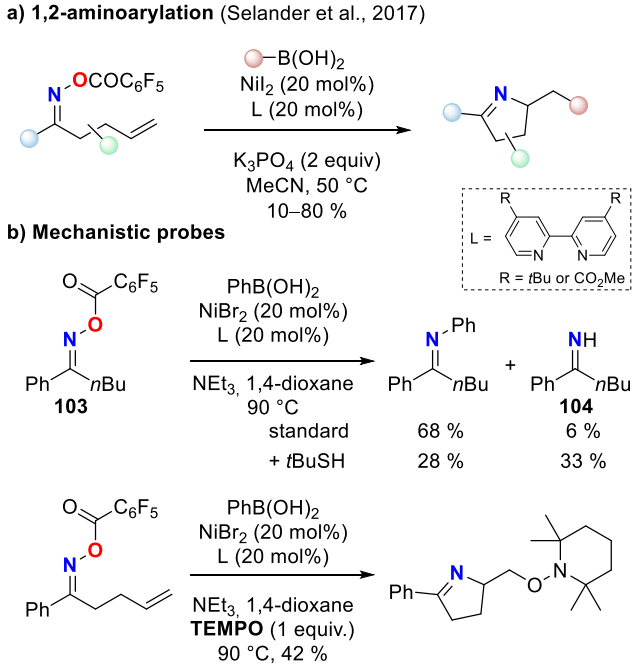


Scheme 24. Pd-catalyzed reaction of oxime esters reported by the group of Bower. a) Dichotomous reactivity of oxime esters in presence of Pd-catalyst depending on the electronic of the phosphine ligand; b) Estrone mechanistic proof for two different mechanisms involving either a radical or an ionic mechanism.

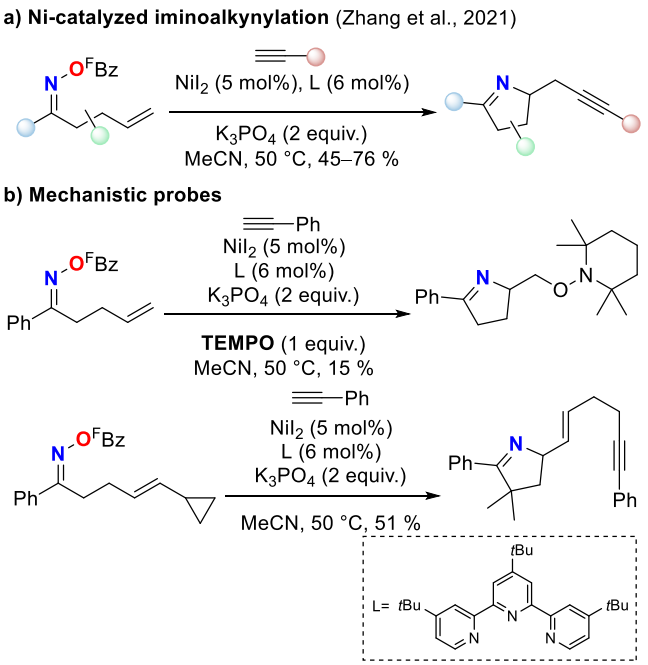
3.4. Ni and Fe catalyzed reactions: amino-arylation and -alkynylation

Inspired by the work of Bower on palladium catalysis, the group of Selander disclosed a Ni-catalyzed 1,2-aminoarylation involving a cascade reaction, where the cyclization of an oxime ester was followed by a cross-coupling with an arylboronic acid (Scheme 25a). The motivation for using a Ni(II) salt was to avoid the *β*-hydride elimination regularly encountered with Pd-catalysis, and facilitate the cascade post-functionalization. Reacting saturated oxime ester **103** with phenyl boronic acid under the standard conditions in presence of *tert*-butylthiol as hydrogen donor resulting in an increased yield of the NH-imine **104**. This result suggests the involvement of a single electron transfer from a Ni(I) or a Ni(II) species to the N–O bond, forming an iminyl radical which could rapidly cyclize in a 5-*exo*-*trig* fashion to give a free carbon radical. A radical trapping experiment with TEMPO also hinted at the involvement of the latter (Scheme 25b). Nevertheless, these experiments did not rule out other pathways where the iminyl radical is directly trapped by the Ni-catalyst and the cyclization occurs in the coordination sphere of the metal through an aminometalation step of the pendant alkene.[95] Recently, Zhang and coworkers reported a Ni-catalyzed iminoalkynylation based on a similar mechanistic rational. Likewise, a radical clock experiment, where the pendant cyclopropyl underwent ring opening, and a radical trapping experiment with TEMPO hinted at a carbon radical intermediate in the reaction (Scheme 26). Here again however, these experiments cannot completely rule out a cyclization in the coordination sphere of the metal and give little information on the activation of the N–O bond itself.[96]

