ORGANIC CHEMISTRY
FRONTIERS

CHINESE CHEMICAL SOCIETY

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Org. Chem. Front.*, 2020, **7**, 1948

Recent advances in cyclization reactions of unsaturated oxime esters (ethers): synthesis of versatile functionalized nitrogen-containing scaffolds

Chen Chen, *[a] Jinghui Zhao,[a] Xiaonan Shi,[a] Liying Liu,[a] Yan-Ping Zhu,[b] Wan Sun[a] and Bolin Zhu *[a]

Received 30th March 2020,
Accepted 5th June 2020

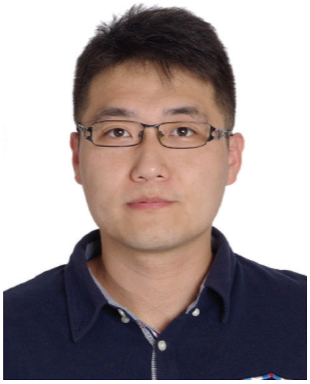
DOI: 10.1039/d0qo00397b

rsc.li/frontiers-organic

Cyclization/functionalization of unsaturated oxime esters (ethers) is a powerful strategy for the synthesis of versatile functionalized nitrogen-containing scaffolds, which are valuable structural motifs in numerous bioactive molecules. This review provides an overview of the recent advances in cascade cyclization of unsaturated oxime esters (ethers) with different functional group reagents. Typical examples are listed and mechanistic aspects are discussed in detail. Moreover, the remaining challenges and future perspectives are presented at the end.

1. Introduction

Nitrogen-containing molecules have gained great attention over the past few decades, as they constitute the core structure of drugs, materials and agrochemicals.[1,2] In particular, they hold a dominant position in drug discovery. It is known that approximately eighty percent of the top 20 best-selling brand name drugs incorporate nitrogen atoms, in which two-thirds of them contain N-heterocycles.[3] Among them, functionalized pyrrolines and related scaffolds are valuable structural motifs in numerous bioactive molecules, pharmaceuticals and alkaloid natural products.[4–6] Therefore, the development of effective synthetic methodologies for rapidly constructing various functionalized pyrrolines and related scaffolds from simple and readily available starting materials has been of great interest to many organic chemists.


Chen Chen

Chen Chen was born in Tianjin, China, in 1986. He pursued his PhD studies with Prof. Xiaofeng Tong at the East China University of Science and Technology (ECUST) from 2010 to 2015. Then he worked as a postdoc with Prof. Bert Maes in Antwerp University (Belgium) from 2015 to 2016. In 2017, he joined the College of Chemistry at Tianjin Normal University (TJNU) to start his independent career. His current research interests include free radical chemistry and new methods for the synthesis of organofluorine and organophosphorus compounds.


Jinghui Zhao

Jinghui Zhao was born in Hebei Province, China, in 1999. She is now pursuing her undergraduate studies in the College of Chemistry at Tianjin Normal University. She is interested in organic chemistry and has been working in Dr Chen Chen's lab for two years and is looking forward to further studies.

---

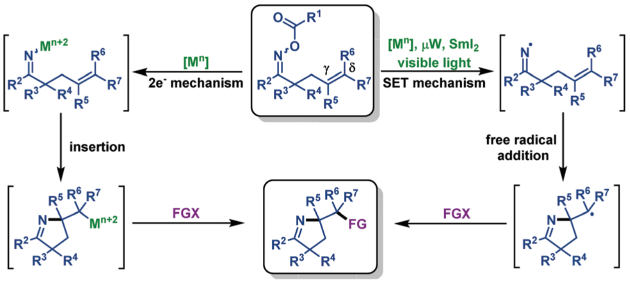
[a] *Tianjin Key Laboratory of Structure and Performance for Functional Molecules, College of Chemistry, Tianjin Normal University, Tianjin 300387, P. R. China. E-mail: hxxycc@tjnu.edu.cn, hxxyzbl@tjnu.edu.cn*

[b] *School of Pharmacy, Key Laboratory of Molecular Pharmacology and Drug Evaluation, Ministry of Education, Collaborative Innovation Center of Advanced Drug Delivery System and Biotech Drugs in Universities of Shandong, Yantai University, Shandong, Yantai, 264005, P. R. China*

Over the past few decades, oxime esters (ethers) have been one of the most widely used starting materials for the synthesis of small molecule nitrogen-containing heterocycles,[7–31] which can be easily prepared from the corresponding ketones. This is mainly due to the viable and facile oxidative addition of the N–O bond to low valent transition metal centers. In addition, an iminyl radical could be generated *via* N–O bond homolytic cleavage. In particular for γ,δ-unsaturated oxime esters (ethers), the N–O bond cleavage is followed by an intramolecular imino-functionalization process, which delivers diverse functionalized nitrogen-containing scaffolds. Recently, great progress has been made in this field. In this review, we mainly focus on the recent advancements in the study of the synthesis of versatile functionalized nitrogen-containing scaffolds from unsaturated oxime esters (ethers). We hope that this review would serve as a reference for organic chemists who are interested in developing novel synthetic methodologies using unsaturated oxime esters (ethers).

2. Cyclization reactions of γ,δ-unsaturated oxime esters (ethers)

γ,δ-Unsaturated oxime esters (ethers) are important starting materials and useful building blocks in organic synthesis, which can undergo N–O bond cleavage followed by an intramolecular imino-functionalization process, delivering diverse functionalized pyrroline moieties. Recently, much progress has been achieved in this field. In the section, we mainly focus on the recent advances in the synthesis of diverse functionalized pyrrolines and related scaffolds from γ,δ-unsaturated oxime esters. These reactions are classified by the type of N–O bond cleavage, including N–O bond homolytic cleavage and N–O bond oxidative addition (Scheme 1).

