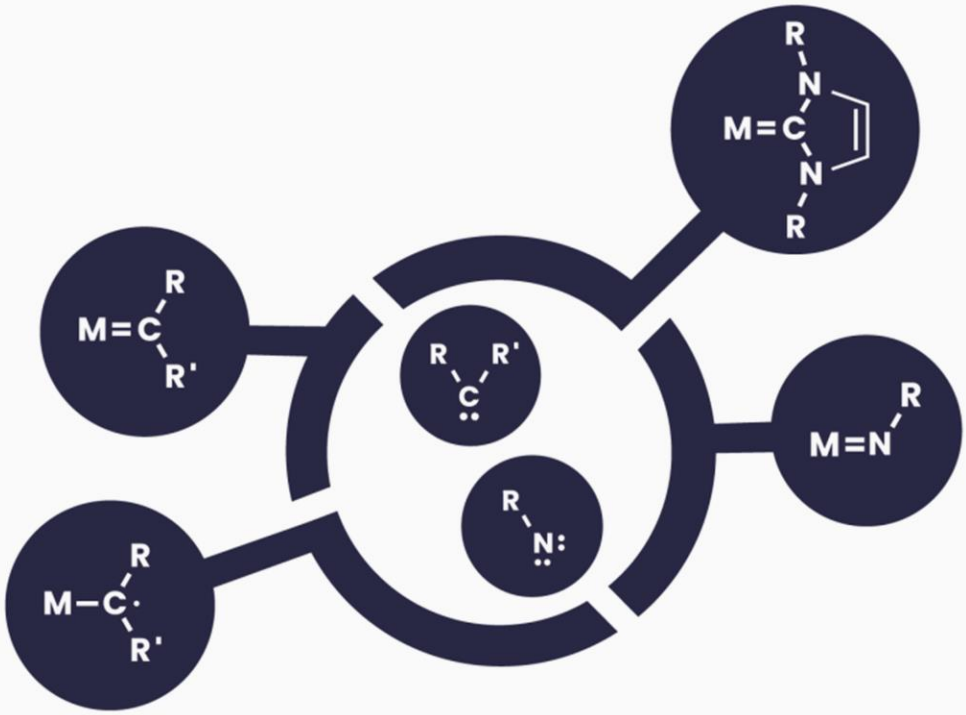
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ABSTRACT BOOK

POSTERS

Utilization of Sulfoxonium Ylides and Anthranils in Transition Metal-Catalyzed C–H Activation/Annulation Reaction

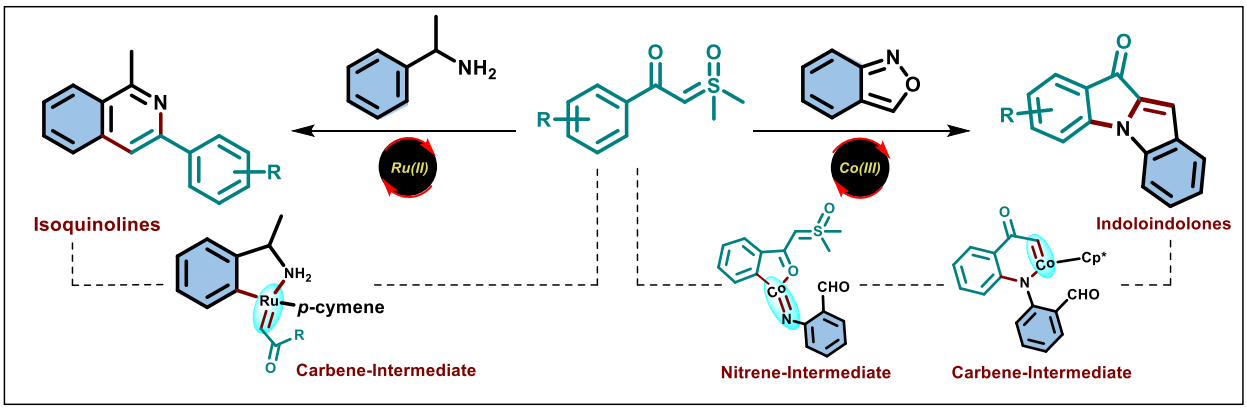
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Transition metal-catalyzed carbene and nitrene transfer reactions have been used extensively as tools to construct carbon and nitrogen containing scaffold using various directing groups including isoxazoles, dioxazolones, azides, iodonium ylides, diazo compounds, etc. Amongst these, sulfoxonium ylides and anthranils have been used as traceless directing groups and investigated as safer alternatives carbene and nitrene precursor of above compounds for carbenoid and nitrenoid transfer reactions. Until now, limited groups have disclosed the utilization of sulfoxonium ylides and anthranils in C–H activation reactions. However, utilization of sulfoxonium ylides and anthranils as alternative carbene and nitrene precursors or traceless directing groups under Cp*Co(III) and Ru(II)-catalysis is rather finite. We attempted to demonstrated Cp*Co(III)-catalyzed [4+1] C–H functionalization/annulation cascade between sulfoxonium ylide and anthranil towards synthesis of indoloindolone derivatives. Moreover, we could also display free amine directed Ru(II)-catalyzed redox-neutral [4+2] C–H activation/annulation of sulfoxonium ylides with benzylamines.

Keywords: Sulfoxonium ylides, Anthranils, Benzylamines, C–H Activation, Cobalt, Ruthenium.



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Skeletal Editing by Single-Carbon Insertions in Single C–C Bonds

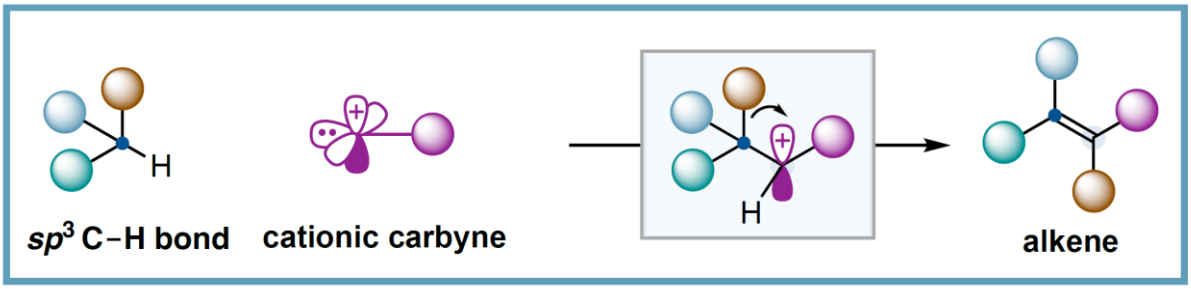
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The interest for the development of skeletal editing processes that selectively insert, delete or exchange an atom in organic molecules has witnessed a significant increase over the last years.[1] However, while single-carbon insertions in doble C–C bonds have been reported,[2] there is still limited research exploring methods for single C–C bond functionalization. Herein, we would like to present the discovery and development of a new platform for single-carbon atom insertions in single C–C bonds. Our work was driven by the photochemical generation of a cationic carbyne equivalent that selectively inserts in aliphatic C–H bonds. The resulting intermediate evolves into a tetrasubstituted alkene *via* a cationic [1,2]-sigmatropic rearrangement and proton elimination. This newfound synthetic strategy not only represents a new olefination reaction using C–H bonds as functional groups but also underscores an opportunity as a tool in skeletal editing. These insights will be relevant to reach previously unattainable chemical space in drug discovery.[3]



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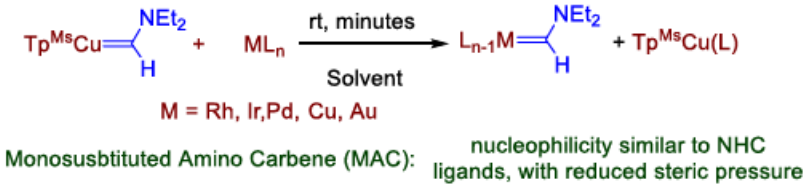
A copper-masked monosubstituted carbene as a general transmetalating agent

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Metal complexes containing $LnM{=}CR_1R_2$ carbene ligands are relevant intermediates in many catalytic transformations. Although examples of isolated complexes are known, their stability significantly decreases when one of the carbene substituents is a hydrogen, i.e., in the case of monosubstituted carbenes. We have discovered that the copper complex $Tp^{Ms}Cu(C(H)NEt_2)$[1] easily transfers the aminocarbene $:C(H)NEt_2$ to other metal complexes such as rhodium, iridium, palladium, copper, or gold, resulting in stable complexes containing the $M\text{-}C(H)NEt_2$ moiety. Experimental data allow us to propose that this monosubstituted amino carbene (MAC) ligand shows electrophilicity similar to NHC ligands bearing bulky substituents, despite its considerably low bulk.[2] These characteristics enable unprecedented reactivity patterns, such as the generation of the first stable monosubstituted carbene adduct of $Rh_2(OAc)_4$, a known catalyst for carbene transfer reactions



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A Supramolecular Approach for Enantioselective C-H Amination with Iron Phthalocyanine as Catalyst

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The development of transition metal catalysts for asymmetric catalysis is of current interest in view of their potential usefulness in organic synthesis.[1] In the case of non-directed C-H functionalization, the overwhelming majority in literature have been applying chiral ligands in design of asymmetric catalysts like $Rh_2(CO_2R)_4$,[2] M(D_4-Por)X (M = Ru, X = CO and M = Ir, X = CH_3),[3] Co(D_2-Por)[4] and M(Salen)X (M = Ru, X = CO and M = Ir, X = CH_3).[5] However, developing asymmetric ligand frameworks is a non-trivial task.[6]

Herein, we report a supramolecular system consisting of iron phthalocyanine and chiral templates (10 derivatives) for highly enantioselective C-H amination. This system was applied to a range of C-H bond substrates, yielding C-H aminated products at moderate yield and high enantioselectivity (16 intermolecular examples, 10 intramolecular examples, conversion up to 70%, yield up to 98%, e.r. up to 98:2). Mechanistic studies (KIE and racemization of stereogenic centers) suggest a stepwise reaction with iron-nitrenoid intermediates. The supramolecular self-assembly mechanism was examined with ^{1}H NMR, UV, 2D NMR and CD spectroscopic techniques. GFN2-xTB computational models were optimized and proposed for the optimum **Fe-1**-**T2h**$_2$ structure.

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A Phosphinidene-Capped Pd_8 Cluster

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Herein, we report the synthesis of a novel Pd cluster stabilized by phosphinidene (PR), ligands species analogous of nitrenes and carbenes.[1] When organocyclophosphine compound $(PDip)_3$ reacts with 2 equivalents of $Pd_2(dba)_3$, (**Figure 1**) an insertion reaction takes place, affording the previously unreported $[Pd_8(PDip)_6]$ cluster. The X-ray structure of the Pd_8 cluster (**Figure 2**) exhibits a cubic core, where each phosphinidene unit binds four Pd centers, placed at the vertexes of the cube. If, instead of $Pd_2(dba)_3$, a (Py)Pd(CAAC) complex is exploited as starting reagent, other insertion products can be obtained, such as $[(Py)_2Pd(P_3Dip_3)]$ or $[(P_3Dip_3)(PyPd)_2(P_2Dip_2)]$, reported in **Figure 3**. In these products, P-P bonds are still present in the ligand moieties derived from $(PDip)_3$, in contrast with the Pd_8 cluster. It is possible to tune the synthesis towards different products, changing the reagent stoichiometry and the reaction conditions. For instance, when the molar ratio $[(PDip)_3]$:[(Py)Pd(CAAC)] is 1:4, the Pd_8 cluster is again obtained. From the X-ray structure of the cluster, it is possible to note that the Pd centers are coordinatively unsaturated, in contrast with similar Ni clusters obtained with the same method.[2] Consequently, it is possible to further functionalize the cluster by adding 2,6-xylylisocyanide (CNPh). The NMR characterization of the isocyanide-stabilized cluster highlights the presence of four CNPhs anchored to the core, likely forming a symmetrical motif on it, since only one shifted singlet is evident in the ^{31}P NMR spectrum.

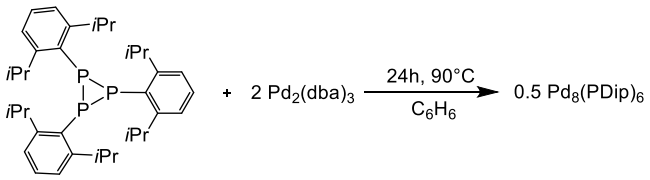


Figure 1: Synthesis of $Pd_8(PDip)_6$ cluster

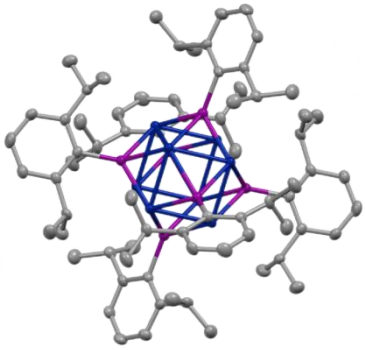


Figure 2: X-ray structure of $Pd_8(PDip)_6$ cluster

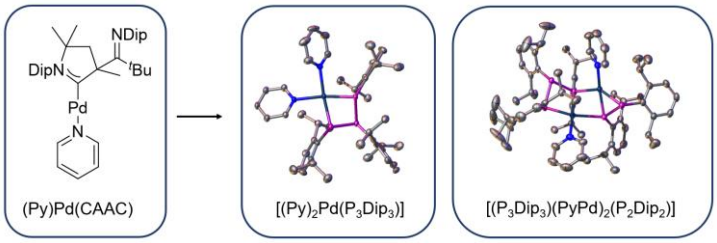


Figure 3: CAAC-Pd(0) complex used in this work and X-ray structures of complexes obtained from its reaction with $(PDip)_3$

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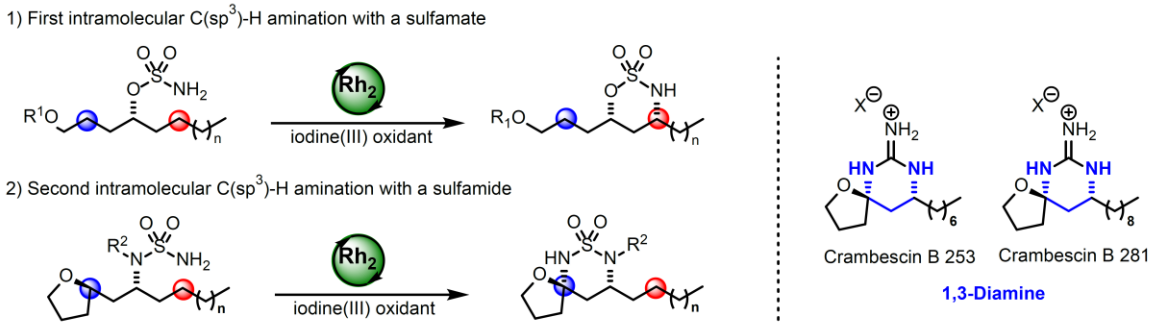
Diamine in Organic Synthesis: Towards the Total Synthesis of Crambescins B 281 and B 253

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Crambescins are cyclic guanidine alkaloids of marine origin (Marine Sponge *Crambe crambe*) that exhibit notable biological activities.[1] Two new members from this family of natural products, Crambescins B281 and B253, were recently isolated at ICSN by the group of Dr. J. Ouazzani and Dr. G. Le Goff.[2] Interestingly, these potent antibacterial products display a spirocyclic motif that combines a tetrahydrofurane ring with a cyclic guanidine deriving from a 1,3-diamine unit.