A similar iminoarylation was reported using Fe(II)-based catalysts by the group of Ohe (Scheme 27). Consistent with preliminary



Scheme 25. a) 1,2-aminoarylation under Ni-catalysis involving a single-electron transfer as described by the group of Selander; b) Mechanistic investigations on the catalytic system. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

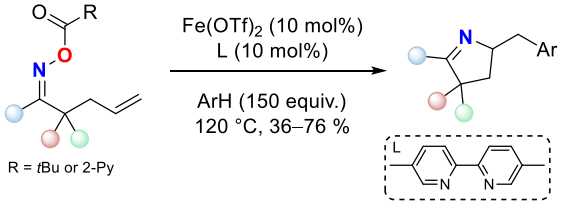


Scheme 26. a) Iminoalkynylation developed by the group of Zhang under Ni-catalysis; b) Mechanistic probes for this reaction. ^{F}Bz = 3,5-bis(trifluoromethyl)benzoyl; TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl.

mechanistic studies (TEMPO inhibition, kinetic isotopic effect, reaction in presence of a hydrogen atom donor), the authors proposed a carbon radical intermediate. The reaction is thus believed to go through single electron transfer from the metallic species to the N–O bond, forming either an iminyl radical or iron-ketimido intermediate, which would cyclize to form the C–N bond and carbon radical. The nature of the intermediate prior cyclization is yet unknown.[97]

Radical mechanistic pathways thus occur essentially in reactions of oxime esters (or ethers) or phthalimide derivatives, which are both well-known as electrophores. Seminal examples involved the use of stoichiometric amounts of metals and a 5-exo cyclization of a nitrogen radical on a pendant alkene.

Apart some examples, the following catalytic transformations also include intramolecular reactions where a putative nitrogen radical cyclizes in a 5-exo-fashion. The resulting carbon radical can then be involved or not in a cascade reaction allowing further functionalization of the 5-membered ring.



Scheme 27. Fe-catalyzed iminoarylation of oximes with a pendant alkene as disclosed by Ohe and coworkers.

Conclusion

Since the seminal examples of reactions with hydroxylamine derivatives, plethora of synthetic transformations have made use of the versatile reactivity of N–O σ bonds. Indeed, these weak bonds which readily breaks in a homolytic fashion, are also easily reducible, undergoing single electron transfer from metallic species. Their radical reactivity goes along with an electrophilic reactivity, most of the time borne by the nitrogen atom. So far, the high reactivity of N–O bonds has already further improved on many classical methods such as syntheses of *N*-heterocycles, olefin amino-functionalization, or C–H amidation. More than making them react, the difficulty relies in obtaining the desired outcome. As highlighted in this review, transition metal catalysis helped finely tuning this reactivity, allowing the development of new synthetic methodologies for the formation of C–N bonds.
Compared to the tremendous amount of literature making use of N–O bonds reactivity, few mechanistic investigations are reported. Due to their high reactivity, the isolation of intermediate species is not always possible, therefore mechanistic details of multiple transformations are not very clear. The borders between two different pathways are often faint, as exemplified by Bower and coworkers with the dichotomous reactivity of Pd-catalysts in presence of oxime derivatives.[26] To investigate mechanistic features, characterization of intermediates through X-Ray analysis when doable, radical-clock experiments to distinguish between ionic and radical pathways (with a careful attention at kinetics), or DFT computational studies are the most employed. One could also make use of kinetic, labelling experiments and/or advanced spectroscopic analyses to identify the mechanisms at play.
Interestingly, although a large amount of transformations are reported, intermolecular reactions in the case of oxidative additions or radical reactivity are rather rare. Most reactions also lack atom-economy since a sacrificial *O*-substituent (benzoate, electron-poor aromatic ring, pivalate…) is most of the time required. In only few cases both nitrogen and oxygenated moieties are incorporated in the final molecule either through amino-oxygenation pathways with alkenes,[86,98] or, upon decarboxylation of the carboxylate moiety, in alkylation reactions.[93] One can expect that understanding the key features of the catalytic mechanistic pathways will offer more possibilities, such as intermolecular reactions, using more available transition metals, and improving the atom-economy by using more systematically both parts of the molecule like in the case of the recently emerged photoexcited energy transfer reactions.[82] All the described methodologies thus set the stage for more challenging reactions.