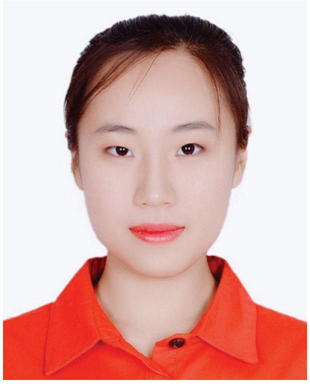


Scheme 1 Cyclization/functionalization of γ,δ-unsaturated oxime esters.

2.1 Cyclization reactions involving iminyl radical intermediates

Iminyl radical cyclizations have emerged as an important tool that allows the efficient construction of nitrogen-containing heterocycles. During the past few decades, several important advancements in iminyl radical cyclizations of γ,δ-unsaturated oxime esters (ethers) have been made by organic chemists. Iminyl radicals are useful intermediates that can be generated from the N–O bond homolytic cleavage of γ,δ-unsaturated oxime esters (ethers). Typical conditions for generating iminyl radicals include microwave heating,[32–36] transition metal catalysis,[37–54] light irradiation[55–62] and SmI_2 irradiation.[63]

2.1.1 Generation of iminyl radicals *via* microwave heating. The first microwave-assisted imino-functionalization of γ,δ-unsaturated oxime ethers was developed by Walton and coworkers.[32,33] They discovered that N–O bond homolytic cleavage could be realized by microwave heating. Compared with conventional heating, microwave irradiation is more practical to produce iminyl radicals from γ,δ-unsaturated oxime ethers due to higher yields and shorter reaction times. Moreover, they realized microwave-assisted hydroimination of γ,δ-unsaturated oxime ethers to synthesize various pyrroline derivatives in just 15 min. The addition of ionic liquid ($emimPF_6$) was proved to be useful to promote efficient microwave heating in the nonpolar solvent (Scheme 2a).[34] When alkyne-tethered unsaturated oxime ether was used as the substrate, the expected pyrroline product was not formed; however, the corresponding pyrrole was obtained in 72% yield. The aromatisation of the heterocycle might be the driving force for this transformation (Scheme 2b).[35]

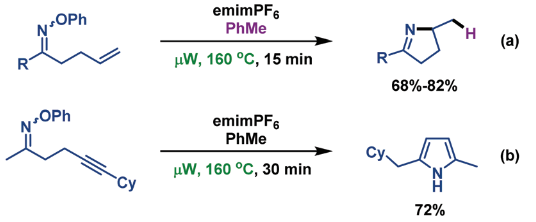


Xiaonan Shi

Xiaonan Shi was born in Tianjin, China, in 1999. She is now pursing her bachelor's degree in the College of Chemistry at Tianjin Normal University. She is interested in organic chemistry and is currently conducting research under the direction of Dr Chen Chen.

Liying Liu

Liying Liu was born in Hebei Province, China, in 1996. She obtained her bachelor's degree from the Qingdao University of Science and Technology in 2019. She is currently studying towards a master's degree in the College of Chemistry at Tianjin Normal University under the supervision of Dr Chen Chen. Her current research interests focus on the synthesis of organic compounds by transition-metal-catalyzed coupling reactions.

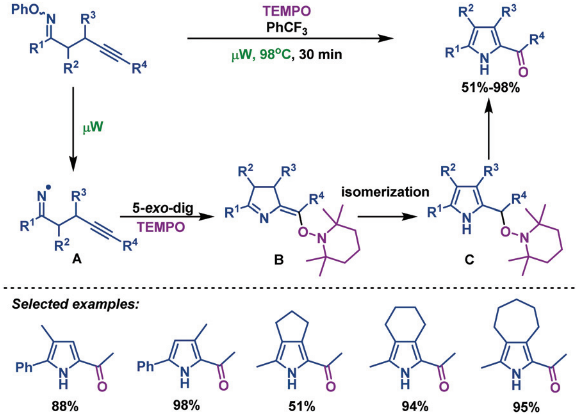


Scheme 2 Walton's microwave-assisted cyclization of γ,δ-unsaturated oxime ethers.

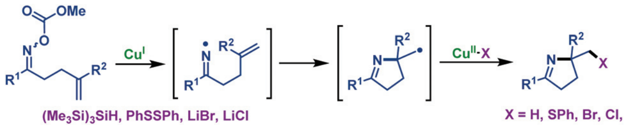
In 2015, Castle *et al.*[36] reported a microwave-promoted iminyl radical cyclization of γ,δ-unsaturated oxime ethers with TEMPO, which afforded a variety of 2-acylpyrroles in moderate to good yields (Scheme 3). $PhCF_3$ was used as a solvent to effectively facilitate radical cyclization and avoid hydrogen atom abstraction. Mechanistically, N–O bond homolytic cleavage of γ,δ-unsaturated oxime ethers was induced by microwave heating to afford iminyl radical intermediate **A**. Then **A** undergoes an intramolecular 5-*exo-dig* radical cyclization to generate a vinyl radical intermediate, which could be captured by TEMPO to afford **B**. Subsequently, isomerization of **B** delivers the more stable pyrrole intermediate **C**, which undergoes H abstraction to furnish the desired 2-acylpyrroles.

2.1.2 Generation of iminyl radicals *via* transition metal catalysis

2.1.2.1 Copper-catalyzed/promoted reactions. Copper-catalyzed/promoted cascade radical cyclization/functionalization reactions of γ,δ-unsaturated oxime esters are the most effective and practical synthetic strategies to synthesize versatile functionalized pyrrolines. For instance, Narasaka and co-workers[37] developed a novel copper-catalyzed imino-functionalization of γ,δ-unsaturated oxime esters with different radical trapping reagents, such as $(Me_3Si)_3SiH$, PhSSPh, LiBr and LiCl (Scheme 4). By using this protocol, a variety of functionalized pyrrolines are thus prepared catalytically, whereas the formation of tetrahydropyridine is hard to proceed from δ,ε-unsaturated oxime esters.



Scheme 3 Castle's microwave-promoted cyclization of γ,δ-unsaturated oxime ethers with TEMPO.



