

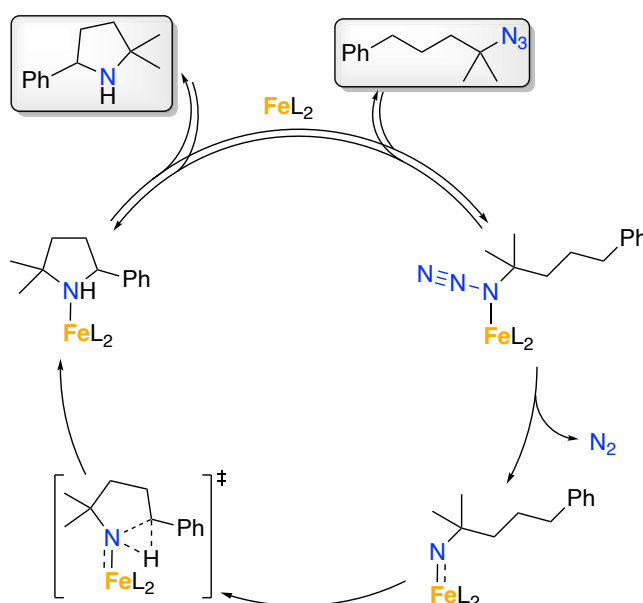
Using Carbenes to Make Reactive Nitrenes

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The formation of C–N bonds via the activation of unfunctionalized C–H bonds offers great synthetic potential to access N-heterocyclic compounds. Pioneering work by Betley demonstrated the suitability of iron complexes as catalysts and the feasibility of organic azides as substrates for this challenging reaction. Subsequent developments have shown that ligand tailoring as well as modulation of the metal center provide opportunities for enhancing the catalytic activity, and for avoiding the use of additives. Moreover, the imidyl/nitrene intermediate, assumed to be the critical species to induce C–H bond activation, has been stabilized and characterized in bespoke complexes. Inspired by these achievements, we have been searching for new catalyst precursors based on iron complexes. We will discuss both, our strides to shed light on some of the mechanistic aspects of this reaction as well as our efforts to improve the catalytic activity of the metal center. We will present our studies to identify azide coordination to the iron center as well as dinitrogen loss to form the critical nitrene. In particular the introduction of carbene ligands yielded catalytic systems that show remarkable performance in the formation of pyrrolidines via the activation of aliphatic or benzylic C–H bond activation.



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Can a free carbene do the job of a transition metal?

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Our recent results dealing with the development of catalytic processes promoted by carbenes, which are genuine organic compounds, will be discussed. This approach could address the major drawbacks of current transition metal catalysis technology that are the excessive cost of metal complexes (metal + ligands) and in many cases the toxicity of the metal.^[1-4]

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Stabilizing Radical Intermediates

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We sought to emulate the C–H bond hydroxylation reaction chemistry of Cytochrome P450s by generating metal-ligand multiple bonds (MLMBs) featuring open-shell configurations. We hypothesize that open shell MLMBs would diminish bond covalency as well as render the multiply bonded functionality highly electrophilic. Pursuant to this goal, we have explored the chemistry of C–H bond amination mediated through transition metal bound nitrenoids. Using weak-field ancillary ligands, we have been able to isolate examples of terminal nitrenoids that exhibit imido ($M^{2+}(NR^{2-})$),^[1] imidyl ($M^{+}(^2NR^{-})$),^[2] and nitrene ($M(^3NR)$)^[3] character. The spectroscopic signatures of these materials, their attendant reactivity with C–H bonds, and their efficacy in C–H bond amination catalysis will be described.^[4]

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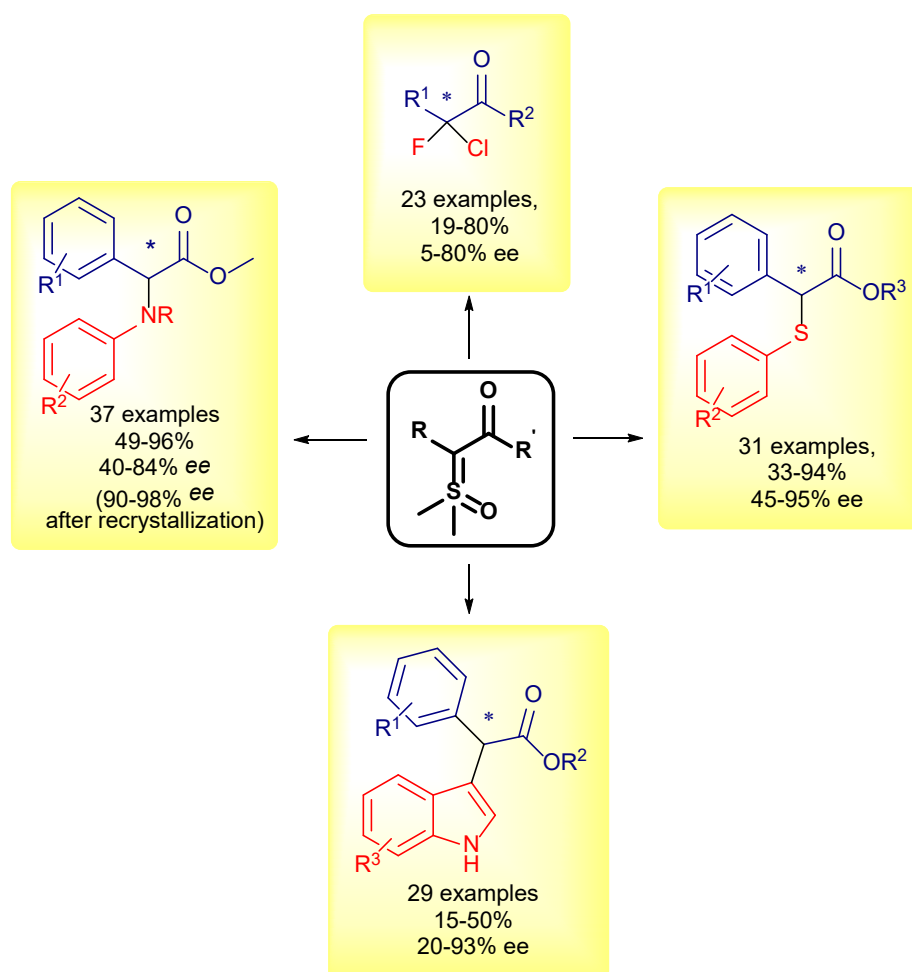
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Enantioselective Transformations from α -Carbonyl Sulfoxonium Ylides

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Sulfoxonium ylides have been employed in a plethora of new and intrinsic chemistry, especially in the last years. Bench stability and handling are also advantages of this class of organosulfur, and its use in industry as safer alternatives to diazo compounds has been evaluated during several years. Despite all that, efficiently asymmetric transformations, specifically catalytic enantioselective versions, have only emerged in the last years. This work will discuss the main results of our laboratory in the enantioselective formal N-H, S-H and C-H insertion reactions from carbonyl sulfoxonium ylides, as well as fluorination reactions, employing non-covalent and covalent catalysis.¹ These methods permitted the synthesis of several α -difunctionalized carbonyl compounds, containing heteroatoms, in an enantioenriched fashion.



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Towards A Multivariate Linear Regression Workflow to Design Catalysts with Few-Entry Datasets

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One of the major goals in catalysis is to move beyond the empirical trial-and-error approach and to explore catalysts space efficiently. This would allow discovering catalysts outperforming those already known, while minimizing experimental costs and time to target. In this context, data-driven machine learning approaches are emerging as powerful tools for screening and predicting catalysts behavior. These approaches rest on the availability of large datasets allowing to explore catalysts space using physico-chemical features characterizing catalysts diversity. Building these datasets using high-throughput experimentation and analysis platforms is possible, but it requires slow and multi-steps synthesis of new catalysts. Consequently, the most common case for the ordinary laboratory is having at hand only a few dozens of catalysts. However, the accuracy of ML models trained on few-entry datasets to identify improved catalysts is unclear.

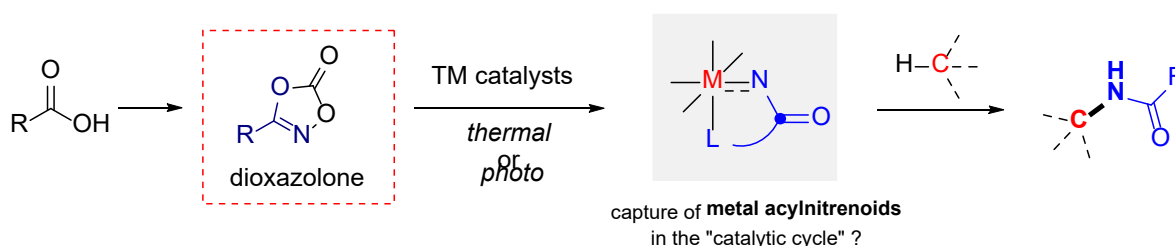
With the aim of solving this problem, we introduce here a series of tests to assess the robustness of a ML-model trained on a few-entry dataset to reproduce known data and to predict catalysts with performance beyond those in the training dataset. These tests are condensed into a confidence score aimed at estimating the expected prediction capability of a new model. To achieve robust validation of the workflow we applied it to a variety of different cases. We thus assembled 29 reaction classes and experimental reaction properties into 29 training datasets, and we trained and tested ML models to identify the top performing catalysts in each dataset. Due to the small size of these datasets, as ML engine we rested on classic multivariate linear regression. We will also show a potential application of this protocol by leveraging few experimental data to screen new N-heterocyclic carbenes, by using in sequence DFT calculations and ML-methods.

C-H Amidation Reactions via Amino Group Transfer Pathway: Validation of Metal Acylnitrenoid Intermediacy

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Direct amidation of C–H bonds is a highly desirable reaction considering high utility of amidated products in total synthesis, medicinal chemistry and materials science.¹⁻² Although tremendous research efforts have been made especially in recent years, the current status enabling such C–H reactions in excellent stereoselectivity and high efficiency is still rather limited. In this context, we have developed a novel methodology that employs tailor-made Ir-based catalysts in combination with dioxazolone substrates to access a short-lived metal-nitrenoid intermediate, thereby eventually leading to a construction of γ -lactams via an outer-sphere C–H insertion pathway.³ The scope was found to be broad and a range of carboxylic acids could be readily utilized for the lactam formation. More recently, we have successfully introduced an iridium-based catalyst system for asymmetric C–H amidation that enables facile construction of chiral γ -lactams starting from commodity chemicals. Various types of secondary C–H bonds, such as being positioned at the benzylic, unactivated aliphatic, propargylic, and allylic sites, were all smoothly reacted in a regio- and stereoselective manner.⁴⁻⁵ More recently, this strategy of C–N bond formation has been also successfully demonstrated to work with basic transition metal catalysts.⁶⁻⁸ The nitrenoid intermediacy was extensively investigated using mechanistic experiments, photocrystallography, and computational studies.⁹ The present approach will find broad applications in medicinal chemistry, and the mechanistic insights may provoke further developments in related asymmetric catalysis.



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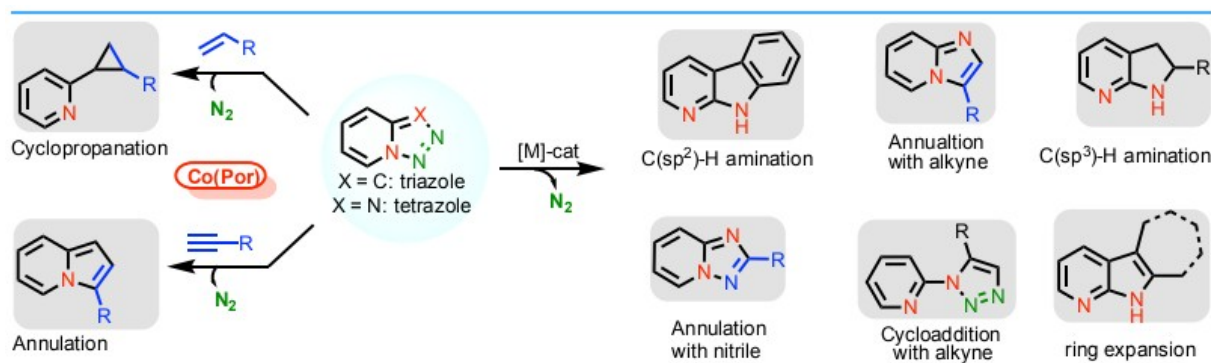
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Catalysis for Denitrogenative Transformation of 1,2,3,4-Tetrazoles

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The quest for the discovery of new and powerful synthetic methods to access high-valued *N*-heterocycles¹ have been at the forefront of organic chemistry research for more than a century. Over the past few decades, great research efforts have made to develop efficient synthetic methods for the construction of high-valued *N*-heterocycles. Among many efforts, transition metal-catalyzed denitrogenative transformation^{1,2,3} has emerged as a cornerstone due to its innate versatility and wider scope of application. In this context, while catalysis for the denitrogenative transformation of the 1,2,3-triazole via metal carbene intermediate sparked significantly in the application of various important heterocycles synthesis,¹⁻³ unfortunately, the catalytic denitrogenative transformation of 1,2,3,4-tetrazole via metal nitrene remains a big challenge. Interestingly, this chemistry was reported⁴ more than 50 years back by Huisgen and Fraunberg using a stoichiometric amount of Cu powder at high reaction temperature. Subsequently, Wentrup group studied⁵ extensively the thermal and photochemical nitrene–nitrene rearrangement of this tetrazole. Unfortunately, since these reports, the process had never been considered to make either catalytic or to use this tetrazole as a synthetic precursor in organic synthesis. Thus, we thought that if we can generate a productive metal-nitrene intermediate, it will enable a new area for the catalysis research and that was the starting point to begin this chemistry. Initially we developed a method that produced a productive metal-nitrene intermediate⁶ and using this nitrene, we then developed a series of new reactions.^{1,2,9,10} In this conference, I would like to talk some of them.