Acknowledgements

For financial support, we aknowledge CEA, CNRS, the University Paris-Saclay, and ANR (project TransferNO, ANR JCJC Grant no. ANR-21-CE07-0060-01).

Keywords: metal catalysis • N–O bonds • mechanisms • electrophilic amination • hydroxylamines

[1] a) R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284-287; b) A. Ricci, *Amino group chemistry: from synthesis to the life sciences*, John Wiley & Sons, **2008**; c) S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451-3479.

[2] a) P. W. Neber, A. V. Friedolsheim, *Justus Liebigs Ann. Chem.* **1926**, *449*, 109-134; b) C. O'Brien, *Chem. Rev.* **2002**, *64*, 81-89.

[3] E. Ciganek, in *Organic Reactions*, **2009**, p. 1-366.

[4] K. S. Williamson, D. J. Michaelis, T. P. Yoon, *Chem. Rev.* **2014**, *114*, 8016-8036.

[5] Y.-R. Luo, *Comprehensive Handbook of chemical Bond Energies*, 1st edition ed., CRC Press, **2007**.

[6] a) D. H. R. Barton, D. Crich, W. B. Motherwell, *J. Chem. Soc., Chem. Commun.* **1983**, 939-941; b) D. H. R. Barton, D. Crich, W. B. Motherwell, *Tetrahedron Lett.* **1983**, *24*, 4979-4982.

[7] a) M. Hasebe, K. Kogawa, T. Tsuchiya, *Tetrahedron Lett.* **1984**, *25*, 3887-3890; b) M. Hasebe, T. Tsuchiya, *Tetrahedron Lett.* **1986**, *27*, 3239-3242.

[8] a) J. A. Labinger, *Organometallics* **2015**, *34*, 4784-4795; b) L. Vaska, J. W. Diluzio, *J. Am. Chem. Soc.* **1961**, *83*, 2784-&.

[9] A. J. Deeming, D. W. Owen, N. I. Powell, *J. Organomet. Chem.* **1990**, *398*, 299-310.

[10] C. M. P. Ferreira, M. F. C. G. da Silva, V. Y. Kukushkin, J. J. R. F. da Silva, A. J. L. Pombeiro, *J. Chem. Soc., Dalton Trans.* **1998**, 325-326.

[11] A. Tillack, P. Arndt, A. Spannenberg, R. Kempe, U. Rosenthal, *Zeit. Anorg. Allg. Chem.* **1998**, *624*, 737-740.

[12] P. Arndt, C. Lefeber, R. Kempe, U. Rosenthal, *Chem. Ber.* **1996**, *129*, 207-211.

[13] T. Shimbayashi, K. Okamoto, K. Ohe, *Chem. Eur. J.* **2017**, *23*, 16892-16897.

[14] A. N. Desnoyer, W. Chiu, C. Cheung, B. O. Patrick, J. A. Love, *Chem. Commun.* **2017**, *53*, 12442-12445.

[15] M. K. Bogdos, P. Muller, B. Morandi, *Organometallics* **2023**, *42*, 211-217.

[16] H. Tsutsui, K. Narasaka, *Chem. Lett.* **1999**, *28*, 45-46.

[17] a) M. Kitamura, K. Narasaka, *Chem. Record* **2002**, *2*, 268-277; b) K. Narasaka, *Pure Appl. Chem.,* **2003**, *75*, 19-28; c) K. Narasaka, M. Kitamura, *Eur. J. Org. Chem.* **2005**, *2005*, 4505-4519.

[18] a) M. Kitamura, S. Zaman, K. Narasaka, *Synlett* **2001**, *2001*, 974-976; b) S. Zaman, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1055-1062.

[19] a) M. Kitamura, S. Chiba, O. Saku, K. Narasaka, *Chem. Lett.* **2002**, *31*, 606-607; b) S. Chiba, M. Kitamura, O. Saku, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 785-796.