Scheme 4 Narasaka's copper-catalyzed imino-functionalization of γ,δ-unsaturated oxime esters.

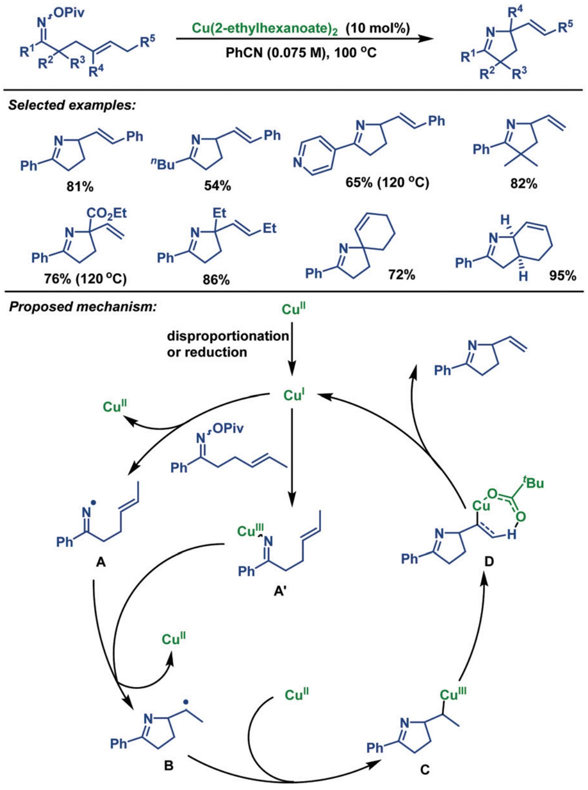
Later, Bower and colleagues[38] described nice copper-catalyzed Heck-like cyclizations of γ,δ-unsaturated oxime esters in 2014, furnishing a series of structurally diverse alkene-containing pyrrolines in moderate to good yields (Scheme 5). Notably, this protocol tolerates less activated *O*-pivaloyl oxime. This facet is in stark contrast to the work with Pd-systems,[39–41]

Yan-Ping Zhu

Yan-Ping Zhu was born in Wuhan, China. He obtained his Ph.D. (Organic Chemistry) in 2013 under the supervision of Prof. An-Xin Wu at Central China Normal University (CCNU). He then moved to Antwerp University, Belgium, and worked with Prof. Bert Maes as a postdoctoral researcher. In 2015, he was rewarded by The Marie Curie Actions Individual Fellowships and worked at Antwerp University, Belgium. He started his independent research in 2017 at the School of Pharmacy, Yantai University, China. His recent research focuses on heterocycle synthesis, domino reactions, transition metal catalysis and medicinal chemistry.

Wan Sun

Wan Sun was born in Liaoning Province, China, in 1995. She obtained her bachelor's degree at Linyi University in 2017. She is currently studying towards a master's degree at Tianjin Normal University under the supervision of Dr Chen Chen and Dr Bolin Zhu. Her current research interest includes free radical chemistry and transition metal catalysis.



Scheme 5 Bower's copper-catalyzed Heck-like cyclizations of γ,δ-unsaturated oxime esters.

where *O*-pentafluorobenzoyl oximes are necessary for efficient cyclization. The reaction mechanism may involve the following steps: firstly, Cu^I species was formed *in situ via* disproportionation or reduction of $Cu(2\text{-ethylhexanoate})_2$. Next, pathways proceed *via* either the generation of imino-Cu^{III} intermediate **A′** or iminyl radical intermediate **A**; in the former case cyclization occurs by the homolytic cleavage of the N–Cu bond. Subsequently, alkyl radical intermediate **B** is trapped by Cu^{II} species to provide alkyl-Cu^{III} intermediate **C**, followed by *syn* β-H elimination to generate alkene-containing pyrrolines.

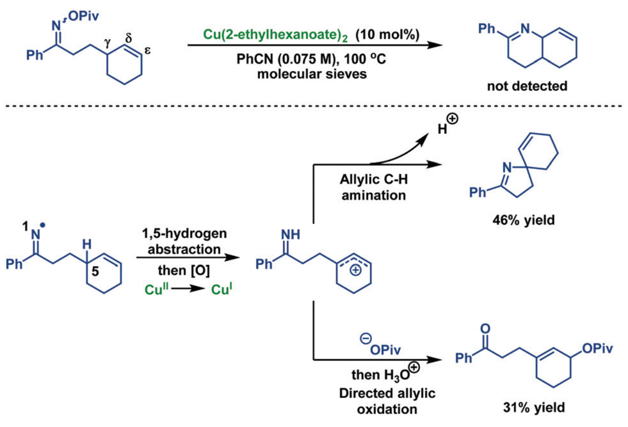
The author then explored the possibility of 6-ring cyclization of δ,ε-unsaturated oxime esters (Scheme 6). Surprisingly, exposure of δ,ε-unsaturated oxime esters under optimal conditions did not afford the Heck-type product. Instead, the allylic C–H amination or oxidation products were achieved in 46% and 31% yields, respectively.

In 2018, the group of Zhu[42] realized a copper-catalyzed domino cyclization/trifluoromethylthiolation of γ,δ-unsaturated oxime esters for the synthesis of a variety of SCF_3-containing pyrrolines (Scheme 7). A series of γ,δ-unsaturated oxime esters were investigated, leading to SCF_3-substituted pyrrolines in good yields. The reaction enables the simultaneous formation of a $C(sp^3)–SCF_3$ bond and a C–N bond, and is amenable for gram-scale synthesis. Mechanistically, the N–O bond of γ,δ-unsaturated oxime esters was cleaved by $CuSCF_3$, which was generated from the metathesis between Cu(I) and $AgSCF_3$. Consequently, iminyl radical intermediate **A** and $Cu(II)SCF_3$ species were formed. Next, **A** underwent 5-*exo-trig* cyclization to afford alkyl radical intermediate **B**, which could be captured by $Cu(II)SCF_3$, followed by $C–Cu(III)–SCF_3$ reductive elimination to construct a $C–SCF_3$ bond. Alternatively, **B** could be oxidized to carbocation **D** by $Cu(II)SCF_3$, which can react with the SCF_3 anion to give the SCF_3-substituted pyrrolines (Scheme 7).