With the aim to perform SAR studies and determine the functional groups responsible for the antibacterial activity of Crambescins B 281 et B 253, we proposed a retrosynthetic analysis likely to give access to a large variety of analogues of the natural products. The strategy relies on two key steps of rhodium(II)-catalyzed intramolecular C(sp^3)-H amination in the presence of an iodine(III)oxidant for the formation of the 1,3-diamine unit.[3] The first reaction involves a sulfamate and raises the question of the site-selectivity, an issue that was addressed by screening the reaction parameters. The second reaction is performed from a sulfamide. In this communication, we will present our synthetic strategy for the preparation of Crambescins B281 and B253, and then will discuss the optimization of both catalytic intramolecular C-H amination reactions.



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Silver complexes as efficient catalysts for the regioselective C-H bond functionalization of light alkanes

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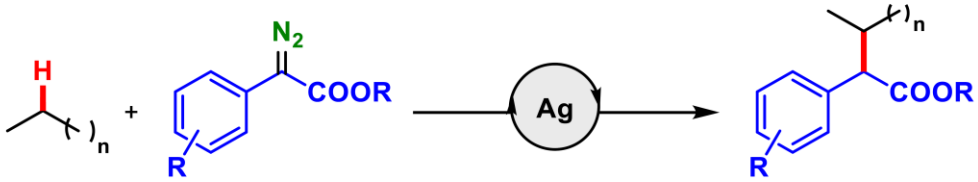
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Despite the fact that alkanes C_nH_{2n+2} are inexpensive and available raw materials, their conversion into value-added compounds remains a challenge due to their chemical inertness (high bond dissociation energies and low C-H bond polarity, particularly the gaseous members of the series.[1] Among the synthetic strategies, the catalytic functionalization of C-H bonds via carbene insertion from a diazo reagent or its precursors is one the most developed in homogeneous conditions.[2] However, the examples of different catalytic systems capable of inducing selective functionalization toward a specific C-H bond in alkanes are still scarce.[3]

Our research group has reported a series of silver complexes bearing hydrotrispyrazolylborate ligands (Tp^x) as efficient catalysts for the functionalization of C_{sp3}-H bonds via carbene insertion,[4] including the regioselective functionalization of linear alkanes.[5] In this contribution, we expand the use of this methodology to gaseous alkanes employing donor-acceptor aryl diazocompounds.



propane, butane

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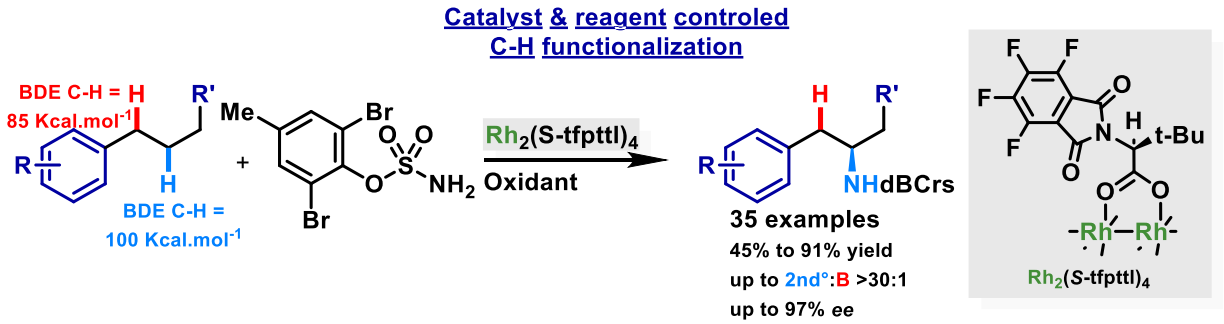
Selective catalytic amination of unactivated C(sp^3)–H bonds in the presence of electronically activated sites.

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Designing site-selective C(sp^3)–H functionalization reactions is a significant challenge in organic synthesis, with broad implications for pharmaceutical and agrochemical research.[1] A first approach to meet this goal relies on directed functionalization reactions through the use of coordinating groups or intramolecular reactions. Though efficient in many cases, directed functionalization reactions can suffer from limitations such as low substrate scope, poor reactivity, and the requirement for specific functional groups. A second strategy to control the site-selectivity is to rely on the innate reactivity of the substrate, particularly by playing with the C-H bond dissociation energies (BDEs).[2] Again, limitations in terms of scope are often met. Moreover, many C-H bonds remain inaccessible with the application of both approaches. Catalyst-controlled site-selective C(sp^3)-H functionalization reactions is a third strategy that has recently emerged to go beyond the limitations of substrate-controlled reactions.[3]

In this context, our group recently initiated studies[4] to address the issue of the selective intermolecular amination of unactivated secondary (BDE of 100 kcal.mol^{-1}) C(sp^3)−H bonds in the presence of an activated benzylic site (BDE of 85 kcal.mol^{-1}). In this communication, we thus will describe the discovery of a highly discriminating rhodium-bound nitrene species resulting from the synergistic combination of a dirhodium(II) complex and a sulfamate.[5] The use of these reagents allows for selective conversion of secondary C(sp^3)−H bonds to afford α,α-disubstituted amides, with high yields and good regioselectivity. The scope of these reactions, including their application to the late-stage functionalization and their potential extension to the stereoselective amination, will be discussed.



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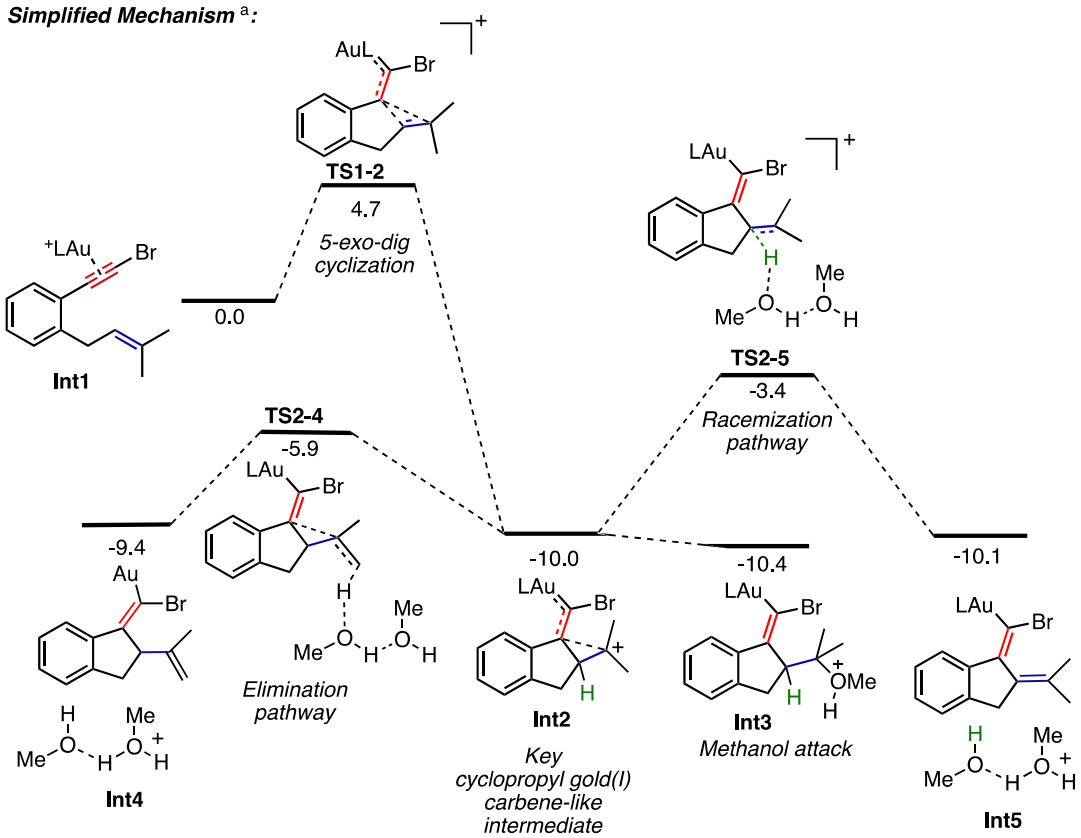
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Racemization Pathways in Enantioselective Cyclizations of Enynes Mediated by Cyclopropyl Gold(I) Carbene Intermediates

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The enantioselective gold(I)-catalyzed alkoxycyclization of 1-bromo-1,6-enynes was achieved using a modified JohnPhos ligand with a distal C_2-2,5-diarylpyrrolidine previously designed in our group.[1] Different alcohols could be used as nucleophiles in the formal *5-exo-dig* cyclization of 1-bromo-1,6-enynes. At lower concentrations of alcohol, the elimination product was also formed with a lower enantiomeric excess than that of the alkoxycyclization product. Moreover, the *er* of the latter results to be strictly dependent on the amount of nucleophile. Control experiments and DFT calculations performed first on bromoenynes and then with other internal alkynes support the hypothesis of an in-cycle racemization process through cyclopropyl-gold(I) carbene intermediates,[2] which shed light on the mechanism of gold(I)-catalyzed cyclizations of enynes.



[a] L = PMe_3. DFT calculations performed with B3LYP/6-31G(d) (C, H, P, O), LANL2DZ (Br) and SDD (Au) in CH_2Cl_2 (PCM). Free energies in Kcal/mol.

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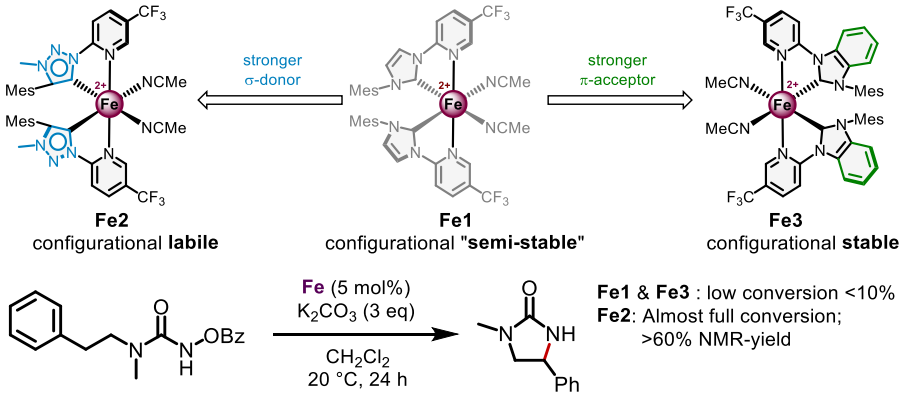
Chiral-at-Iron Complexes: A journey between reactivity and stability

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In 2019 we introduced the first examples of chiral iron catalysts that exclusively use achiral ligands. In this approach, the overall chirality arises from the asymmetric coordination of the achiral ligands around the central metal, resulting in metal-centered chirality.[1] These catalysts demonstrated activity in various asymmetric reactions. Despite modifying the N-heterocyclic carbene substituents, certain noncoordinating solvents, water, or air led to significant racemization of the iron center over time.[2]

Consequently, we became intrigued by the factors that dictate the configurational stability of chiral-at-iron complexes. My research demonstrates how the σ-donor and π-acceptor properties of NHC ligands affect the configurational stability of chiral-at-iron complexes. By replacing imidazole-2-ylidene (**Fe1**, nNHC) with a 1,2,3-triazolylidene (**Fe2**), we increased the σ-donor properties while decreasing the π-acceptor properties, resulting in a completely configurational labile complex. Conversely, replacing nNHC with a benzimidazole-2-ylidene (**Fe3**), which mainly increased the π-acceptor properties, yielded a significantly more configurational robust chiral-at-iron catalyst. This catalyst was capable of catalyzing an asymmetric hetero-Diels-Alder reaction with high stereoselectivity even under open-flask conditions.[3]



Serendipitously, we observed an enhanced activity of the more electron-rich iron complex **Fe2** towards the nitrene-mediated ring-closing C(sp^3)-H amination of urea compounds. This shows us the influence of the electronic properties of the ligands on the activity of these iron complexes toward nitrene reactions.

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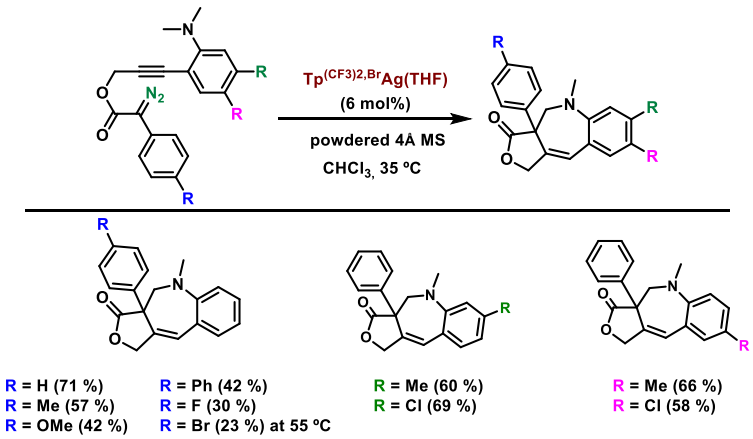
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Intramolecular Interception of the Remote Position of Vinylcarbene Silver Complex Intermediates by C(sp3)−H Bond Insertion

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Within the field of metal carbenes, vinylcarbene metal complexes have become one of the most intriguing subclass of metal carbenes. Pionered by Prof. Davies in the 90's, [1] vinylcarbenes display two potential reactive sites: the more common carbenic position or the less studied vinilogous one. Studies carried out by Davies, [2] and Harada and Nemoto [3] have shown that rhodium favors the reactivity at the carbenic site while silver promotes remote functionalization in O-H and N-H insertions. Carbene alkyne/methathesis (CAM), [4] has become one of the most powerful tools for *insitu* generation of vinylcarbenes. Starting from an initial diazo compound, a first carbene is formed then reacting with an alkyne unit generating the desired vinylcarbene, which can further react in a cascade manner. In this basis, Xu and Doyle have shown how selective carbenic C_{sp3}-H selectivity can be achieved employing dialkyl amino derived diazo compounds under rhodium catalysis in a CAM process.[5] Herein we wish to report the first example of silver catalyzed selective vinylogous C(sp3)-H bond insertion, starting from a dimethylamino derived diazo compound, leading to the synthesis of a new family of benzoazepines.[6] Several substitiuents could be employed showing the scope of the transformation. Morover, DFT studies unraveled the whole reaction profile including an stepwise C-H insertion mechanism involving a zwitterionic intermediate as the rate determing step of the transformation.