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Iron-Catalyzed Nitrene and Carbene Transfer and Insertion Reactions

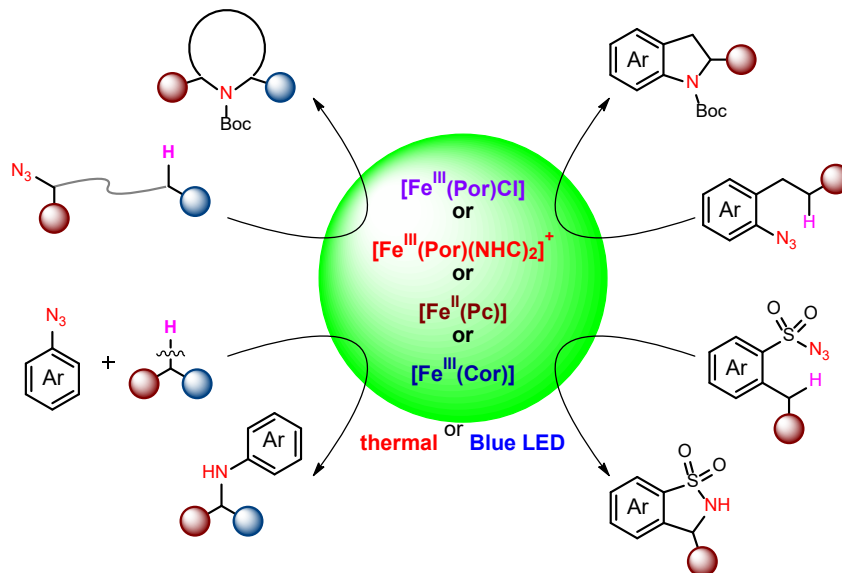
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Iron complexes have been shown to be effective catalysts for nitrene C–H bond functionalization reactions and carbene insertion reactions.[1] In this presentation, our recent works on iron complexes supported by chiral macrocyclic ligands (e.g. Fe(III) porphyrin, Fe(II) phthalocyanine, Fe(IV) corrole etc) for alkylnitrene, aryl nitrene and sulfonylnitrene transfer/insertion reactions are described.[2–4] These reactions can be applied to the synthesis of various natural products and bioactive compounds.[5] Under visible-light-irradiation, these iron-catalyzed nitrene C–H insertion reaction could proceed at a much lower reaction temperature,[6] which greatly facilitate asymmetric nitrene C–H functionalization reactions (up to 99% yield with 93% ee).[7] The reaction mechanism of these nitrene transfer reactions has been studied experimentally and theoretically. We have been able to capture and spectroscopically characterized a reactive alkylimido Fe(V) species, which can react with C–H bonds via an H-atom abstraction mechanism. Our recent work shows that highly enantioselective carbene cyclopropanation reactions can be achieved using chiral iron porphyrins as catalysts.



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Elusive Intermediates and NMR signatures of Active Sites in Heterogeneous Olefin Metathesis Catalysts

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Olefin metathesis has become a prominent reaction in organic synthesis. It is certainly a key process of the petrochemical industry for decades, enabling to interconvert olefins on large scale. Prominent examples are i) the production of propene by cross-metathesis of ethene and 2-butenes and ii) the SHOP process. These processes rely on catalysts based on supported group 6 metal oxides, WO₃/SiO₂ and MoO₃/SiO₂-Al₂O₃. Despite years of research and the development of well-defined homogeneous catalysts based on the Chauvin mechanism, the structure of the active sites and reaction intermediates (alkylidenes and metallacyclobutanes) have remained elusive for the corresponding heterogeneous catalysts. Notably, it is not clear how the expected metathesis intermediates are generated in these heterogeneous catalysts from the olefins and the metal oxides. This contribution will discuss how Surface Organometallic Chemistry (SOMC) anchored on molecular chemistry, solid-state NMR spectroscopy and computational studies have enabled to generate and characterize highly active supported catalysts based on well-defined alkylidenes, detect metathesis reaction intermediates, and develop detailed structure-activity relationships.[1] This approach has most recently been used to understand initiation mechanism in classical heterogeneous catalysts.[2] In that context, we will discuss how NMR spectroscopic signatures can provide key information about electronic structures and reactivity of metal sites.[3]

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Naturally-based heterogenized iron porphyrins for the efficient and eco-compatible transfer of C1 and carbene units

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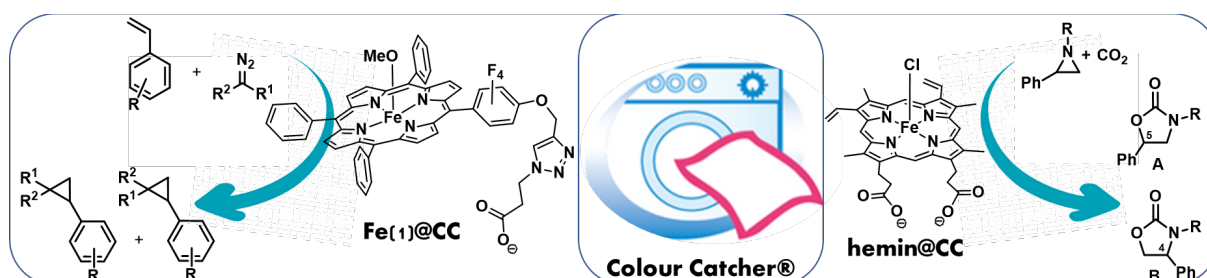
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For answering to the society's demand for eco-friendly chemical processes, high interest has been recently devoted to the use of naturally derived and recyclable catalytic systems for the synthesis of useful fine-chemicals. In this view, the heterogenization of homogenous catalytic systems have gained the chance to anchor, through covalent bondings or non-covalent interactions, active catalysts on suitable solid supports allowing the recyclability and the eco-compatibility of the resulted catalytic systems.

To combine the transfer of carbon units from sustainable sources with the eco-compatibility of the employed catalytic system, both naturally and synthetically derived iron porphyrins were anchored onto Colour Catcher® sheets, a well-known cellulose-based material usually employed during the laundry to capture the colours released by tissues.^[1]

The anchorage of the naturally derived hemin, active centre of many protein families such as cytochromes, peroxidases, myoglobins, and hemoglobins, onto the Colour Catcher® surface allowed easily obtaining the heterogeneous **hemin@CC** (Scheme 1). The latter system efficiently promoted the transfer of C1 carbon units from carbon dioxide to *N*-alkyl aziridines yielding the corresponding *N*-alkyl oxazolidinones^[2] in yields up to 99% and A/B ratios up to 99:1.

On the other hand, according to capability of *meso*-substituted iron porphyrins to transfer the carbene functionality to C=C double bonds^[3], a negatively charged iron porphyrin was synthesized and anchored onto the Colour Catcher® surface to develop the catalytically active material **Fe(1)@CC** (Scheme 1). The latter is a promising heterogeneous system able to transfer 'R¹CR²' unit from diazo reagents to double bonds affording cyclopropanes.



Scheme 1: transfer of C1 and R¹CR² units promoted by heterogenized iron porphyrins.

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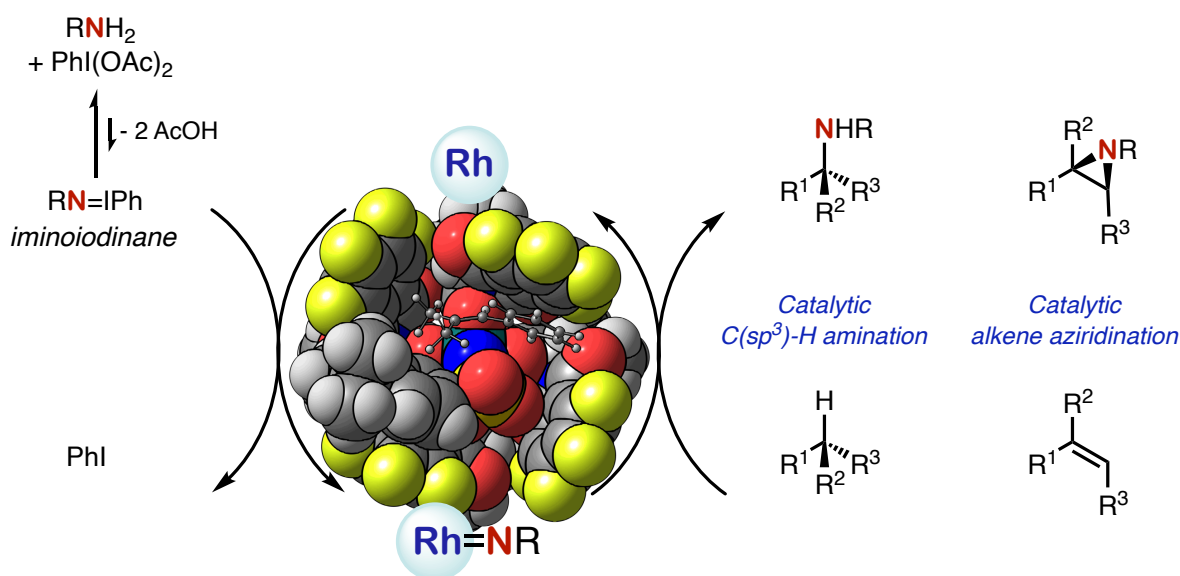
Catalyst- and Reagent-Controlled Selective Nitrene Additions

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The importance of nitrogen in nature, life sciences, and asymmetric catalysis has translated into the development of a wide range of C-N bond forming reactions.^[1] Among these methods, the search for catalytic nitrene additions led to the discovery of efficient transformations for the direct functionalization of C(sp³)-H bonds or the aziridination of alkenes. Particularly, synthetically useful methods were reported through the combination of hypervalent iodine chemistry and dirhodium(II) catalysis.^[2]

Despite many achievements, the questions of enantioselectivity and site-selectivity remain to be solved in catalytic intermolecular nitrene additions. In this lecture, we will give an overview of our latest investigations aimed to address these issues with the design of new rhodium-bound nitrene species. These led to the development of catalyst- and reagent-controlled selective C-N bond forming reactions.^[3]



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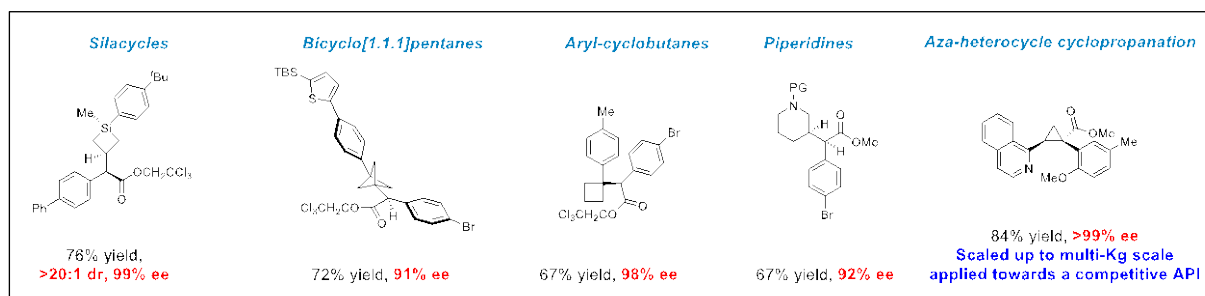
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Pharmaceutical Applications of Rhodium Carbene Chemistry

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Transient donor/acceptor carbenes are capable of undergoing a wide range of selective transformations such as cyclopropanation, cyclopropenation, C-H functionalization and various ylide transformations. We have enhanced the effectiveness of this chemistry by designing a collection of chiral catalysts that control the outcome of the site selectivity, diastereoselectivity and enantioselectivity of the reactions. We have conducted extensive studies in recent years to increase the industrial practicality of this chemistry. We have developed a safe diazo transfer reagent, three methods for generating the diazo compounds in flow, methods to increase compatibility with heterocycles, and procedures for rhodium catalysis using extremely low catalyst loading (0.001 mol % or below). This presentation will describe the practical advances of this chemistry and its application to the synthesis of chiral pharmaceutically relevant scaffolds and as an enabling process in a drug discovery program.



