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# Intramolecular C(sp$^3$)–H Bond Amination Strategies for the Synthesis of Saturated N-containing Heterocycles

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Dedicated to the memory of Prof. Kilian Muñiz

*Abstract:* The selective functionalization of C(sp$^3$)–H bonds *via* intramolecular amination reactions represents a very attractive strategy for the construction of saturated N-containing heterocycles (SNHets). Over the past decades, the chemical community has devoted its efforts towards expanding the synthetic toolbox with the aim of facilitating access to these key fragments in a controllable, reproducible and efficient manner. This review covers selected examples of the most recent advances in intramolecular C(sp$^3$)–N bond-forming reactions by three main approaches: (1) the Hofmann-Löffler-Freytag (HLF) reaction; (2) transition-metal-catalyzed nitrene C(sp$^3$)–H insertion; and (3) transition-metal-catalyzed ligand-assisted C(sp$^3$)–N bond-forming reactions *via* a reductive elimination step. We will discuss reactivity, selectivity and the major mechanistic insights into these transformations.

**Keywords**: Amination · C–H functionalization · Catalysis · Cyclization · Heterocycle

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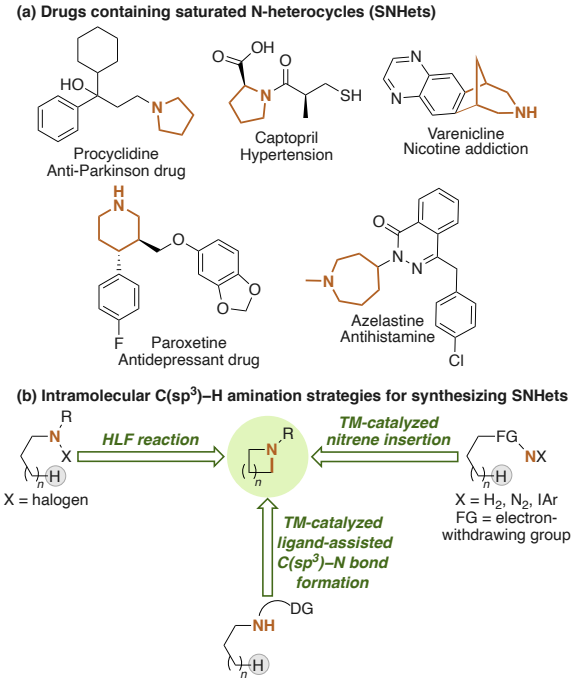
## 1. Introduction

Saturated nitrogen-containing heterocycles (SNHets), such as azetidine, pyrrolidine or piperidine are among the most prevalent molecular fragments in chemical space, especially in medicinal chemistry.[1] Their presence in druglike architectures usually enhances their biological activities, so these motifs are found in a wide variety of top-selling pharmaceuticals (Scheme 1a). Despite their prevalence and importance, the synthesis of these cyclic amines is far from trivial. In this context, intramolecular C(sp$^3$)–N bond-forming processes represent a very efficient and practical route for accessing these attractive moieties. These approaches pose different initial challenges such as *(i)* the thermodynamic and kinetic stability of the C(sp$^3$)–H bonds or *(ii)* the site-selectivity control of the C–H bond cleavage. Therefore, the synthetic community has devoted tremendous efforts to tackle them, providing a versatile toolkit for streamlining the construction of these molecules.[2] In this work, we cover the principal intramolecular C(sp$^3$)–H amination strategies. We have classified the methods into three categories (Scheme 1b): (1) the Hofmann-Löffler-Freytag (HLF) reaction; (2) transition-metal-catalyzed nitrene C(sp$^3$)–H insertion; and (3) transition-metal-catalyzed ligand-assisted C(sp$^3$)–H activation. We will mainly focus on selected and representative synthetic examples reported over the past 5 years, since different reviews have revised these reactions previously.[3] We will also gather the most relevant mechanistic information on the operative pathways behind each of these reactions.

## 2. Hofmann-Löffler-Freytag (HLF) Reaction

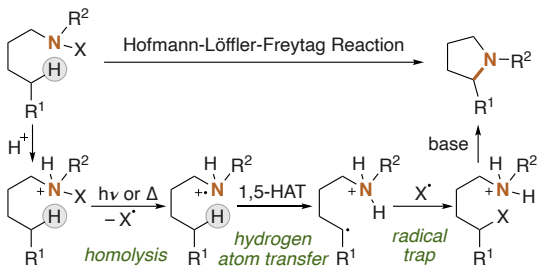
Intramolecular amination of remote aliphatic C–H bonds *via* hydrogen atom transfer (HAT) reactions stands out as a very attractive and general procedure for generating mainly pyrrolidine derivatives.[4] These transformations are triggered by the thermal or photochemical homolysis of the N–X bond of an *N*-halogenated amine in acidic media.[5] The protonated aminyl radical thus generated participates in an intramolecular 1,5-HAT to give a carbon-centered radical.[6] Subsequently, this species is trapped by recombination




Scheme 1. (a) Bioactive molecules containing saturated *N*-containing heterocycles (SNHets). (b) Current synthetic strategies for accessing SNHets *via* intramolecular C(sp$^3$)–H amination reactions.

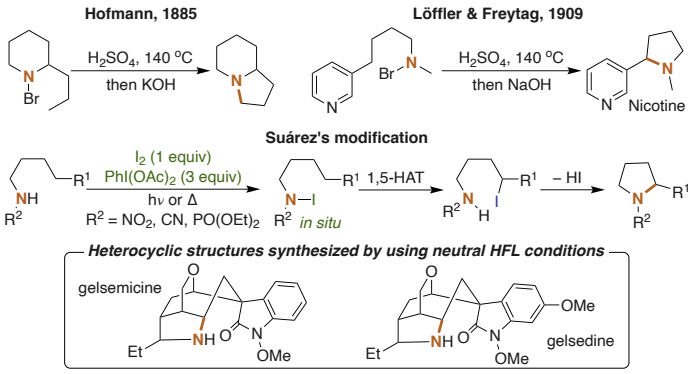
with a caged X$^{\bullet}$, or participates in halogen atom abstraction from the protonated starting material, usually to generate a δ-halogenated amine. The final cyclization proceeds *via* an $S_N2$ reaction, usually upon treatment with a base (Scheme 2). The formation of six-membered rings is rare and is typically observed in systems where the formation of pyrrolidine derivatives is not viable.