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Photocatalytic Generation of Free Triplet Carbenes and their Application

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The indole heterocycle represents one of the most important motifs in natural product and drug discovery. Especially the alkylation of unprotected indoles is a key question in organic synthetic methodology and only recently the reaction of diazoalkanes with indoles emerged as a promising tool to conduct selective alkylation reactions.[1,2] Surprisingly, the reaction mechanism of the C3 alkylation of indole is not yet fully understood and direct functionalization of the C3 position or the ring-opening of a cyclopropane intermediate are under discussion.[3]
Herein, we report on the selective C3-H functionalization of unprotected indole heterocycles under photocatalytic reaction conditions. Detailed experimental and theoretical calculations uncover an unexpected reaction mechanism via a 1,2-alkyl radical migration.[4] Furthermore, we expanded the reactivity of free triplet carbenes towards the stereoconvergent cyclopropanation of β-substituted styrenes.[5]

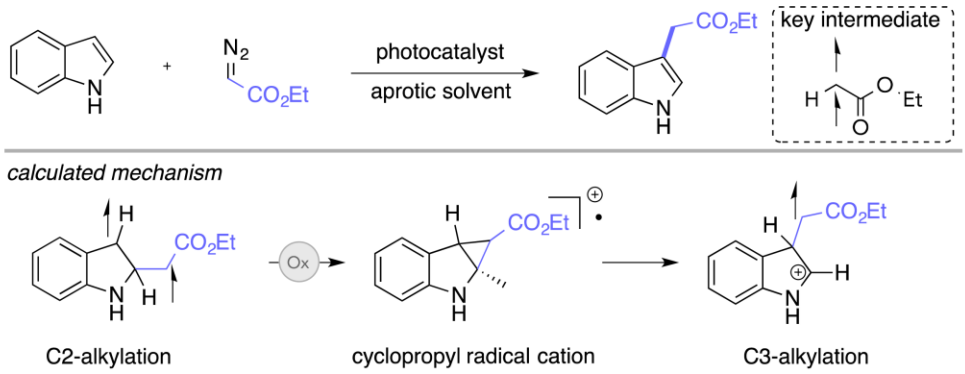


Figure 1. Photocatalytic C-H Functionalization of Indole.

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Iron-Catalyzed C(sp^3)-H Lactonization Using Hydroxylamine Derivatives

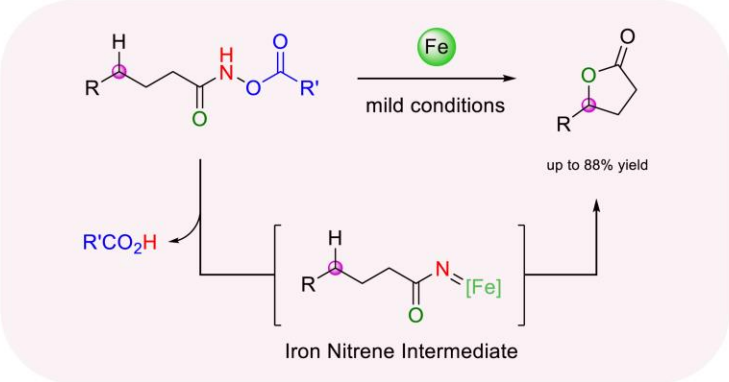
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Lactones are highly valuable intermediates in the synthesis of many natural products, as well as prominent scaffolds in bioactive compounds.[1] Direct functionalization of C-H bonds represents the most straightforward route to these compounds in the context of sustainable chemistry. There has thus been an ongoing effort into the development of efficient and robust methodologies for C-O bond formation.[2] However, most of these developed processes are poorly atom economical, require external oxidants, and are based on the use of rare and expensive transition metals such as palladium.[3]

Nitrenes are well-known for their ability to perform aziridination, alkene difunctionalization and C-H amination.[4] Our group aims to achieve sustainable nitrene transfer processes using iron as the catalyst and hydroxylamines as the nitrogen source.[5] Iron is cheap, abundant, and non-toxic while hydroxylamines are bench-stable, easily accessible, and can form a metallonitrene intermediate in the presence of a transition-metal without the addition of external oxidants.[6] During our investigation on C-H amination, we hypothesized that we could deviate the reactivity of nitrenes to favour a C-H oxygenation process.

In this communication, we will present in detail our recently developed iron-catalyzed lactonization using hydroxylamine derivatives. This sustainable process allows for an efficient access to new C(sp^3)-O bonds, yielding various lactone derivatives in good-to-excellent yields using very mild conditions.



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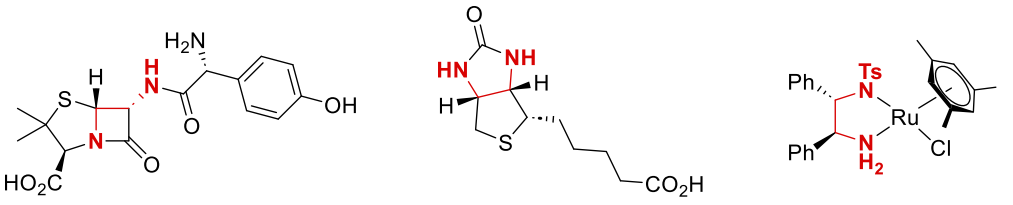
Iridium(III)-catalyzed intermolecular C(sp^3)–H amidation for the synthesis of chiral 1,2-diamines

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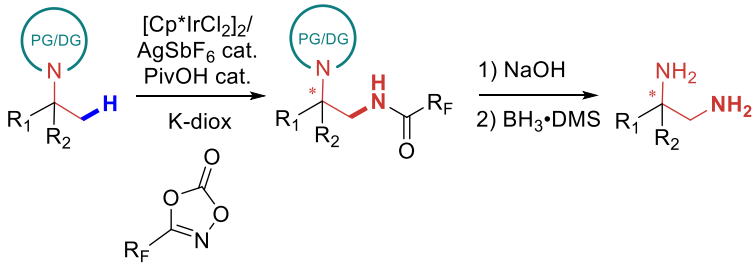
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Chiral 1,2-diamines are privileged scaffolds among bioactive natural products, active pharmaceutical ingredients, ligands for transition-metal-based asymmetric catalysis and organocatalysts (Scheme 1)[1]. Although a few traditional approaches have facilitated their synthesis[2], the construction of chiral 1,2-diamine motifs remains still a challenge. Lately, transition-metal-catalyzed C(sp^3)–H amination reactions have witnessed impressive advances, providing powerful, straightforward and unconventional strategies to forge new C(sp^3)–N bonds[3]. Motivated by the lack of direct methods to access such a useful scaffold, we developed an iridium(III)-catalyzed intermolecular C(sp^3)–H amidation for the synthesis of chiral 1,2-diamines (Scheme 2). This method takes advantage of the high reactivity of K-Diox[4], a bench-stable 1,4,2-dioxazol-5-one-based nitrene precursor and relies upon the design of a new, cheap and cleavable *exo*-protecting/directing group derived from camphorsulfonic acid, furnishing free enantiopure diamines upon cleavage of both nitrogen substituents[5]. Kinetic and computational studies served as supportive tools to gain further insights into the reaction mechanism, which proceeds through a sequence of C(sp^3)–H activation (CMD) and inner-sphere nitrene transfer. Moreover, in order to achieve the synthesis of chiral α-tertiary-1,2-diamines, a two-steps protocol involving intermolecular regioselective hydroamination of an unactivated olefin / C(sp^3)–H amidation was developed.

Scheme 1



Scheme 2



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Access to Carbazoles and related Heterocycles from Sulfilimines

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Carbazoles and related heterocycles can be synthesized through light-induced intramolecular C–H amination using aryl sulfilimines, which offer promising alternatives to hazardous azides. A comprehensive exploration of different catalysts and light sources led to the successful development of a broad reaction scope, featuring consistently high yields. When subjected to transition metal catalysts or light, aryl sulfilimines generate nitrene intermediates with phenyl sulfide as the leaving group. The formed nitrene species can subsequently insert into a C–H bond, leading to the formation of indoles and carbazoles. This process can be easily scaled up to gram scale without the risks associated with potential explosive decomposition, as observed with azides. Notably, sulfilimines exhibit superior reaction speeds compared to their azide counterparts.[1]

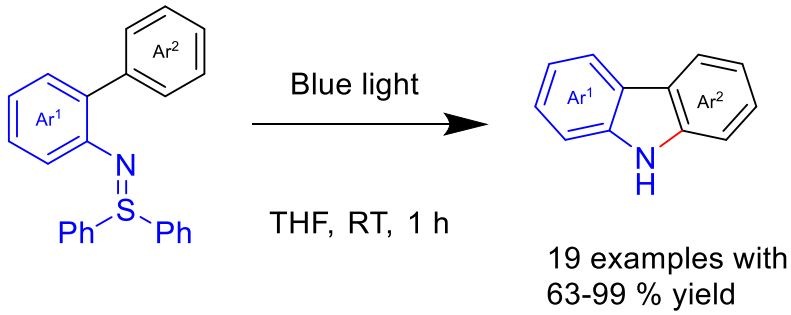


Figure 1 Synthesis of carbazoles from aryl sulfimines by C–H-amination.[1]

References

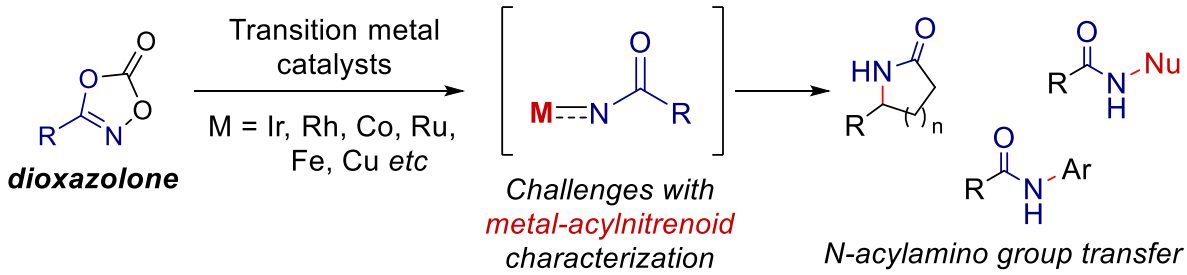
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Mechanism-driven development of metal-acylnitrene transfer catalysis using dioxazolone as nitrene precursor

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Catalytic C–H amination is an efficient method for synthesizing valuable N-functionalized molecules. Recent advancements in group 9 transition metal-catalyzed C–H amidations using dioxazolone as the nitrenoid precursor have facilitated a wide range of hydrocarbon amidations. In this study, we have explored the reactivity nature of proposed metal-acylnitrenoid species for diverse transformations. By utilizing the mechanistic characteristics of key metal-nitrenoid intermediates, we have devised a novel ruthenium catalyst system capable of achieving high benzylic C–H selectivity, surpassing the competing tertiary C–H positions when employing dioxazolone as the nitrenoid precursor.[1] Additionally, taking advantage of the electrophilic properties exhibited by proposed metal-acylnitrenoid intermediates, we have successfully demonstrated the trapping of acyl nitrenoids with external amines as nucleophiles, resulting in the formation of hydrazides.[2] Finally, through the design of a new rhodium catalyst system, we have explored the mechanism of Rh-acylnitrene transfer process.[3]



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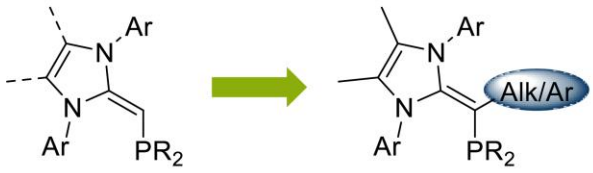
Influence of the Backbone Substitution of *N*-Heterocyclic Olefin-Substituted Phosphine Ligands on Their Catalytic Activity

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In the last decades phosphines have emerged as widely used ligand class for homogeneously catalyzed cross-coupling reactions.[1] Especially electron-rich phosphines are capable of supporting the often difficult oxidative addition step in the catalytic cycle of Pd-catalyzed transformations of aryl chlorides, which are of high interest for chemical industry.[2] Unsymmetrical phosphine ligands that are substituted with an electron donating moiety are able to exceed the donor properties of symmetrical trialkylphosphines[3] or even *N*-heterocyclic carbenes (NHC), resulting in an accelleration of the oxidative addition step. Following this approach, ylide-substituents delivered strong electron donating ligands (YPhos) that we successfully applied in a seris of catayltic transformations.[4] A further approach from Beller *et al.* relies on the usage of *N*-heterocyclic olefins (NHO) as electron-donating moiety in phosphine ligands (NHOP).[5] To this day, the structural motive of NHOP ligands is limited to monosubstituted olefines[6], leaving a second substitution site as shown in Figure 1 to further increase the donor ability.

Here, the synthesis and characterization of multiple ligands containing an additional backbone modification are reported to provide a better understanding of the behavior of this ligand class in catalytic processes. The ligands were investigated in several Pd-catalyzed cross-coupling reactions and the different behavior examined by investigation of the molecular structures of the ligands and palladium complexes.



Established **Novel**

Figure 1 : Novel structural motive of the investigated NHOP ligands.

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Iron-Catalyzed Intermolecular Nitrene Transfer Reactions Using Hydroxylamine Derivatives as Clean Nitrogen Sources

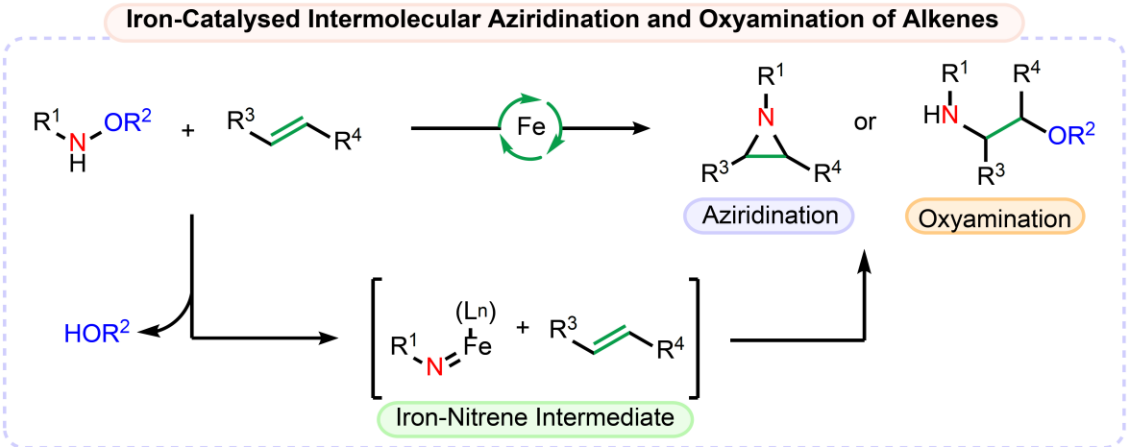
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Nitrogen-containing molecules are incredibly valuable in the organic synthesis due to their ubiquity within pharmaceuticals, chiral ligands and as synthetic intermediates. There has thus been an ongoing effort into the development of new, efficient, and robust methodologies for C-N bond formation.

Metallonitrenes are a powerful tool for the formation of C-N bonds and their use has led to the development of a variety of amination processes such as aziridination, alkene difunctionalisation and C-H functionalization.[1] However, many of these processes are poorly atom economical, and are based on the use of non-sustainable materials such as rare and expensive transition metals (Rh, Pd, etc.). Hydroxylamine derivatives, in the presence of a transition-metal, can form a metallonitrene intermediate where the N-O bond acts and an endogenous oxidant, forgoing the use of external additives.[2] In comparison, the generation of such intermediates from hydroxylamine derivatives coupled with the use of cheap, abundant, and non-toxic iron sources has been narrowly studied, however, is increasing in interest.[3]

Following our previous work on the reactivity of iron-nitrenes deriving from hydroxylamine derivatives,[4] we will present our recently developed intermolecular iron-catalysed aziridination and oxyamination of alkenes using hydroxylamine derivatives as a nitrogen source.[5] These sustainable processess allows for efficient access to a variety of useful nitrogen-containing scaffolds in good-to-excellent yields.