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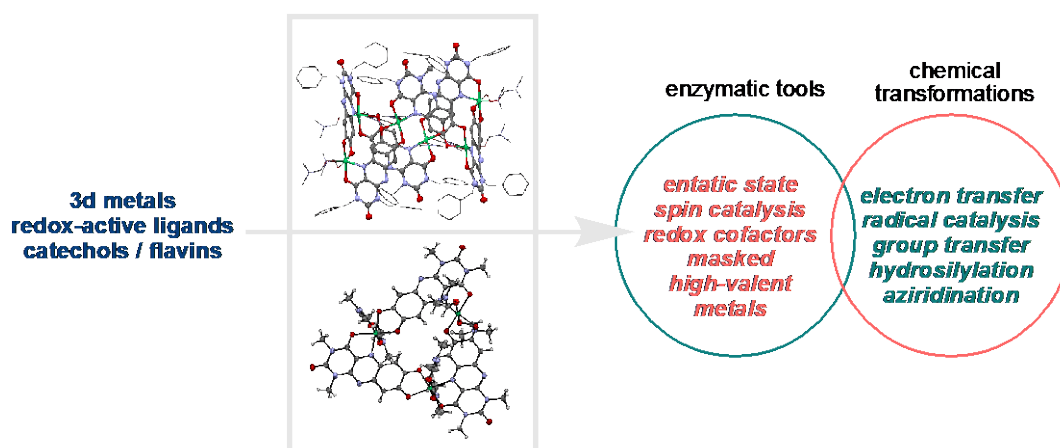
Interfacing redox catalysis with the metalloenzymatic reactivity toolbox

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The exquisite efficiency of biological systems relies on the use of reactivity-enhancing tools to perform chemical reactions with unrivalled efficiency.¹ Among these tools, redox cofactors present near metalloenzymatic active sites provide electron storage and release to assist the neighboring metal center in performing the reactions.

Emulating such systems, the development of catalysts bearing redox-active ligands is a blossoming research field.² Our contribution in this area has dealt with the transfer of CF₃ groups³ and the stabilization of masked high-valent metallic oxidation states.⁴ We will present our results on the transfer of nitrene and carbene moieties by redox-active copper complexes bearing iminosemiquinone ligands, and focus on our efforts to cross-fertilize the field of bioinspired catalysis with redox-active ligands with other bioinspired reactivity-enhancing strategies such as spin catalysis,⁵ entatic state reactivity⁶ and new ligand design.⁷



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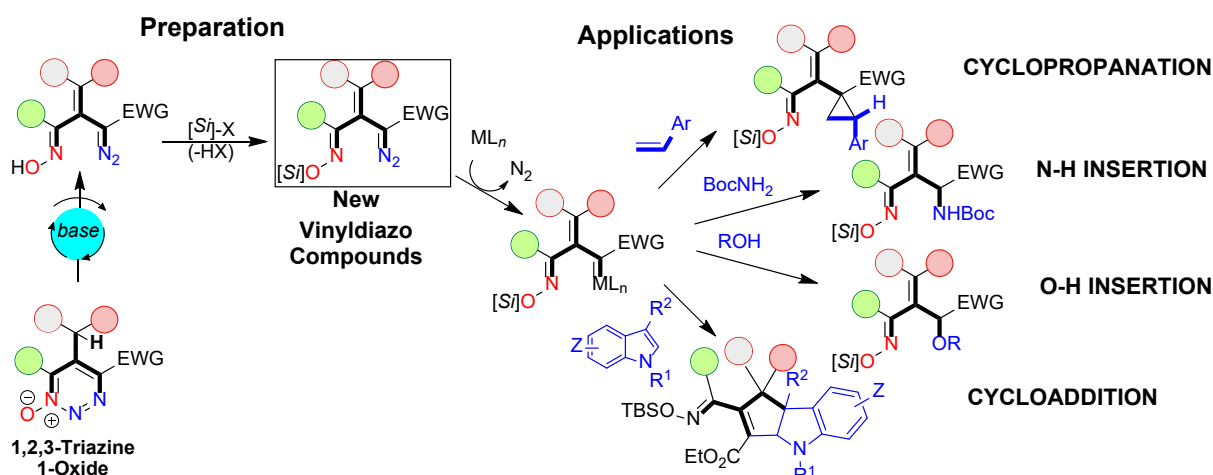
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Expanded Access to Vinyldiazo Compounds from 1,2,3-Triazine 1-Oxides and Their Enantioselective Metal Carbene Applications

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The catalytic use of metal carbenes for addition, insertion, and cycloaddition reactions is dependent on their carbene precursor. The limited methods available for the preparation of diazo esters, which are the most common carbene precursors, restricts their ability to impart structural diversity in metal carbene reactions. We have discovered a new methodology for the preparation of diverse vinyldiazoacetate esters and report their effective uses in highly enantiocontrolled cyclopropanation, N-H insertion, O-H insertion, and [3+2]-cycloaddition reactions. 1,2,3-Triazine 1-oxides [1] with a sp^3 -C-H bond at the 5-position undergo base-catalyzed Dimroth-type rearrangement to form oximido-vinyldiazoacetates in high yields at or below room temperature. These diverse diazo compounds undergo catalytic metal carbene transformations to produce oximidovinylcyclopropanes, α -oximidovinyl- α -amino acids and α -hydroxy acids, as well as tricyclic indole derivatives in high yields and enantioselectivities. The new access to vinyldiazo compounds has applicability to a vast array of metal carbene transformations with greatly expanded structural versatility.



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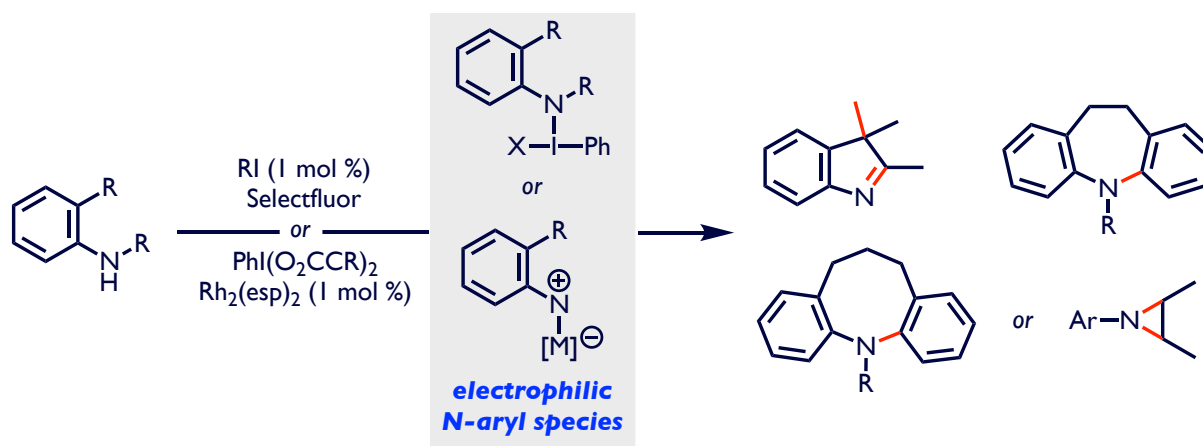
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Non-Activated Anilines as *N*-Atom Precursors in Aziridination and C–H Bond Amination Reactions

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Our research program is centered on the the development of new methods to construct *N*-heterocycles by leveraging the reactivity embedded in aryl amines or nitroarenes. Our recent efforts have shown that electrophilic divalent *N*-aryl nitrogen reactive species can be accessed from aryl amines using an iodine(III) oxidant to synthesize 3*H*-indoles, dibenzazepines, or dibenzazocines. Intermolecular *N*-atom transfer can be triggered from aryl- or heteroaryl amines using the combination of a stoichiometric iodine(III) oxidant and a Rh₂(II)-carboxylate catalyst to enable site-selective, chemoselective, and diastereoselective aziridination of di-, tri-, or tetrasubstituted olefins.



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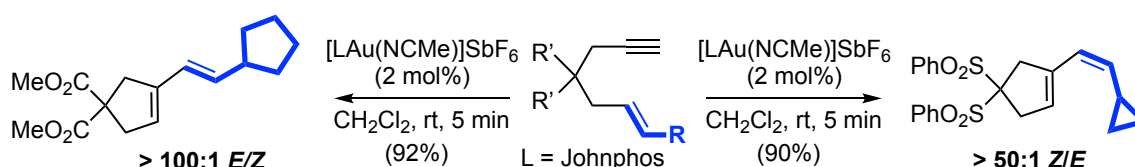
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On the Structure of Key Gold(I) Catalytic Intermediates

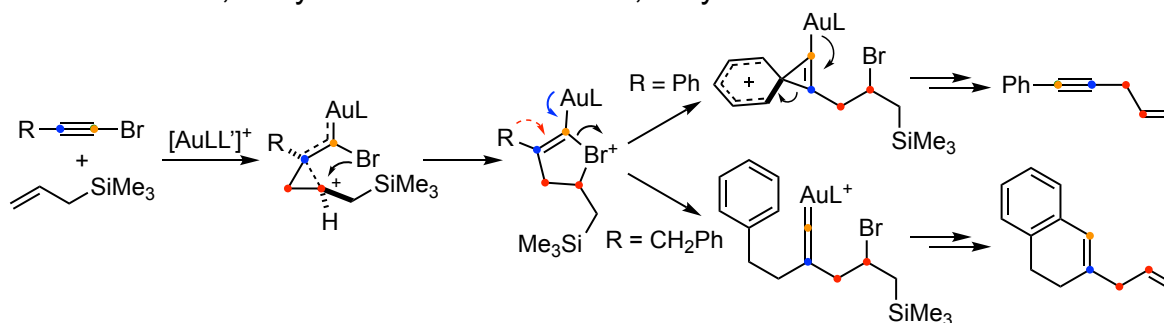
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Gold(I) carbenes have been proposed as key intermediates in cycloisomerizations of 1,n-enynes and in many other gold(I) catalyzed transformations.^[1] We described examples of skeletal rearrangement of 1,6-enynes leading to the selective formation *E*- or *Z*-configured 1,3-dienes as a function of the alkene substituent.² Selective formation of less stable *Z*-configured 1,3-dienes has also been observed in the gold(I)-catalyzed metathesis-type reaction of alkenes with acetylene.³



On the other hand, we have also reported the formation of 1,4-enynes in a formal cross-coupling reaction by gold(I)-catalyzed reaction of bromoalkynes with allylsilanes.⁴ Our mechanistic studies suggested the involvement of gold(I) vinylidenes or vinylidenephonium gold(I) cations depending on the substituent on the bromoalkyne. In the case of bromo arylalkynes, the vinylidenephonium gold(I) cations lead to 1,4-enynes via a remarkable 1,2-aryl shift.



We have now reexamined the surprising formation of *Z*-configured 1,3-dienes to clarify the reactivity of the cyclopropyl gold(I) carbenes. In addition, we have studied the formation of gold(I) vinylidenes under stoichiometric conditions and their evolution to form (η^2 -alkyne)gold(I) complexes. Results of these two experimental and computational studies will be presented.

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Chemomimetic Biocatalysis: Selective C(sp³)-H Functionalization via Metalloenzyme-Catalyzed Carbene and Nitrene Transfer Reactions

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Expanding the reaction scope of biological catalysts beyond the realm of enzymatic transformations occurring in nature can offer new opportunities for leveraging biocatalysis for asymmetric synthesis. Our group has been engaged in the design, investigation, and application of engineered metalloenzymes for enabling the construction of new carbon-carbon and carbon-nitrogen bonds via ‘abiological’ enzyme-catalyzed carbene and nitrene transfer reactions. In this contribution, we will present recent progress made by our group toward the development of efficient and stereoselective metalloprotein catalysts for the asymmetric synthesis and C–H functionalization of N-containing heterocycles. These methodologies provide an attractive avenue for the chemoenzymatic synthesis and late-stage C–H functionalization of pharmaceuticals and other biologically active molecules.

Photochemical transformations of diazo compounds

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The development of new, sustainable reactions and protocols is essential to meet the growing demands of every branch of organic chemistry for greener synthetic methods. In this context, the use of visible light as the only source of energy is very attractive.