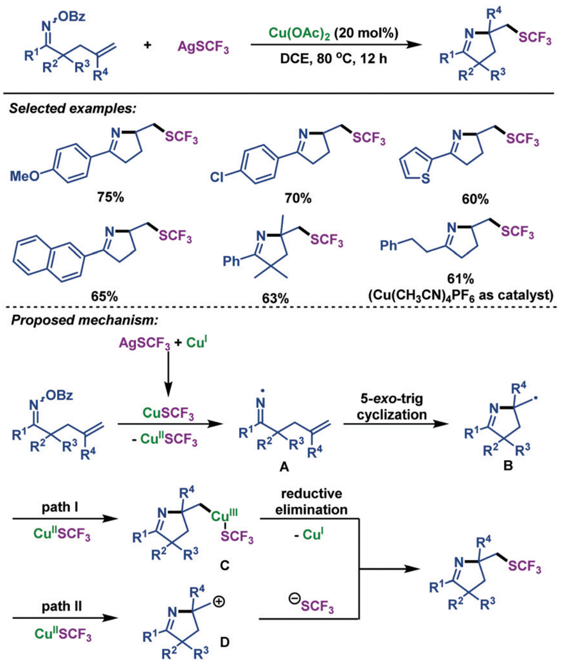
In 2019, our group[43] reported a highly efficient approach for the cascade radical cyclization/sulfonylation of γ,δ-unsaturated oxime esters with sodium sulfinates (Scheme 8). Both sodium arylsulfinates and sodium alkylsulfinates were compatible in this reaction, and the desired iminosulfonylation products were obtained in moderate to excellent yields. Notably, sodium heteroarylsulfinate was also tolerated in this transformation. Based on the control experimental results and previous reports, we proposed a plausible mechanism. First, sodium sulfinate was oxidized by Cu(II) to give a sulfonyl radical and Cu(I) species. Then, an iminyl radical intermediate was formed through N–O bond homolytic clea-

Bolin Zhu

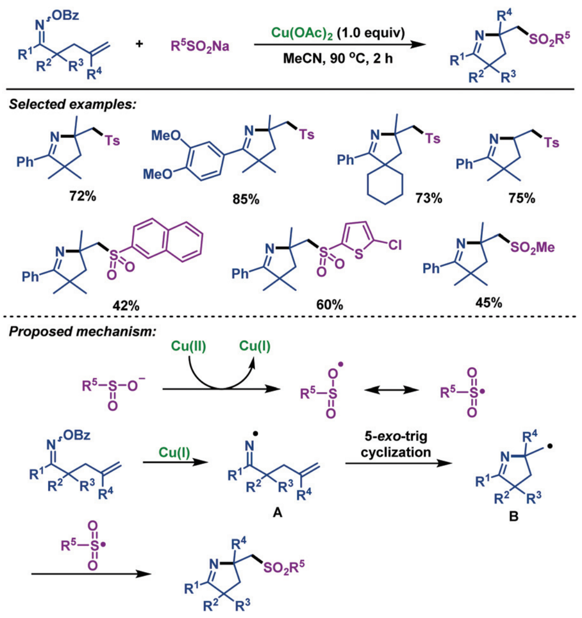
Bolin Zhu was born in Jiangsu Province, China, in 1977. He obtained his BS and PhD in Chemistry from Nankai University in 1999 and 2004. After spending five years at UC-Berkeley, Iowa State University and UW-Madison as a postdoc, he then joined the faculty of Tianjin Normal University as an associate professor in 2009. He was promoted to professor in 2014. His main research areas are synthetic organometallic chemistry and transition-metal-catalyzed methodologies.



Scheme 6 Bower's methodology applied to δ,ε-unsaturated oxime esters.



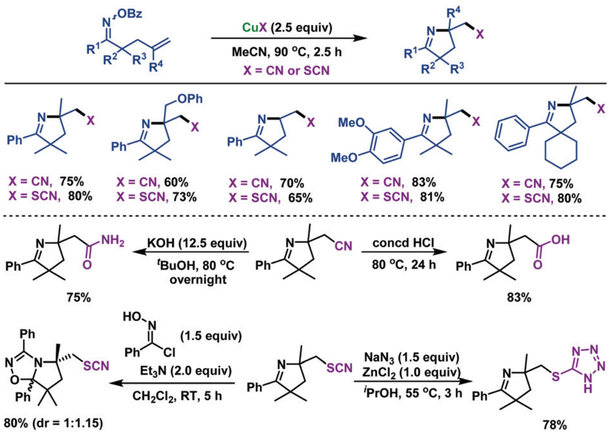
Scheme 7 Zhu's copper-catalyzed imino-trifluoromethylthiolation of γ,δ-unsaturated oxime esters with $AgSCF_3$.



Scheme 8 Zhu and Chen's copper-promoted imino-sulfonylation of γ,δ-unsaturated oxime esters with sodium sulfinates.

vage with the assistance of Cu(I). Next, it underwent an intramolecular 5-*exo-trig* radical cyclization to form carbon radical intermediate **B**, which was trapped by the sulfonyl radical to afford the sulfonyl-containing pyrrolines.