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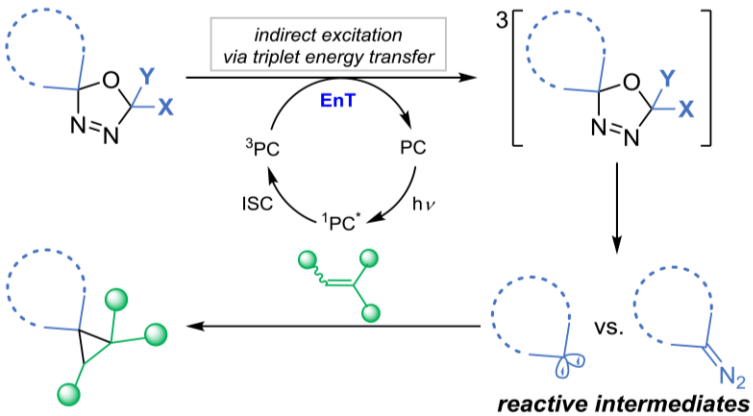
Visible Light-Induced Activation of 1,3,4-Oxadiazolines via Triplet Energy Transfer

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The chemistry of diazo compounds gives access to diverse reactive species and represents extremely valuable branch of organic synthesis. While a number of reports on stabilized diazo compounds is constantly growing, the reactivity of non-stabilized diazoalkanes lacks exploitation. [1-2] Numerous precursors are known for the generation of nonstabilized carbenes i.a. hydrazones, diazirines, and 1,3,4-oxadiazolines.[3-5] The access to alkylidene carbenes remains, hovewer, challenging and their application in organic transformations has been poorly investigated. Among others, 1,3,4-oxadiazolines proved to serve as precursors of versatile intermediates under variable reaction modes.[5] While under UV light irradiation photolysis to non-stabilized diazo compounds occurs, thermolysis leads to heteroatom-substituted carbenes. Ley proposed to use oxadiazolines in UV light-induced aryl-alkyl cross-coupling and aldehyde C-H functionalization reactions.[6-7] Nevertheless, the development of milder approach that would broaden their applicability to UV light-sensitive substrates is still missing.

To reveal their full chemical potential, we have explored the reactivity of 1,3,4-oxadiazolines under visible light irradiation in the presence of electron-deficient olefins with the use of triplet energy transfer catalysis. Mechanistic experiments support energy transfer events and identify both carbene and diazoalkane as reaction intermediates.The designed procedure is efficiently leading to valuable spirocyclic products.



Visible light-mediated iridium-catalyzed formation of spirocyclic compounds with 1,3,4-oxadiazolines.

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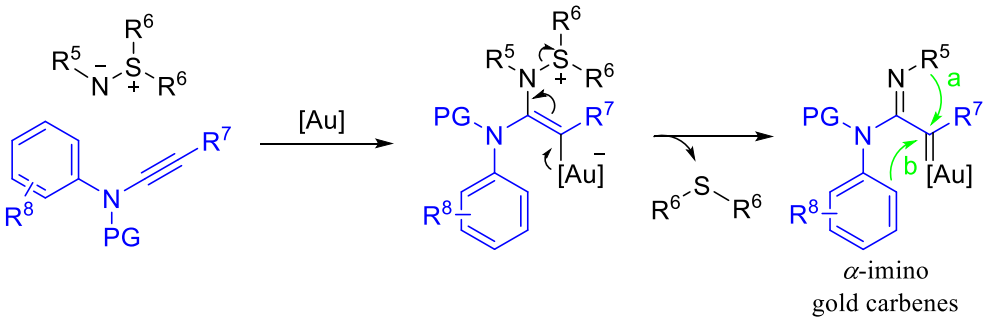
Sulfilimines in gold catalysis: a powerful tool for heterocycle synthesis

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Due to its operational simplicity and unique reactivities, gold catalysis has emerged as effective tool for the synthesis of various heterocycles with high interest for academia and industry.[1] The ability of gold catalysts to activate unsaturated bonds offers a broad synthetic spectrum of possible cyclization paths. Among them, α-iminocarbene intermediates have contributed essentially to the synthesis of bioactive nitrogen-containing skeletons. However, existing carbene precursors have limitations in terms of functional group tolerance, synthetic methods and safety concerns.[2]

Sulfilimines as gold nitrene transfer reagents:



Adressing these challenges, sulfilimines represent a new easy-to-handle generation of nitrene transfer reagents which can be synthesized from inexpensive, readily available starting materials.[3] Upon activation by gold catalysts, ynamides were shown to react with sulfilimines to pivotal α-iminocarbene intermediates by a formal nitrene transfer. This synthetic intermediate opens up various downstream transformations such as 1,2-H insertion[3], attack of nitrogen or oxygen nucleophiles[4,5], cyclopropanation[3] and C-H insertion[3,6] offering a library of functionalized heterocycles.[3,7]

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Catalytic asymmetric transformations of α-diazo carbonyl compounds involving metal or free carbene intermediates

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Metal carbenes have demonstrated to be versatile intermediates in organic synthesis, which are typically generated *in situ* from diazo precursors with various transition metal salts.[1] Among the numerous metal carbenes-based transformations, the asymmetric ylide rearrangements provide a facile access to chiral heteroatom-containing molecules (e.g. sulfur), but the enantiocontrol of this type of rearrangement through a catalyst-free and stable ylide intermediate is challenging. Our group tackled this issue by using a new kind of α-diazo pyrazoleamides and a dual-task chiral *N*,*N*'-dioxide-nickle(II) or cobalt(II) complex. Wherein, a metal carbene- and a Lewis acid-bonded sulfonium ylide intermediate were formed, triggering a series of highly enantioselective rearrangements processes, including Doyle−Kirmse reaction,[2b] [2,3]-Stevens and Sommelet−Hauser rearrangement,[2c] thio-Claisen rearrangement,[2d] as well as formal vinylogous N−H insertion[2f] and (2+1) cycloaddition[2g]. Moreover, we also made a breakthrough on the application of chiral guanidine-metal complex as a promotor in the metal carbenes-mediated asymmetric multicomponent reaction (AMCR) involving C-H insertion of α-diazoesters.[3] Very recently, a visible light-induced enantioselective C-C and C-H insertion of α-diazoesters through a free carbene was established as well by utilizing such a chiral bifunctional guanidine-amide organocatalyst.[4]

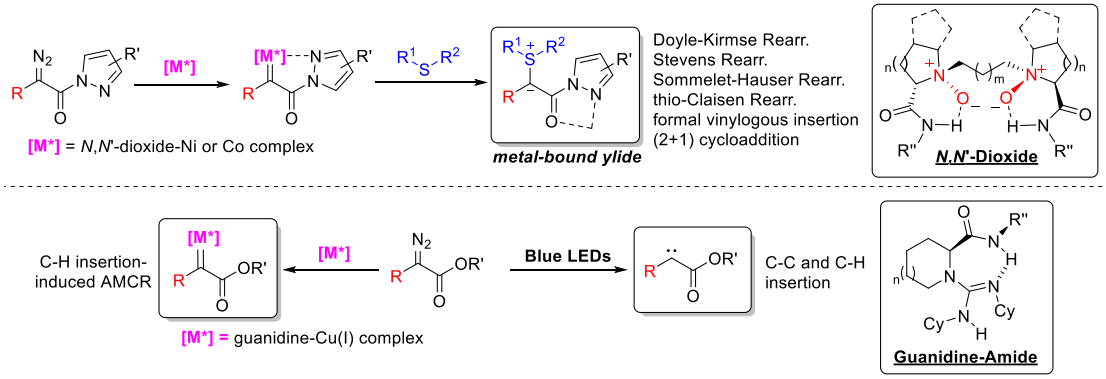


Figure 1 Catalytic asymmetric transformations of α-diazo carbonyl compounds through carbene intermediates

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Red light catalyzed functionalization of diazo compounds

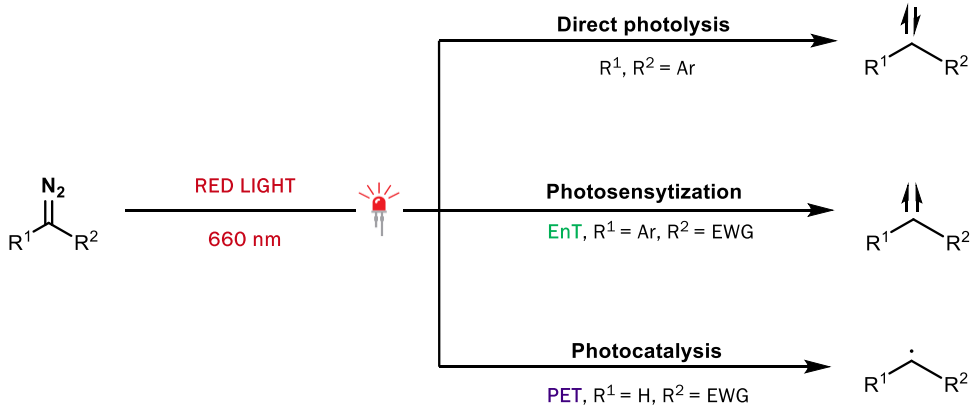
Katarzyna Orłowska,[1] Piotr Krajewski,[1] Joao Victor Santiago da Silva,[1] Katarzyna Rybicka-Jasińska*,[1] Dorota Gryko*,[1] Klaudia Łuczak[1]

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Diazo compounds, next to azides and diazirines, have reserved special place in organic and bioorganic chemistry. As biorthogonal chemical reporters those molecules can hastly be connected to particles and selective products, can take part in metabolic pathways.[1] In last decades meaningful synthons in modern organic chemistry are often generated from diazo compounds.[2-4] These include carbenes that react with wide range of substrates, forming products of insertions, Doyle-Kirmse rearrangement or cycloaddition. Diazo reagents can also generate another species such as radicals (with use the use of photoredox catalyst), or act as nucleophile for cross- dehydrogenative crosscoupling.

Most of organic substrates absorb in the ultraviolet (UV), blue and green spectral regions, warranting sensitization with long wavelength absorbing chromophores.[5] However, low energetic red and infrared light is safer to apply with low health risk and penetreates relatively deep in scattering in media.[6] Therefore, in our work sensitization and near-red absorbers are essential for activating with low-energy red light radiation. Despite the undeniable utility of porphyrins in blue- and green-light-induced energy- and electron-transfer processes, they are also perfectly suited for red light applications.

Herein, we use red light to drive photolysis of diazo molecules, and by adding porphyrins as photocatalyst we are able to prompt photoredox and photosensitizing processes. Direct photolysis transforms diazo compounds to singlet carbene species that then reacted with X-H donors. Tetraphenylporphyrins enable photosensitisation of diazo compounds not absorbing the red region leading to triplet carbenes, that engage cycloaddition and insertion reactions. Likewise, we proved universal utility of porphyrins in photoredox catalysis, where they catalyse formation of radicals from diazo compounds.



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A Palladium(II) Metallocarbene with Triplet Ground State

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Transition metal (TM) carbyne complexes ($L_nM{\equiv}C{-}R$) are key intermediates in alkyne metathesis and Fischer-Tropsch synthesis. Their chemistry has been extensively examined[1] since the first synthesis of a group 6 carbyne complex by Fischer et al in 1973.[2] Triple bonding of TM ions with terminal carbyne ligands requires vacant or partially filled d-orbitals with suitable σ- and π-symmetry, respectively . However, for low-valent late TM ions, high d-electron configurations reduce π-bonding and carbyne complexes with significant metallocarbene ($L_nM{-}C{-}R$) character are expected. which feature a metal-carbon single bond and adopt electronic singlet or triplet ground state. The Liu group has recently reported a gold(I) metallocarbene with singlet ground state, which was stabilized by π-donation of a phosphino substituents ($Au{-}C^{-}{=}P^{+}_2$).[3] However, authentic triplet metallocarbenes, that would be expected in the absence of π-stabilization remain elusive.

Here, we report the synthesis of a formal palladium(II) carbyne complex upon photolysis of trimethylsilyl-substituted diazomethanide precursor (Figure 1). Photocrystallographic, magnetic and computational characterization support nearly linear coordination of the singly-bonded carbon ligand and an electronic triplet ground state with predominant metallocarbene ($L_nPd^{II}{-}C{-}SiMe_3$), carbon-centred diradical character. Intramolecular decay by selective carbyne C–H insertion, as well as intermolecular trapping reactions with CO and phenol are reported.

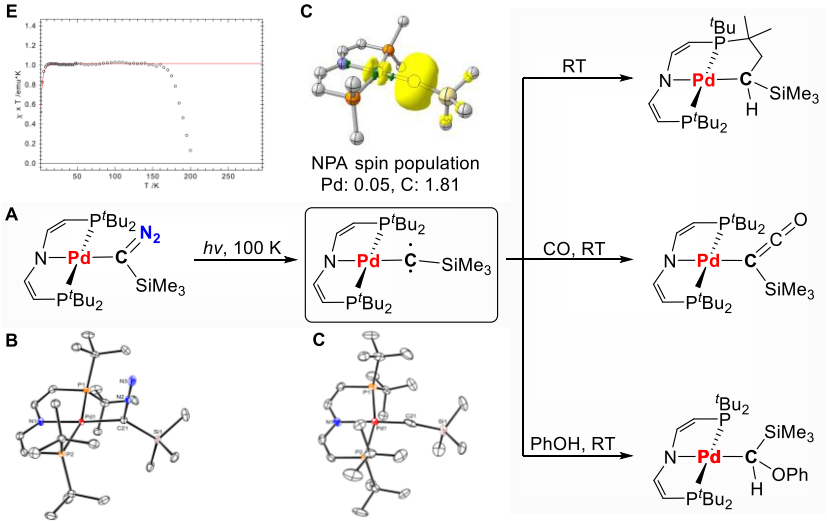


Figure 1. Synthesis, characterization and reactivity of the palladium(II) carbyne.

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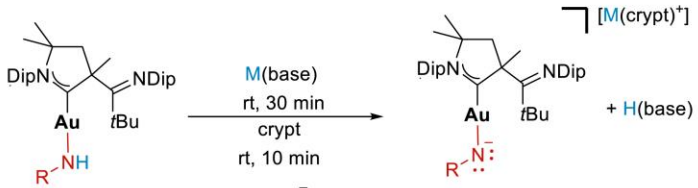
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Gold Terminal Imido Complexes

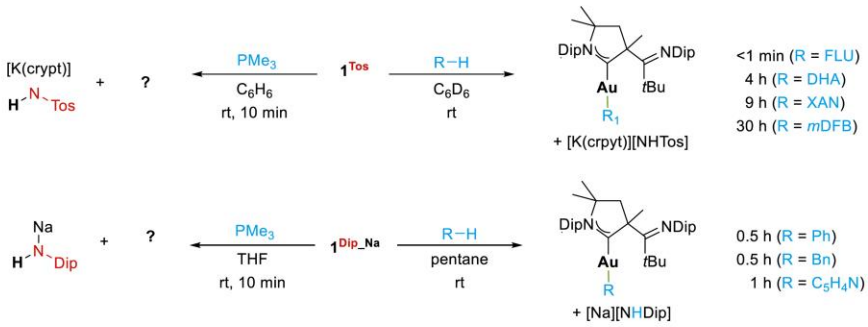
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Despite the application of transient gold nitrenes in catalysis, the isolation of gold terminal imido complexes remains hitherto elusive.[1-3] Following our work with palladium,[4,5] I will present on Au(I) terminal imido complexes. The synthesis of [K(crypt)][(CAAC)Au^{I}(NTos)] (**1^{Tos}**) was achieved *via* deprotonation of (CAAC)Au^{I}(NHTos), followed by removal of the coordinating potassium ion by the 2.2.2-cryptand. Following the same route, **1^{ArNO2}** and thermolabile **1^{Dip_Na}** could be isolated as well.