Diazo compounds are valuable reagents in organic synthesis and their transformations carried out in a sustainable manner are of great interest. High reactivity and easy availability make them suitable for solar-powered transformations. Indeed, their photochemical transformations under visible light irradiation have recently emerged as a valuable alternative to transition metal catalysis.[1] Though UV-light-induced carbene generation has been well known, only recently it became clear that these reactive intermediates can be formed under blue-light irradiation via direct photolysis.² *We have shown that in the presence of photocatalysts diazo compounds or its surrogates can be activated either via energy or electron transfer generating carbenes or radicals.*[3-7]

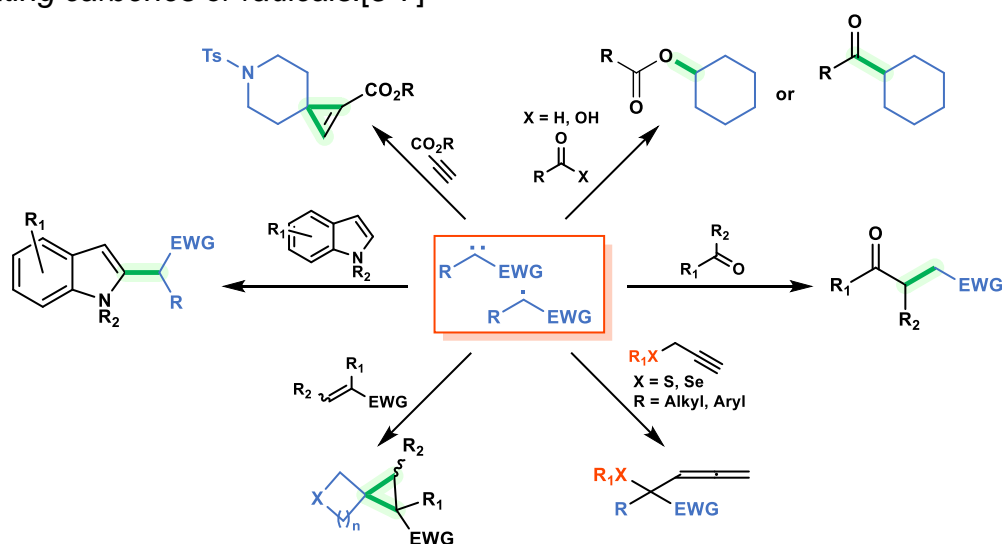


Figure. Photochemical transformations of carbene surrogates developed by Gryko group

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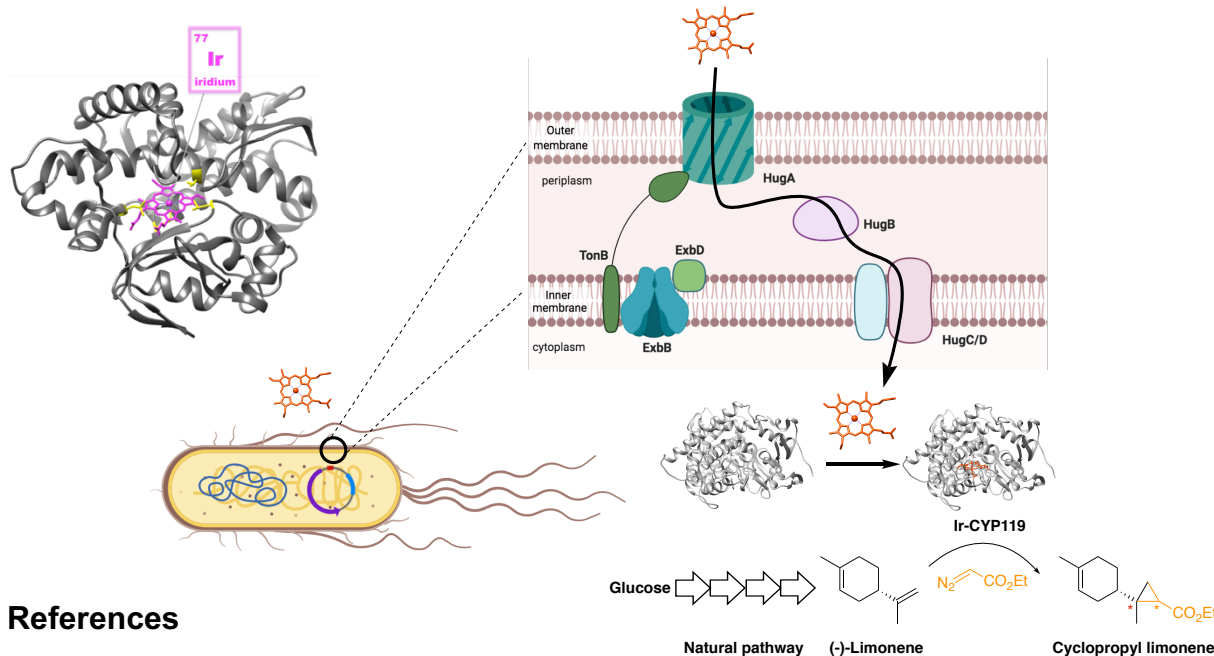
Selective Abiotic Carbene Transfers Catalyzed Natural and Unnatural Metalloenzymes *in vitro* and *in vivo*

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The introduction of functional groups at the positions of typically unreactive C-H bonds site-selectively and the stereo- and regio-selective functionalization of unconjugated C=C bonds have been longstanding challenges in catalysis. To this end, our group has been motivated by the limits of small-molecule catalysts for such reactions to begin to investigate artificial metalloenzymes. These artificial metalloenzymes contain synthetic cofactors possessing abiotic metal centers that catalyze unnatural reactions with control over selectivity resulting from the protein environment. In the best-case scenario such reactions could occur within the cells of *E. coli* or other microorganisms and in the long-term to occur as part of an unnatural biosynthetic pathway to produce unnatural products by fermentation.

This talk will include results on new transformations, new mechanisms, new reactive intermediates, and new methods for *in vivo* assembly of artificial metalloenzymes. This combination of results has enabled us to combine an unnatural carbene-transfer reaction catalyzed by natural and artificial metalloenzymes with the biosynthesis of diazo compounds and natural reactions of a heterologous biosynthetic pathway to create engineered microorganisms that produce unnatural products by artificial biosynthesis encompassing organometallic chemistry.¹



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Gold Catalysis: Carbene Intermediates

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The first publications demonstrating a high increase in molecular complexity in gold-catalyzed organic reactions,[1,2] triggered the development of homogeneous gold catalysis to a frequently used tool in different sectors of organic synthesis, e.g. for total synthesis or materials science and related fields.[3,4] The reactivity patterns in the field are fascinating, reaching from pi-coordination[5] for the activation of nucleophilic additions to “gold only” photoreactions[6,7] and even radical chains combined with gold-based catalytic cycles.[8]

The crucial influence of reactive intermediates like gold vinylidene intermediates[9,10] or other functionalized gold carbene/nitrene intermediates[11] on the outcome of gold-catalyzed reactions will be presented. This includes the methodology development, mechanistic studies and synthetic applications.

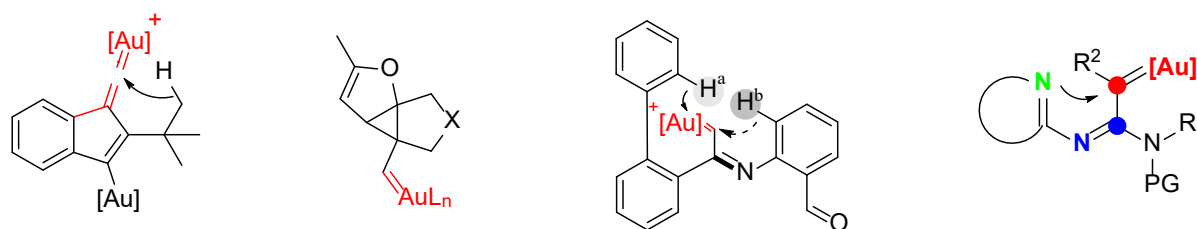


Figure 1. Gold Carbene Intermediates, from left to right: Vinylidene, carbene, alpha-imino carbene, functionalized alpha imino carbene (the latter two via nitrene transfer reagents)

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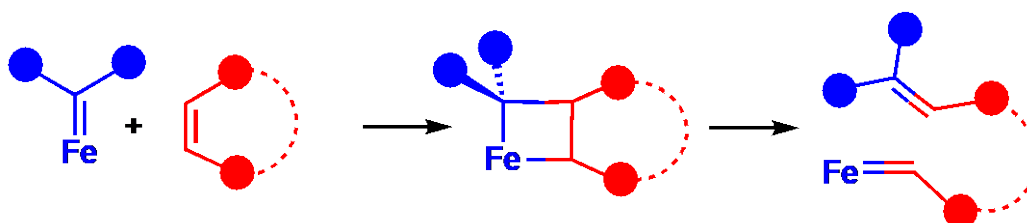
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Olefin Metathesis with Iron Carbenes

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Ruthenium carbenes are ubiquitous in olefin metathesis reactions. Iron based catalysts for the same reactions are of great interest because of iron's natural abundance and non-toxicity compared to ruthenium. Despite extensive efforts into this endeavor, iron carbenes have not displayed similar reactivity to their group congener, owing to their tendency to undergo reductive elimination from metallacycle intermediates, instead of cycloreversion. We will discuss the reactions of a discrete and stable iron carbene toward a variety of olefins, revealing unprecedented formation of metathesis products. Reaction with a strained olefin results in the isolation of a ring-opened iron alkylidene, reminiscent of proposed intermediates in ruthenium catalyzed reactions. Furthermore, this alkylidene can undergo ring closing with the formation of the corresponding olefin. This work reveals fundamental insight into development of iron catalysts for olefin metathesis.



Formation and reactions of iron imide (and carbene) complexes supported by macrocyclic tetra-N-heterocyclic carbene ligands

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The catalytic synthesis of aziridines from alkenes and an oxidant (a C₂+N₁ reaction) is a critical underdeveloped reaction in organometallic chemistry.¹ Not only are these small rings featured in natural products and pharmaceuticals, but they are widely employed as intermediates in synthesis due to their ring strain. Since metal imide species are often described as intermediates for this reaction, it is critical to understand both their formation and subsequent reactivity.

Macrocyclic tetra-NHC ligands are effective auxiliary ligands to support high oxidation state intermediates on late transition metals such as iron. NHC's strong sigma donor strength promotes high oxidation state intermediates (e.g. iron(IV)) and the NHCs are generally resistant to oxidative degradation. As such, our group has been able to stabilize low spin and intermediate spin iron(IV) imides² and alkylidene³ complexes on iron (Figure 1). In addition to the aforementioned complexes, we have also prepared complexes that show competing reactions within the catalytic aziridination cycle starting from iron imides. The synthesis, spectroscopy, and structural characterization of these complexes as well as relevant computation results will be presented.

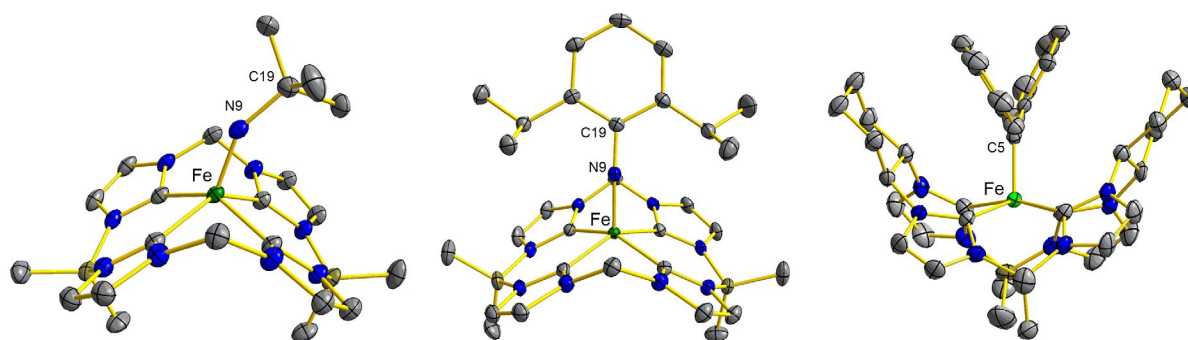


Figure 1. X-ray crystal structures of iron imides (left and center) and iron alkylidene (right) supported by macrocyclic tetra-NHCs.^{2,3} Green, blue, gray, and olive ellipsoids (50% probability) represent Fe, N, C, and B atoms, respectively.

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From Ylides to Carbenes and Phosphines, and their Application in Catalysis

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Phosphonium ylides are most prominently known for their use in olefination reactions such as the Wittig reaction.^[1] Their α -metalated congeners, the so called yldiides, have long remained elusive species and their applications have therefore remained scarce, due to their high reactivity, difficult handling, and rather challenging synthesis.^{[2][3]} However, recent reports of easily accessible systems have opened up new possibilities for their use as ligands and substituents for a variety of reactive compounds containing main group elements and metals.^[4]

Our group has investigated a variety of different applications of ylides and yldiides, ranging from stabilizing main group compounds, to the formation of stable ketenyl moieties and also the formation of strongly donating phosphine ligands for transition metal catalysis, namely the ylide-substituted phosphines (YPhos).^[5] These ligands have showcased remarkable activity in catalytic transformations on par with current state of the art systems.

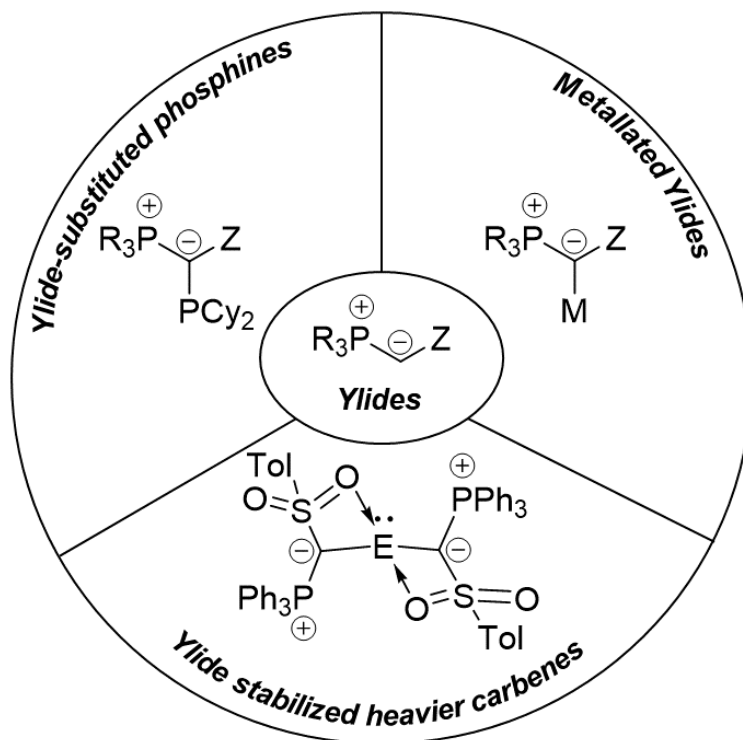


Figure 1. Application of phosphonium-ylides by our group.