The first example of the conversion of an *N*-halogenated amine into a SNHet was reported in the early 1880s by Hofmann. In this seminal work, the treatment of *N*-bromo-2-propylpiperidine with hot sulfuric acid, and subsequent basification, afforded the formation of a bicyclic tertiary amine.[7] In 1909, Löffler and Freytag extended the scope to the use of secondary amines, providing a versatile method for the synthesis of pyrrolidines.[8] In the 1960s, Corey and Wawzonek provided the first experimental evidence supporting the radical reaction pathway, such as the observation of no cyclized product in the absence of radical initiators.[9] Despite these remarkable synthetic advances, the early reports on HLF reactions were limited by the pre-formation of the haloamine and/or the harsh acidic reaction conditions. In this context, Suárez and co-workers surmounted these limitations by two major breakthroughs (Scheme 3). First, the authors were capable of generating the N–halogen bond *in situ* from the corresponding amine in the presence of iodine and hypervalent iodine reagents. Second, the use of electron-withdrawing groups (–CN, –$NO_2$, *etc.*) on the nitrogen atom makes the resulting N-centered radical reactive enough to participate in the HAT process under neutral conditions.[10] Due to these improvements, it has been possible to apply these methodologies to more complex




Scheme 2. Hofmann-Löffler-Freytag mechanism.

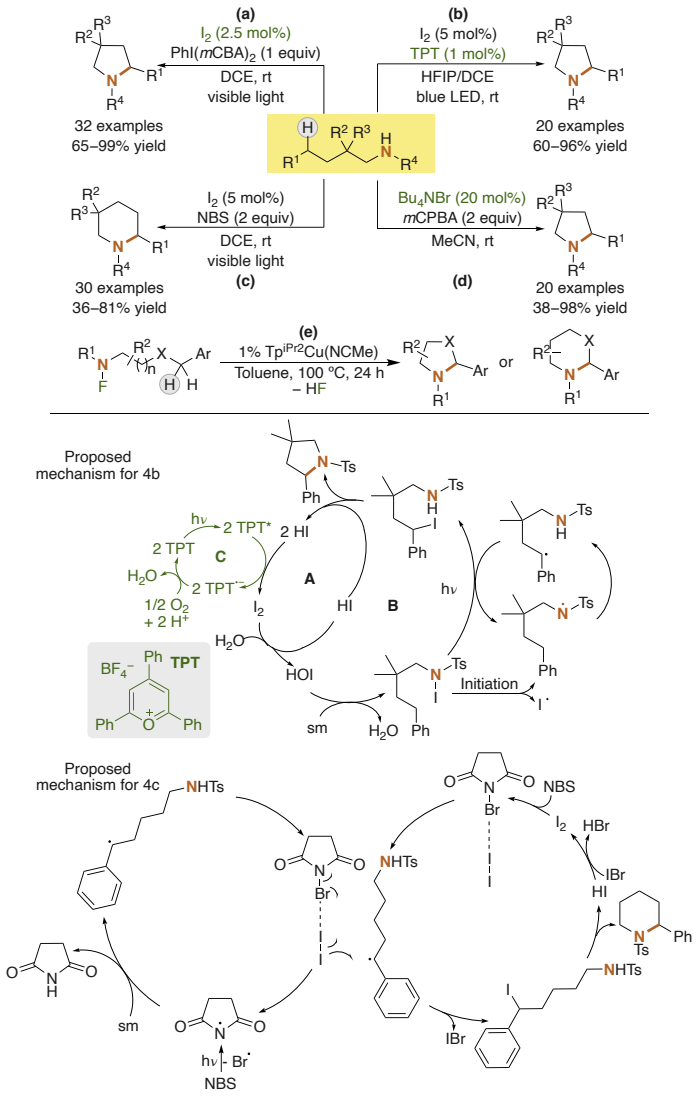
scaffolds such as starting materials containing acid-sensitive groups or to the synthesis of key natural product intermediates.[3b]




Scheme 3. Seminal reports on δ C(sp$^3$)–H amination *via* *N*-centered radicals *via* N–X homolysis.

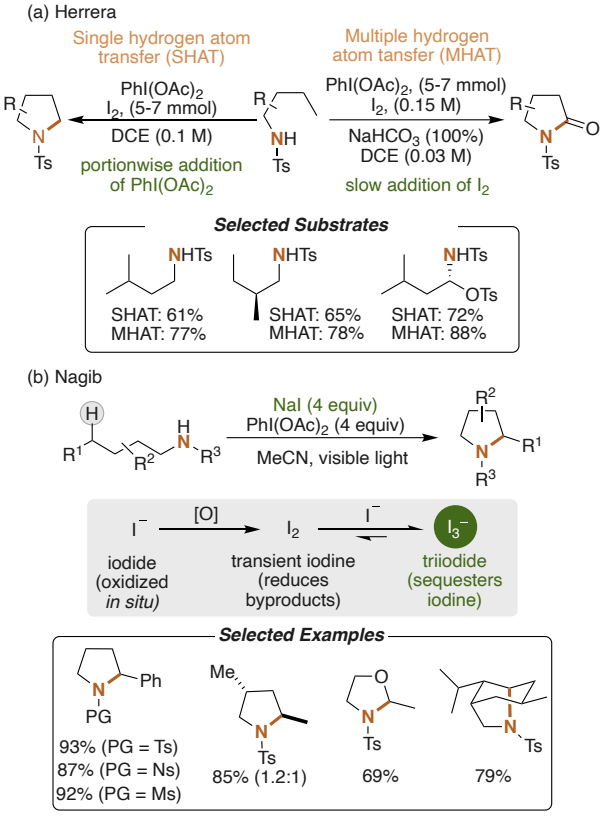
Inspired by these literature precedents, over the past years, different research groups have contributed to develop more robust and straightforward cyclization events. For example, major accomplishments have been made in developing iodine-catalyzed methodologies. The presence of stoichiometric amounts of $I_2$ tends to provide undesired oxidation reactions of weaker α-aminyl C–H bonds, which compete with 1,5-HAT processes, due to the AcOI homolysis-derived radicals.[11] In this context, Muñiz and co-workers designed very elegant strategies to suppress these side-reactions. In 2015, they reported the first example of an HLF reaction using iodine as a catalyst (Scheme 4a). In this work, the authors used 10 mol% of $I_2$ in the presence of a hypervalent iodine oxidant, PhI(*m*CBA)$_2$ (*m*CBA = 3-chlorobenzoate).[12a] This method is applicable to the amination of a wide variety of primary, secondary, and tertiary C(sp$^3$)–H bonds in excellent yields. From a mechanistic perspective, this reaction is proposed to proceed by two interconnected catalytic cycles encompassing a radical chain reaction induced by visible light. In 2017, the same group reported a dual light-activated cooperative iodine and photoredox catalysis protocol for the synthesis of 2-arylpyrrolidines (Scheme 4b).[12b] In this work, the iodine catalyst activates a remote C(sp$^3$)–H bond (1,5-HAT process) under visible light irradiation, while the organic photoredox catalyst (TPT) allows the regeneration of $I_2$, after the product release. In order to overcome the unfavorable kinetics of 1,6-H abstraction from aminyl radical,[6a] the Muñiz group fine-tuned the reaction conditions of their previous iodine-catalyzed methodologies to access six- and seven-membered rings in a selective manner (Scheme 4c).[12c] In this report, the authors envisioned the synergistic cooperation of two catalytic cycles. In the first cycle, an N-centered succinimidoyl radical, generated from NBS, abstracts a hydrogen atom from the benzylic position of the corresponding starting material, which is the weakest C–H bond. In the second one, the resulting benzylic radical abstracts an I atom from an $I_2$–NBS adduct, affording a benzyl iodide intermediate that undergoes cyclization. In a follow-up work, Muñiz explored, as a proof of principle, the use of bromine as catalyst in the intramolecular amination of C(sp$^3$)–H bonds (Scheme 4d).[12d] It is worth noting that bromine-based procedures usually provide low turnover rates, associated with catalyst deactivation through different side reactions (overoxidation to unreactive $Br^V$ species and/or disproportionation). However, after careful optimization of the reaction conditions, combining 20 mol% of $NBu_4Br$ and 2 equiv of *m*CPBA, the authors were able to develop an efficient protocol upon photochemical activation with normal daylight. In addition, in this work it was possible to detect and unambiguously characterize, for the first time, the *N*-halogenated intermediate in a catalytic HLF reaction. More recently, the group accomplished the formation of SNHets involving the unprecedented homolytic