Interestingly, the addition of Lewis-Bases such as PMe_3 to **1** leads to the quantitative formation of the free amides. Complexes **1** are superbasic and metalate fluorene (FLU), 1,10-dihydroanthracene (DHA), xanthene (XAN) and 1,3-difluorobenzene (*m*-DFB). Complex **1^{Dip}** even metalates unactivated arenes such as toluene, benzene, and pyridine. Oxidation experiments of **1** are currently ongoing and point at the generation of Au(III) nitrenes.



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Styrene Aziridination with $[Co^{III}(TAML^{red})]^-$ in Water

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Enabling radical-type nitrene transfer reactions in water can open up a more comprehensive range of applications, such as the in vivo synthesis of medicines. However, these reactions typically suffer from oxygen-containing side-product formation, of which the origin is not fully understood. Therefore, we investigated aqueous styrene aziridination using a water-soluble $[Co^{III}(TAML^{red})]^-$ catalyst known to be active in radical-type nitrene transfer in organic solvents. The cobalt-catalyzed aziridination of styrene in water (pH = 7) yielded styrene oxide as the major product, next to minor amounts of aziridine. Based on ^{18}O-labeling studies, catalysis, and mass spectrometry experiments, we demonstrate that styrene oxide formation proceeds via hydrolysis of the nitrene radical complex $[Co^{III}(TAML^{sq})(N^{\bullet}Ts)]^-$. Computational studies support that this process is facile and yields an oxyl radical complex $[Co^{III}(TAML^{sq})(O^{\bullet})]^-$ active in oxygen atom transfer to styrene. Motivated by these mechanistic insights, we found that adjusting the pH affords selective aziridination (>99%) in water with respectable yields (up to 56%).

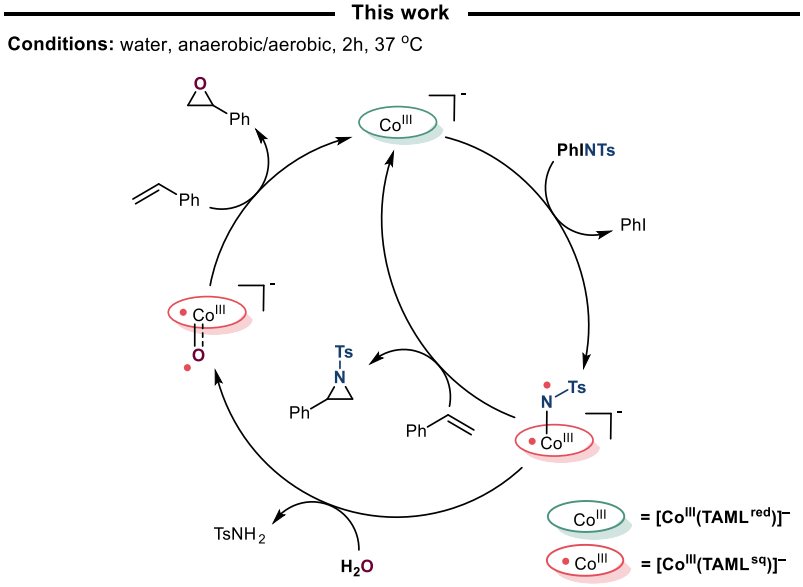


Figure 1: Competitive hydrolysis of the $[Co^{III}(TAML^{sq})(N^{\bullet}Ts)]^-$ complex yields a reactive $[Co^{III}(TAML^{sq})(O^{\bullet})]^-$ complex responsible for styrene oxide formation in water.

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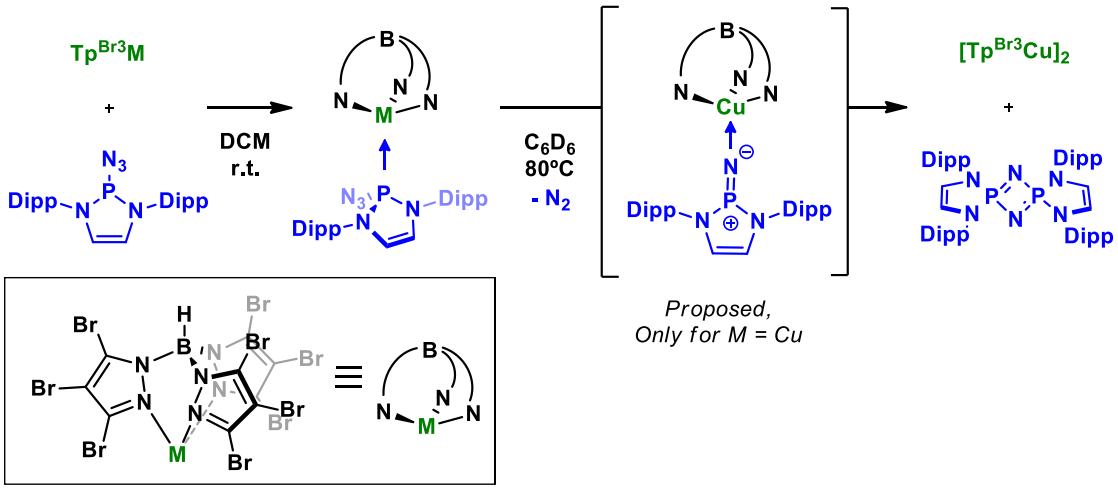
$Tp^{X}M$ (M= Cu, Ag) Complexes Bearing Phosphinoazide Ligands as Precursors of Metal-Nitrene Species

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During the last years, our research group has developed several catalytic systems based in a family of copper and silver complexes bearing hydrotrispyrazolylborate ligands (Tp^{x}) as efficient catalysts for the transfer of a nitrene unit to several substrates.[1] This transformation occurs through metal-nitrene intermediates which have been detected or isolated only in a few cases.[2]

In this contribution, we describe the synthesis and characterization of two $Tp^{Br3}M$-L adducts with a phosphoazide ligand (M = Cu, Ag and L = 2-azido-1,3-bis(2,6-diisopropylphenyl)-2,3-dihydro-1H-1,3,2-diazaphosphole). Thermal decomposition of both complexes has been studied, finding that copper promotes the formation of the corresponding cyclodiphosphazene by the formal dimerization of two phosphinonitrene units.[3] In addition, this process has been further explored in a catalytic manner by the decomposition of the phosphinoazide in the presence of the $Tp^{Br3}Cu(NCMe)$ complex.



$Tp^{Br3}M$ complexes (M= Cu, Ag)

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Stereoselective synthesis of pyrrolidines *via* two consecutive C(sp^3)-H aminations

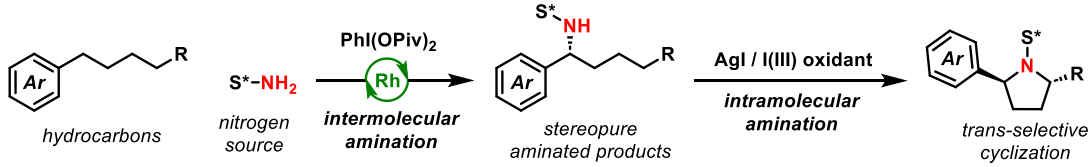
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Nitrogen containing heterocycles are ubiquitous in natural products, pharmaceuticals and agrochemicals. In particular, pyrrolidines are found in a range of bioactive compounds and are a privileged motif for catalyst design in asymmetric catalysis.[1] Herein, we present the asymmetric synthesis of enantiopure 2,5-disubstituted pyrrolidines *via* a streamlined strategy relying on two sequential C(sp^3)-H aminations of simple hydrocarbons.[2]

The first step of our strategy was a stereoselective intermolecular C-H amination reaction catalyzed by rhodium(II) complexes and mediated by a iodine(III) oxidant. Along this line, we performed a nitrene C-H insertion on benzylic positions using the synergistic combination of a chiral rhodium(II) catalyst and an enantiopure sulfonimidamide as chiral auxiliary.[3] When applied to 1,4-diarylbutane derivatives, this catalytic system gave stereochemically pure aminated products awaiting for cyclization.

The second step relied on a Hofmann-Löffler-Freytag (HLF) reaction involving a 1,5-HAT followed by a diastereoselective cyclization. Inspired by the recent work of Nagib and coworkers on HLF reactions,[4] we optimized a protocol based on a tailored hypervalent iodine oxidant and AgI as iodide source that led to *trans*-pyrrolidines with good diastereoisomeric ratios. Conveniently, the chiral auxiliary could be removed under reductive conditions (Mg in MeOH or Li/naphthalene) to afford the corresponding unprotected enantiopure pyrrolidines.



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Synthesis Reactivity of a Pincer-Stabilized Nickelacyclobutane

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Metallacyclobutanes are important reactive intermediates present in catalytic cycles such as olefin metathesis and cyclopropanation.[1-3] They can undergo reductive elimination yielding cyclopropane derivatives or cycloreversion and β-hydride elimination/reductive elimination yielding different types of alkenes (Figure 1).[2-4] However, a general understanding of what governs their reactivity towards each route is lacking. For nickel, early studies reported the influence of the coordination number of the nickel center in the major product of decomposition of nickelacyclobutanes by the identification of the resulting organic products. It was suggested that transient pentacoordinated nickelacycles enhanced the formation of metathesis products, an uncommon pathway for nickel complexes.[5,6]

In this contribution, we report the isolation and characterization of an unusual pentacoordinated nickelacyclobutane incorporated in a pincer complex. The nickelacyclobutane is stable in weakly coordinating solvents allowing the isolation and full characterization including an X-ray crystal structure. The rich reactivity of the isolated nickelacyclobutane includes cyclopropanation, carbene transfer, metathesis, and formal β-hydride elimination. With the help of DFT calculations, the factors controlling the selectivity of nickelacyclobutane decomposition are investigated.[2]

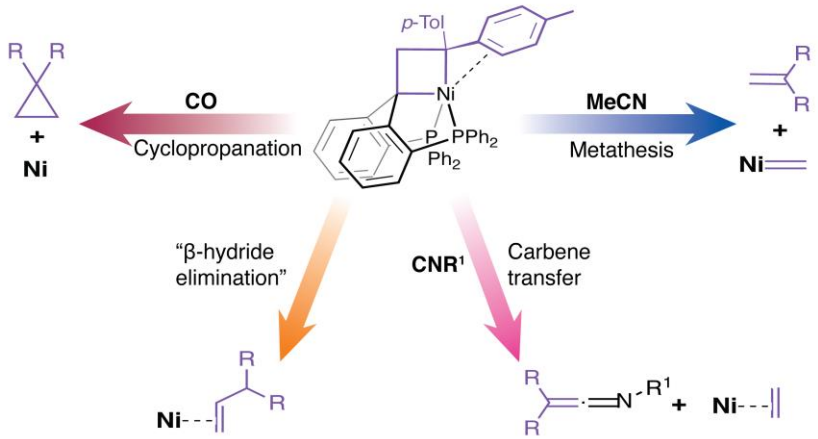


Figure 1. Decomposition routes of a nickelacyclobutane in a pincer ligand framework.

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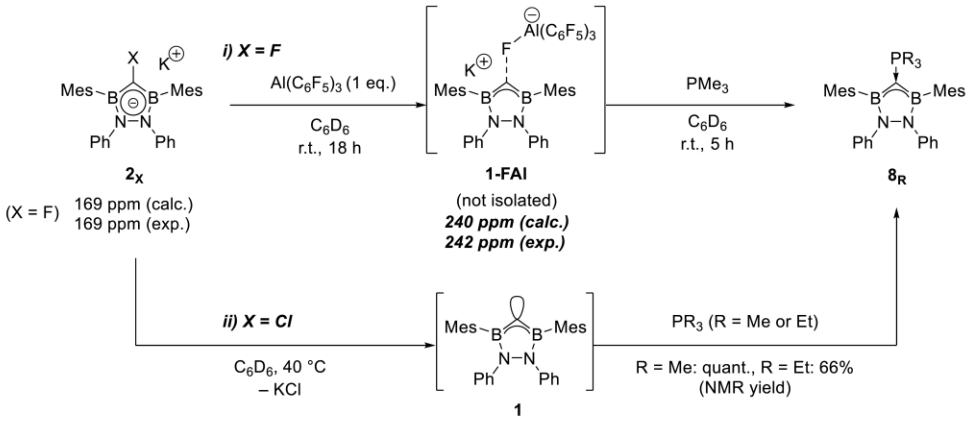
Synthesis, Characterization and Trapping of a Cyclic Diborylcarbene, an Electrophilic Carbene

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Carbene is a neutral and divalent carbon species possessing two unshared electrons. Singlet carbene has one vacant orbital and one lone pair on the carbene carbon, thus can exhibit both Lewis acidity and basicity. However, as represented by N-heterocyclic carbene, highly Lewis basic carbenes stabilized by π-donating substituent(s) on the carbene carbon have mainly been focued on in the chemistry of carbene[1]. The situation would be completely opposite in case both substituents on the carbene carbon are π-accepting ones. Diborylcarbene (DBC) wherein the carbene carbon has two boryl substituents is the representative of Lewis acidic carbene. DBC has been examined only by theoretical calculations[2–4] and trapping reactions[2, 5–9], and never been isolated or even observed in a matrix-isolated state due to its instability.

Herein, we develop novel chemical equivalnets of DBC **1**, K/X-diborylcarbenoids $\mathbf{2_X}$ (X = F or Cl). Diborylcarbenoids $\mathbf{2_X}$ can afford DBC **1** by releasing the halogen atom on the carbenoid carbon. Treatment of $\mathbf{2_F}$ with $Al(C_6F_5)_3$ yielded $[AlF(C_6F_5)_3]^-$-stabilized DBC **1-FAl**, which showed a significant low-field shift of the carbenoid carbon from 169 ppm (doublet, coupling with ^{19}F) to 242 ppm (singlet) as shown in Scheme i). The loss of halogen was also detected through ESI-TOFMS analysis of $\mathbf{2_X}$ only in the presence of $Al(C_6F_5)_3$. Generated DBC **1** from **1-FAl** or $\mathbf{2_{Cl}}$ was successfully trapped with excess amounts of trialkylphosphines (PR_3, R = Me or Et), which afforded the corresponding DBC-PR_3 adducts $\mathbf{1\text{-}PR_3}$. In addition, the Lewis acidity of DBC **1** was evaluated both experimentally and theoretically to reveal that **1** is one of the most Lewis acidic species among neutral molecules.



Scheme. i) Fluoride abstraction and trapping reaction from $\mathbf{2_F}$; ii) Trapping reactions from $\mathbf{2_{Cl}}$.