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Lighting up carbene and nitrene transfer reactions

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Carbenes and nitrenes are versatile reactive intermediates that find widespread application in organic synthesis and drug discovery.^[1] Their high reactivity, however, often necessitates the use of metal complexes for stabilization of such species. Only recently, the photolysis of diazoalkanes, which are usually intensely colored, using visible light attracted the interest of synthetic chemistry and many groups contributed to broaden applications of photochemical, catalyst-free carbene transfer reactions.^[2,3] These reactions most typically proceed via a singlet carbene intermediate. In the presence of a photocatalyst, however, new reaction pathways via redox chemistry or energy transfer can be opened-up.^[2c]

In this context, we recently reported on the photocatalytic generation of triplet carbenes from diazoalkanes. This approach opens distinct pathways and does not react along a classic singlet carbene reaction pathways, instead, e.g., *gem*-difluorolefination reactions can be accessed in the reaction with trifluoromethylated olefins or C-H functionalization with heterocycles.^[4] In a related fashion, we could show that iodinanones can be used as simple, but versatile reagents, to access a nitrene or a nitrene radical anion under photochemical or photocatalytic conditions, respectively. These intermediates show a distinct reactivity in the reaction with olefins and give either the product of C-H functionalization or aziridination.^[5]

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Elucidating the Electronic Structure of Cobalt(III) Nitrene Radical Complexes

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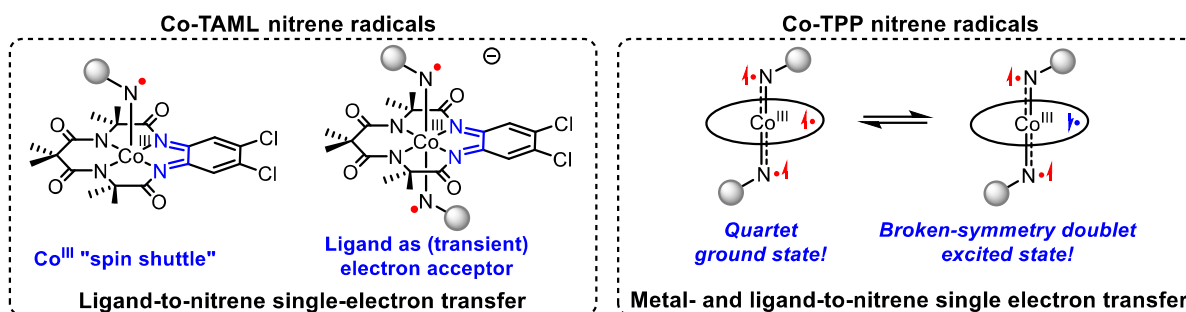
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Metal-nitrene radical $[M(^{\bullet}NR)]$ complexes are excellent catalytic intermediates for the direct transfer of an *N*-group to C–H bonds, alkenes or heteroatoms, and can be formed via usage of a redox-active metal, ligand and/or substrate. To control, predict, and steer their reactivity, a thorough understanding of the (electronic) structure is of pivotal importance. However, a correct description of their often complicated (open-shell electronic) structure relies on a combination of nontrivial spectroscopic and computational tools.

We investigated the electronic structure of cobalt-TPP (TPP = tetraphenylporphyrin) and cobalt-TAML (TAML = Tetra-Amido Macrocyclic Ligand) nitrene complexes with XRD, XAS, EPR, μ_{eff} , HRMS, UV-Vis, DFT and NEVPT2-CASSCF methods. Interestingly, we found that the electronic ground state of $[\text{Co}^{\text{III}}(\text{TPP}^{\bullet+})(^{\bullet}NR)_2]$ is more intricate than previously assumed, and has a quartet ($S = 3/2$) spin ground state, with a thermally accessible multireference and multideterminant “broken-symmetry” doublet spin excited state.^[1]

We also describe how the oxidation state of the TAML dictates whether mono- or bis-nitrene complexes are formed onto a Co^{III} center.^[2] These nitrene radicals are reactive under mild (and even aerobic) conditions in catalytic chemoselective aziridination^[3] and sulfimidation reactions.^[4] Close inspection of their electronic structure reveals an interesting interplay between (partial) electron and spin transfer processes during *electronically asynchronous transition states* that give rise to *N*-group transfer.



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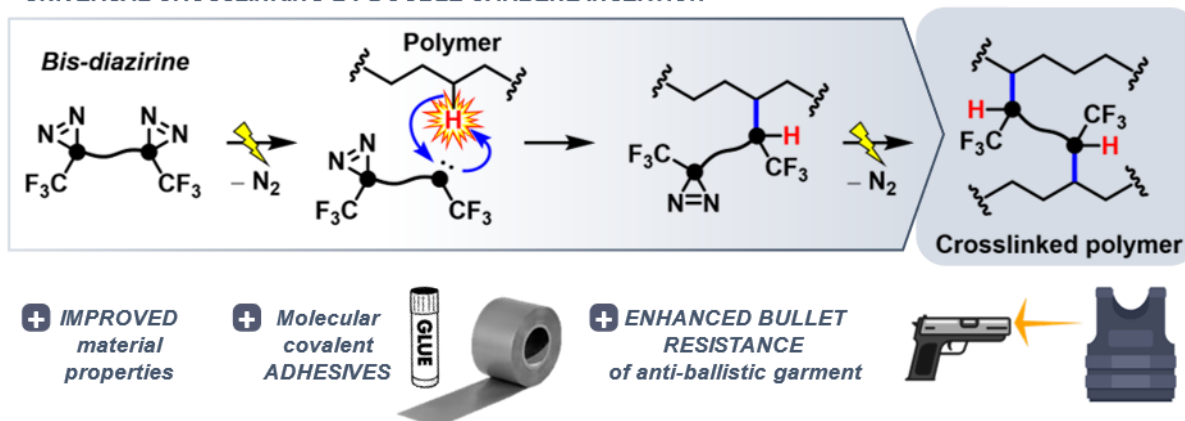
Diazirine-born carbenes for (near-)universal crosslinking

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While polymer cross-linking is a well-studied field, it remains challenging to create 3-dimensional networks of low-functionality macromolecules without the use of co-polymers and/or the introduction of orthogonal reactive groups. Most methods employ irradiation by gamma rays or embedded peroxides to generate highly reactive radicals in situ, allowing only a limited control over the degree and type of crosslink. To tackle these difficulties, we used bis-diazirines as a new class of additives whose mild and controllable activation enables the crosslinking of almost any organic polymer, even those lacking reactive functional groups, through C–H, O–H or N–H insertions of free carbenes. After demonstrating the feasibility of our approach in a simple model system,^[1] we used a few optimized molecules as broadly applicable crosslinkers in several relevant applications.

UNIVERSAL CROSSLINKING BY DOUBLE CARBENE INSERTION



First, bis-diazirine crosslinkers were introduced as curing agents into bulk, off-the-shelf polymeric materials and elicited chain elongation and/or thermosetting behavior, thereby demonstrating efficient crosslinking.^[1] Second, they were efficiently used as adhesives for polyethylene and/or polypropylene, two materials of low surface energy and for which adhesion is typically challenging.^[1-2] Third, treatment of a fabric made of ultra-high-molecular-weight polyethylene strands led to a significant increase in strength against tearing and perforation, which we translated into an improved resistance of bulletproof jackets.^[1,3] The fine-tuning of linker flexibility, physico-chemical properties of the crosslinkers, as well as carbene electronics proved essential to success in each application, emphasizing the importance and relevance of controlling the molecular structure of additives in the upgrading of organic materials.

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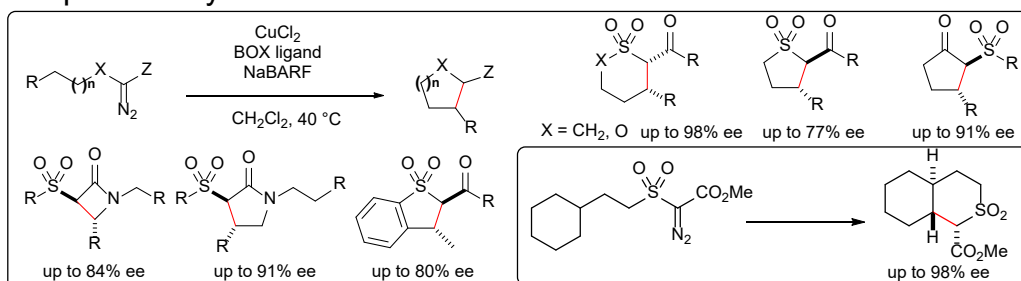
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Synthetic and stereochemical aspects of intramolecular C–H insertions of α -diazocarbonyl compounds

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Metal-catalysed transformations of α -diazocarbonyl compounds have a proven track record in organic synthesis, allowing the rapid build-up of molecular complexity, often in a highly chemo-, regio-, and stereoselective manner, under mild conditions.¹ Intramolecular C–H insertion of α -diazosulfones and related compounds in the presence of copper or rhodium catalysts lead efficiently to cyclopentanones, sulfolanones, thiopyranones, sultones, and lactams.² The selectivity patterns seen in the copper- and rhodium-catalyzed reactions are often complementary.



Despite the versatility of metal-carbene chemistry at a laboratory scale, there are challenges in extending this to large scale synthesis for safety reasons. Continuous flow processing can potentially reduce the barrier to use of this chemistry at large scale by eliminating the need to isolate and handle high-energy species. Methods for *in situ* generation of sulfonyl azides coupled with their direct application to diazo transfer, have been developed, and successfully telescoped with subsequent carbene reactions.³

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DFT modelling of catalytic nitrene transfers by high-valent Fe active species: mechanistic insights and rationalization

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Computational approaches rooted in Density Functional Theory (DFT) are widely exploited for the design and optimization of molecular catalysts.[1] Theoretical modelling offers the opportunity to grasp mechanistic details and information on the active species involved in reaction processes. This is especially true when the catalytic reaction is too fast to isolate transient species. Such information is yet essential to rationalize the catalytic efficiency and thus to provide a support for further optimizations of catalysts.

We will illustrate these aspects with some issues around nitrene transfer reactions catalyzed by high-valent Fe species (see fig. 1).

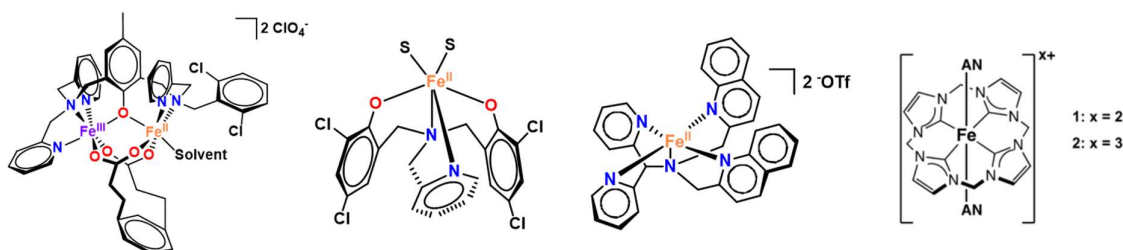


Figure 1. Schematic view of some of the Fe catalysts investigated in DFT studies of nitrene transfers.