cleavage of N–F bonds (Scheme 4e).[12e] This elegant copper(I/II) catalysis manifold allows the construction of both pyrrolidine and piperidine cores, under uniform reaction conditions using fluorinated starting materials.




Scheme 4. Iodine-catalyzed HLF approaches by the Muñiz group.

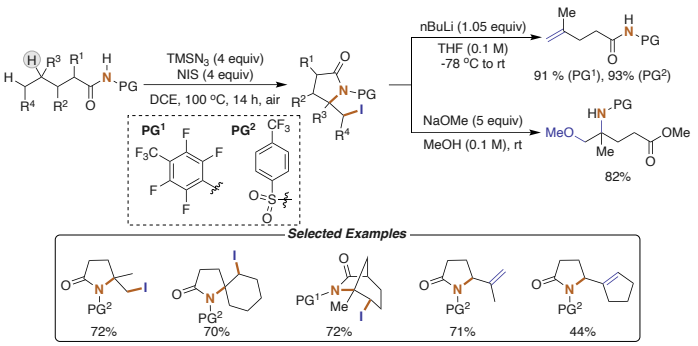
At the same time that Muñiz reported the first catalytic HFL methodology, Herrera and co-workers described the chemoselective amination of primary C(sp$^3$)–H bonds by using sulfonamides as N-centered radical precursors (Scheme 5a).[13] This work showed the potential of these reactions beyond traditional weak aliphatic C–H bonds (benzylic, tertiary, α-oxy). In addition, it also demonstrated that it is possible to obtain pyrrolidine or 2-pyrrolidinone derivatives selectively, *via* single or multiple HAT processes (SHAT or MHAT) respectively, by controlling the addition of oxidant. Therefore, this work offers an alternative to avoid undesirable $I_2$-mediated oxidations. In this regard, in 2016, Nagib and co-workers reported another strategy to circumvent the side-reactions associated to the employment of excess of $I_2$.[14] The authors described a triiodide-mediated amination strategy where $I_3^-$ acts as a $I_2$ reservoir (Scheme 5b). Triiodide is generated *in situ* by the oxidation of NaI to $I_2$, which in the presence of excess of $I^-$ forms $I_3^-$. This dynamic equilibrium reduces the amount of available $I_2$ in the reaction media, attenuating the negative effect of the excess of AcOI in solution. Nagib applied this strategy to a wide variety of scaffolds containing biologically relevant motifs, such as esters, ketones and arenes.




Scheme 5. Alternative approaches for overcoming undesired $I_2$-mediated reactions.

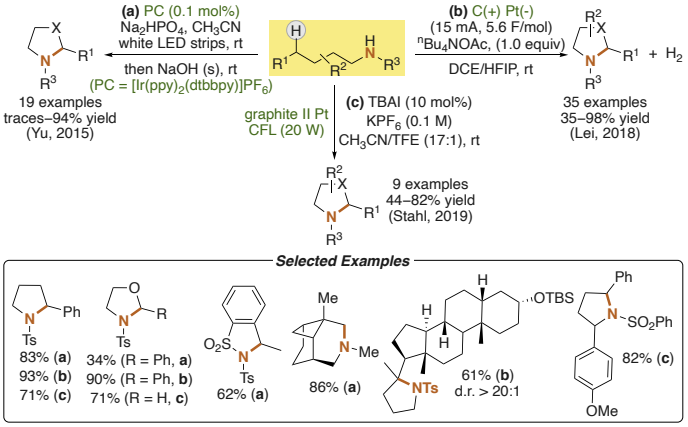
In 2015, Yu and co-workers uncovered a novel protocol for the δ-iodo-γ-lactamization of aliphatic amides by reaction with *N*-iodosuccinimide (NIS) and trimethyl azide ($TMSN_3$), *via* 1,5- and 1,6-abstractions (Scheme 6).[15] The proposed mechanism, for this unexpected transformation, involves the iodination of the starting amide by treatment with NIS to give an N–I intermediate that, following the Suárez-HLF method, provides the corresponding lactam. Subsequently, an azide radical generated *in situ* promotes a β-C–N bond scission, to afford a terminal olefin. The final iodinated product is obtained after radical 5-exo-trig cyclization and recombination with an iodo free radical. The authors exploited this reactivity not only to synthesize a wide variety of iodolactams, but also to subsequently diversify them into 1,2-amino alcohol and allylic amide derivatives, some of them closely related to drug analogs, such as vigabatrin.

Over the past years, the use of photocatalyst and the implementation of electrochemical strategies have opened innovative and appealing avenues in the context of HFL transformations. In 2015, Yu reported a visible light photoredox-mediated protocol for




Scheme 6. γ,δ,ε-C(sp$^3$)–H functionalization through directed radical H-abstraction.