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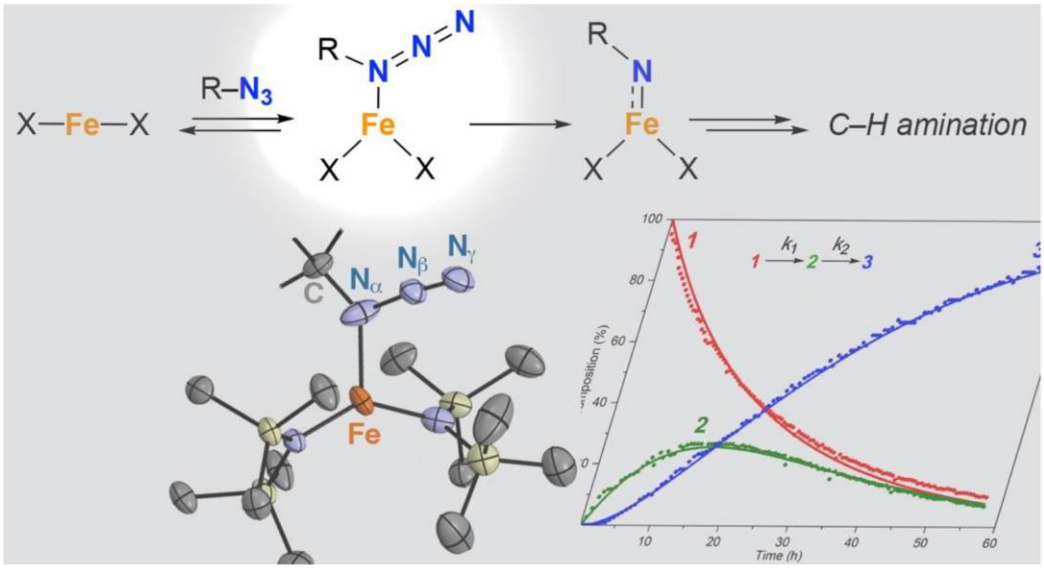
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Synthesis and Reactivity of a Stable Organoazide Iron Complex and its Relevance to C–H Bond Amination

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The formation of C–N bonds is of paramount importance for synthesis of pharmaceuticals, agrochemicals and natural products.[1] Complexes with organic azides are critical precursors for the formation of nitrene systems en route to the direct C–H amination, forming C–N bonds very efficiently and sustainably. Despite their relevance, first-row transition metals with α-organoazide coordinated are extremely rare,[2,3] and they have been elusive so far for iron, even though iron complexes are by far the most active C–H amination catalysts with organic azides.[4-6]



In this contribution we will show the first example of the full characterization of such an organoazide iron complex. We will demonstrate the further reactivity to a transient nitrene intermediate and discuss reactivity of the azide both in solution and in crystallo. The characterization of both these intermediates is of paramount importance for understanding the catalytic C–H amination reaction and for designing new and improved catalytic systems.

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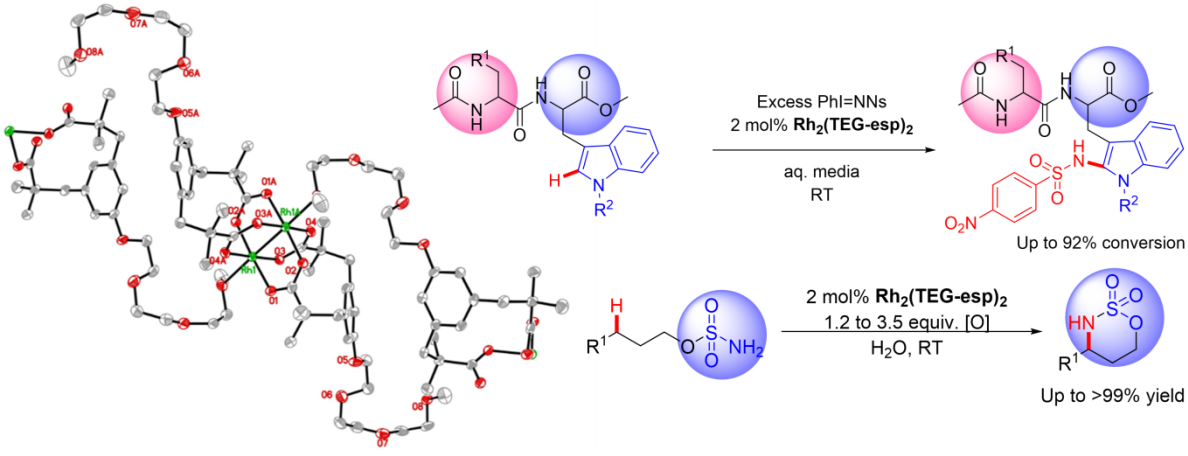
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Nitrene Transfer Mediated by a New Water-soluble Dirhodium (II) Carboxylato Complex in Aqueous Media

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Dirhodium-catalyzed C–H amination has been a promising and versatile tool in the construction of a vast array of organic molecules containing C–N bonds. However, the use of water as solvent for nitrene transfer has almost been underexplored, as the active intermediates were most prone to decomposition in the aqueous environment. In this work, we report a new water-soluble dirhodium (II) paddlewheel complex, **Rh_2(TEG-esp)$_2$**, that efficiently catalyzes C–H amination in the aqueous media under ambient conditions. Using the hypervalent iodine reagent PhI=NNs, the N-protected tryptophan residues on various short peptides were successfully modified with conversion up to 92%. Meanwhile, **Rh_2(TEG-esp)$_2$** also serves as a competent catalyst in the intramolecular cyclization of sulfamate ester to form the corresponding six-membered cyclized product in water. These results demonstrate the potential of applying metal-mediated nitrene transfer chemistry in water for both greener organic synthesis and bioconjugation reactions.



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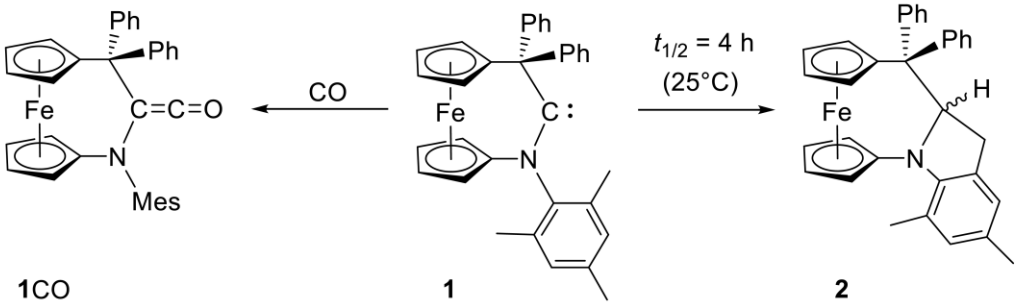
Highly Ambiphilic Cyclic (Alkyl)(amino)carbenes with a 1,1'-Ferrocenylene Backbone

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Standard five-membered N-heterocyclic carbenes (NHCs) are almost exclusively nucleophilic and hence lack the ambiphilic profile necessary for small-molecule activation.[1] In contrast, we found that formally six-membered NHCs with a 1,1'-ferrocenylene backbone (fcNHCs) react readily with fundamentally important small molecules like NH_3 and CO.[2] This unconventional reactivity may be ascribed to the large $C_{carbene}$ bond angle (ca. 120°), which causes a small HOMO–LUMO gap, leading to an ambiphilicity similar to that of cyclic (alkyl)(amino)carbenes (CAACs), which are famous for reacting with NH_3, CO, and even H_2 under mild conditions.[3]

In this contribution we report on a combination of fcNHCs and CAACs, namely cyclic (alkyl)(amino)carbenes with a 1,1'-ferrocenylene backbone (fcCAACs). We have prepared the crystalline fcCAAC **1** (see Figure). While its nucleophilicity is similar to that of standard CAACs, **1** exhibits an electrophilicity higher than that of any previously reported CAAC. Consequently, the HOMO–LUMO gap is unprecedentedly small for a CAAC,[4] which augurs well for a high competence of fcCAACs in small-molecule activation chemistry. In fact, **1** reacts readily with CO even below room temperature to yield the thermally stable ketene **1**CO. No reaction of **1** was observed with H_2, because an intramolecular C–H insertion reaction affording compound **2** is kinetically preferred.



1CO **1** **2**

Currently, we are working on homologues with *N*-substituents not prone to undergo intramolecular reactions leading to compounds of type **2** in order to achieve unprecedented intermolecular reactivity with fcCAACs.

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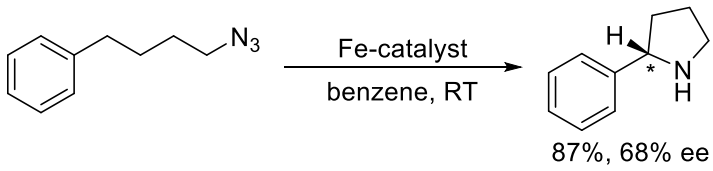
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Developing a Novel Iron Catalyst for Enantioselective C-H Bond Amination

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The challenge of efficiently and reliably forming C–N bonds remains a prominent issue in organic synthesis. In order to address this challenge, the functionalization of C–H bonds through amination reactions has garnered attention due to their abundance in organic molecules.[1] This research focuses on synthesizing and characterising a novel iron catalyst for enantioselective C-H bond amination reactions. The catalyst was designed to enable efficient nitrene formation without the need for additional additives, offering a sustainable and practical approach to access chiral amine derivatives. To demonstrate the effectiveness of the catalyst, it was tested against various azides, leading to high yields of desired products and achieving impressive enantiomeric excesses. The influence of steric side groups on the enantioselectivity was investigated, revealing a relation between the introduction of sterical hindrance and enhanced enantioselectivity. Furthermore, the isolation and characterization of the nitrene species was accomplished. Additionally, a kinetic isotope effect (KIE) experiment was performed to gain further insights into the reaction mechanism.



87%, 68% ee

References

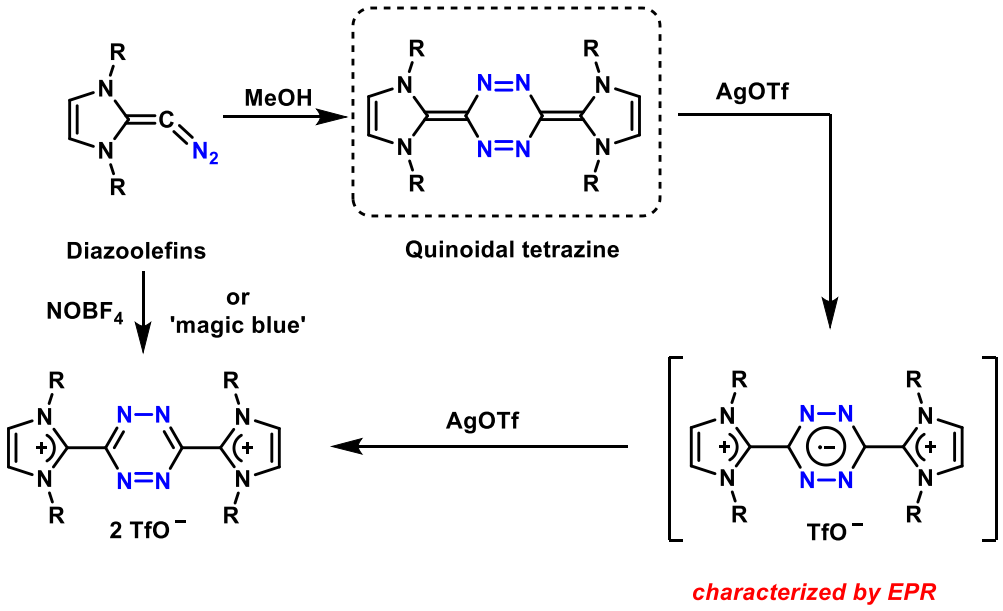
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Head-to-Tail Dimerization of N-Heterocyclic Diazoolefins

Paul Varava, Tak Hin Wong[1], Zhaowen Dong, Anastasia Yu. Gitlina, Andrzej Sienkiewicz, Wolfram Feuerstein, Rosario Scopelliti, Farzaneh Fadaei-Tirani, Kay Severin*

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Room temperature stable N-heterocyclic diazoolefins were isolated by our group[1] and by Hansmann's group[2] in 2021. N-heterocyclic diazoolefins can undergo [2+3] cycloaddition reactions. The ylidic carbon can also coordinate with metal complexes and Lewis acids. Our group recently discovered an unprecedented type of cycloaddition reaction for N-heterocyclic diazoolefins: the head-to-tail dimerization.[3] This formal [3+3] cycloaddition gives strongly reducing quinoidal tetrazines. The oxidation of quinoidal tetrazines proceeds in a stepwise manner, with an isolable and room temperature-stable radical cation as an intermediate. The radical could be characterized by EPR spectrometry, and a singlet with hyperfine splitting due to the coupling to four ^{14}N nuclei was observed. The final oxidation product contains a tetrazine core with two imidazolium substituents. The dication can also be prepared from diazoolefins directly by reactions with oxidants like nitrosonium tetrafluoroborate or 'magic blue'.



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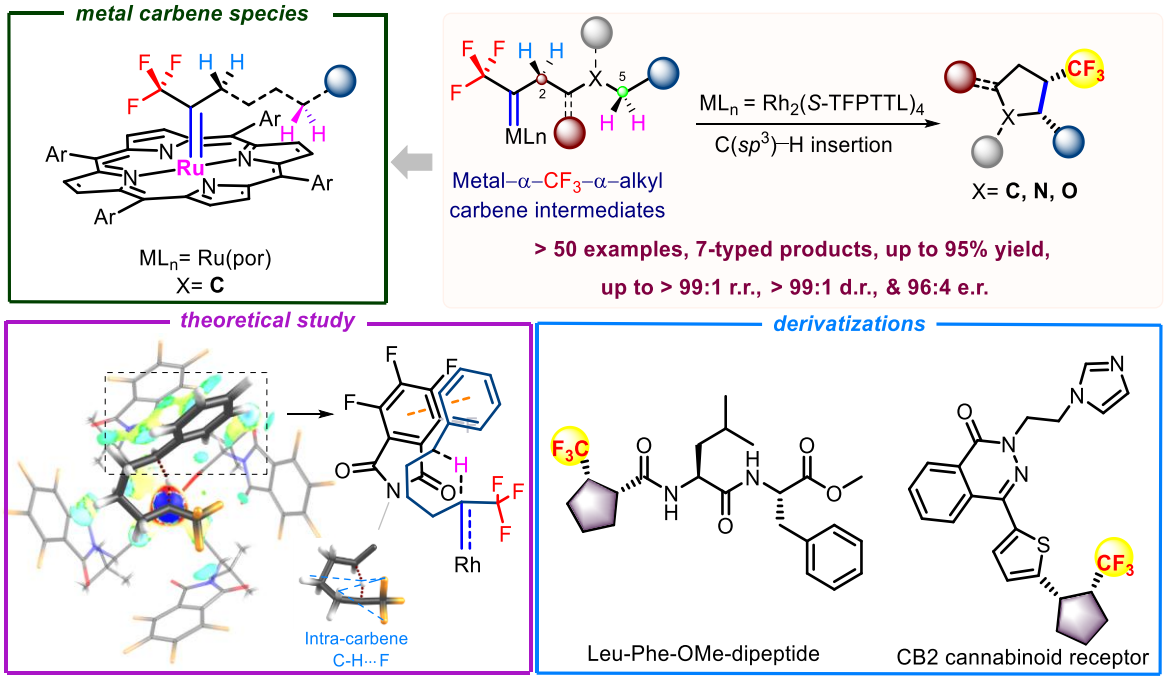
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A Convergent, Modular Approach to Trifluoromethyl-Bearing 5-Membered Rings via Catalytic C(sp^3)-H Activation

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Trifluoromethyl-bearing 5-membered rings are prevalent in bioactive molecules,[1] but modular approaches to these compounds by functionalization of robust C(sp^3)-H bonds in a direct and selective manner are extremely challenging.[2] Herein we report the rhodium-catalyzed α-CF_3-α-alkyl carbene insertion into C(sp^3)-H bonds of a broad range of substrates to access 7 types of CF_3-bearing saturated 5-membered carbo- and heterocycles. The reaction is particularly effective for benzylic C-H insertion exerting good site-, diastereo- and enantiocontrol, and applicable to the synthesis of chiral CF_3 analogues of bioactive molecules. Ruthenium α-CF_3-α-alkyl carbene complexes underwent stoichiometric reactions to give C-H insertion products, lending evidence for the involvement of metal α-CF_3-α-alkyl carbene species in the catalytic cycle. DFT calculations revealed that the π···π attraction and intra-carbene C H···F hydrogen bond elucidate the origin of selectivity of the benzylic C H insertion reactions.



