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Understanding the Chemistry of Nitrene and Highlighting its Remarkable Catalytic Capabilities as a Non-Heme Iron Enzyme

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Nitrogen is a crucial ingredient for biological processes and is necessary for several cellular activities, including metabolic processes, nucleic acid generation, and protein synthesis. Herein we looked at the intricate chemical properties of nitrene, a molecule that contains nitrogen at its core. Nitrene, akin to carbene, exhibits unique reactivity as an electrophile due to its unpaired octet. The

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electrical arrangement of nitrene, namely in its most basic form as imidogen (HN), is analyzed, with an emphasis on its sp hybridization and spin density characteristics. The formation of nitrene, which is known for its strong reactivity, occurs as an intermediate species through two primary mechanisms: the photolysis or thermolysis of azides, and the decomposition of isocyanates. This study offers a concise elucidation of significant chemical occurrences involving nitrenes, such as the incorporation of C-H bonds, cycloaddition reactions, the observed phenomena of ring contraction and ring expansion in aryl nitrenes and the catalytic reactions through Nitrene radical. The final section of the paper provides a summary focused on a specific study involving the transfer of nitrene, which is assisted by a non-heme iron enzyme. The research examines the catalytic prowess of PsEFE, a non-heme iron enzyme derived from Pseudomonas savastanoi, in nitrene transfer processes. Through the utilization of directed evolution and the introduction of non-native small-molecule ligands, PsEFE demonstrated an elevated level of aziridination activity. This emphasizes the capability to enhance catalysis by modifying the reliance on ligands. This study advances the understanding of nitrene chemistry and highlights the remarkable catalytic capabilities of a non-heme iron enzyme, opening possibilities for further exploration in the area of biocatalysis with transition metals.

Keywords: Cycloaddition reactions; imidogen; spin density characteristics; nitrene radical; absolute metabolite concentration.

1. INTRODUCTION

Nitrogen is essential in most living organisms in existence. It makes up a major constituent of several known organic and inorganic compounds that are useful for supporting the continuity and existence of most life forms [1]. Additionally, nitrogen is involved in various reactions in enzymes catalyzing the reaction, as a constituent of the substrates that take part in reactions, or as an additive during the reaction process to yield varying species of products [2]. In cells, generally, nitrogen is involved in metabolic processes such as cell growth, biosynthesis of Nucleic Acids, protein synthesis, removal of cell waste, etc. [3]. Nitrene is a Nitrogen-centered compound, hence, one of the reasons for this paper.

While it is likely not exactly acknowledged, nitrogen-based radicals' usage in synthesis has existed since as far back as the Hofmann-Loffler-Feytag reaction of the 19th century, which was used to synthesize pyrrolidines [4]. The organic free radicals these reactions entailed are usually related to low selectivities [5]. Indeed, organic free radicals usually result in the disproportionation of radicals and other reactions on the side, which produces insoluble materials [6]. Notwithstanding, several selective reactions that have their basis in N-centered free radicals have been accomplished ever since, exploiting kinetic control – undesired reactions outcompeted by desired ones [7].

There is better control accomplished in a metal's coordination sphere, and N-centered radical-binding transition metals are identified more as crucial intermediates to facilitate the regulated bond formation reactions of the C–N radical type [8]. N-centered radicals bound to transition metals are generated catalytically, in little and regulated quantities, thus leading to much higher selectivities than commonly accomplished with organic free radicals [9].

Metals surrounded by ligands are employed in fine-tuning these intermediate's reactiveness – electronically and sterically [10]. Nitrene/imido-centered nitrogen-based radicals M–N.R – that is, complexes of nitrene and imidyl radicals – bound to transition metals, have gained significant attention because they facilitate diverse useful nitrene-transfer and nitrene-insertion reactions. This paper aims to assess the chemistry of Nitrene by investigating its electronic configuration, formation, and chemical reactions.

2. OVERVIEW OF NITRENE

Nitrene, also referred to as imene and denoted by the configuration R–N is the nitrogen analogue of a carbene, a methylene (CH_2) compound. The nitrogen atom of nitrenes is univalent and uncharged [11], thus the nitrene simply has 6 electrons in its level of valence – two electrons covalently bonded and four electrons that are not non-bonded. Hence, it is regarded as an electrophile because of its unbound octet, based on the *octet rule*. Nitrene takes part in many reactions as a reactive intermediate [12]. Nitrene exists in its simplest form as HN, which is termed an "imidogen," and

that name is at times used when referring to the class of nitrenes [13].

2.1 Electronic Configuration

Considering the simplest nitrene form, the imidogen (N–H molecule) has an sp hybridized nitrogen atom, possessing two of its four electrons that are not bonded, in an sp orbital, as a lone pair as well as the other two electrons occupying the p orbitals' degenerative pair. This electron configuration aligns with Hund's rule – a triplet with a single electron in each of the p orbitals as the low energy form as well as a singlet with one pair of electrons occupying a p orbital and the other p orbital unoccupied as the high energy form.

As is common with carbenes, there is a solid relationship between the density of spin on the nitrogen atom that is determined in "silico" and the experimentally derived "zero-field splitting parameter *D*" from the electron spin resonance [14]. Simple Nitrene forms like NH or CF_3N possess values of D at around 1.6cm-1 having densities of spin nearing "2" as the maximum value. Molecules with low D values, that is, less than 0.4 (< 0.4) are found at the scale's lower end and with a 1.2 to 1.4 spin density as in 9-phenanthrylnitrene and 9-anthrylnitrene.

3. FORMATION OF NITRENE

Nitrenes are not isolated due to their high reactivity. Rather, their formation is as a reaction's reactive intermediates. Typically, nitrenes can be formed in two ways. They are:

1. Nitrene formation from Azides

Nitrenes are formed from Azides by the process of photolysis or thermolysis, with nitrogen gas expelled from the reaction. This technique is like that used in carbene formation from diazo compounds.

2. Nitrene formation from isocyanates

Nitrenes can also be formed from isocyanates, with the carbon monoxide gas expelled from the reaction. This technique of nitrene formation is related to carbene formation from ketenes.

4. CHEMICAL REACTIONS OF NITRENE

In this section, some of the reactions involving Nitrene are examined for a better understanding of Nitrene chemistry.

4.1 The Insertion of the C-H Bond by Nitrene

Nitrene easily inserts into a covalent bond of carbon to hydrogen to yield products such as amides or amines. The retention of configuration is reacted with one singlet nitrene. In research, nitrene was observed to be formed by carbamate oxidation with potassium persulfate, which offers an insertion reaction into the reaction product's palladium to nitrogen bond of palladium(ii) acetate and 2-phenylpyridine to methyl *N*-(2-pyridylphenyl) carbamate in a cascade reaction [15].

Also, in the example below, in the insertion of a C–H bond that involves an oxime, acetic anhydride, a nitrene intermediate is suspected, yielding an isoindole [16].

4.2 The Cycloaddition of Nitrene

Nitrenes interact with alkenes to yield aziridines, usually together with a nitrenoid precursor like nosyl- or tosyl-substituted [*N*-(phenylsulfonyl) imino]phenyliodinane (PhI=NNs or PhI=NTs respectively)), however, the interaction is recognized to take place with the sulfonamide directly in the presence of a catalyst which is transition metal based like gold, copper or palladium [17].

Typically, there is however an initial separate preparation of [*N*-(*p*-nitrophenylsulfonyl) imino] phenyliodinane (PhI=NNs) as shown in Fig. 6.