[20] a) H. Tsutsui, K. Narasaka, *Chem. Lett.* **2001**, *30*, 526-527; b) C. A. Ramsden, M. Kitamura, D. Kudo, K. Narasaka, *Arkivoc* **2005**, *2006*, 148-162.

[21] S. Zaman, K. Mitsuru, A. D. Abell, *Org. Lett.* **2005**, *7*, 609-611.

[22] M. Kitamura, Y. Moriyasu, T. Okauchi, *Synlett* **2011**, *2011*, 643-646.

[23] T. Gerfaud, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 572-577.

[24] a) T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2000**, *122*, 12049-12050; b) T. Nishimura, Y. Nishiguchi, Y. Maeda, S. Uemura, *J. Org. Chem.* **2004**, *69*, 5342-5347.

[25] a) A. Furstner, K. Radkowski, H. Peters, *Angew. Chem. Int. Ed.* **2005**, *44*, 2777-2781; b) A. Furstner, K. Radkowski, H. Peters, G. Seidel, C. Wirtz, R. Mynott, C. W. Lehmann, *Chem. Eur. J.* **2007**, *13*, 1929-1945.

[26] N. J. Race, A. Faulkner, M. H. Shaw, J. F. Bower, *Chem. Sci.* **2016**, *7*, 1508-1513.

[27] H. Tsutsui, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1451-1460.

[28] a) A. Faulkner, J. S. Scott, J. F. Bower, *Chem. Commun.* **2013**, *49*, 1521-1523; b) A. Faulkner, J. F. Bower, *Angew. Chem. Int. Ed.* **2012**, *51*, 1675-1679; c) N. J. Race, J. F. Bower, *Org. Lett.* **2013**, *15*, 4616-4619; d) A. Faulkner, J. S. Scott, J. F. Bower, *J. Am. Chem. Soc.* **2015**, *137*, 7224-7230; e) For a recent and detailed review on Narasaka-Heck type reactions work, see: N. J. Race, I. R. Hazelden, A. Faulkner, J. F. Bower, *Chem. Sci.* **2017**, *8*, 5248-5260.

[29] X. Bao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9577-9581.

[30] C. Chen, L. Hou, M. Cheng, J. Su, X. Tong, *Angew. Chem. Int. Ed.* **2015**, *54*, 3092-3096.

[31] I. R. Hazelden, X. Ma, T. Langer, J. F. Bower, *Angew. Chem. Int. Ed.* **2016**, *55*, 11198-11202.

[32] a) I. R. Hazelden, R. C. Carmona, T. Langer, P. G. Pringle, J. F. Bower, *Angew. Chem. Int. Ed.* **2018**, *57*, 5124-5128; b) X. Ma, I. R. Hazelden, T. Langer, R. H. Munday, J. F. Bower, *J. Am. Chem. Soc.* **2019**, *141*, 3356-3360.

[33] a) S. A. Shuler, G. Yin, S. B. Krause, C. M. Vesper, D. A. Watson, *J. Am. Chem. Soc.* **2016**, *138*, 13830-13833; b) R. D. Gao, S. A. Shuler, D. A. Watson, *Chem. Sci.* **2021**, *12*, 8859-8864.

[34] F. Xu, S. A. Shuler, D. A. Watson, *Angew. Chem. Int. Ed.* **2018**, *57*, 12081-12085.

[35] a) A. M. Berman, J. S. Johnson, *J. Am. Chem. Soc.* **2004**, *126*, 5680-5681; b) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2005**, *70*, 364-366; c) A. M. Berman, J. S. Johnson, *J. Org. Chem.* **2006**, *71*, 219-224.

[36] M. J. Campbell, J. S. Johnson, *Org. Lett.* **2007**, *9*, 1521-1524.

[37] S. Tobisch, *Chem. Eur. J.* **2016**, *22*, 8290-8300.

[38] Y. Miki, K. Hirano, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2013**, *52*, 10830-10834.

[39] S. Zhu, N. Niljianskul, S. L. Buchwald, *J. Am. Chem. Soc.* **2013**, *135*, 15746-15749.

[40] N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449-6457.

[41] For an early example of nitrene formation starting with dioxazoles under thermo- and photolysis, see: J. Sauer, K. K. Mayer, *Tetrahedron Lett.* **1968**, *9*, 319-324.