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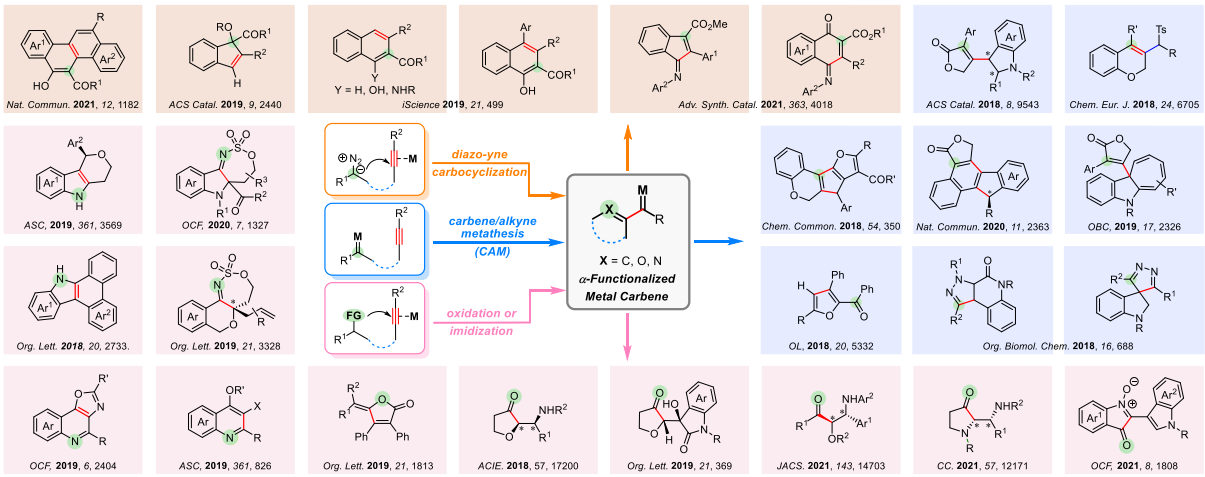
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Catalytic Alkyne Functionalization Involving Metal Carbene Species

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Catalytic alkyne transformations have demonstrated broad applications in synthetic chemisty.[1] Especially, alkyne has heavily emerged as a practical and safe carbene precursor in recent two decades. Generally, catalytic oxidation, imidization, diazo-yne carbocyclization and carbene/alkyne metathesis(*CAM*) are four general types of protocols for the generation of *α*-oxo metal carbene, *α*-imino metal carbene, and *α*-vinyl metal carbene species from readily avaibale alkynes.[2] Metal carbene mediated catalytic alkyne transformations have offered an efficient tool box for the expeditious construction of various heterocyclic skeletons and carbocyclic skeletons.[3,4] Moreover, through the introduction of metal and chiral organocatalyst cooperative catalysis stratagy, a series of asymmetric transformations for the multi-functionalization of alkynes have been achieved, thus efficiently constructing chiral poly-functionalized molecules with structural diversity.[5] Further applications based on this strategy could be envisioned for the novel methodology development and expeditious construction of complex and polyfunctionalized molecules, which might led to the discovery of unique molecules with remarkable anti-cancer activities.



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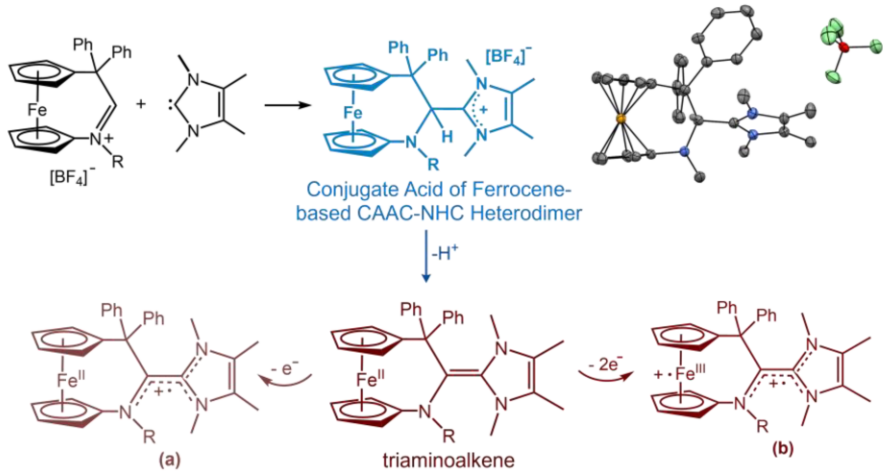
Conjugate Acids of Ferrocene-based CAAC-NHC Heterodimers

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Cyclic (alkyl)(amino)carbenes (CAACs) have a significantly more pronounced ambiphilic character in comparison to traditional N-heterocyclic carbenes (NHCs).[1] CAAC scaffolds are highly suitable for stabilizing carbon-based radicals.[2] CAAC-NHC heterodimers (triaminoalkenes) play a prominent role in this context.[3] They can show several stable redox states, which augurs well for a broad range of applications similar to tetrathiafulvalenes, as was noted in a seminal paper.[4] We envisage that their fascinating redox properties may be extended even further by using a CAAC with a redox-active 1,1´-ferrocenediyl backbone, giving rise to additional redox states.

We recently reported a CAAC with a 1,1´-ferrocenediyl backbone, which shows a particularly pronounced ambiphilicity in comparison to other isolable CAACs.[5] We have synthesized conjugate acids of CAAC-NHC heterodimers with ferrocene-based CAAC precursors and sterically less demanding N-methyl substituted five-membered NHCs. The suitability of these compounds for the synthesis of the corresponding ferrocene-based triaminoalkenes as well as their possible organoradicals (**a** and **b**) are presently under investigation.



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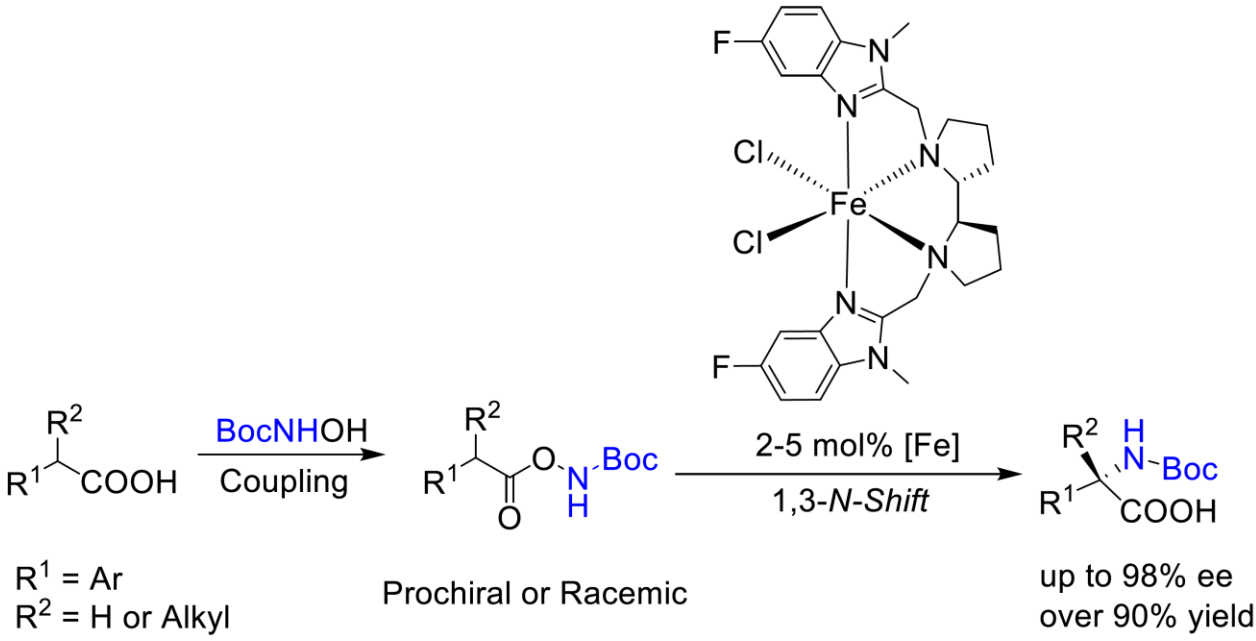
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Iron(II)-Catalyzed Synthesis of Chiral α-Amino Acids by 1,3-Nitrogen Migration

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Asymmetric functionalization of C−H bonds, especially the radical type, is one of the most attractive and efficient strategies in asymmetric synthesis, which has received increasing attention in recent years.[1] Amino acids have encountered widespread applications for the preparation of biologically active molecules and peptidomimetic drugs.[2] Here we describe our progress in asymmetric C(sp^3)−H activation catalyzed by a class of chiral Iron(II) complexes, which provides a straightforward and highly efficient method for the enantioselective synthesis of unnatural α-amino acids.[3] This method displays a broad scope, providing rapid access to optically active *N*-Boc-protected α-amino acids with aryl, heteroaryl, and alkyl side chains, and both α-monosubstituted and α,α-disubstituted α-amino acids exhibit high activity (over 90% yield) and high Enantioselectivity (up to 98% ee).



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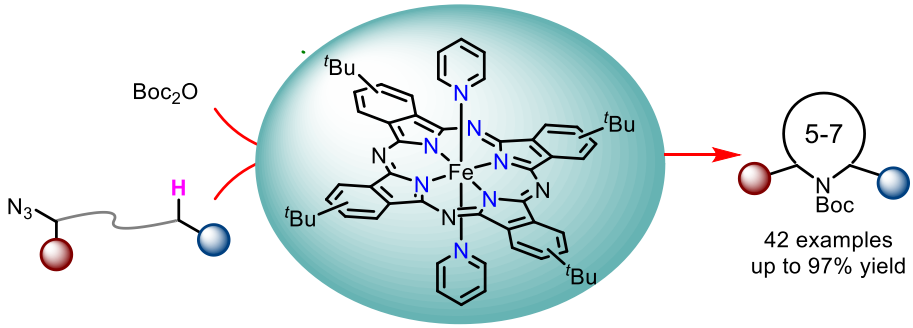
A Soluble Iron(II)-Phthalocyanine-Catalyzed Intramolecular C(sp^3)–H Amination with Alkyl Azides

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Abstracts

Direct C(sp^3)–H bond amination via metal-catalyzed alkylnitrene C–H insertion is a powerful tool for accessing *N*-heterocycles,[1] which are ubiquitous in pharmaceuticals and natural products. Herein, we described a soluble iron(II)-phthalocyanine, [Fe^{II}(^{t}Bu$_4$Pc)(py)$_2$] (Pc = phthalocyaninato(2–)), as an effective catalyst in intramolecular C(sp^3)–H bond amination of alkyl azides, to afford various types of *N*-heterocycles in moderate to excellent yields with a broad substrate scope.[2] We also applied this practical method for late-stage functionalization of pharmaceuticals and the preparation of natural product derivatives, which were generated with good product yields.



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Artificial Metalloenzyme-Catalyzed Enantioselective Amidation via Nitrene Insertion in Unactivated C(sp^3)–H Bonds

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Enantioselective C–H amidation offers attractive means to assemble C–N bonds to synthesize high-added value, nitro-gen-containing molecules. In recent decades, complementary enzymatic and homogeneous-catalytic strategies for C–H amidation have been reported. Herein, we report on an Artificial Metalloenzyme (ArM) resulting from anchoring a biotinylated Ir-complex within streptavidin (Sav). The resulting ArM catalyzes the enantioselective amidation of un-activated C(sp^3)–H bonds. Chemogenetic optimization of the Ir cofactor and Sav led to significant improvement in both activity and enantioselectivity. Up to > 700 TON and 92% ee for the amidation of unactivated C(sp^3)–H bonds was achieved. The single crystal X-ray analysis of the artificial nitrene insertase (ANIase) combined with quantum me-chanics-molecular mechanics (QM-MM) calculations sheds light on critical second coordination sphere contacts lead-ing to improved catalytic performance.

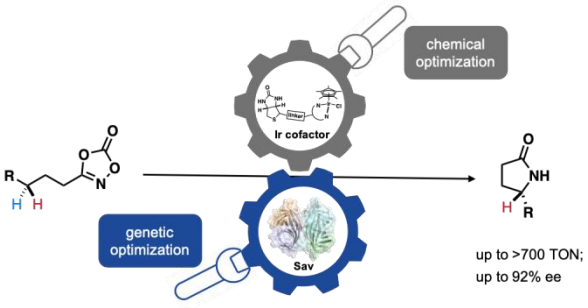


Figure 1. Artificial Metalloenzyme (ArM)-Catalyzed Enantioselective Amidation via Nitrene Insertion in Unactivated C(sp^3)-H Bonds

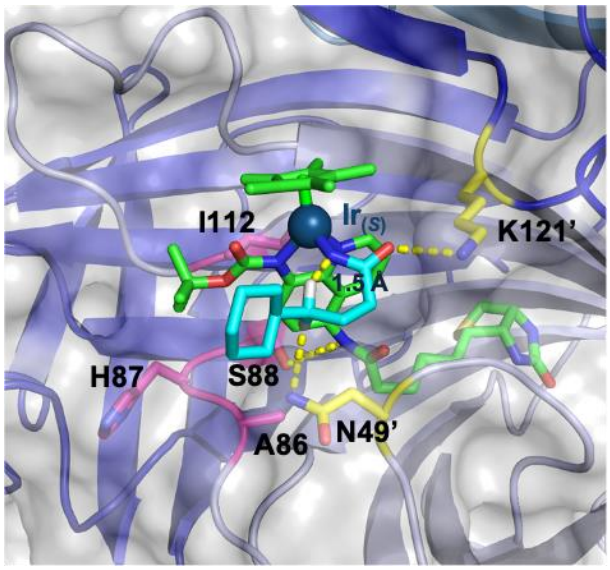


Figure 2. QM-MM calculations of the reaction path leading to the enantiopure product based on crystal structures of the ANIase.