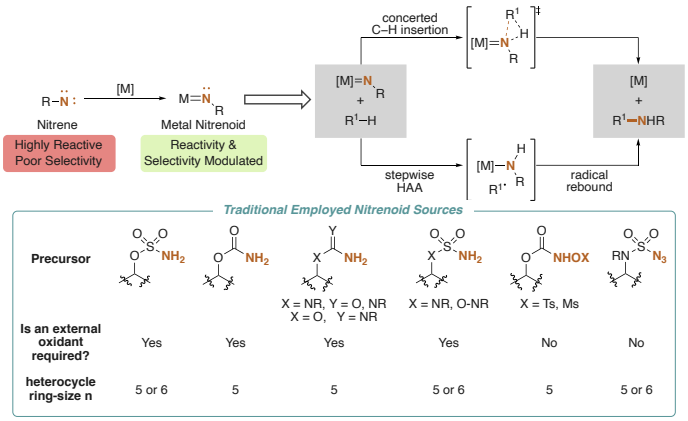
the remote amination of *N*-chlorosulfonamides (NCSs) (Scheme 7a).[16] This methodology proceeds with good to excellent yields at room temperature, under mildly basic conditions, and using very low catalyst loading (0.1 mol%) of $Ir(ppy)_2(dtbbpy)PF_6$. In this transformation, the nitrogen-centered radical is proposed to be generated through an oxidative quenching of the excited state $Ir^{III*}$ with the corresponding NCS. The authors demonstrated the synthetic potential of this approach by (i) scaling up the reaction to gram scale and (ii) applying it to the late-stage functionalization of complex and biologically relevant N-containing compounds, such as (–)-*cis*-myrtanylamine or (+)-dehydroabietylamine. Another major breakthrough in the field is the use of electric current as reagent, which has the potential of obviating the need for metal catalysts, halogenated reagents, and/or stoichiometric amounts of chemical oxidants. For example, in 2018 Lei and co-workers disclosed an electrochemical oxidatively induced amination of primary, secondary and tertiary C($sp^3$)–H bonds (Scheme 7b).[17] This site-selective electrosynthetic protocol enables the access to a wide variety of pyrrolidine derivatives and is compatible with different N-protecting groups. A plausible mechanism for this electro-oxidative HLF reaction involves the generation of the aminyl radical by a single-electron oxidation at the anode. After 1,5-HAT, the corresponding C-centered radical undergoes another anodic oxidation to afford a carbocation intermediate that provides the desired product after nucleophilic attack by the sulfonamidyl group. Recently, Stahl and co-workers have combined photo- and electrochemical strategies to promote the intramolecular amination of C($sp^3$)–H bonds (Scheme 7c).[18] A key feature of this iodide-mediated process is its broad functional group compatibility due to the combination of low applied potentials and the photochemically induced cleavage of intermediate N–I bonds.




Scheme 7. Visible light- and electrochemical oxidation-induced remote intramolecular C($sp^3$)–H aminations.

## 3. Transition-Metal-catalyzed Nitrene C($sp^3$)–H Insertion Reactions

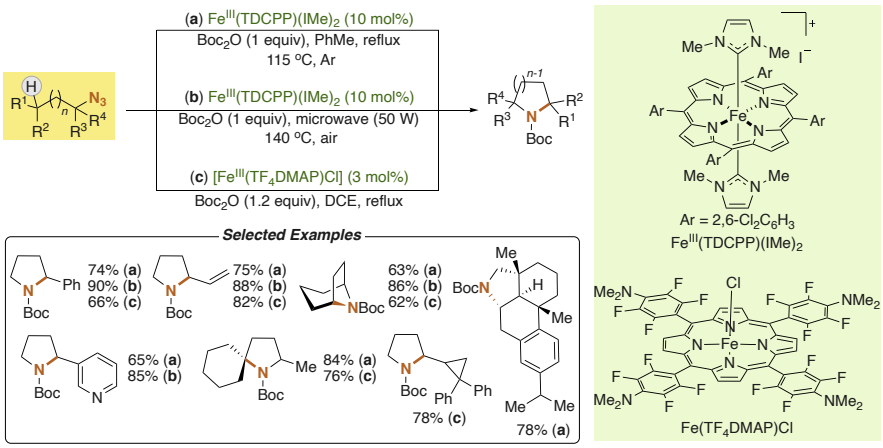
Since the seminal example reported by Breslow in the early 1980s,[19] TM-catalyzed intramolecular nitrene transfer processes have become a very powerful and useful method for the synthesis of saturated N-containing heterocycles.[2d,20] The proposed mechanisms involve the formation of a metal–nitrenoid species which is responsible for the subsequent cleavage of the C($sp^3$)–H bond. This step can occur *via* a concerted C–H insertion, preferred for singlet species, or a stepwise hydrogen atom abstraction (HAA), usually followed by triplet intermediates (Scheme 8). Since the pioneering finding that iminoiodinanes ($ArSO_2N$=IPh) could serve as nitrene precursors,[21] the field has evolved to the use of readily available nitrogen sources such as azides, sulfonamides, or carbamates.[20] The synthetic methods developed over the past decades comprise a wide variety of transition-metal-based systems, ranging from catalysts based on noble metals, such as Rh or Ru,[22] to more sustainable ones, such as Mn or Fe. Here, we will highlight a selection of the most relevant works over the past few years, paying special attention to first-row-transition-metal-catalyzed methodologies.




Scheme 8. Overview of C–H amination reactions *via* intramolecular nitrene insertion.