Thereafter there is a transfer of Nitrene (Fig. 7).

In the reaction above, the shown cis-stilbene and the 'trans' form, which is not shown, both yield the product, that is, trans-aziridine, positing a mechanism of reaction in two steps. The differences in the energy of the singlet and triplet nitrenes can be negligible in certain instances, enabling the process of interconversion at room temperature. Nitrenes in triplet form have more stability, thermodynamically but interact in a stepwise manner enabling rotation to take place freely and therefore yielding a stereochemistry mixture [18].

4.3 The Ring-Contraction and Ring-Expansion of Arylnitrene

There is a ring expansion to 7-membered ring cumulenes, reactions of ring opening, and formations of nitrile shown by aryl nitrenes,

several times in reaction paths that are complex. For example, the azide 2 in the reaction shown in Fig. 8 below [19] confined in a matrix of argon at 20 K during photolysis releases nitrogen to the triplet nitrene 4, experimentally detected using an ESR and ultraviolet-visible spectroscopy, which equilibrates with the product 6 ring-expansion.

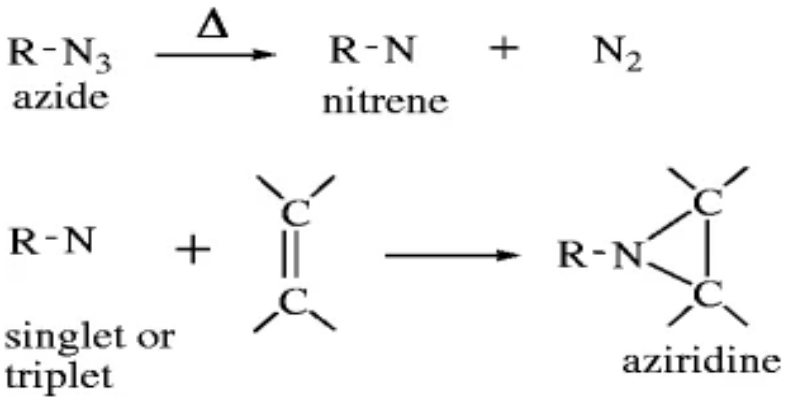


Fig. 1. Nitrene Formation from an Azide
Source: Devi et al., 2016

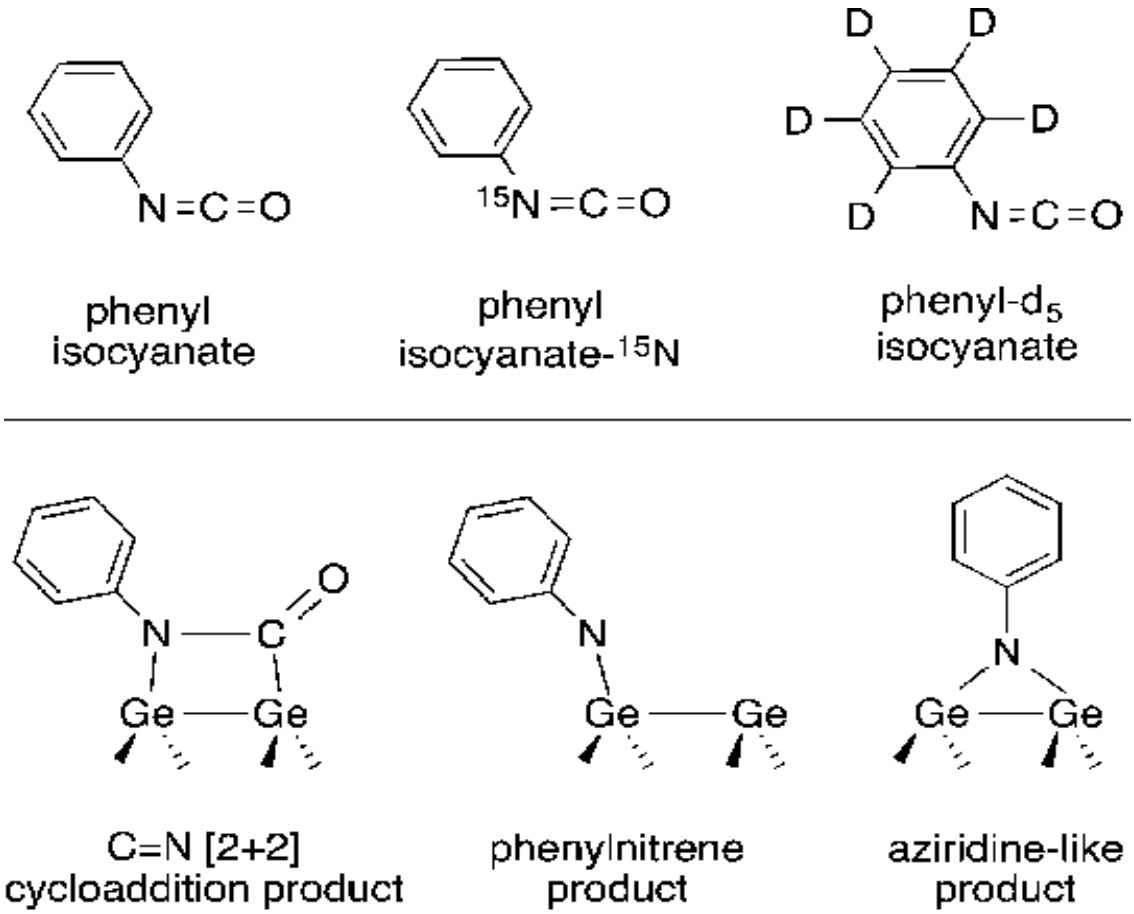


Fig. 2. Nitrene Formation from isocyanates
Source: Wong et al., 2013

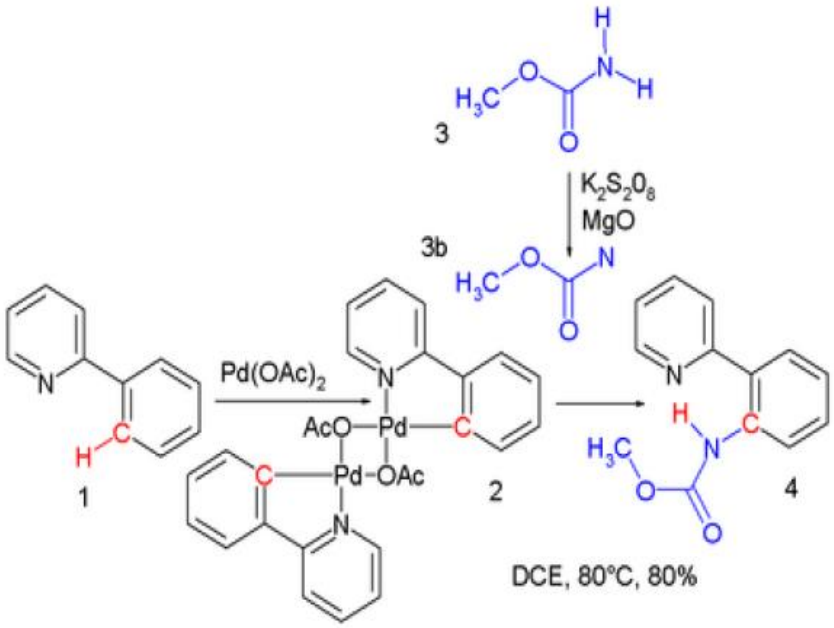


Fig. 3. Insertion reaction by carbamate oxidation with potassium persulfate
Source: (Thu et al., 2006).