Indeed their high efficiency preclude any isolation of intermediates during reaction. Their identity and mode of action could be disclosed only by DFT modelling supported by tricky experimental probes such as Hammet plots, labellings and monitored spectroscopies. Such combined approaches allowed to identify the actual active species,[2] rationalize the catalytic mechanism[3] and explain some particular behaviours due to side reactions or generation of the active species.[3, 4, 5]

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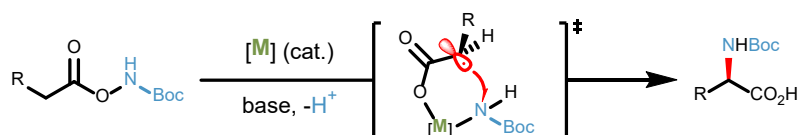
Nitrene-Mediated C–H Functionalization: New Directions

Eric Meggers

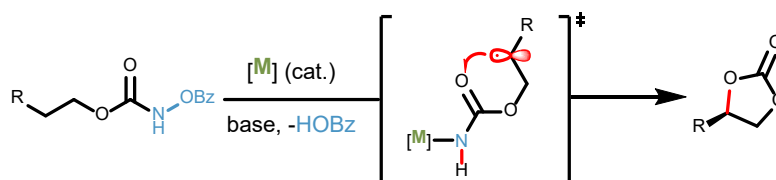
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Over the past ten years, our laboratory has advanced the design and application of a novel class of powerful asymmetric catalysts in which the required overall chirality originates solely from a stereogenic metal center.^[1,2] Recently, we introduced chiral-at-ruthenium catalysts for nitrene-mediated C–H functionalizations.^[3] Intermediate ruthenium nitrene species are generated from organic azides and hydroxylamine derivatives followed by ring-closing C–H aminations to afford chiral cyclic pyrrolidines, ureas, or carbamates in high yields and with excellent enantioselectivities.^[3–8] In addition, we discovered novel reaction patterns and reactivities of intermediate transition metal nitrenes. This includes intramolecular nitrene-mediated C(sp³)–H oxygenations,^[9,10] which allow for the construction of chiral cyclic carbonates and lactones via nitrene chemistry, a ruthenium or iron-catalyzed novel 1,3-migratory nitrene C(sp³)–H insertion,^[11] and a one-step conversion of carboxylic acids into α -amino acids by directed nitrene-mediated C–H insertion.^[12]

■ Nitrene-mediated C–H amination towards acyclic products



■ Nitrene-mediated C–H oxygenation



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Palladium-, Gold- and Phosphonio Nitrenes

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We reported the isolation of palladium terminal imido complexes with aliphatic, aromatic, as well as sulfonyl substituents.^[1,2] The reactivity with nucleophiles such as phosphines and olefins as well as Hydrogen-Atom-Abstraction reactivity suggest that the nitrene character is weak for the latter, yet substantial if not strong for the former. In this talk, I will present on their electronic structure based on – among others – ¹⁵N CP-MAS spectra of isotopically enriched congeners, XAS measurements, and quantum chemical calculations.^[3] As such, I will elaborate why we tentatively understood some of these compounds as singlet-nitrene complexes, which will put into perspective with a high-valent cobalt terminal imido complex.^[4] Further, I will report on our progress with terminal gold imido complexes.^[5] If time allows, I will also present on an isolable bis-(phosphonionitrene), which activates small molecules and engages in Hydrogen-Atom-Abstraction as well.

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Diazoalkanes and Diazirines as Valuable Synthetic Intermediates for Si–H Insertions and Cycloadditions

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Recent synthetic methods for the synthesis of diazoalkanes will be first disclosed [1]. The insertion reaction of diazo compounds into X–H bonds will be presented using copper and iron catalysis. A C₂-symmetric copper(I) diimine complex enables the asymmetric insertion reaction of 1-aryl-2,2,2-trifluoro-1-diazoethanes to give enantioenriched (1-aryl-2,2,2-trifluoroethyl)silanes with enantioselectivities *up to* 96% ee [2]. An efficient synthesis of 3-trifluoromethyl-3-aryl-cyclopropenes *via* the cyclopropanation reaction of alkynes with photolytically-generated carbenes from diazirines will be disclosed. This reaction is performed in continuous flow using readily available LEDs in mild reaction conditions. This new and efficient method describes the synthesis of 3-trifluoromethyl-3-aryl-cyclopropenes with yields *up to* 97%, achieved in continuous flow with 5 min residence time. The cyclopropanation reaction of alkenes with photolytically-generated halocarbenes from halodiazirines is also presented as an effective way to prepare 3-halo-3-aryl-cyclopropanes in continuous flow [3].

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Catalytic and stoichiometric carbene and nitrene transfer reactions

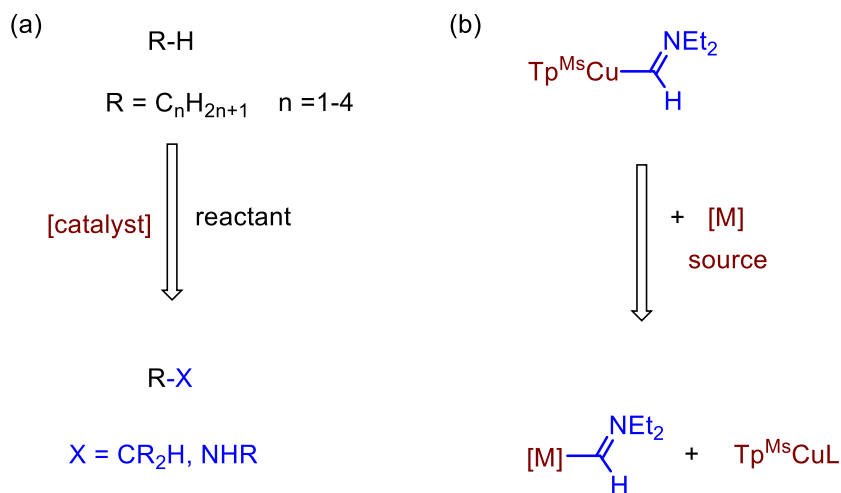
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In the context of the functionalization of C-H bonds by processes involving the transfer of carbene or nitrene units, a plethora of substrates have been employed.[1] Among them, examples involving alkanes and, more specifically, the gaseous alkanes C1-C4, are yet reduced. Our group has provided several examples of the functionalization of methane and light alkanes leading to products derived from the formation of C-C and C-N bonds (Scheme, a).[2] The latest results involving the functionalization of such substrates involving carbene and nitrene units will be presented.

In a second approach, we have recently reported the formation of a stable copper-monosubstituted carbene complex upon a decarbonylation process of a diazoacetamide.[3] We have found that this complex is an excellent transmetallating reagent for the aminocarbene ligand, that can be transferred to an array of metal centers (scheme, b). An account of this stoichiometric carbene transfer process will be also presented.



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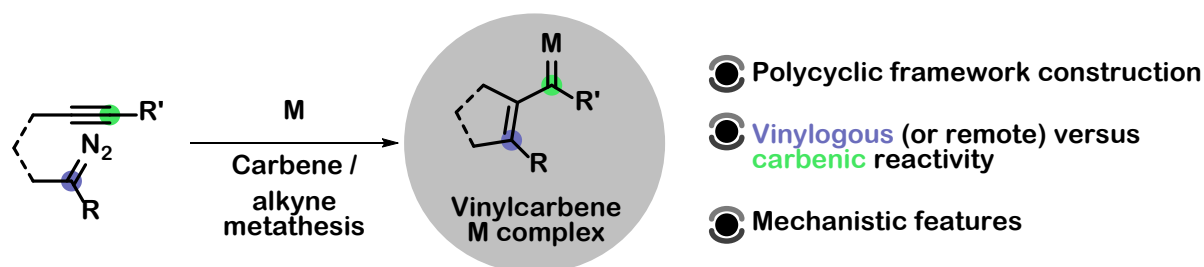
Reactivity of *in situ* generated vinylcarbene silver complexes

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Vinylcarbene metal complexes, a fascinating subclass of metal carbene complexes, are extremely powerful reagents in cycloaddition reactions. Furthermore, they have the particularity of displaying electrophilic reactivity at the vinylogous (or remote) position in addition to the typical carbene position, making them extremely versatile reaction intermediates.

Carbene/alkyne metathesis (CAM)^[1] is a simple method for the *in situ* preparation of vinylcarbene metal complexes. In this transformation, a metal carbene complex reacts with an alkyne transferring the carbene character to one of the alkyne's carbon atoms thus generating a vinylcarbene metal complex. Construction of polycyclic frameworks can be efficiently achieved via CAM cascades terminated by various carbene reactions.^[2]



Scheme 1

In this communication, we will present our most recent efforts towards the study of the reactivity of vinylcarbene silver complexes towards the selective vinylogous C-H bond insertion,^[3] and the mechanistic intricacies of vinylcarbene silver complex preparation and its subsequent reactivity.

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Copper Nitrene Cores in Aziridination and Amination reactions

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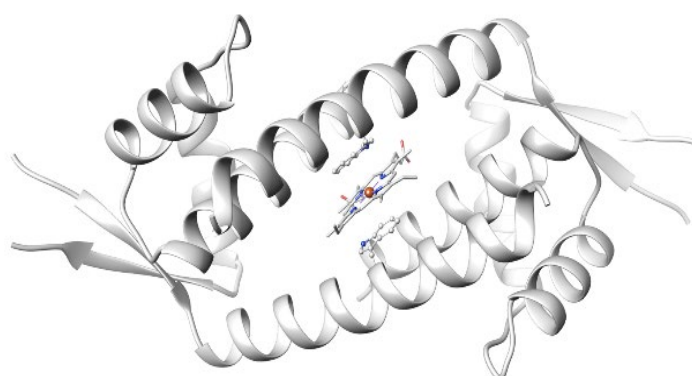
Chemists had previously suggested that certain copper-catalyzed reactions might involve high-valent, terminal copper–nitrene units in aziridination and amination reactions, but these species had remained elusive for decades ensuring that the mechanism of such reactions remained hidden. In this talk we summarize some of our efforts to trap one such intermediate, a copper–tosylnitrene, in presence of different Lewis acids. The research suggests that Cu(III)NTs – an unusual oxidation state for the metal two levels above copper(I) – are the core component of the copper-based oxidation catalysis used in aziridination and amination reactions. Two-state reactivity, in which a singlet ground state and a nearby triplet excited-state both contribute, provides a useful model for interpreting reactivity trends of the high-valent copper intermediates.

Artificial Metalloenzymes for Catalysis of Carbene Reactions

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The catalytic efficiency and high selectivities achieved by natural metalloenzymes are a source of inspiration for the design of novel bio inspired catalysts. A powerful approach for creating artificial metalloenzymes involves incorporating an biological metal cofactor into a protein or other biomolecular scaffold. Here we will present two classes of artificial metalloenzymes that we have developed for catalysis of carbene transfer reactions. The first class is based on DNA, with bound metal complexes.[1][2] The second is based on the transcription factor LmrR (Lactococcal multidrug resistance Regulator).[3] LmrR was selected as the protein scaffold because it contains an unusual large hydrophobic pocket on the dimer interface, which can be used both to bind catalytic active metal complexes, such as hemin, to create a novel active site, or a new substrate binding pocket.[4] A comparison of the different designs will be made and some general lessons about rate acceleration in artificial metalloenzyme catalyzed carbene transfer reactions will be presented.[5]



Structure of an LmrR-based artificial carbene transferase.

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Nitrene intermediates

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Direct C-H to C-N transformation is usually accomplished by reacting organic substrates with nitrene intermediates. Unstabilized nitrene intermediates can be generated photochemically. Metal-nitrene intermediates can be generated from various precursors thermally or photochemically. The common feature is that they are highly reactive and often difficult to characterize. We have developed methods based on mass spectrometry that allow us to investigate these reactive intermediates' formation, structure, and reactivity.^[1,2]

In the presentation, I will show our findings about a series of different nitrene intermediates spanning from highly reactive sulfonyl nitrenes^[3] via cobalt and iron imido complexes^[4] to relatively stable copper-nitrene complexes. I will present a portfolio of methods that allow the characterization of these species in the gas phase and the bridging of the results to their solution reactivity.

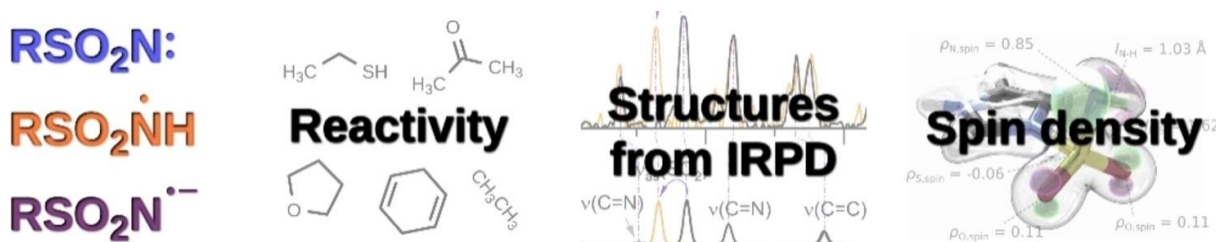


Figure 1. A combined experimental and computational approach to study reactive intermediates' formation, structure, and reactivity.

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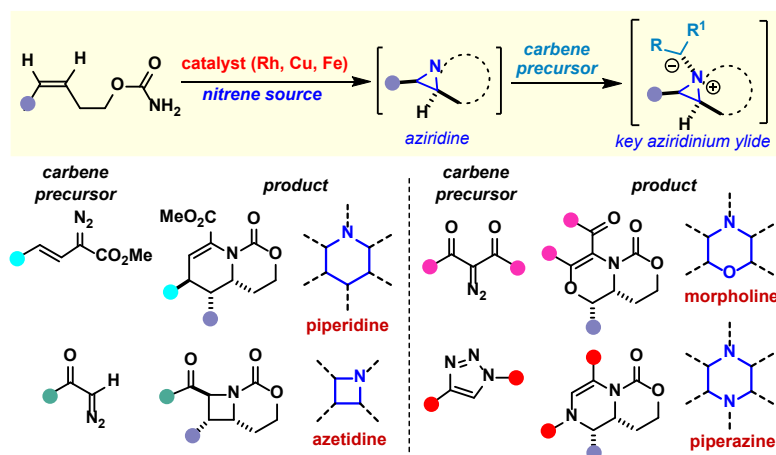
Merging nitrene and carbene transfer for the syntheses of complex *N*-heterocycles

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Stereochemically complex molecular space is underrepresented in typical compound screening libraries. Recently, there has been a resurgence of interest in the exploration of more diverse molecular scaffolds containing multiple sp³ stereocenters. In this context, densely functionalized *N*-heterocycles and aminated carbocycles are particularly attractive targets, as they are prevalent in drugs, natural products, and other biomolecules. A modular and unified platform capable of flexibly transforming readily available precursors into heavily functionalized azetidines, pyrrolidines, piperidines and amine-bearing carbocycles could speed the identification of new amine chemical space with useful bioactivity.