[42] G. Dequirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384-7395.

[43] C. Wentrup, *Acc. Chem. Res.* **2011**, *44*, 393-404.

[44] a) For one historical example of such reactivity, see: G. Smolinsky, B. I. Feuer, *J. Am. Chem. Soc.* **2002**, *86*, 3085-3088; b) for a comprehensive insight, see: M. M. Díaz-Requejo, A. Caballero, M. R. Fructos, P. J. Pérez, in *Alkane C-H Activation by Single-Site Metal Catalysis* (Ed.: P. J. Pérez), Springer Netherlands, Dordrecht, **2012**, p. 229-264; c) for an example where product selectivity is highly tuned, see: S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M. H. Baik, S. Chang, *Science* **2018**, *359*, 1016-1021.

[45] Y. Ding, S. K. Sarkar, M. Nazish, S. Muhammed, D. Luert, P. N. Ruth, C. M. Legendre, R. Herbst-Irmer, P. Parameswaran, D. Stalke, Z. Yang, H. W. Roesky, *Angew. Chem. Int. Ed.* **2021**, *60*, 27206-27211.

[46] a) P. F. Kuijpers, J. I. van der Vlugt, S. Schneider, B. de Bruin, *Chem. Eur. J.* **2017**, *23*, 13819-13829; b) For a review of electrophilic reactivity, see: P. Starkov, T. F. Jamison, I. Marek, *Chem. Eur. J.* **2015**, *21*, 5278-5300.

[47] H. Noda, X. X. Tang, M. Shibasaki, *Helv. Chim. Acta* **2021**, *104*, e2100140.

[48] K. Okamoto, T. Oda, S. Kohigashi, K. Ohe, *Angew. Chem. Int. Ed.* **2011**, *50*, 11470-11473.

[49] H. J. Xie, F. R. Lin, L. Yang, X. S. Chen, X. C. Ye, X. Tian, Q. F. Lei, W. J. Fang, *J. Organomet. Chem.* **2013**, *745*, 417-422.

[50] K. Okamoto, K. Sasakura, T. Shimbayashi, K. Ohe, *Chem. Lett.* **2016**, *45*, 988-990.

[51] T. Shimbayashi, G. Matsushita, A. Nanya, A. Eguchi, K. Okamoto, K. Ohe, *ACS Catal.* **2018**, *8*, 7773-7780.

[52] W. Rong, T. Zhang, T. Li, J. Li, *Org. Chem. Front.* **2021**, *8*, 1257-1266.

[53] K. Okamoto, T. Shimbayashi, M. Yoshida, A. Nanya, K. Ohe, *Angew. Chem. Int. Ed.* **2016**, *55*, 7199-7202.

[54] K. Okamoto, T. Shimbayashi, E. Tamura, K. Ohe, *Chem. Eur. J.* **2014**, *20*, 1490-1494.

[55] T. Shimbayashi, K. Okamoto, K. Ohe, *Synlett* **2014**, *25*, 1916-1920.

[56] C. L. Zhong, B. Y. Tang, P. Yin, Y. Chen, L. He, *J. Org. Chem.* **2012**, *77*, 4271-4277.

[57] Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534-4542.

[58] P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon, J. Seayad, *Angew. Chem. Int. Ed.* **2017**, *56*, 16550-16554.

[59] K. S. Halskov, H. S. Roth, J. A. Ellman, *Angew. Chem. Int. Ed.* **2017**, *56*, 9183-9187.

[60] R. H. Mei, J. Loup, L. Ackermann, *ACS Catal.* **2016**, *6*, 793-797.

[61] J. Park, S. Chang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14103-14107.

[62] S. Lee, T. Rovis, *ACS Catal.* **2021**, *11*, 8585-8590.

[63] G. N. Hermann, C. Bolm, *ACS Catal.* **2017**, *7*, 4592-4596.

[64] V. Bizet, L. Buglioni, C. Bolm, *Angew. Chem. Int. Ed.* **2014**, *53*, 5639-5642.

[65] X. Lyu, J. Zhang, D. Kim, S. Seo, S. Chang, *J. Am. Chem. Soc.* **2021**, *143*, 5867-5877.

[66] H. Lei, T. Rovis, *J. Am. Chem. Soc.* **2019**, *141*, 2268-2273.