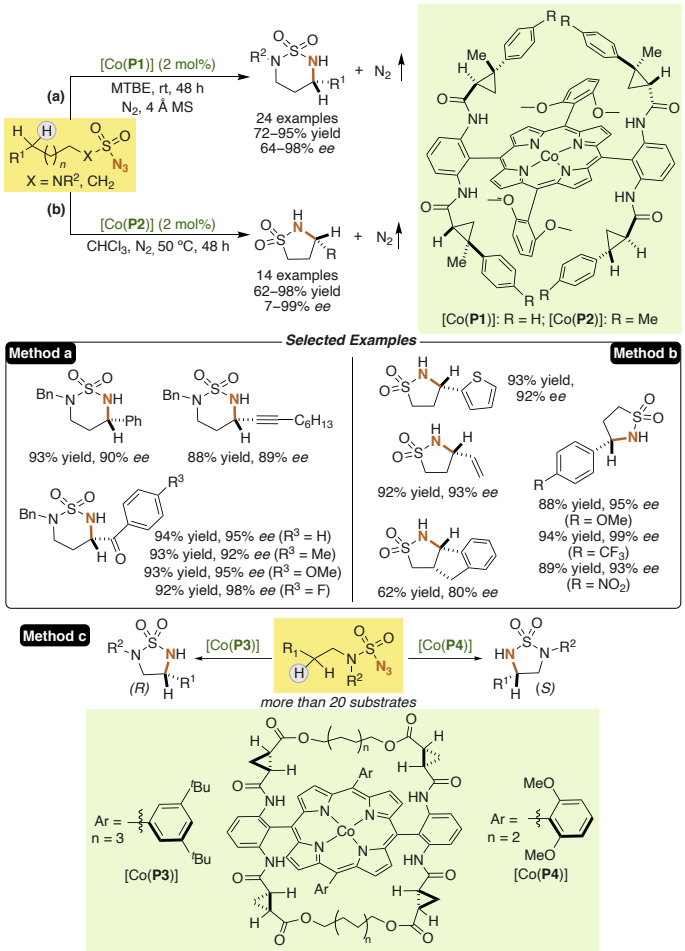
In the context of direct intramolecular C($sp^3$)–H amination *via* nitrenoid insertion, one of the most efficient and robust catalytic systems is metalloporphyrin complexes (MPC), a biomimetic model of the cytochrome P450.[2b,23] These systems present unique ligand environment and metal coordination modes, often leading to high selectivity and turnover number (TON). This is associated with longer catalyst lifetime and/or the minimization of side-reactions due to the absence of vacant coordination sites. Since the seminal report by Che, in 2002, of a direct intramolecular C($sp^3$)–H amidation with ruthenium porphyrins, by the reaction of sulfamate esters with $PhI(OAc)_2$,[24a] this group and others have exploited different porphyrin-based catalytic systems for the synthesis of SNHets (Scheme 9). The current state of the art, especially involving 3d metalloradical catalysis, shows how tailor-made changes in the porphyrin system enhance the efficiency, regio- and stereoselectivity, enabling their application to the late-stage functionalization of complex scaffolds. For example, in 2018, Che disclosed an iron(III)-porphyrin system bearing axial *N*-heterocyclic carbene ligands, [$Fe^{III}$(TDCPP)$(IMe)_2$] (10 mol%), for the intramolecular amination of alkyl azides.[24b] In this work, the authors achieved the selective functionalization of benzylic, allylic, tertiary, secondary, and even primary C($sp^3$)–H bonds, in good to excellent yields, under thermal (Scheme 9a) or micro-wave irradiation conditions (Scheme 9b). This protocol was applied to the preparation of relevant alkaloids, such as leelamine derivatives and nornicotine. In a follow-up paper, the group was capable of reducing the catalyst loading to just 3 mol% for the synthesis of 5- and 6-membered ring heterocycles using a biocompatible iron complex, [$Fe^{III}(TF_4DMAP)Cl$] ($TF_4DMAP$ = *meso*-tetrakis(*o,o,m,m*-tetrafluoro-*p*-(dimethylamino)phenil)porphyrinato dianion) (Scheme 9c).[24c] This work demonstrated the profound effect of ligand on metalloporphyrin catalysis (MPC).

Another first-row metal that has been widely exploited in MPC is cobalt. Since 2007, Zhang and co-workers have reported multiple $Co^{II}$ porphyrin-catalyzed examples of intramolecular amination of aliphatic C–H bonds using organic azides as nitrenoid precursors.[23] In this regard, their recent advances on the use of chiral $D_2$-symmetric cobalt(II)-amidoporphyrins for controlling the enantioselectivity of 1,5- and 1,6-radical processes is particularly noteworthy (Scheme 10).[25] Very recently, the authors developed a new generation of chiral ligands to accomplish enantiodivergent radical 1,5-C($sp^3$)–H amination reactions of sulfamoyl azides. In




Scheme 9. Iron(III)-porphyrin-catalyzed intramolecular C(sp³)–H amination of alkyl azides.

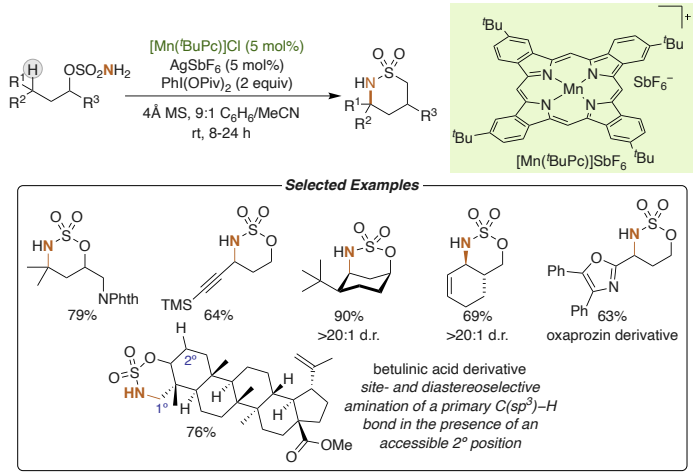
this work, the authors fine-tuned the cavity size and environment of the cobalt-amidoporphyrin complexes by modifying the length of the distal alkyl bridges along with the nature of the remote nonchiral substituents.[25c] Based on detailed mechanistic studies performed by the group, these cobalt-catalyzed transformations are proposed to occur through a stepwise radical reaction pathway, wherein a α-Co$^{III}$-aminyl radical intermediate cleaves the aliphatic C–H bond by HAA. Besides Zhang, de Bruin and co-workers have also explored the activity of Co$^{II}$ porphyrins for constructing saturated heterocycles from aliphatic azides.[26] In this work, the authors used di-tert-butyldicarbonate ($Boc_2O$) to enhance the reaction rate by preventing the competitive coordination of the final amine product.




Scheme 10. Cobalt(II)-based metalloradical approaches for intramolecular heterocyclization of sulfamoyl and sulfonyl azides.

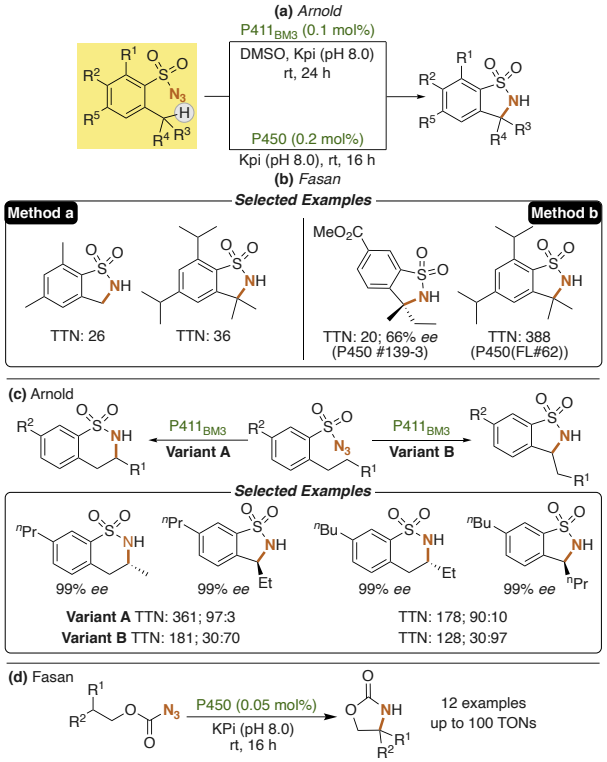
In 2015, White and co-workers reported a very remarkable manganese-based catalyst, containing a nitrogen porphyrin analogue, for the synthesis of dioxooxathiazinanes (Scheme 11).[27] This system exhibits an exquisite chemoselectivity towards the amination of strong primary C–H bonds over weaker secondary/tertiary C–H bonds, surmounting one of the major historical limitations associated with C(sp³)–H amination reactions. This protocol features a broad functional group tolerance, enabling the late-stage functionalization of complex architectures. Interestingly, based on different mechanistic studies, the authors proposed an unusual reaction pathway for the nitrene transfer, which lies between a concerted insertion, usually operative for $Rh_2$(II) catalytic systems, and the stepwise HAA/rebound process, proposed for iron(III) complexes. (Scheme 11)