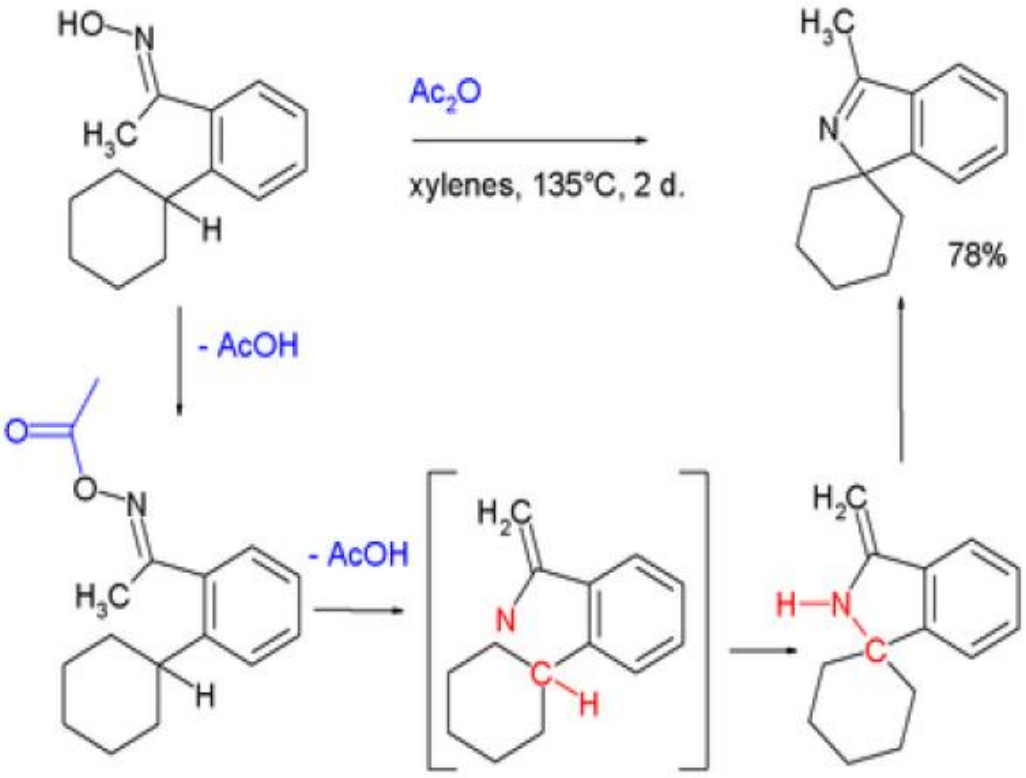


Fig. 4. Suspected Nitrene intermediate in C–H bond insertion that involves oxime, acetic anhydride

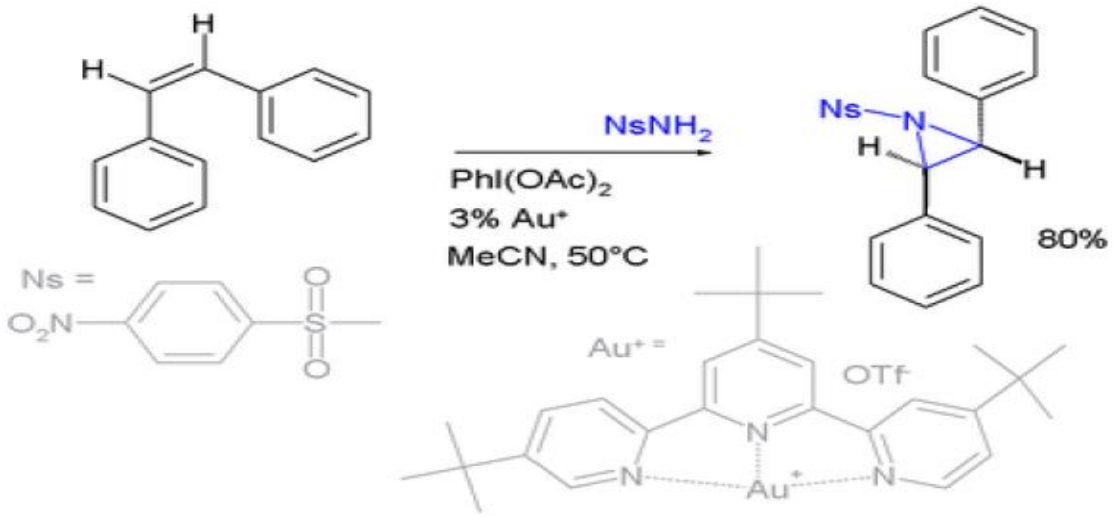


Fig. 5. A Nitrene Cycloaddition Reaction
Source: Li et al., 2006

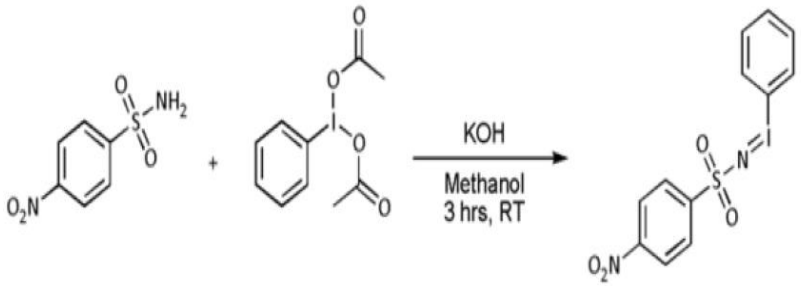


Fig. 6. Initial separate preparation of [*N*-(*p*-nitrophenylsulfonyl)imino]phenyliodinane (PhI=NNs)
Source: Yudin, 2007