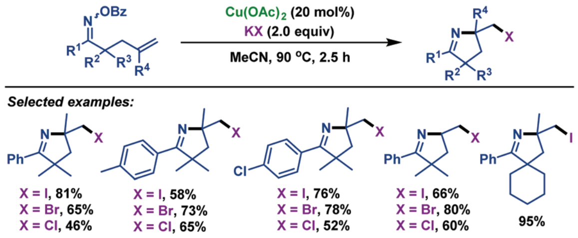
In addition, we also reported CuX-promoted (X = CN, SCN) imino-thiocyanation and imino-cyanogenation of γ,δ-unsaturated oxime esters to furnish a series of cyano- and thiocyano-containing pyrrolines in good yields (Scheme 9).[43] The limitation of this transformation was that γ,δ-unsaturated oxime ester without geminal disubstitution failed to undergo the cyclization reaction. This was probably due to the lack of the Thorpe–Ingold effect, which aided *gem*-dimethyl substrates, thus favoring radical cyclization. Notably, a series of synthetic transformations were carried out, which illustrated the synthetic potential of our prepared cyano- and thiocyano-functionalized pyrrolines.



Scheme 9 Zhu and Chen's CuX (X = CN or SCN) promoted imino-cyanogenation and imino-thiocyanation of γ,δ-unsaturated oxime esters.

Soon afterwards, our group[44] reported a copper-catalyzed imino-halogenation of γ,δ-unsaturated oxime esters with KX (Scheme 10). A variety of structurally diversiform 2-halomethyl pyrrolines were efficiently synthesized by using this protocol. We proposed that a Cu(I)-initiated iminyl radical cyclization process was involved in this transformation.

Although an array of methodologies are available for imino-functionalization of γ,δ-unsaturated oxime esters for the synthesis of versatile functionalized pyrrolines, the leaving group was not effectively utilized in the imino-functionalization process, leading to reduced atom economy. Therefore, the utilization of the leaving group as the coupling partners in the imino-functionalization of γ,δ-unsaturated oxime esters needs to be investigated. In 2019, our group[45] realized an atom-economical copper-catalyzed group-transfer radical cyclization (GTRC) of γ,δ-unsaturated oxime esters, during which a five-membered ring, a new C–O bond and a new C–N bond were



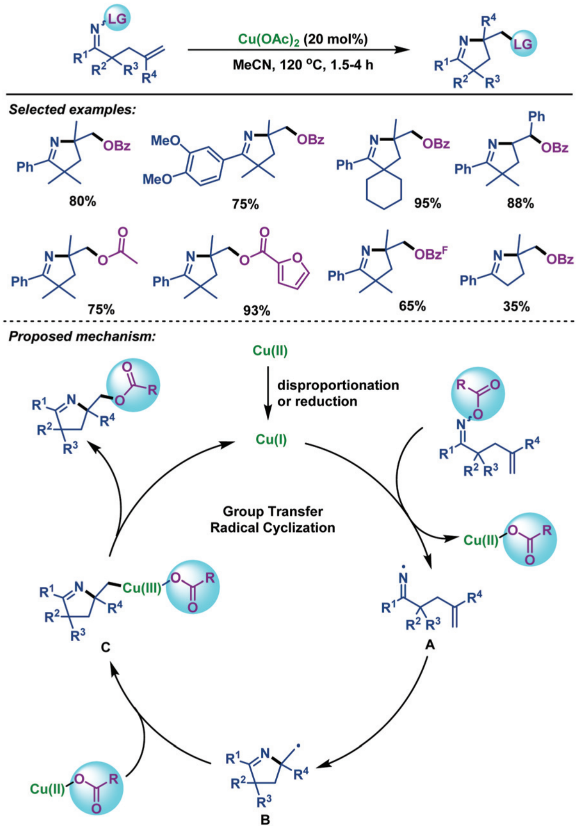
Scheme 10 Zhu and Chen's copper-catalyzed imino-halogenation of γ,δ-unsaturated oxime esters with KX.

formed in a one-step manner. This reaction effectively utilizes the leaving group as the ArC(O)O source for the first time, avoiding the use of additional reagents. A variety of ester-containing pyrrolines were obtained under oxidant-free and ligand-free conditions in good yields (Scheme 11). The possible mechanism for this copper-catalyzed GTRC reaction was proposed. Initially, a Cu^I species was formed *in situ via* the reduction or disproportionation of $Cu(OAc)_2$. Next, N–O bond homolytic cleavage led to the formation of iminyl radical intermediate **A**, which underwent 5-*exo-trig* radical cyclization to form alkyl radical intermediate **B**. Finally, intermediate **B** is trapped by $Cu^{II}OCOR$ to produce Cu^{III} intermediate **C**, followed by reductive elimination to provide ester-functionalized pyrrolines and Cu^I species.

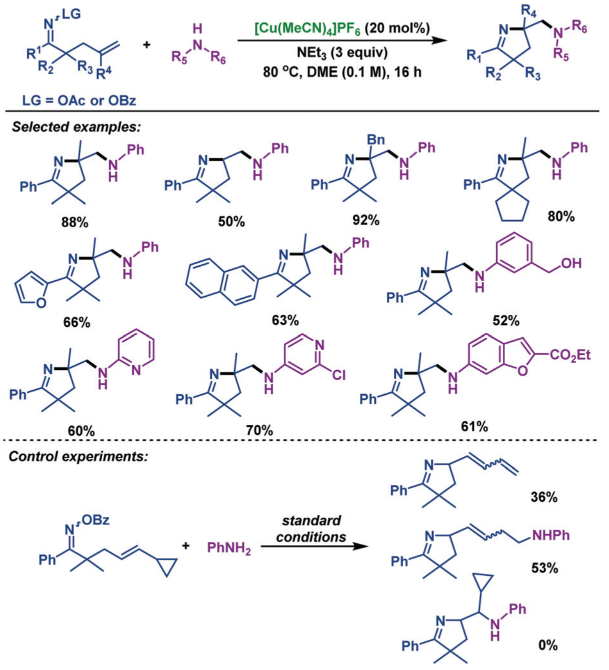
In the same year, Wang and colleagues[46] illustrated a redox-neutral copper-catalyzed diamination of γ,δ-unsaturated oxime esters with various unprotected amines. This reaction offers an efficient entry to various amine-containing pyrrolines under ligand- and oxidant-free conditions, and employs readily available unprotected amines as the nucleophilic nitrogen source. The radical clock experiment was conducted and the radical pathway for the cyclization step was proposed (Scheme 12).