Apart from synthetic metalloporphyrins, over the past few years, the implementation of directed evolution strategies for the intramolecular amination of C(sp³)–H bonds has opened very interesting avenues (Scheme 12). Dawson and Breslow reported, for the first time in 1985, the participation of microsomal cytochrome P450 in intramolecular C(sp³)–H amination reactions.[28] However, it was not until very recently that Arnold and Fasan revisited, independently, the catalytic potential of mutated cytochromes ($P411_{BM3}$ and $P450_{BM3}$, respectively) in the synthesis of benzosultam derivatives (Schemes 12a and 12b).[29a,30a] These works display high enantioselectivities along with high turnover numbers with catalyst loadings lower than 0.5 mol%. Since then, both groups have showcased the tremendous potential of biocatalytic nitrenoid C(sp³)–H insertions. For example, Arnold has employed two different engineered variants of $P450_{BM3}$ to provide divergent reactivity patterns from sulfonyl azide substrates (Scheme



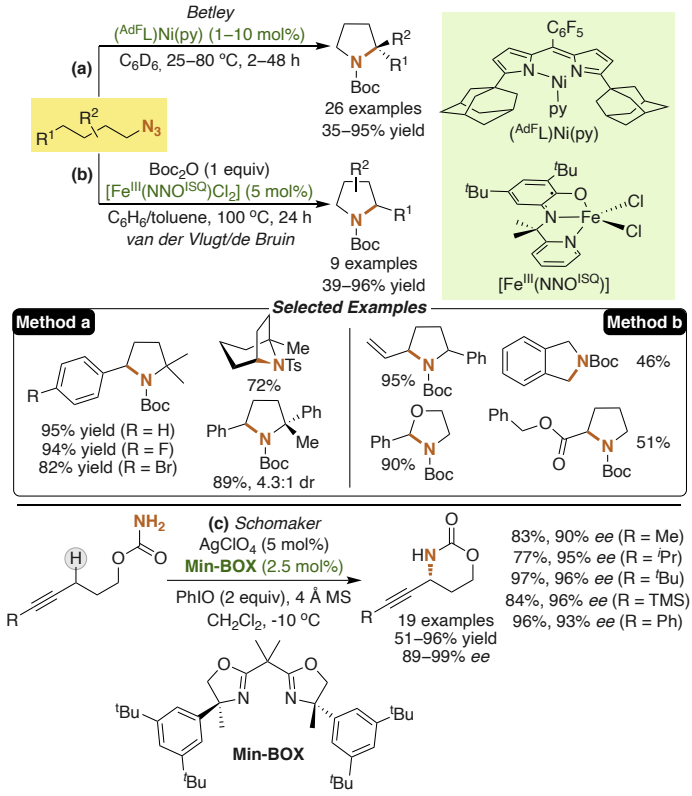

Scheme 11. Manganese-catalyzed intramolecular C(sp³)–H amination of sulfamate esters.

12c).[29b] Fasan has also reported the efficient C($sp^3$)–H activation and subsequent cyclization of carbonazidate scaffolds to afford oxazolidinones by the involvement of a nitrene-heme intermediate (Scheme 12d).[30b] More recently, the same group has reported a mechanism-driven approach to rationally design and develop a series of $P450_{BM3}$ variants for increasing the efficiency of intramolecular C($sp^3$)–H aminations. Currently, these engineered catalysts are among the most active nitrene tranfererases reported to date, with over 10,000 turnovers.[30c] Interestingly, Hartwig and co-workers reported in 2017 that while a Ir-porphyrin was inert in the intramolecular amination of sulfonyl azides, artificial P450 metalloenzymes containing an abiological Ir(Me) mesoporphyrin IX cofactor provide yields up to 98% with good turnover (approx. 200 TON).[31] This work demonstrates the potential of engineered biocatalysts versus more traditional porphyrin-based systems.




Scheme 12. Enantioselective intramolecular C($sp^3$)–H amination catalyzed by engineered cytochrome.

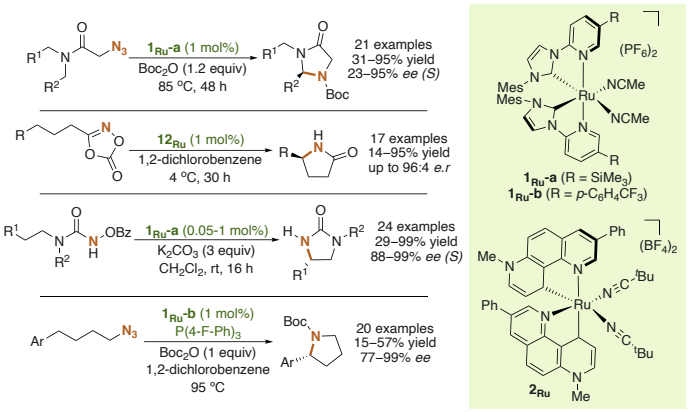
Over the past 5 years, transition metal-based systems bearing other types of ligands have also participated in intramolecular nitrene transfer processes, exhibiting very interesting reactivity patterns and broad substrate scope. Inspired by previous iron-based systems,[32a] Betley and co-workers have reported the employment of nickel-dipyrrin complexes as catalysts in the intramolecular ring-closing C–H bond amination of unactivated aliphatic azides (Scheme 13a).[32b] This procedure proceeds under mild reaction conditions, with high chemoselectivity and broad substrate scope. Van der Vlugt and de Bruin have also demonstrated the participation of an air-stable iron(III) complex, containing a redox-active pyridine-aminophenol ligand in intramolecular nitrene transfer events (Scheme 13b).[33] This system catalyzes efficiently the synthesis of pyrrolidine and piperidine derivatives using alkyl azides as substrates with high turnover numbers ( >600). Plieker and co-workers have applied a nucleophilic Fe complex, $Bu_4N[Fe(CO)_3(NO)]$, to the construction of substituted indoline and tetrahydroquinoline derivatives.[34] Schomaker and co-workers have designed novel bis(oxazoline) (BOX) ligands for achieving a general silver-catalyzed intramolecular asymmetric C($sp^3$)–H amination involving a nitrene transfer pathway. This protocol allows the access to γ-alkynyl γ-aminoalcohols with excellent yields and enantioselectivity (90–99% ee) (Scheme 13c).[35] DFT calculations support that the structural modifications introduced into the BOX-type ligand facilitate the differentiation between prochiral protons during the enantio-determining HAT step.