Few productive reactions involving aziridinium ylides as key intermediates have been reported. Our group has developed tandem nitrene/carbene transfer sequences that provide a versatile approach to stereochemically complex 4-7-membered *N*-heterocycles from simple allene and alkene precursors. Aided by computational studies, we have shown that we can manipulate the identity of the substrate, carbene precursor, catalyst, and reaction conditions in a predictable manner to divert the aziridinium ylide along different mechanistic pathways. Asymmetric and visible-light photocatalyzed variants of this tandem nitrene/carbene transfer strategy will also be discussed.



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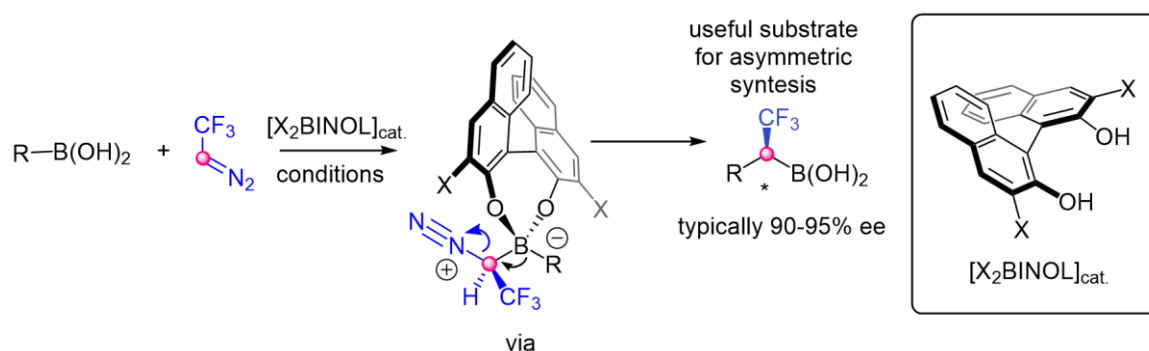
Asymmetric catalysis via carbene insertion into C-B bond

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Asymmetric homologation of alkenes, aryl and alkenyl boronic acid derivatives with trifluoromethyl diazomethane was performed using BINOL derivatives as organocatalysts.^[1] The reaction was suitable for synthesis of α -CF₃ boronic acid derivatives via stereoselective ate complex formation followed by 1,2-borotropic rearrangement.

The enantioenriched α -CF₃ organoboronic acids are very useful synthons in organic synthesis. In particular allylboronic acid derivatives are useful precursors in stereoselective organic synthesis. Allylboration of aldehydes, ketones, indole derivatives and imines proceeds with high level of chirality transfer. In addition Se-catalysed ^[2] sulfenofunctionalization could be performed with high stereoselectivity to obtain chiral SCF₃, SCN and SR compounds. In addition, oxidation and halogenation of organoboron compounds also proceeds with high levels of stereoselectivity.



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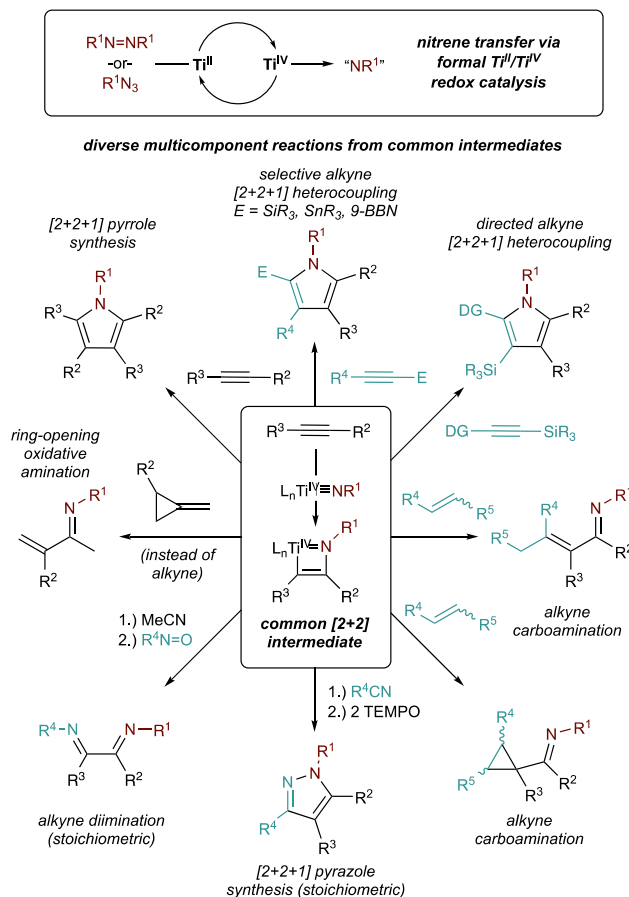
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Strategies for Catalytically Breaking and Making N-N Bonds with Ti

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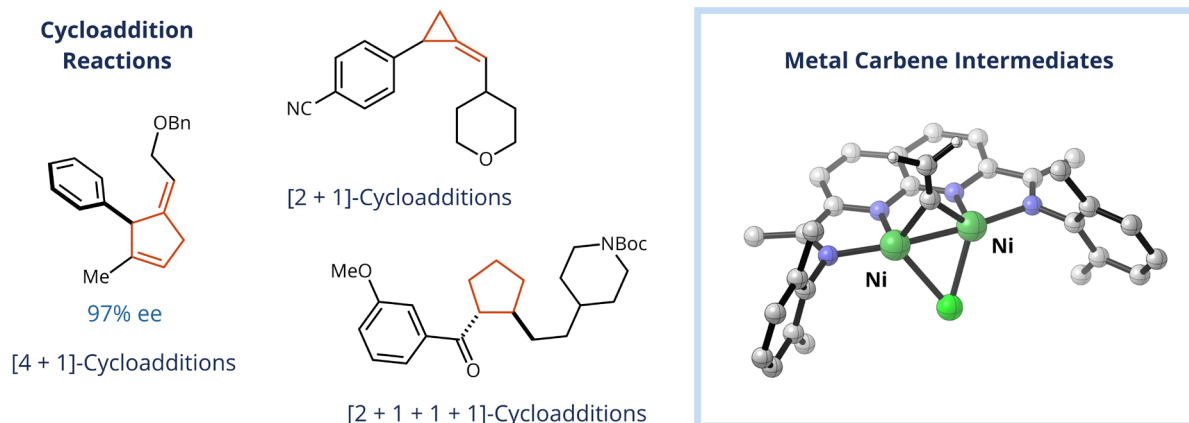
Titanium is an ideal metal for green and sustainable catalysis—it is the 2nd most earth-abundant transition metal, and the byproducts of Ti reactions (typically TiO₂) are nontoxic. Our group has a longstanding interest in developing oxidative nitrene transfer reactions using Ti imidos (L_nTi=NR). In the course of these studies, we have developed a suite of reactions that capitalize on the catalytic cleavage of N-N and N=N bonds. In this talk, our latest synthetic and mechanistic discoveries related to Ti nitrene transfer catalysis and other amination reactions will be discussed, with a specific focus on how we can leverage mechanistic understanding to design new reactions. An emerging theme in this research area is the close relationship of organometallic amination reactions to catalytic inorganic nitrogen fixation reactions (ammonia oxidation, nitrogen reduction), which will be highlighted in a discussion of new examples of Ti-catalyzed N-N bond formation in heterocycle synthesis.



Catalytic Transfer Reactions of Non-Stabilized Carbenes

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Carbenes are versatile reactive intermediates that display orthogonal reactivity to common nucleophilic and electrophilic functional groups. Homogeneously catalyzed carbene transfer reactions were first discovered over 50 years ago, and numerous examples of $[n + 1]$ -cycloaddition reactions have now been developed, often with control over diastereo- and enantioselectivity. Nearly all of these reactions rely on the controlled decomposition of diazoalkane precursors as a central strategy for accessing reactive carbene equivalents.

Despite the utility of diazoalkanes in organic synthesis, they are inherently limited by the need for stabilizing substituents such as aryl or carbonyl groups. In order to develop transfer reactions of non-stabilized carbenes, such as methylene, isopropylidene, and vinylidene, it would be necessary to identify an alternative set of precursors. Our group has shown that nickel and cobalt catalysts can promote reductive $[n + 1]$ -cycloaddition reactions using readily available and indefinitely stable 1,1-dichloroalkanes and 1,1-dichloroalkenes as carbene precursors. In this seminar, I will describe our development of new cycloaddition methods and our current hypotheses about the mechanisms of these reactions.

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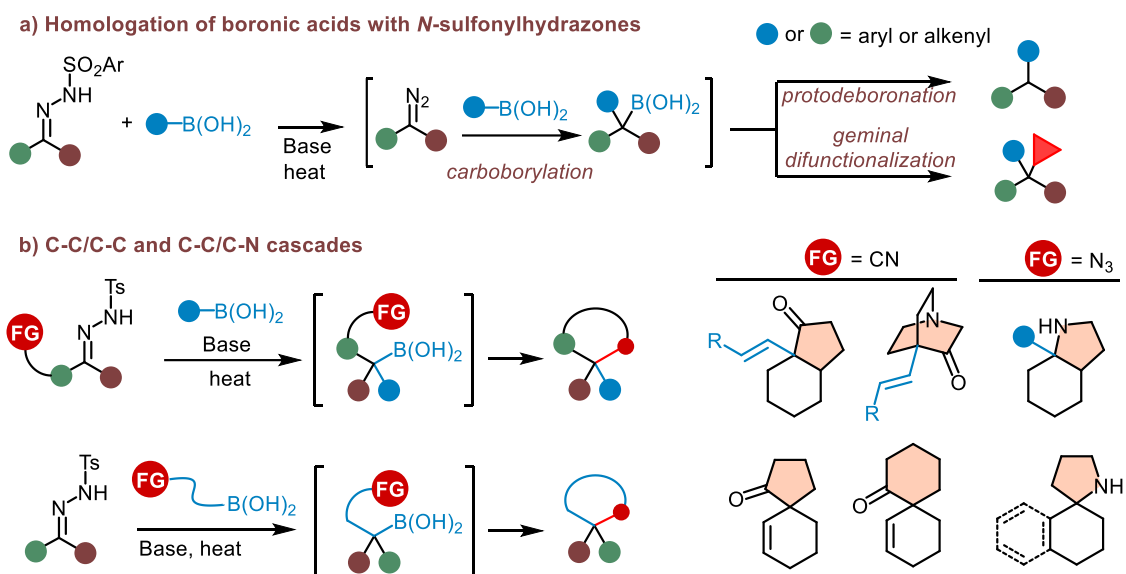
Building Csp³-rich Molecular Complexity by Geminal Difunctionalizations with *N*-Sulfonylhydrazones

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The generation of three-dimensional molecular complexity is currently an area of very active research, oriented to the discovery of new lead structures for medicinal chemistry. In this context, geminal difunctionalizations of carbenes or carbene precursors represent a very attractive opportunity for incorporating Csp³-rich complexity. We have faced this challenge by employing diazoalkanes generated from *N*-sulfonylhydrazones in Pd-catalyzed as well as in transition metal-free reactions. In particular, we have shown that the reaction between boronic acids and *N*-sulfonylhydrazones is a very appropriate transformation towards this goal. In this processes a homologated boronic acid is formed upon carboborylation of the diazoalkene, which may suffer protodeboronation,^[1] or alternatively may be trapped through a subsequent inter^[2] or intramolecular reaction.

Taking advantage of this concept, we have designed several C-C/C-C^[3] and C-C/C-N^[4] bond forming cascades that have allowed for synthesis of a variety of bicyclic and spirocyclic structures. Overall, these methods can be seen as geminal difunctionalizations of carbonyls *via* their sulfonylhydrazones. Indeed, the reactions have been applied to the modification of carbonyls obtained from several natural products and biologically active drugs.



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Iron catalyzed C(sp³)-H Amination

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The development of efficient methods for the formation of carbon–nitrogen (C–N) bonds is one of the most crucial tasks in chemical synthesis. The installment of C–N bonds by direct functionalization of C(sp³)–H bonds is a powerful and atom-efficient transformation for chemical synthesis. Although the direct installation of nitrogen into a C(sp³)–H bond is extremely challenging due to the thermodynamic and kinetic stability of the C(sp³)–H bond, intra- and intermolecular C(sp³)–H amination has seen much progress in the past decade.^[1] Particularly, intramolecular C(sp³)–H amination as an atom-economical strategy has found extensive applications for the construction of varieties of important N-heterocycles.^[2]

Fe-mediated catalysis has slowly made its way to various important classes of organic chemical transformations, including hydroaddition chemistry and recently also C–H activation,^[3] but the Fe-mediated functionalization of aliphatic C(sp³)–H bonds is still a formidable challenge.^[4]

Nitrene (in situ generated) insertion into a C(sp³)–H bond is an efficient and perhaps the best studied approach for C(sp³)–N bond formation. In situ generation of a metal-bound nitrene species from readily available aliphatic organoazides, releasing only molecular nitrogen as the side product, followed by selective insertion into a C(sp³)–H bond would constitute an efficient approach for catalytic C–H amination. Synthesis of N-heterocycles via direct C(sp³)–H amination using aliphatic azide substrates is an appealing strategy, given that N-heterocycles are prevailing building blocks in natural products, pharmaceuticals, and functional material.