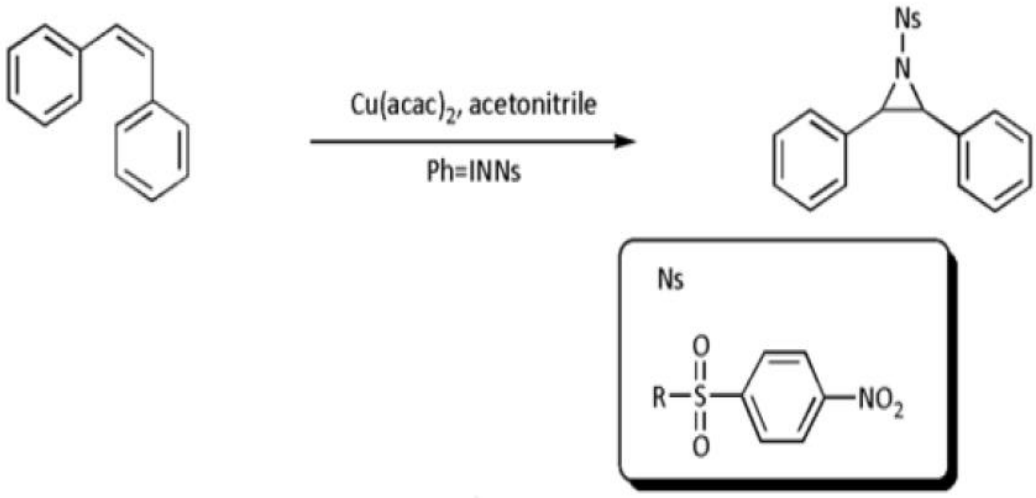


Fig. 7. The Nitrene transfer reaction
Source: Yudin, 2007

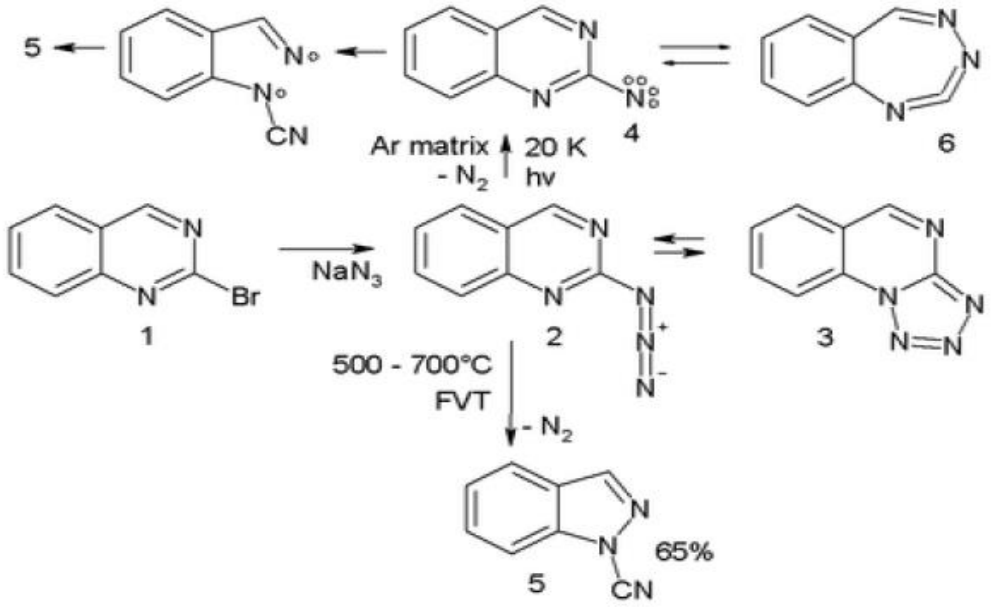


Fig. 8. Arylnitrene ring-contraction and expansion reaction
Source: Kvaskoff et al., 2006

Ultimately, the nitrene is converted to the ring-opened nitrile 5 via the intermediate 7 which is diradical. In an interaction with high temperature, 500-600^{O}C of FVT produces nitrile 5 as well in a yield of 65 per cent [20].

5. NITRENE RADICAL INTERMEDIATES IN CATALYTIC SYNTHESIS

From as far back as the 19th century, radicals that are nitrogen-centred have been used in synthesis, though it was not identified as such initially as observed in the pyrrolidine's synthesis via the Hofmann-Lcffler-Freytag reaction [21]. The organic radicals which are free and participate in these reactions are usually related to low selectivity [22]. Undoubtedly, the free organic radicals usually result in the disproportionation of radicals as well as other reactions that lead to insoluble materials generation. Notwithstanding, several reactions selective on free N-centered radicals' basis have been since, by kinetic control – preferred reactions overcoming less-preferred ones [23].

Improved regulation can be accomplished in a metal's coordination sphere, and N-centered radicals bound to transition metal are regarded more as key intermediates to allow the formation reactions of the C-N bond (a controlled radical type) [24]. In regulated and low amounts, the N-centered radicals bound to transition metals can be formed catalytically, thus resulting in increased selectiveness than commonly accomplished using free organic radicals.

The metal-surrounding ligands are employed in honing both the electronic and steric intermediates, reactiveness [25]. Nitrene/imido-centred nitrogen-based radicals M-N-R bound to transition metals, that is, radical complexes of imidyl and nitrene; Fig. 9&10), have gained certain consideration, since they allow various relevant reactions involving nitrene-transfer and nitrene-insertion. Commonly, these reactions have more selectivity than those utilizing free nitrenes or free N-centered radicals.

5.1 Catalytic Reactions through Nitrene Radical Species Generated using Activated Precursors of Nitrene

Various reactions involving nitrene-insertion and nitrene-transfer, plus C-H amination [26], aziridination [27], and C-H amidation [28] have utilized cobalt porphyrins. Like the aforementioned, radical complexes of cobalt (III) nitrene precursors are posited as important reactive intermediates (Fig. 12). Commonly, they are produced from the interaction of nitrene precursors and cobalt (II)-porphyrin complexes, like activated organic azides or iminiodanes. The discrete radical-type mechanisms are involved in the reaction of cobalt (III) nitrene radical

intermediates. The addition of radical to hydrogen atom transfer (HAT) or C=C double bonds from C-H bonds (activated allylic or benzylic) Fig. 12, results in various preferable organic products containing nitrogen like cyclic and linear amines [29], dihydrobezoxazie, amides [30], azabenzenes [31] and aziridines [32].

Zhang et al in 2005 explained the first aziridation catalyzed by cobalt-porphyrin, wherein they utilized Bromamine-T as the precursor of nitrene [33]. Although, earlier Cenini et al (2000) have demonstrated that organic azides are fit agents of nitrene transfer in C-H bond amination reactions catalyzed by cobalt (II)-porphyrin [34]. In comparison to Bromamine-T, they can be more easily worked with, viable, and possess a wider scope, synthetically. Consequently, in many successive types of research comprising cobalt (II)-porphyrin-mediated reactions of nitrene-transfer and nitrene-insertion, the preferred nitrene precursor selected was the organic azides (plus most C-H bond amination and aziridination research described by Zhang et al (2005). The aziridination reaction mechanism was scrutinized by de Burin et al (2010) through DFT techniques, corroborating nitrene radical intermediates' formation as the important reactive species in the cycle of catalysis (Fig. 12).

5.2 Catalytic Reactions through Nitrene Radical Species Generated using Aliphatic Precursors of Nitrene

Several of the aforementioned catalytic reactions need pre-activated or aromatic organic azided, i.e. $ROSO_2N_3$, $(RO)_2P(=O)N_3$, $ROC(=O)CN_3$ etc., to accomplish selective and effective turnover. Commonly, these azides are activated more easily than aliphatic azides, and therefore, at lower temperatures, more effective reactions occur are possible with these pre-activated compounds. Such reactions using aliphatic azides are more complex, and typically necessitate higher temperatures and more reactive catalysts. However, using aliphatic azides significantly widens these reactions' scope, resulting in a wide range of fascinating cyclic products containing nitrogen. Therefore, attempts at novel protocols' development for activating aliphatic azides are preferable. In catalysis, advances in the field undoubtedly indicate the possibility of converting aliphatic (less reactive) azides – processes that all have the nitrene radical complexes' intermediacy involved.