[67] J. L. Jat, M. P. Paudyal, H. Gao, Q. L. Xu, M. Yousufuddin, D. Devarajan, D. H. Ess, L. Kurti, J. R. Falck, *Science* **2014**, *343*, 61-65.

[68] D. F. Lu, C. L. Zhu, Z. X. Jia, H. Xu, *J. Am. Chem. Soc.* **2014**, *136*, 13186-13189.

[69] a) For some examples, see: E. T. Hennessy, T. A. Betley, *Science* **2013**, *340*, 591-595; b) Y. Liu, X. Guan, E. L. Wong, P. Liu, J. S. Huang, C. M. Che, *J. Am. Chem. Soc.* **2013**, *135*, 7194-7204.

[70] L. Legnani, B. Morandi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2248-2251.

[71] a) L. Legnani, G. Prina-Cerai, T. Delcaillau, S. Willems, B. Morandi, *Science* **2018**, *362*, 434-439; b) E. Falk, S. Makai, T. Delcaillau, L. Gurtler, B. Morandi, *Angew. Chem. Int. Ed.* **2020**, *59*, 21064-21071.

[72] S. Makai, E. Falk, B. Morandi, *J. Am. Chem. Soc.* **2020**, *142*, 21548-21555.

[73] a) H. Yu, Z. Li, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 324-327; b) S. Chatterjee, S. Makai, B. Morandi, *Angew. Chem. Int. Ed.* **2021**, *60*, 758-765.

[74] S. Chatterjee, I. Harden, G. Bistoni, R. G. Castillo, S. Chabbra, M. van Gastel, A. Schnegg, E. Bill, J. A. Birrell, B. Morandi, F. Neese, S. DeBeer, *J. Am. Chem. Soc.* **2022**, *144*, 2637-2656.

[75] Y. Zhou, J. Ni, Z. Lyu, Y. Li, T. Wang, G. J. Cheng, *ACS Catal.* **2023**, *13*, 1863-1874.

[76] a) C. Chen, J. H. Zhao, X. N. Shi, L. Y. Liu, Y. P. Zhu, W. Sun, B. L. Zhu, *Org. Chem. Front.* **2020**, *7*, 1948-1969; b) J. C. Walton, *Molecules* **2016**, *21*, 63.

[77] The use of phthalimide derivatives as redox-active esters has been recently reviewed: S. K. Parida, T. Manda, S. Das, S. K. Hota, S. De Sarkar, S. Murarka, *ACS Catal.* **2021**, *11*, 1640-1683.

[78] K. Okada, K. Okamoto, M. Oda, *J. Am. Chem. Soc.* **1988**, *110*, 8736-8738.

[79] a) For some selected examples, see: J. Boivin, A. C. Callier-Dublanchet, B. Quiclet-Sire, A. M. Schiano, S. Z. Zard, *Tetrahedron* **1995**, *51*, 6517-6528; b) K. Uchiyama, Y. Hayashi, K. Narasaka, *Chem. Lett.* **1998**, *27*, 1261-1262; c) F. Portela-Cubillo, J. S. Scott, J. C. Walton, *J. Org. Chem.* **2008**, *73*, 5558-5565; d) S. J. Markey, W. Lewis, C. J. Moody, *Org. Lett.* **2013**, *15*, 6306-6308; e) Y. Cai, A. Jalan, A. R. Kubosumi, S. L. Castle, *Org. Lett.* **2015**, *17*, 488-491.

[80] a) For recent reviews, see: J. Davies, S. P. Morcillo, J. J. Douglas, D. Leonori, *Chem. Eur. J.* **2018**, *24*, 12154-12163; b) X. Y. Yu, Q. Q. Zhao, J. Chen, W. J. Xiao, J. R. Chen, *Acc. Chem. Res.* **2020**, *53*, 1066-1083; c) M. Latrache, N. Hoffmann, *Chem. Soc. Rev.* **2021**, *50*, 7418-7435; d) For selected examples on photoirradiation, see: R. Alonso, P. J. Campos, B. Garcia, M. A. Rodriguez, *Org. Lett.* **2006**, *8*, 3521-3523; e) F. Portela-Cubillo, E. M. Scanlan, J. S. Scott, J. C. Walton, *Chem. Commun.* **2008**, 4189-4191; f) R. T. McBurney, J. C. Walton, *J. Am. Chem. Soc.* **2013**, *135*, 7349-7354; g) M. Kitamura, Y. Mori, K. Narasaka, *Tetrahedron Lett.* **2005**, *46*, 2373-2376; h) M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 539-547; i) F. Gagosz, S. Z. Zard, *Synlett* **1999**, *1999*, 1978-1980.