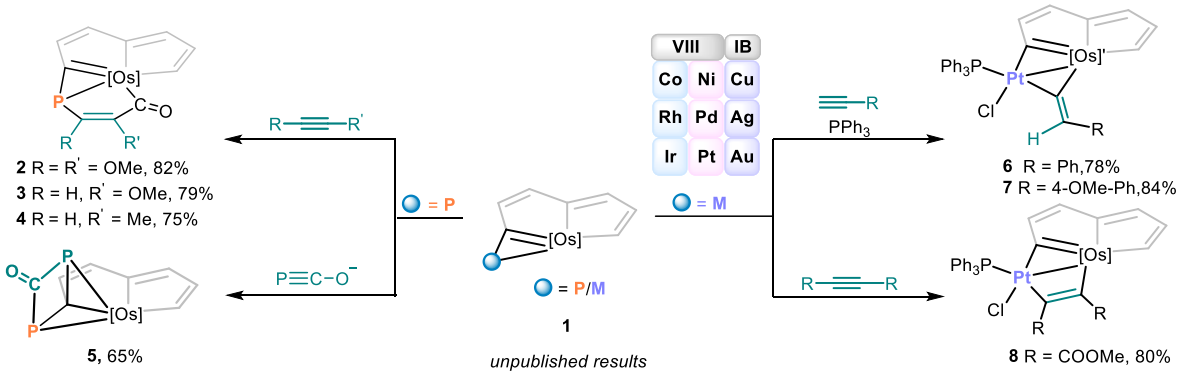
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Small Rings Containing Metal-Carbene Bonds

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Metallaaromatics represent a distinct species of aromatics, which have been broadly recognized as compounds structurely 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 bonds[2-10]. Very recently, the synthesis of strained bimetallacyclopropenes and phospha-metallacyclopropenes 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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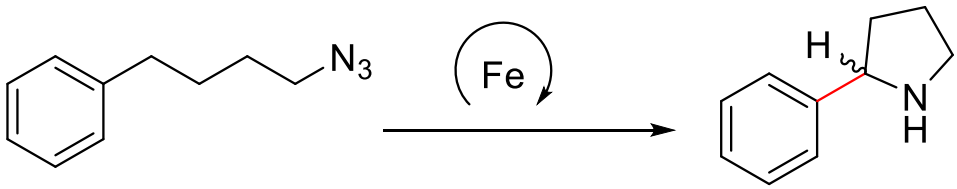
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Iron-catalyzed Asymmetric Intramolecular Nitrene Transfer Reactions

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N-heterocycles play a crucial role in the realm of bioactive molecules. The utilization of iron-catalyzed intramolecular C-H amination through organic azides offers an invaluable and sustainable approach for the targeted and atom-efficient synthesis of these heterocyclic motifs.[1] Following up on previous work from our group,[2] we herein investigate several iron-based catalysts capable of facilitating catalytic nitrene group transfer under mild reaction conditions, without the need for additives, while maintaining high chemoselectivity. Notably, by tuning the ligand, we are able to also achieve high levels of asymmetric induction in the resulting product - asymmetric C(sp^3)-H aminations are still scarce.[3,4] Furthermore, our study includes mechanistic investigations, employing several analyticaltechniques.



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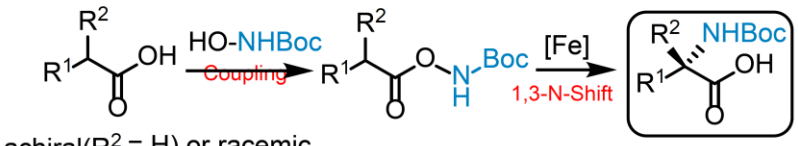
N-Boc Protected α-Amino Acids by 1,3-Migratory Nitrene C(sp^3)-H Insertion

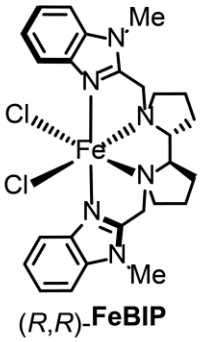
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Recently, we invented a new strategy for the synthesis of α-amino acids in which carboxylic acids are ligated to a nitrene precursor followed by a stereocontrolled 1,3-nitrogen shift from the carboxylic acid oxygen to the α-carbon.[1] Mechanistically, after ligation to an azanyl ester, the transition metal catalyst inserts into the O-N bond to form a transition metal nitrene which undergoes a stereocontrolled intramolecular C(sp^3)-H insertion into the coordinated carboxylate fragment, which constitutes an unprecedented 1,3-migratory nitrene C(sp^3)-H insertion reaction. This surprisingly simple and straightforward new two-step protocol has several attractive features: (1) it employs carboxylic acids as abundant and easily accessible feedstock molecules, (2) inexpensive and environmentally benign iron[2] can serve as the catalytic metal for the stereocontrolled nitrogen migration, and (3) the method displays a very broad scope providing rapid access to non-racemic α-monosubstituted α-amino acids with aryl, allyl, propargyl, and alkyl side chains, and even α,α-disubstituted α-amino acids. However, our previous work was limited to the synthesis of α-amino acids containing the 2,2,2-trichloroethoxycarbonyl (Troc) protecting group at the α-amino group, although the *tert*-butyloxycarbonyl (Boc) protecting groups are far more common in amino acid chemistry including peptide couplings.[3]

Herein, we introduce a two-step protocol to access non-racemic *N*-Boc-protected α-amino acids. In the first step, the carboxylic acid is coupled with *tert*-butyl aminocarbonate (BocNHOH) to generate azanyl ester (acyloxycarbamate) RCO_2NHBoc. In the second step, this azanyl ester undergoes a stereocontrolled iron-catalyzed 1,3-nitrogen migration to generate the *N*-Boc-protected non-racemic α-amino acid. The straightforward protocol is applicable to the catalytic asymmetric synthesis of α-monosubstituted α-amino acids with aryl, alkenyl, and alkyl side chains. *N*-Boc- protected α-amino acids synthesized using this two-step protocol are ready-to-use building blocks.





(*R*,*R*)-**FeBIP**

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Photoredox-Enabled Self-[3 + 2] Cyclization of Vinyldiazo Reagents: Synthesis of Cyclopentenyl α-Diazo Compounds

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Vinyldiazo compounds have a rich and varied reactivity due to the presence of conjugated alkene and diazo group in their structure, rendering themselves prominent building blocks for organic synthesis.[1] The major use involves the facile decomposition of vinyldiazo compounds by transition metal catalysts to form electrophilic vinylmetal carbenes species. Recently, we have demonstrated that vinyldiazo compounds could be used as three-carbon radical acceptors under visible light conditions (Figure 1, a).[2] However, the conservation of the reactive vinyldiazo functional group, while manipulating the remaining molecular skeleton, is significantly underdeveloped.

Herein, we present a photocatalytic self-[3 + 2] cycloaddition of vinyldiazo compounds is described, which provides cyclopentene derivatives with retention of one diazo functionality (Figure 1, b). Experimental insights and DFT calculations implicate that the reaction is triggered by the single electron oxidation of vinyldiazo compounds in the presence of an iridium photocatalyst, while another molecule of vinyldiazo reagents serves as a nucleophilie to intercept the radical cations. The synthetic applications of the resultant cyclopentenyl α-diazo compounds were demonstrated based on the rich chemistry of diazo group.

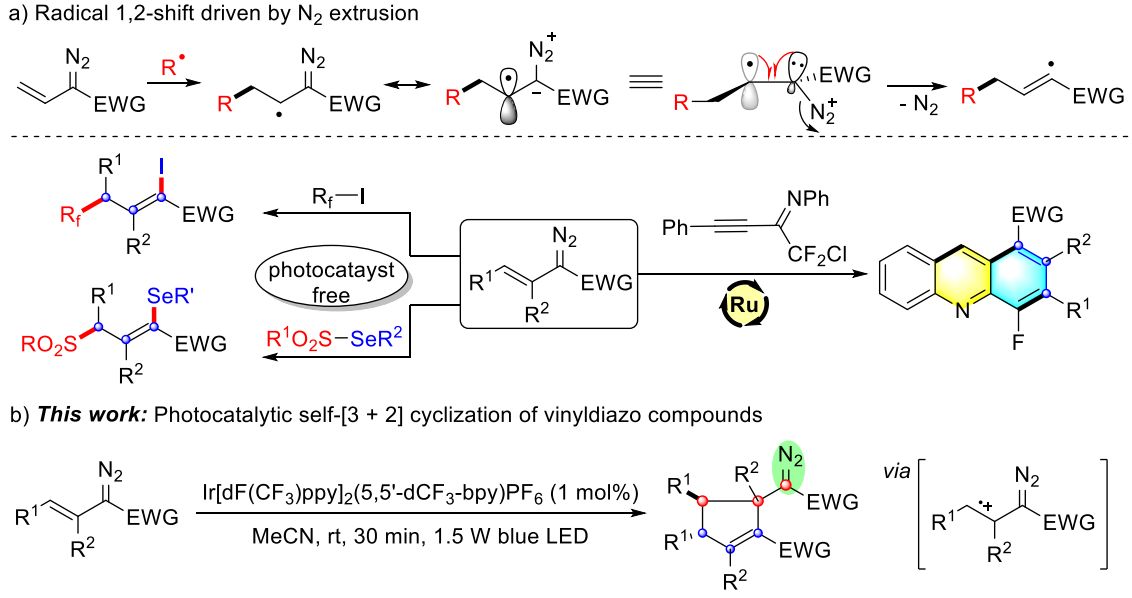


Figure 1 Visible light-promoted radical reactions of vinyldiazo compounds

References

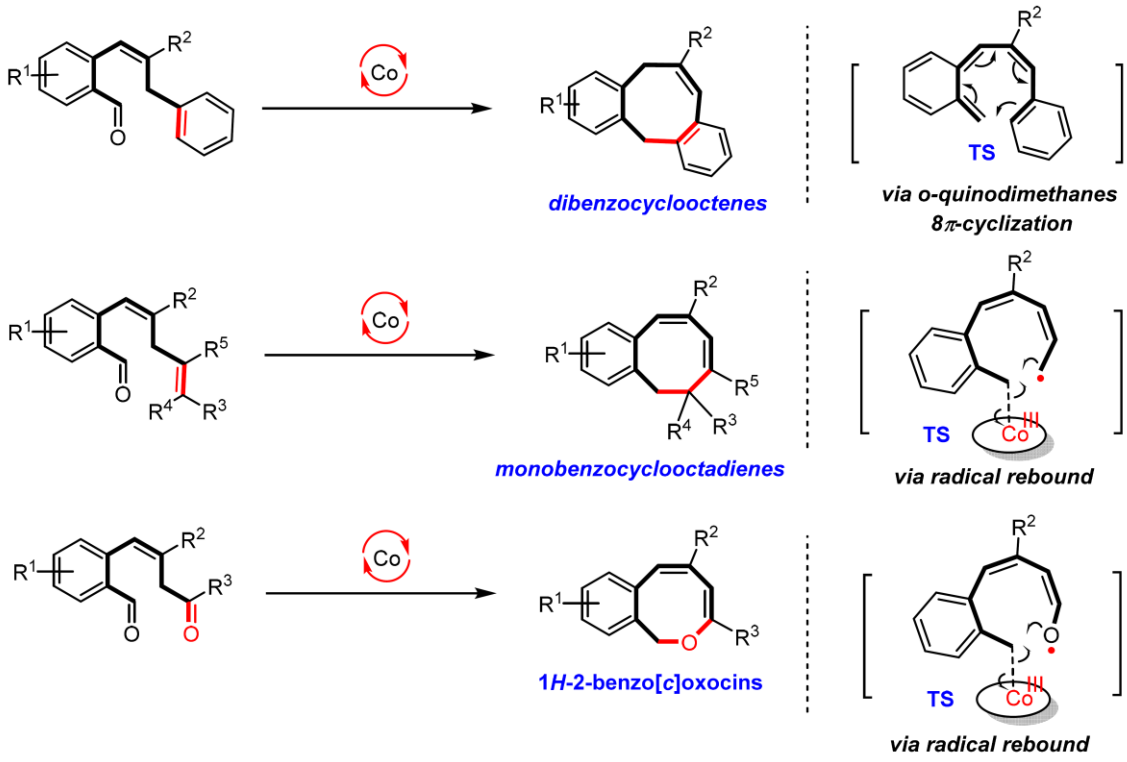
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Catalytic Synthesis of Medium-Sized Ring Systems via Cobalt(III)-Carbene Radicals

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The metalloradical activation of *o*-aryl aldehydes with tosylhydrazide and a cobalt(II porphyrin catalyst produces cobalt(III)-carbene radical intermediates, providing a new and powerful strategy for the synthesis of medium-sized ring structures. Herein we make use of the intrinsic radical-type reactivity of cobalt(III)-carbene radical intermediates in the [Co^{II}(TPP)]-catalyzed (TPP = tetraphenylporphyrin) synthesis of three types of 8-membered ring systems: dibenzocyclooctenes, monobenzocyclooctadienes, and 1*H*-2-benzo[*c*]oxocins. The method was successfully applied to afford a variety of 8-membered ring compounds in good yields and with excellent substituent tolerance. Density functional theory (DFT) calculations and experimental results suggest that the reactions proceed via hydrogen atom transfer from the bis-allylic/benzallylic C–H bond to the carbene radical, followed by two divergent processes for ring-closure to these 8-membered ring products. While the dibenzocyclooctenes are most likely formed by dissociation of *o*-quinodimethanes (*o*-QDMs) which undergo a non-catalyzed 8π-cyclization, DFT calculations suggest that ring-closure to the monobenzocyclooctadienes and 1*H*-2-benzo[*c*]oxocins involves a radical-rebound step in the coordination sphere of cobalt.



References

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Light Induced Cobalt(III) Carbene Radical Formation from Malonic Esters

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Carbene transfer catalysis enables the direct functionalization of C–H or C=C bonds, which is of great importance for the pharmaceutical and chemical industry. However, pre-activated reagents, such as iodonium ylides or diazo compounds, are often used as carbene precursors, which generate halogenated waste, are dangerous to work with or limit the scope of the reaction. Therefore, our aim is to generate a carbene radical complex from non-prefunctionalized reagents, such as malonic esters, using photochemistry. First, a cobalt-malonate adduct is formed under basic conditions. Upon irradiation of light, this intermediate can undergo hydrogen atom abstraction, forming a cobalt(III) carbene radical complex. In presence of styrene, cyclopropanation occurrs leading to direct C=C bond functionalization, although with stochiometric yields only. This work shows that the desired cobalt(III) carbene radical complex can be formed from commercially avalaible and bench stable malonic esters, replacing the detrimental pre-activated reagents that are commonly used.

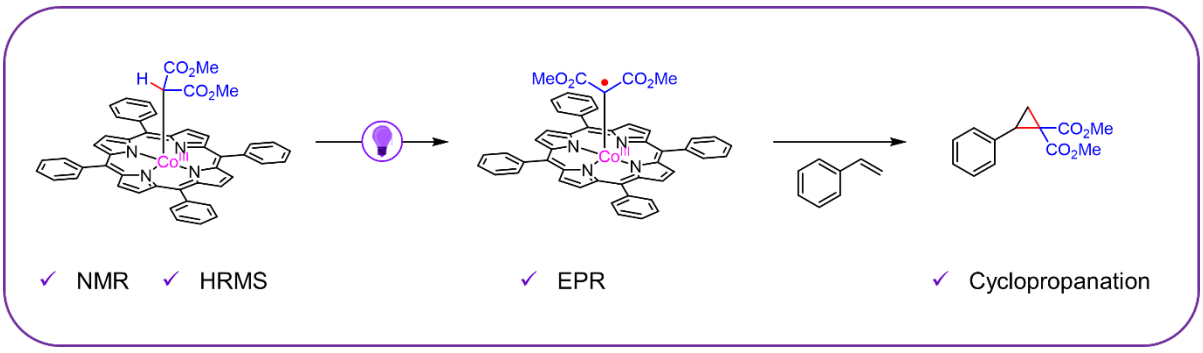


Figure 1. Cyclopropanation reaction via a cobalt(III) carbene radical complex that is generated from the cobalt-malonate adduct upon irradiation of light.

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