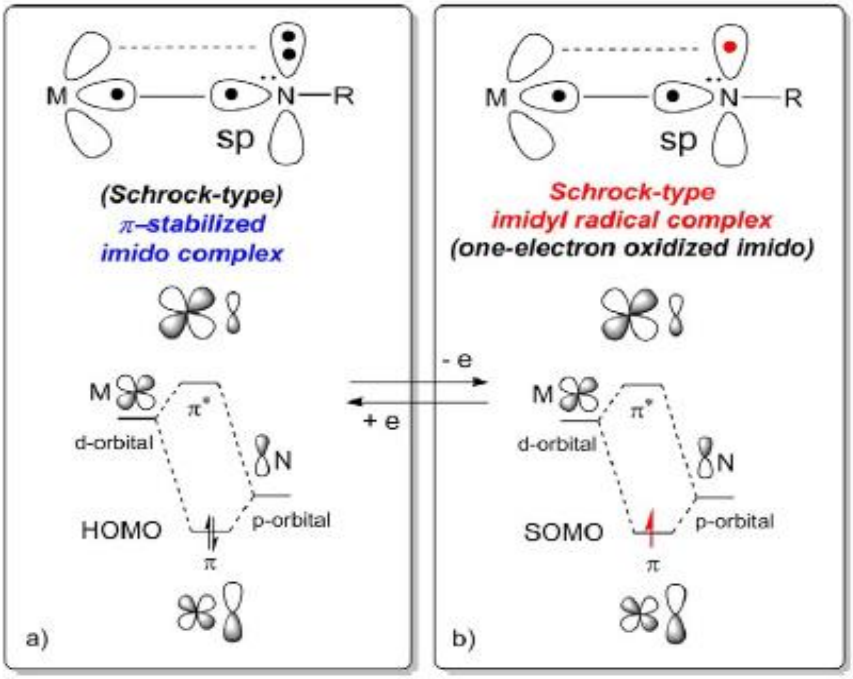


Fig. 9. Basic diagrams of borderline molecular orbital: a) Schrock-type imido complex; b) Schrock-type imidyl radical complex

Source: Kuijpers et al., 2017

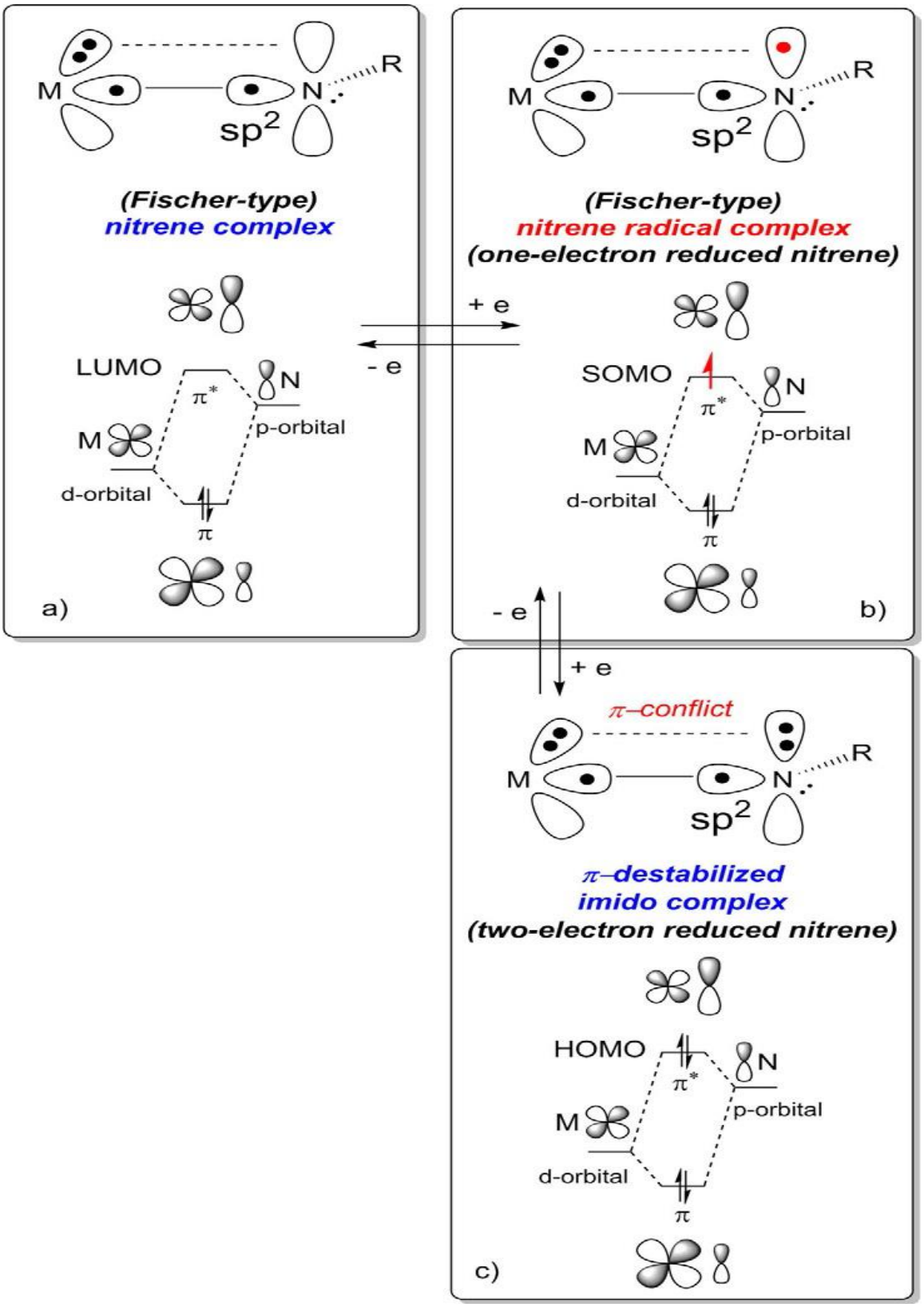


Fig. 10. Basic diagrams of borderline molecular orbital: a) Fischer-type nitrene complex;.b) Nitrene radical complex

Source: Kuijpers et al., 2017

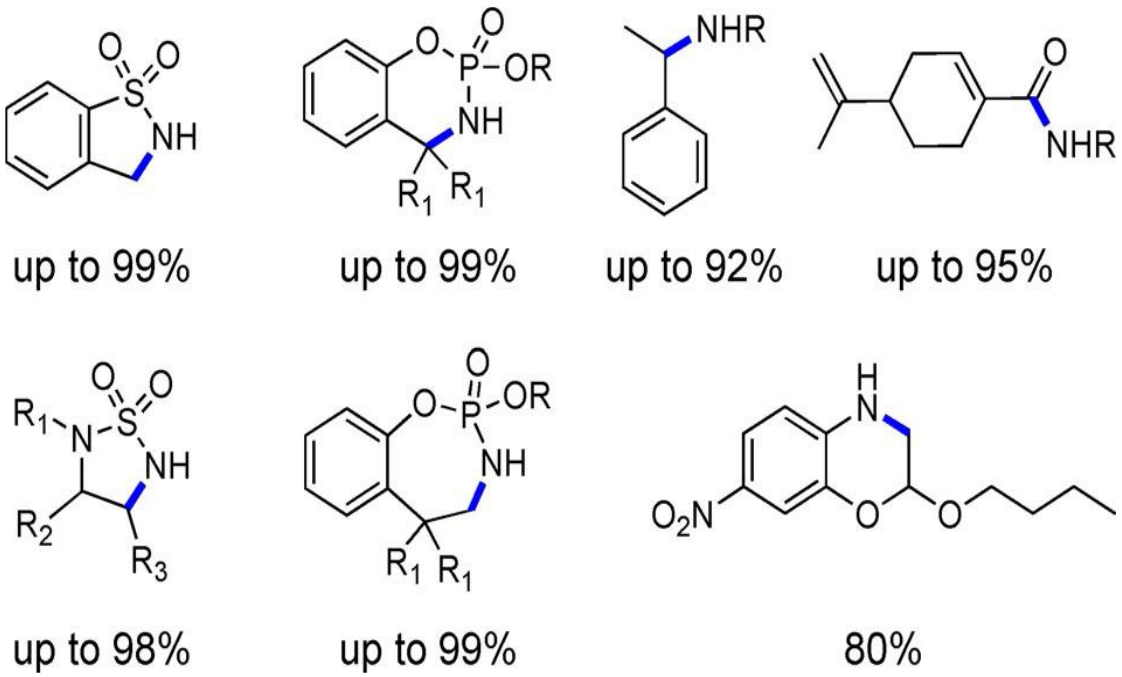


Fig. 11. Selecting diverse products that are produced via protocols of nitrene insertion's catalysis of cobalt (II) porphyrin using nitrene radicals