Scheme 13. TM-catalyzed intramolecular amination.

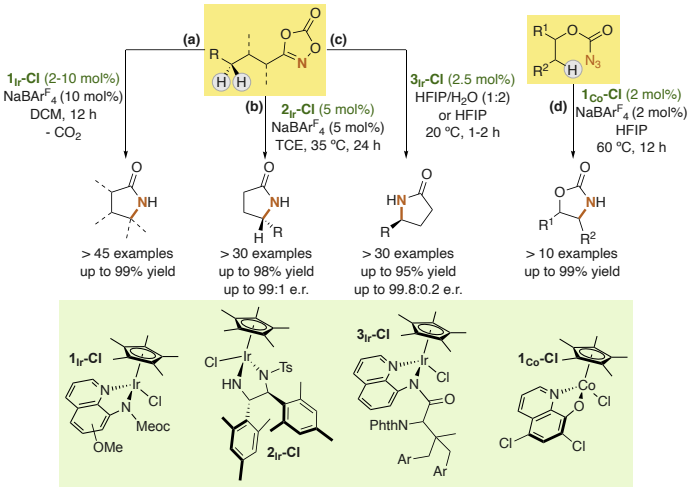
Following an alternative strategy, Meggers and co-workers have accomplished very interesting advances in the stereocontrolled insertion of metal nitrenoids into C($sp^3$)–H bonds by the utilization of chiral-at-metal catalysts (Scheme 14).[36a–c] Although all the ligands are achiral, the stereogenicity of the metal center is responsible for the overall helical chirality of the catalyst. The authors have demonstrated the potential of different bis(pyridyl-NHC) ruthenium complexes for accessing chiral Boc-protected imidazolidine-4-ones, γ-lactams and cyclic ureas in excellent yields and enantioselectivities. In the synthesis of 2-aryl pyrrolidines, Meggers and co-workers proposed a dual ruthenium and phosphine catalysis, where an iminophosphorane intermediate is responsible for transferring the nitrene unit to the metal center.[36d]

One of the major synthetic challenges in intramolecular TM-catalyzed C($sp^3$)–H amination reactions involving nitrene transfer is the construction of γ-lactams. The proposed key carbonyl nitrene intermediates usually participate in competing Curtius-type rearrangements, resulting in the undesired formation of isocyanates. In order to suppress this side-reaction, in 2018, Chang and co-workers engineered a series of Cp*$Ir^{III}$ complexes containing electron-donating auxiliary bidentate ligands, to promote the intramolecular amination by lowering the C–H insertion barrier.[37a] Combining these catalysts with the use of 1,4,2-dioxazol-5-ones as nitrene precursors, the authors successfully achieved the synthesis of a wide variety of racemic γ-lactams (Scheme 15a). This protocol was applied to the activation of primary, secondary and tertiary C($sp^3$)–H bonds in good yields, along with the late-stage functionalization of complex scaffolds such as high-value amino acids. The same type of lactam products can be obtained by the photosensitization




Scheme 14. Enantioselective ring-closing C(sp$^3$)–H amination using chiral-at-metal ruthenium catalysts.

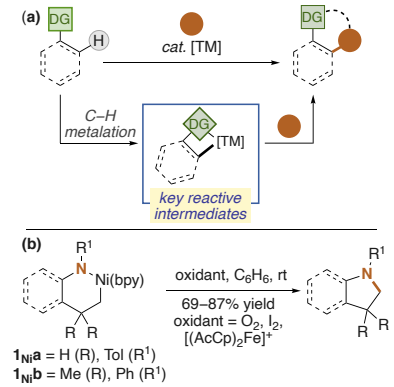
of hydroxamates using 5 mol% of $Ru(bpy)_3(PF_6)_2$.[37b] In 2019, the group accomplished the asymmetric C(sp$^3$)–H amination of dioxazoles, with excellent yields and enantioselectivities, by developing a second generation of iridacycles bearing chiral diamine scaffolds (Scheme 15b).[37c] Computational studies suggest that the exquisite stereoselectivity displayed is associated with an intramolecular hydrogen-bonding interaction between the carbonyl of the starting material and the NH of the chiral ligand. A comparable methodology was simultaneously reported by Yu, using cymene-ruthenium(II) complexes with chelating (*R*,*R*)-diphenyl-1,2-ethylenediamine (dpen) ligands.[38] Subsequently, the Chang group extended the application of their protocols to the synthesis of chiral γ-alkyl-γ-lactams, by using Cp*Ir-based systems containing α-amino-acid-based chiral ligands (Scheme 15c).[37d] The employment of analogous Cp*Co$^{III}$(LX) catalysts containing 8-hydroxyquinoline ligands has enabled the formation of 5- and 6-membered cyclic carbamates using azidoformates as the nitrenoid source (Scheme 15d).[37e]




Scheme 15. Cp*M$^{III}$-catalyzed intramolecular C(sp$^3$)–H amidation processes.