2.1.2.2 *Iron-catalyzed reactions.* Except for the copper catalyst mentioned above, the environmentally friendly and cheap iron catalyst can also realize the imino-functionalization of γ,δ-unsaturated oxime esters. In 2017, the Selander group[47] described an iron-catalyzed coupling reaction of γ,δ-unsaturated oxime esters with silyl enol ethers (Scheme 13a). This protocol provides access to various functionalized pyrrolines *via* alkyl radicals, which are generated from an initially formed iminyl radical by N–O bond homolytic cleavage. It is worth noting that when alkyne-tethered oxime ester was used under optimal conditions, a mixture of products was obtained which demonstrated that the competitive pathways of the intermolecular 1,3-hydrogen transfer and the 5-*exo-dig* cyclization were involved (Scheme 13b).

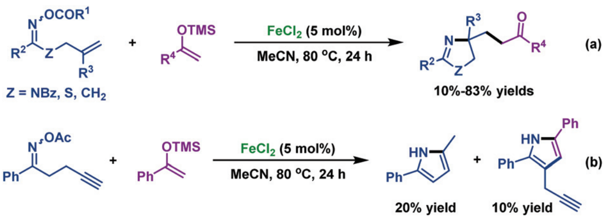
Later, Okamoto and Ohe[48] reported an iron-catalyzed imino-arylation of γ,δ-unsaturated oxime esters with various arenes (Scheme 14). Not only electron-poor and electron-rich arenes, but also heteroarenes were well tolerated in this reaction. Moreover, γ,δ-unsaturated oxime esters bearing sterically hindered alkene moieties were applicable to this reaction system. A plausible mechanism involving an iminyl radical and alkyl radical species was proposed based on radical trap-



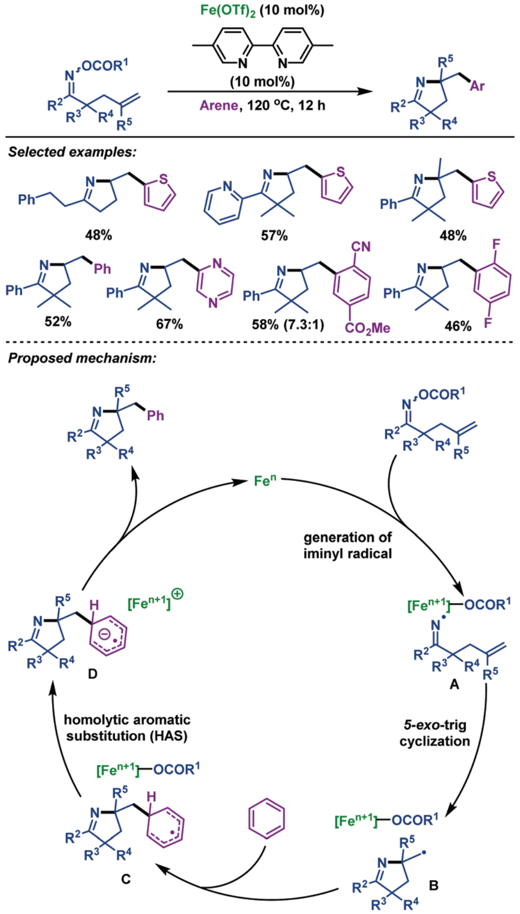
Scheme 11 Zhu and Chen's copper-catalyzed GTRC of γ,δ-unsaturated oxime esters.



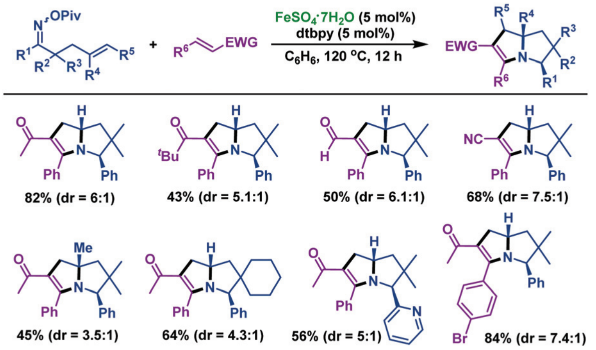
Scheme 12 Wang's copper-catalyzed diamination of γ,δ-unsaturated oxime esters with unprotected amines.



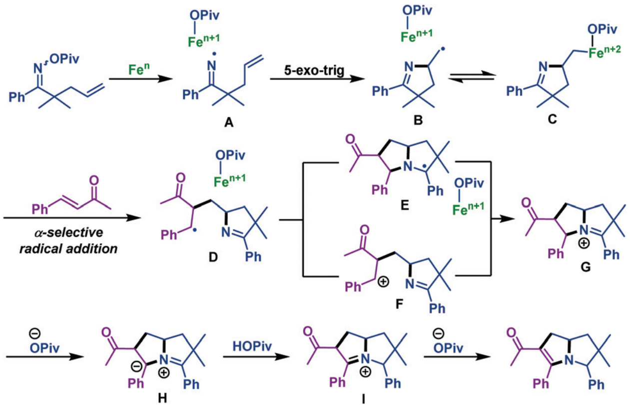
Scheme 13 Selander's iron-catalyzed γ,δ-unsaturated oxime esters with silyl enol ethers.



Scheme 14 Okamoto and Ohe's iron-catalyzed imino-arylation of γ,δ-unsaturated oxime esters with arenes.



Scheme 15 Ohe's iron-catalyzed tetrahydropyrrolizine synthesis from γ,δ-unsaturated oxime esters.