Source: Kuijpers et al., 2017

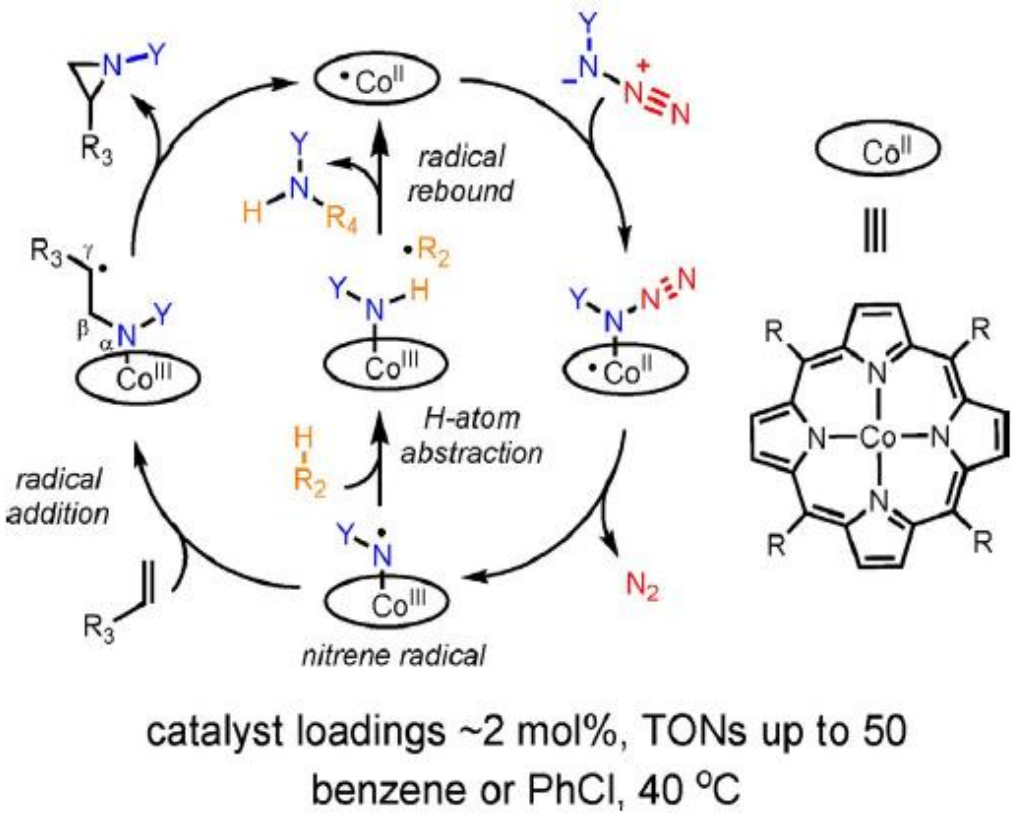


Fig. 12. Comprehensive reactivity of nitrene radical and cobalt (II)–porphyrin metalloradical-catalyzed nitrene-transfer interactions' mechanisms

Source: Kuijpers et al., 2017

The report by King et al (2011), who utilized iron catalysts on "half-porphyrin" dipyrromethane ligands basis, is the first published on aliphatic azides' activation. In both the intramolecular [35]. (Spasyuk, 2016) and intermolecular [36] C-H bond amination reactions, the FeII complexes showed to be active. The first published article in 2011 reported the large aliphatic azides and aromatic intermolecular amination of the C-H bond (Fig. 13) [37]. The electronic structure of the nitrene intermediate is rather complex, having one among the five electrons (unpaired) at the FeIII centre's high spin being antiferromagnetic together with the moiety of nitrene radical, resulting in a ground state S=2. Consequently, it is unclear whether the intermediate should be identified as a nitrene radical Fischer-type (Fig. 10), or instead a Schrock-type imidyl radical complex (Fig. 9). Regardless, the intermediate seems to interact as an N-radical or display discrete nitrogen-based spin density. The posited mechanisms for these interactions have great similarity with those described above for several other catalysts – HAT (from the hydrocarbon by N-radical bound to metal), after by a step of radical rebound to yield the aminated organic product that aligns with the allylic C-H insertion's high chemo-selectivity on aziridination [38].

The trait of the nitrene radical can also result in unwanted side-reaction with nitrene sources – aromatic azides. The phenyl ring of the transitory phenyl-nitrene catalyst species from spin-delocalization lead to the bimolecular integration of two parts of nitrene preventing catalysis [39].

Throughout the previous century, diverse synthetic transition-metal catalysts have been made by chemists in their effort to access novel reactivity modes and chemical transformations. For a much longer time – more than billions of years, nature has been making catalysts and advanced a robust myriad of proteins with performance accrued to majority of the life chemical reactions that exist. However, the intervention brought by nature has no comparison with the renowned inventions made by human chemists. The attempts to combine the nature's broad metalloproteins toolbox with non-biological chemistry of transition metals have concentrated proteins that bind with heme, because in synthetic transition-metal chemistry, the cofactor – heme and analogues are studied in-depth [40]. Although, the proteins that bind to heme depict just a little fraction of the existing chemical diversity in metalloproteins that occur naturally. Over 30 percent of the entire proteins are metalloproteins [41] and they yield most of the primary biological reactions such as synthesis of DNA, nitrogen fixation and photosynthesis. Metalloproteins that occur naturally bind different metals in a broad spectrum of sites for metal binding, which coordinates either a complex metal-containing cofactor or the metal iron itself. A metal and the peptide backbone can be coordinated by almost any side chain containing heteroatoms, enabling many potential environments for coordination [42]. Several environments for coordination in the metalloenzymes lacking heme have many coordination sites which are open at the center of the metal, a vital property of many synthetic transition metal catalysts. Growing catalysts that are new to nature to metalloenzymes lacking heme would create a novel ecosphere of biocatalysis by transition metals. This paper indicates that a non-heme iron enzyme can catalyze the chemistry of nitrene-transfer (Fig. 14). The process which is non-native is facilitated by the non-native small-molecule ligands binding and directed evolution has enhanced it.

Iron enzymes dependent on α-ketoglutarate (α-KG), an enzyme family which demonstrates a metal-binding active site (conserved) with two histidines and one glutamate or aspartate coordinated with iron, was considered to seek the natural metalloproteins abiological catalytic promiscuity [43]. Naturally, the enzymes carry out similar chemistry like the family of the heme-binding cytochrome p450, wherein an iron-oxo intermediate with high valency carries out C–H hydroxylation, olefin epoxidation, or other changes by oxidation [44]. While this enzyme family members have been said to carry out the catalysis of reactions outside their primary functions, every reported reaction occurs via the native iron-oxo mechanism [45]. It was hypothesized that the iron enzymes – non-heme may as well have the ability to catalyze abiological changes like the heme-binding proteins via mechanistic pathway that is not natural.