[81] a) T. Wirtanen, E. Rodrigo, S. R. Waldvogel, *Adv. Synth. Cat.* **2020**, *362*, 2088-2101; b) A. S. Mendkovich, M. A. Syroeshkin, D. V. Ranchina, M. N. Mikhailov, V. P. Gultyai, A. I. Rusakov, *J. Electroanal. Chem.* **2014**, *728*, 60-65; c) H. B. Zhao, P. Xu, J. Song, H. C. Xu, *Angew. Chem. Int. Ed.* **2018**, *57*, 15153-15156; d) X. Chang, Q. Zhang, C. Guo, *Org. Lett.* **2019**, *21*, 10-13.

[82] a) V. K. Soni, S. Lee, J. Kang, Y. K. Moon, H. S. Hwang, Y. You, E. J. Cho, *ACS Catal.* **2019**, *9*, 10454-10463; b) T. Patra, S. Mukherjee, J. Ma, F. Strieth-Kalthoff, F. Glorius, *Angew. Chem. Int. Ed.* **2019**, *58*, 10514-10520; c) T. Patra, P. Bellotti, F. Strieth-Kalthoff, F. Glorius, *Angew. Chem. Int. Ed.* **2020**, *59*, 3172-3177; d) D. S. Lee, V. K. Soni, E. J. Cho, *Acc. Chem. Res.* **2022**, *55*, 2526-2541.

[83] a) C. Pratley, S. Fenner, J. A. Murphy, *Chem. Rev.* **2022**, *122*, 8181-8260; b) S. Z. Zard, *Chem. Soc. Rev.* **2008**, *37*, 1603-1618.

[84] a) J. Boivin, A. M. Schiano, S. Z. Zard, *Tetrahedron Lett.* **1992**, *33*, 7849-7852; b) J. Boivin, A.-M. Schiano, S. Z. Zard, H. Zhang, *Tetrahedron Lett.* **1999**, *40*, 4531-4534.

[85] F. Huang, S. Zhang, *Org. Lett.* **2019**, *21*, 7430-7434.

[86] M. Noack, R. Gottlich, *Chem. Commun.* **2002**, 536-537.

[87] Y. Koganemaru, M. Kitamura, K. Narasaka, *Chem. Lett.* **2002**, *31*, 784-785.

[88] K. Tanaka, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1659-1664.

[89] W. M. Liu, Z. H. Liu, W. W. Cheong, L. Y. T. Priscilla, Y. X. Li, K. Narasaka, *Bull. Korean Chem. Soc.* **2010**, *31*, 563-569.

[90] M. N. Zhao, H. Liang, Z. H. Ren, Z. H. Guan, *Synthesis* **2012**, *44*, 1501-1506.

[91] A. Faulkner, N. J. Race, J. S. Scott, J. F. Bower, *Chem. Sci.* **2014**, *5*, 2416-2421.

[92] J. Ke, Y. Tang, H. Yi, Y. Li, Y. Cheng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 6604-6607.

[93] W. Zhao, R. P. Wurz, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 12153-12156.

[94] L. Wang, C. Wang, *J. Org. Chem.* **2019**, *84*, 6547-6556.

[95] H. B. Yang, S. R. Pathipati, N. Selander, *ACS Catal.* **2017**, *7*, 8441-8445.

[96] X. J. Zhang, D. Qi, C. C. Jiao, Z. G. Zhang, X. P. Liu, G. S. Zhang, *Org. Chem. Front.* **2021**, *8*, 6522-6529.

[97] T. Shimbayashi, K. Okamoto, K. Ohe, *Chem. Asian J.* **2018**, *13*, 395-399.

[98] Such a reaction was reported with perfluorinated carboxylates under palladium catalysis: W. X. Wei, S. Chen, Y. Xia, M. Li, X. S. Li, Y. P. Han, C. T. Wang, Y. M. Liang, *ChemCatChem* **2019**, *11*, 5754-5757.