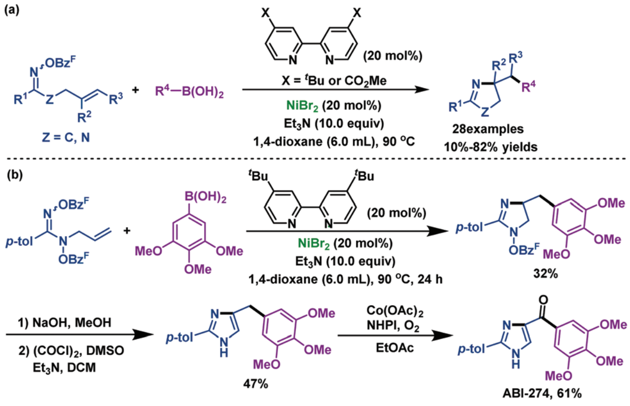
Scheme 16 Proposed mechanism for the synthesis of tetrahydropyrrolizines.

ping experiments. Furthermore, no kinetic isotope effect was observed in C–H bond cleavage, which demonstrated that the general homolytic aromatic substitution process might be involved.

In 2018, the same group[49] realized an iron-catalyzed cycloaddition reaction of γ,δ-unsaturated oxime esters with 1,2-disubstituted alkenes to synthesize diversiform tetrahydropyrrolizines, which are frequently found in bicyclic alkaloids (Scheme 15). A series of γ,δ-unsaturated oxime esters reacted with various 1,2-disubstituted alkenes smoothly, producing tetrahydropyrrolizines in moderate to satisfactory yields. Good functional group compatibility was observed in this transformation.

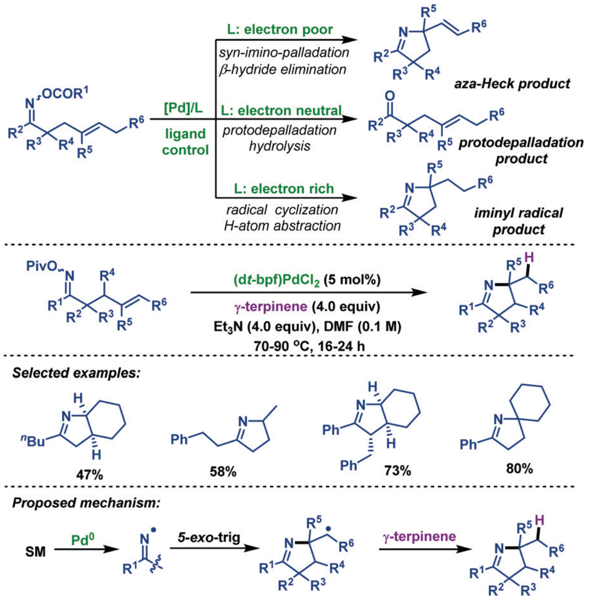
The possible mechanism of this transformation is illustrated in Scheme 16. First, N–O bond homolytic cleavage of γ,δ-unsaturated oxime esters forms iminyl radical intermediate **A**, which undergoes 5-*exo-trig* cyclization to give C-centered radical intermediate **B**. Normally, **B** may be in equilibrium with the corresponding iron adduct **C**. Next, α-selective radical addition with activated alkenes gives radical intermediate **D**, which is demonstrated by DFT analyses. Subsequently, radical cyclization of intermediate **D** with the imine group gives intermediate **E**, which is followed by oxidation to give bicyclic iminium **G**. Alternatively, **D** could also undergo the single electron oxidation by iron to form cation **F**, which is followed by ionic cyclization to **G**. Finally, deprotonation by pivalate gives azomethine ylide **H**, followed by deprotonation and protonation to complete the reaction.

2.1.2.3 Nickel-catalyzed/promoted reactions. Nickel is a powerful catalyst that enables the efficient construction of functionalized pyrrolines from γ,δ-unsaturated oxime esters. Since the pioneering work of the Zard group[50] in 1999, further exploration by Selander's group[51] and Wang's group[52] has enriched and expanded the scope of this method. In 2017, Selander *et al.*[51] reported a nickel-catalyzed imino-arylation of γ,δ-unsaturated oxime esters with boronic acids. Various arylated pyrroline derivatives were synthesized in moderate to good yields *via* the successive formation of C(sp^3)–C(sp^2) and C(sp^3)–N bonds. Moreover, by using this protocol, arylated imidazoline derivatives can also be synthesized from amidooxime (Scheme 17a). It is noteworthy that a potent tubulin inhibitor, ABI-274, was obtained *via* three-step synthesis, as described in Scheme 17b. This strategy offers an alternative route to synthesize ABI analogues.

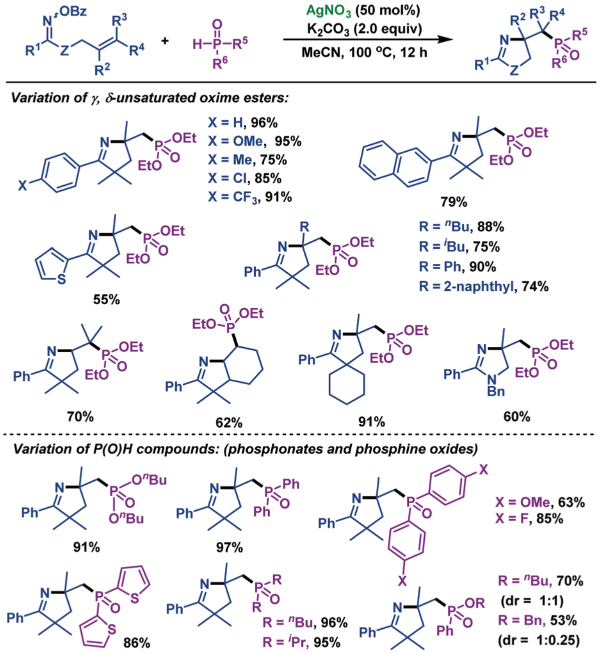


Scheme 17 Selander's nickel-catalyzed imino-arylation of γ,δ-unsaturated oxime esters with boronic acids.