A group of seven purified iron dioxygenases dependent on α-ketoglutarate (α-KG) were screened against the intermolecular styrene aziridination reaction and *p*-toluenesulfonyl azide**.** The insertions of nitrenes carbon-hydrogen (C–H) and aziridination were reported with engineered heme-binding proteins and later posited in a biosynthetic pathway of natural product. According to Chang and co-workers, it

was speculated that there existed a transient iron-nitrene intermediate when they reported the conversion of alkyl azides to nitriles by an iron dioxygenase that is dependent on α-KG, but the reaction still occurs via the canonical iron-oxo cycle of catalysis [45]. Currently, there is no report of non-heme iron enzyme, engineered or natural, that carry out the catalysis of nitrene transfer.

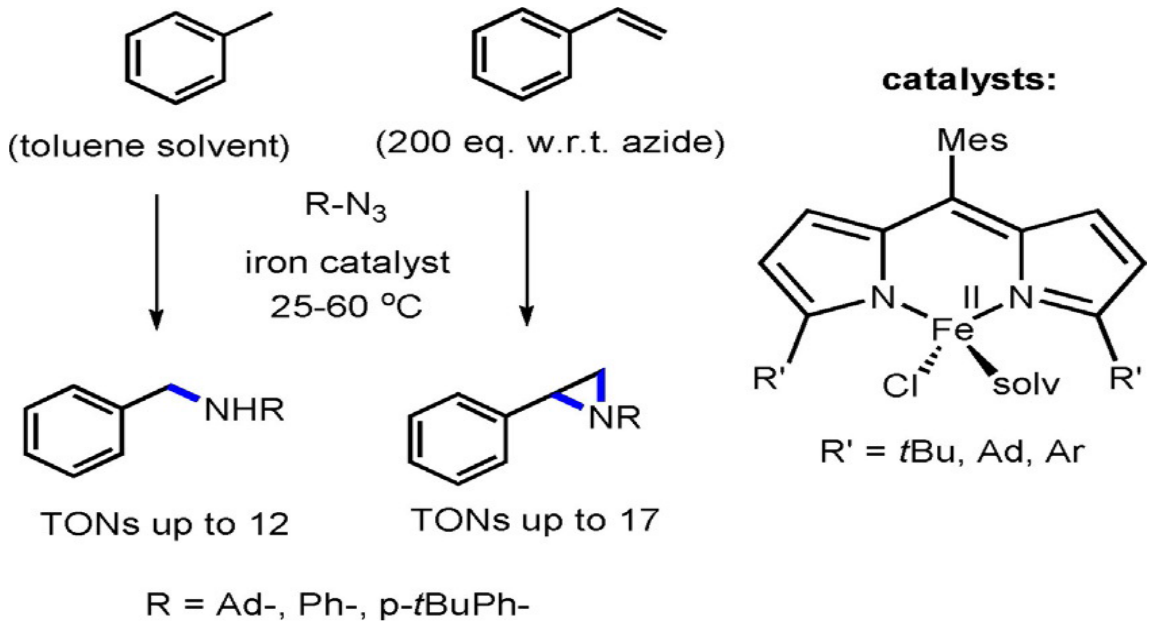


Fig. 13. King et al. (2011) developed reactivity of nitrene-transfer/insertion (left) of the high-spin iron (II) catalyst (right)
Source: Kuijpers et al., 2017

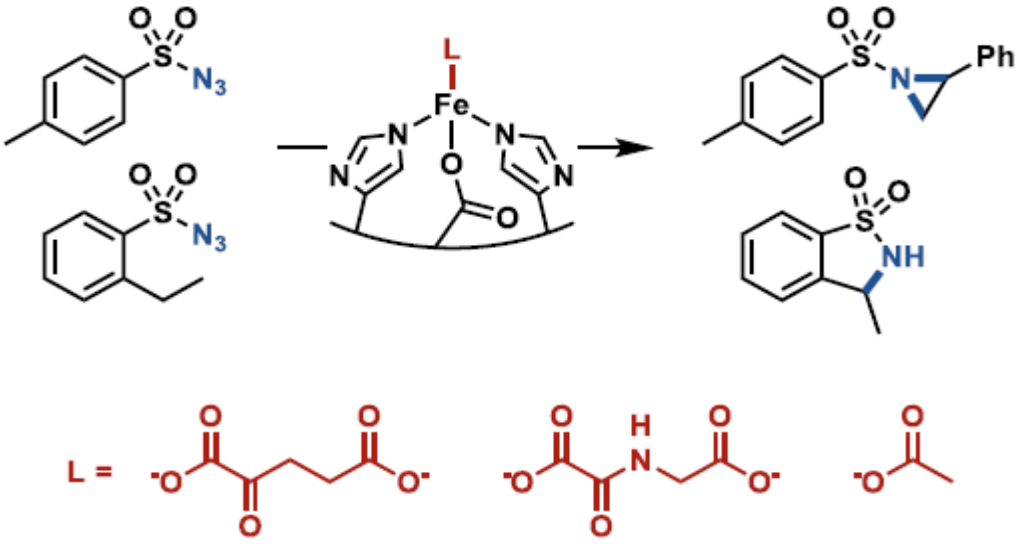
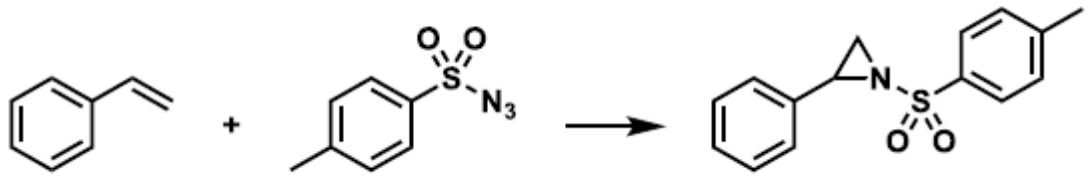


Fig. 14. Small-molecule activation of a non-heme iron center for nitrene transfer. Carboxylate-containing ligands α-ketoglutarate, Noxalylglycine, and acetate modulate the nitrene-transfer activity of variants of P. savastanoi ethylene-forming enzyme
Source: Goldberg et al., (2019)

Pseudomonas savastanoi ethylene-forming enzyme (*Ps*EFE, UniProt ID P32021) was the only tested enzyme from the set that formed aziridine. The iron dioxygenases dependent on α-ketoglutarate (α-KG) in the PsEFE family are structurally and mechanistically unique. Though majority of the enzymes in this family involve in substrate oxidation catalysis, usually C–H hydroxylation, PsEFE is natively involved in the catalysis of the fragmentation process of common co-substrate α-ketoglutarate to ethylene and L-arginine hydroxylation [46]. Normally, *Ps*EFE binds α-ketoglutarate in an atypically hydrophobic pocket is a strained conformation, thus its unusual catalytic activity [47].

Characterizing the needed reaction components was undertaken because the site of *Ps*EFE the binds iron is somewhat different from proteins that bind heme which perform the chemistry of Nitrene transfer. Iron is needed, plus an added equivalent of Iron (II) adequate for a complete wild type apoenzyme restore catalytic activity. There are three sites of coordination in *Ps*EFE occupied by side chains of amino acids (one aspartate and two histidines), making three more binding sites left open to be bound. In the ideal *Ps*EFE mechanism of catalysis, the α-ketoglutarate binds two of the sites and is needed for reaction, because it undergoes oxidative decarboxylation to succinate yielding the reactive iron-oxo intermediate. *Ps*EFE is demonstrated to perform arginine hydroxylation catalysis with α-ketoapidate rather than α-ketoglutarate, but with a lower activity of 500-fold. No activity is yielded from other ketoacids [48]. However, the transfer of nitrene does not follow the normal cycle of catalysis and thus does not need the co-substrate (α-ketoglutarate). The α-ketoglutarate now becomes more of a ligand which can be possibly substituted by small-molecule ligands. *Ps*EFE was tested for aziridination with a group of α-ketoglutarate probes and additives – associated molecules, based on the potential of transforming the reaction of enzyme by primary coordination sphere's change of catalytic iron it was found that while the added carboxylate benefits the reaction, there is a substantially more activity for aziridination by the wild-type enzyme with N-oxaglycine (NOG) or acetate in comparison with α-ketoglutarate (Table 1).