Herein, we discuss the synthesis and detailed characterization of various iron complexes, with different metal oxidation states, and their catalytic performance in the direct C(sp³)–H amination of aliphatic azides to N-heterocycles.

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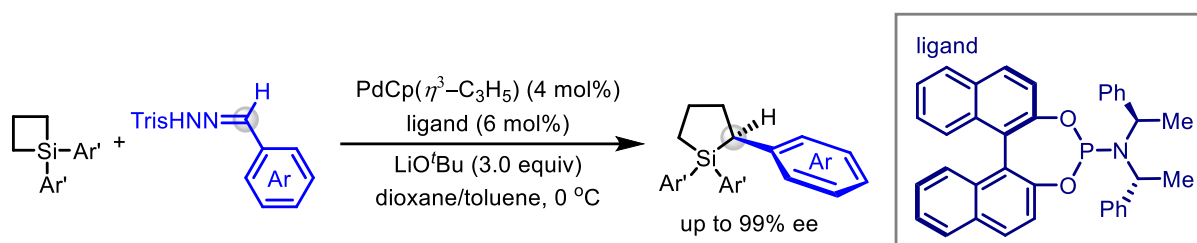
Catalytic Metal Carbene Transformations for Organic Synthesis and Polymer Synthesis

Jianbo Wang

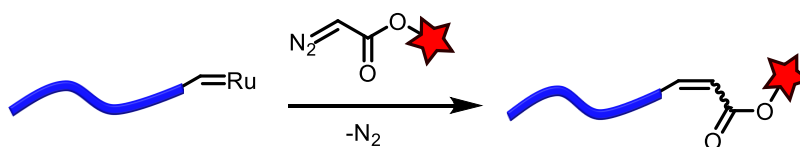
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Carbene-based transformations under transition metal catalysis have been extensively explored in the past decades. The typical carbene transfer reactions involve insertions, cyclopropanations and ylide generations. In the past decade, a new type of transition-metal-catalyzed carbene reactions has emerged, in which the carbene precursors, typically diazo compounds or sulfonylhydrazones, have been explored as the cross-coupling partners in C-C single bond or C=C double bond formations.^[1] Our exploration in this arena has been continued until recently. I present herein our recent studies on highly regio- and enantioselective carbene insertion into strained C-Si bonds, as well as other carbene coupling reactions.^[2]



Moreover, the application of highly efficient transition-metal-catalyzed reactions to the synthesis of polymers has attracted great attentions. In particular, transition-metal-catalyzed cross-coupling and olefin metathesis have been extensively applied in polymerization chemistry. On the contrary, classic carbene transformations have been less utilized in polymer synthesis. We have recently launched a program to systematically explore the application of carbene-based transformations in polymerization chemistry. In this lecture, I would like to present some of our preliminary results along this line.^[3]



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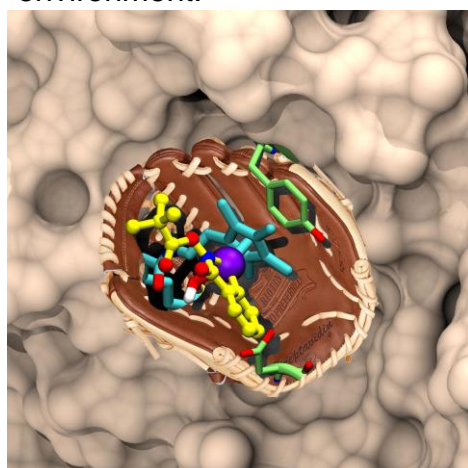
Artificial Metalloenzymes for Carbene and Nitrene Chemistry: Challenges and Opportunities

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Artificial metalloenzymes (ArMs) have attracted increasing attention in the past two decades as attractive alternatives to either homogeneous catalysts or enzymes. Artificial metalloenzymes result from anchoring a catalytically competent abiotic metal cofactor within a host protein, Figure.[1-2] The resulting ArMs combine attractive features of both homogeneous- and bio-catalysts. Most importantly, they enable access to new-to-nature reactions, thanks to the availability of the entire periodic table. In addition, the host protein can be subjected to genetic optimization. Relying on either streptavidin or human carbonic anhydrase as host protein for anchoring the organometallic cofactor, we have optimized the performance of ArMs for sixteen different reactions.

Following a general introduction on the underlying principles of ArMs, this talk will highlight our recent progress in engineering and evolving such hybrid catalysts for olefin metathesis, carbene insertion, and nitrene insertion. A particular emphasis will be set on combining ArMs with natural enzymes and performing catalysis in a cellular environment.



Reactions implemented:

| | |
|--------------------------|-------------------|
| Hydrogenation | Alcohol Oxidation |
| Transfer Hydrogenation | Sulfoxidation |
| Allylic Alkylation | Dihydroxylation |
| Suzuki Cross-Coupling | Peroxydation |
| C–H activation | Michael Addition |
| Enzyme Cascades | Hydroamination |
| Olefin Metathesis | Hydroxylation |
| Carbene Insertion | Cyclopropanation |
| Nitrene Insertion | |

Figure Artificial metalloenzymes result from anchoring an organometallic catalyst in a protein scaffold. The resulting hybrid catalyst can be optimized by combining both chemical and genetic strategies. Reactions implemented in the Ward group.

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Chiral carbenes as unique solution for complex 3d-metal catalyzed asymmetric C-H

Joanna Wencel-Delord

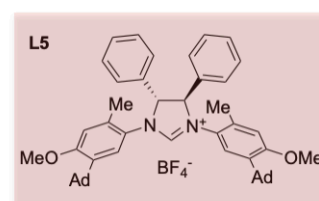
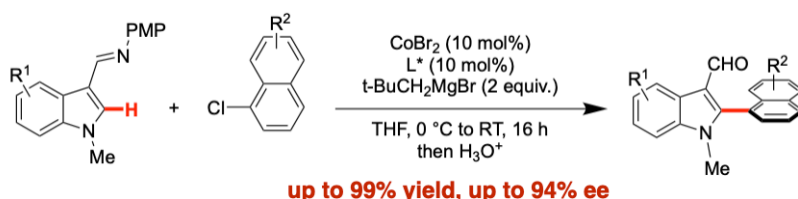
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Chirality is a unique feature of nature that has been attracting the continuously expanding attention of the scientific community. Therefore, not surprisingly, the implementation of chiral information within the design of complex molecules of interest, such as drugs, agrochemicals, and advanced organic materials, is currently a rapidly expanding field. The development of this field requests however, on the one hand, the design of innovative and complex enantiopure structures, and, on the other hand, the development of sustainable and efficient synthetic routes providing access to such compounds.

Following these two objectives, our group has recently focused on the implementation of the asymmetric C-H activation strategy to assemble rapidly complex enantiopure scaffolds. After pioneering use of the sulfoxide moiety as both, a directing group and a chiral auxiliary to prepare atropisomeric biaryls via direct C-H activation, our attention has progressively focused on more available and less toxic 3d-metals. We have thus discovered that the Cobalt catalyst, in combination with a unique NHC-ligand provides an unparalleled catalytic system for the first atroposelective 3d-metal catalyzed direct arylation. Indeed, low-valent Co/NHC catalyst promotes very efficiently and selectively C2-direct arylation of indoles, furnishing atropisomerically pure indole products in high yields and excellent enantioselectivities.

Subsequently, Co- and Fe-catalyst bearing similar *meta*-substituted NHC ligands could be used to assembly unprecedented chiral scaffolds bearing two proximal chirality elements, ie. axial C-C and C-N motifs or atropisomerism and central chirality.

Co-catalyzed atroposelective C-H arylation



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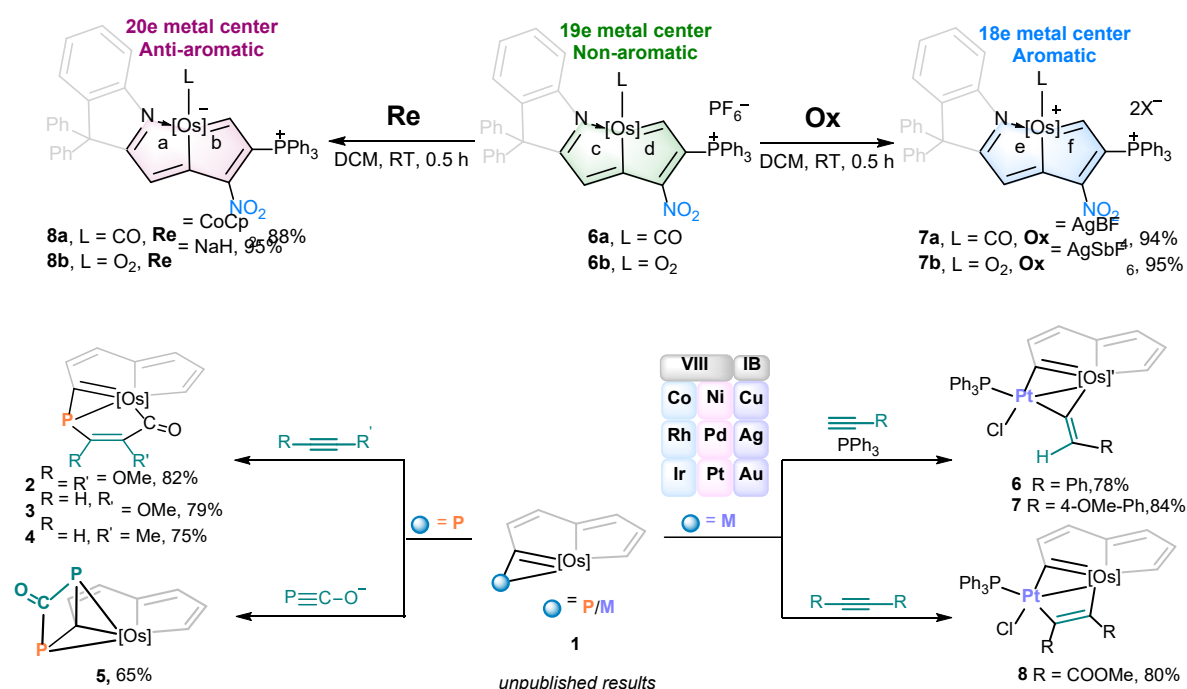
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Metallacycles Containing Metal-Carbene Bonds

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Metallaaromatics represent a distinct species of aromatics, which have been broadly recognized as compounds structurally derived from formal replacement of a C(H) segment in conventional organic aromatic molecules by an isolobal transition metal fragment. In the past decades, metallaaromatics have been attracting extensive interest on account of their unique structural features, aromaticity, and organometallic nature.¹



We attempted to apply several classic organic reactions in metallacyclic compounds, especially those small ring systems with metal-carbon multiple bonds²⁻¹⁰. Very recently, the synthesis of strained bimetallacyclopropenes and phosphametallacyclopropenes has been achieved by reactions of cyclic metal-carbene/carbyne complexes. DFT calculations revealed the stabilization of transition metal in strained ring systems and provided hints for further development of heavy analogs of arenes with strained small rings.

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Metalloradical Catalysis for Carbene and Nitrene Transfers

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Organic synthesis has been dominated by the development of chemical reactions that are based on two-electron heterolytic ionic processes, either stoichiometrically or in catalytic fashion. While one-electron homolytic radical chemistry is equally rich and has been demonstrated with a number of unique features, its application for stereoselective synthesis of organic molecules has been hampered by several enduring challenges. Over the past two decades, my laboratory has been in the process of formulating metalloradical catalysis (MRC) as a general concept to guide the development of fundamentally new approaches for controlling both reactivity and stereoselectivity of radical reactions. In essence, metalloradical catalysis aims for the development of metalloradical-based systems for catalytic generation of carbon- and nitrogen-centered organic radicals from common substrates without the need of radical initiators or the use of light. The subsequent reactions of the resulting organic radical intermediates, which remain covalently bonded or noncovalently associated with the metal center, can be effectively controlled by the catalyst. For achieving enantioselective radical reactions via MRC, we have introduced a family of unique chiral metalloradical catalysts based on structurally well-defined Co(II) complexes of D_2 -symmetric chiral porphyrins with tunable electronic, steric, and chiral environments. These Co(II)-based metalloradical catalysts have demonstrated to be highly effective for a wide range of stereoselective organic reactions, including different carbene and nitrene transfers such as olefin cyclopropanation, olefin aziridination, C–H alkylation, and C–H amination. Due to their distinctive stepwise radical mechanisms that involve α -metalloalkyl and α -metalloaminyll radicals as the key intermediates, the Co(II)-based metalloradical systems enable addressing some long-standing problems in these important organic transformations while offering ample opportunity for invention of new synthetic tools.