## 4. Transition-metal-catalyzed C(sp$^3$)–H Activation

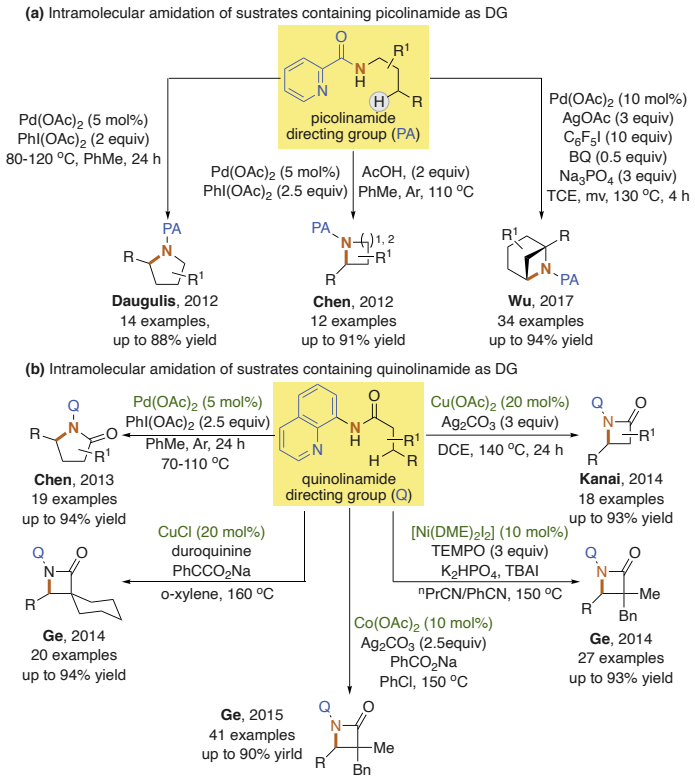
Over the past decades, ligand-assisted transition-metal-catalyzed C–H functionalization reactions have become a cornerstone of modern synthetic organic chemistry.[39] These strategies allow control of the site-selectivity of C–H bond-cleavage by the employment of directing groups (DGs). These chelating moieties are usually Lewis basic groups present in the substrates that bind the metal center, bringing into close proximity a specific C–H bond. After the initial C–H activation step, often *via* a concerted metalation-deprotonation pathway, the resulting metallacycle can participate in a wide variety of bond-forming processes after reacting with the corresponding coupling partner (Scheme 16a). In the context of C(sp$^3$)–H amination processes, one of the major synthetic challenges associated with this approach is the susceptibility of metal–alkyl intermediates to undergo β-hydride elimination instead of C(sp$^3$)–N reductive elimination.[3e] However, inspired by seminal stoichiometric examples of oxidatively-induced intramolecular C(sp$^3$)–N bond-forming reactions from Hillhouse (Scheme 16b),[40] different research groups have surmounted this limitation and developed different catalytic procedures for the synthesis of N-containing heterocycles.



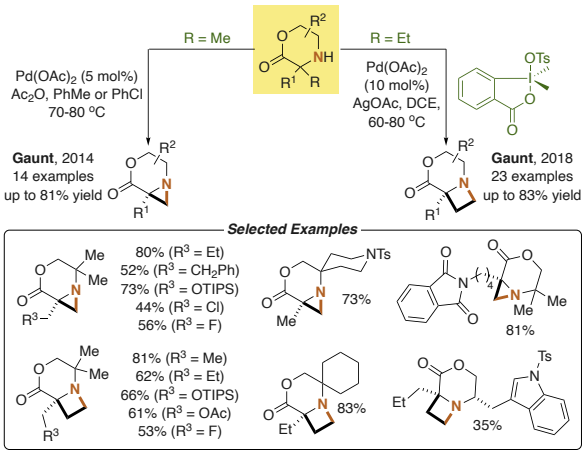

Scheme 16. (a) Mechanism of ligand-assisted TM-catalyzed C–H activation. (b) Early examples of TM-mediated intramolecular C(sp$^3$)–N reductive elimination.

In this context, over the past few years, the use of bidentate directing groups has emerged as a very powerful tool for developing TM-catalyzed intramolecular oxidative C(sp$^3$)–H amination protocols. Taking advantage of the effective chelating behavior of the picolinamide (PA) group (Scheme 17a), Daugulis and Chen reported, independently, access to azetidine and pyrrolidine derivatives, *via* a Pd$^{II/IV}$ catalytic cycle, using $PhI(OAc)_2$ as oxidant.[41,42] Subsequently, Wu applied an analogous methodology for the construction of polycyclic nitrogen-containing heterocycles by activating γ- or δ-C(sp$^3$)–H bonds.[43] 8-Aminoquinoline has also demonstrated its versatility as a bidentate directing group in a wide variety of TM-catalyzed intramolecular C(sp$^3$)–H aminations (Scheme 17b), not only using palladium catalysts,[44] but also those based on earth-abundant metals such as cobalt, nickel and copper.[45,46] Particularly interesting is the ability of these first-row metal-catalyzed protocols to access azetidinone derivatives.

Despite the utility exhibited by these bidentate DGs, they present an obvious disadvantage: the necessity for extra synthetic steps for their installation and removal. To address this limitation, Gaunt and co-workers have exploited the coordinating capability of the nitrogen lone pair to promote the intramolecular cyclization of alkyl amines in the absence of additional chelating moieties (Scheme 18). In 2014, the group reported the first Pd-catalyzed intramolecular C(sp$^3$)–H amination to form strained heterocycles using 2,2,6,6-tetramethylpiperidine derivatives as substrates.[47a] Following this pioneering work, in 2017, Gaunt and co-workers reported the enantioselective version of the aziridination protocol.[47b] The authors achieved high enantioselective ratios by using chiral BINOL-derived phosphoric acid ligands. The same group disclosed in 2018 the synthesis of azetidines by replacing $PhI(OAc)_2$ with the combination of benzidazole tosylate and AgOAc.[47c] This reaction shows broad functional group tolerance, which enabled the application of this protocol to enantioenrich substrates derived from amino alcohols.




Scheme 17. Intramolecular TM-catalyzed C(sp³)–N bond-forming reactions using bidentate directing groups.




Scheme 18. Intramolecular Pd-catalyzed C(sp³)–N bond-forming reactions in the absence of directing groups.

## 5. Conclusions and Outlook

The synthesis of saturated N-containing heterocycles by intramolecular ring-closing C(sp³)–H amination reactions constitutes one of the most active fields in modern synthetic organic chemistry, especially due to the prevalence of SNHets in bioactive molecules. Over the past years, each of the three approaches highlighted in this review – hydrogen atom transfer (HAT), TM-catalyzed nitrene insertion and TM-catalyzed ligand-assisted C(sp³)–N bond-forming reactions – have demonstrated their tremendous potential to broaden the access to more complex architectures by the chemo-, regio- and/or enantioselective functionalization of remote C(sp³)–H bonds. In this context, the implementation of photo- and electrochemical strategies, the employment of new nitrogen sources or the design of more active and selective catalysts, such as engineered TM-containing enzymes, have enabled the development of more efficient methodologies under mild reaction conditions. Despite these important recent accomplishments, there are still unsolved challenges. The use of simple and readily available aliphatic amines as starting materials, without the necessity of converting them into more reactive nitrogen sources, remains extremely limited. In addition, even now it is rare to find synthetic protocols that allow the synthesis of highly substituted SNHets or the formation of usually hindered products, such as three-, four- or seven-membered heterocycles. Further explorations towards tackling these, and other synthetic difficulties, will undoubtedly provoke ground-breaking advances in the field.

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