Table 1. Aziridination Catalyzed by Wild-Type PsEFE



1 2 3

deviation from standard conditions[a]	relative activity
none	1.00
no iron	0.08
no αKG	0.52
acetate[b] instead of αKG	6.72
N-oxalylglycine[c] instead of αKG	7.75
acetate instead of αKG, no ascorbic acid	6.01

[a]Standard conditions: reactions were performed in MOPS buffer (20 mM pH 7.0) with 5% ethanol co-solvent, with 20 μM apoenzyme, 1 mM $Fe(NH_4)_2(SO_4)_2$, 1 mM αKG (as disodium salt), 1 mM L-ascorbic acid, and 10 mM 1 and 2. [b]Sodium salt. [c]Free acid.

Source: Goldberg et al. (2019)

Directed evolution was employed to enhance aziridination of *Ps*EFE by using site-saturation mutagenesis and improved activity screening to target the residues of the active-site. The initial round's first screening was carried out with exogeneous α-ketoglutarate, but exogeneous acetate was used to validate the round and all the screened evolution that followed. The preferred ligand selected was acetate because of its substantial wild-type enzyme activity improvement than the innate α-ketoglutarate; it is cheap and biologically universal. While α-ketoglutarate is the innate ligand and occurs naturally at almost-millimolar intracellular concentration in Escherichia coli [49].

It was rationalized that by reaction medium supplementation with acetate *Ps*EFE can be evolved to depend rather on acetate [50], notwithstanding lysate or whole cell screening conditions [51].

Following two rounds of mutagenesis by site-saturation and one recombination round, it was discovered that a variant having five mutations from the wild type – T97M, R171L, R277H, F314M, C317M, PsEFE MLHMM, which catalyzed the formation of aziridine having total turnover number (TTN) of 120 and 88 percent enantiomeric excess(ee) supporting the (R)-entantiomer (Fig. 15.a) [52]. Among the five mutations introduced, four are in the binding pocket of the innate substrate arginine and apparently take part in substrate binding. The fifth beneficial mutation is at Arg-277 (with guanidino group innately binding the distal carboxylate of α-ketoglutarate (Fig. 15.b). the mutation R277H probably obstructs the binding of the innate α-ketoglutarate; thus, PsEFE MLHMM demonstrates no substantial aziridination activity increase when α-ketoglutarate is included, but an increase by 11-fold when acetate is added. Therefore, the MLHMM variant evolved is activated greatly by acetate but not at all by α-ketoglutarate again, showing that the PsEFE ligand dependence is tunable [53].

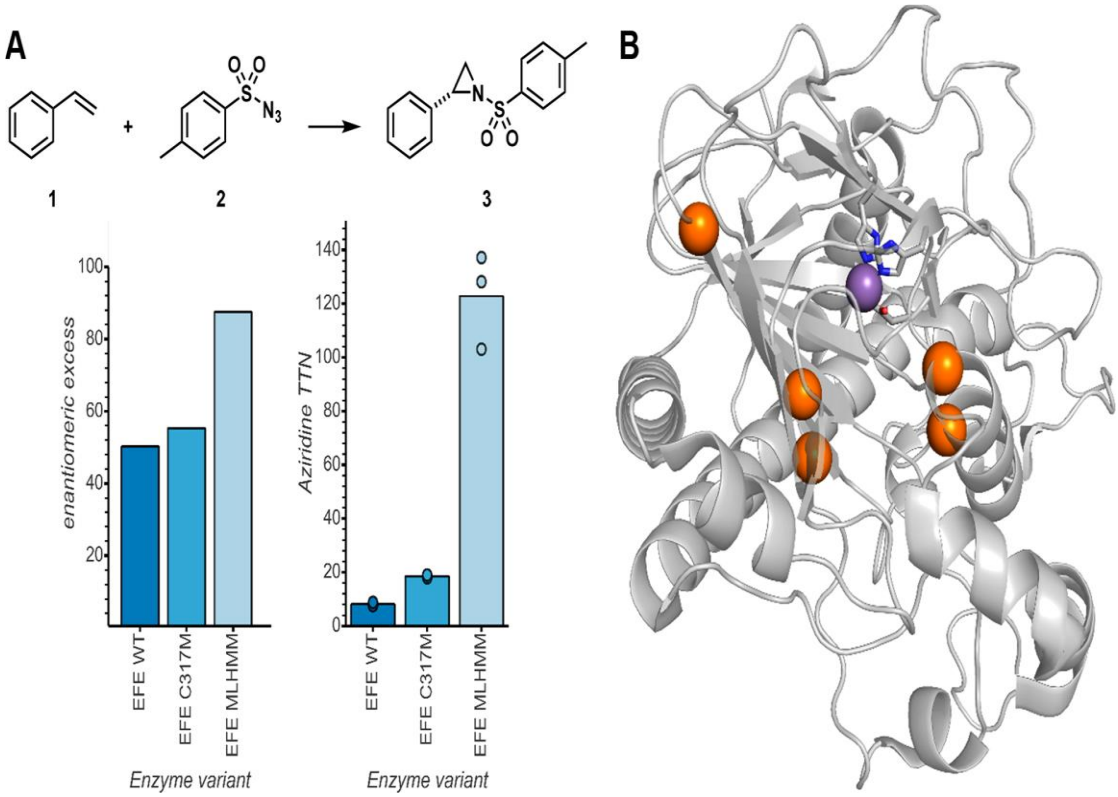


Fig. 15. Directed evolution of PsEFE for aziridination. (a) Evolutionary lineage. Reactions were performed in triplicate anaerobically with acetate and quantified by analytical HPLC-UV. (b) Structural representation of PsEFE with mutated sites highlighted in orange; metal-coordinating residues H189, D191, and H268 are represented in sticks and Mn (the metal with which the protein was crystallized) is represented as a purple sphere (PDB ID: 6CBA)

Source: Goldberg et al. (2019)

6. CONCLUSION

Nitrene is a highly versatile and reactive species derived from nitrogen, playing a pivotal role in many catalytic processes [54]. This review emphasizes the extensive range of states and reactions in which nitrene is instrumental, showcasing its critical role in modern chemical synthesis [55]. As a reactive intermediate, nitrene is involved in various transformations, including the addition to multiple bonds and atom transfer reactions, making it a cornerstone in the synthesis of amines, aziridines, and other nitrogen-containing compounds [56]. The study serves as a foundational reference, paving the way for future research to exploit nitrene's reactivity further [57]. It is anticipated that ongoing and future studies will harness nitrene's diverse capabilities to innovate and enhance the development and synthesis of a wide array of nitrogenous compounds and byproducts [58]. The ability of nitrene to insert into C-H and N-H bonds, among others, provides a powerful tool in the molecular assembly of complex structures, highlighting its significance in advancing the fields of pharmaceuticals, material science, and catalysis. As research progresses, the understanding and application of nitrene in various chemical contexts are expected to expand, driving forward the frontiers of nitrogen chemistry.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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