2.1.2.4 *Palladium-catalyzed reactions.* In 2016, the Bower group[53] illustrated that palladium-catalyzed cyclizations of γ,δ-unsaturated oxime esters are subject to an unusual ligand controlled mechanistic divergence (Scheme 18). Pd-Systems with electron-rich phosphines (such as P(^{t}Bu)$_3$ and d*t*-bpf) promote SET-type oxidative addition. In these cases, C–N bond formation occurs *via* cyclization of an iminyl radical with pendant alkenes. Conversely, for electron-deficient phosphines (such as P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$), N–O oxidative addition proceeds *via* a two-electron pathway to generate imino-palladium intermediates, which employ pendant alkenes in a Heck-type cyclization. They also demonstrated a palladium-catalyzed imino-hydrogenation of γ,δ-unsaturated oxime esters with γ-terpinene, during which the electron-rich ligand, d*t*-bpf, was crucial to promote SET-type oxidative addition. Furthermore, a series of mechanistic experiments were conducted to verify the SET pathway and the scope of imino-hydrogenation was outlined.



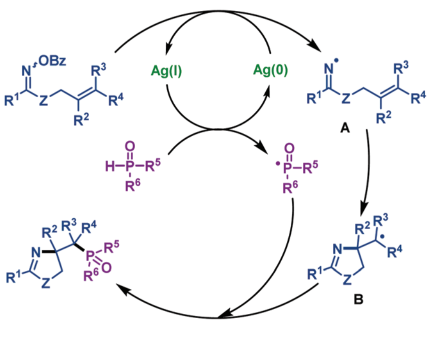
Scheme 18 Bower's palladium-catalyzed imino-hydrogenation of γ,δ-unsaturated oxime esters with γ-terpinene.



Scheme 19 Zhu and Chen's silver-promoted imino-phosphorylation of γ,δ-unsaturated oxime esters with P(O)H compounds.

2.1.2.5 *Silver promoted reactions.* Recently, our group[54] reported the first silver-promoted radical cyclization of γ,δ-unsaturated oxime esters with P(O)H compounds (Scheme 19). Both secondary phosphine oxides and H-phosphinates are compatible with this reaction. γ,δ-Unsaturated oxime esters with both electron-deficient and electron-rich groups could give the corresponding phosphorylated pyrrolines in good to satisfactory yields. Moreover, the heterocycle moiety was compatible with this reaction. Notably, this protocol was also efficient for trisubstituted alkenes. In addition, a phosphorylated imidazoline derivative was obtained from amidooxime under the same conditions.

Based on control experiments, a possible reaction mechanism was proposed (Scheme 20). Initially, iminyl radical inter-



Scheme 20 Proposed mechanism.

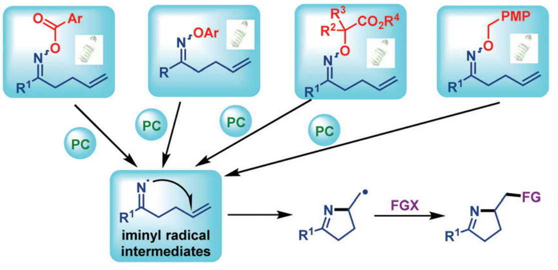
mediate **A** and a phosphinoyl radical were formed with the assistance of AgNO$_3$. Subsequently, the iminyl radical intermediate **A** underwent an intramolecular 5-*exo-trig* cyclization to form a carbon radical intermediate **B**, followed by radical coupling with the phosphinoyl radical to afford the desired phosphorylated pyrrolines.

2.1.3 Generation of iminyl radicals *via* light irradiation.

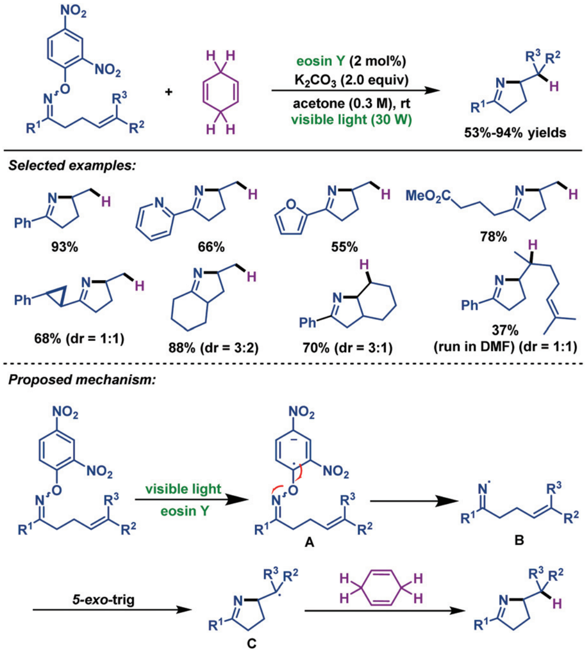
The advent of visible light photoredox catalysis has changed the way of SET processes to access free radical species. Therefore, the nitrogen-centered free radical chemistry has gained remarkable interest. In particular, iminyl radicals can be generated from γ,δ-unsaturated oxime esters (ethers) under visible light photoredox catalysis (Scheme 21). In this section, we discuss the most significant transformations of γ,δ-unsaturated oxime esters (ethers) under light irradiation.

In 2015, Leonori and colleagues[55] devised two complementary visible-light-mediated hydroimination and iminohydroxylation of γ,δ-unsaturated oxime ethers (Schemes 22 and 23). On account of the low reduction potentials of *O*-(2,4-dinitrophenyl)oximes, the cheap and easily available eosin Y could be used as the photocatalyst for hydroimination reaction. A wide range of γ,δ-unsaturated oxime ethers possessing diverse steric and electronic properties participated efficiently in this transformation. Moreover, both internal alkenes and terminal alkenes were suitable substrates for this reaction. Presumably, the reaction was initiated by visible-light promoted single-electron transfer of γ,δ-unsaturated oxime ethers to give radical anion intermediate **A**, followed by fragmentation to form iminyl radical intermediate **B**, which then underwent 5-*exo-trig* cyclization to give alkyl radical intermediate **C**. Finally, **C** abstracts H from CHD to give the desired hydroimination product (Scheme 22).

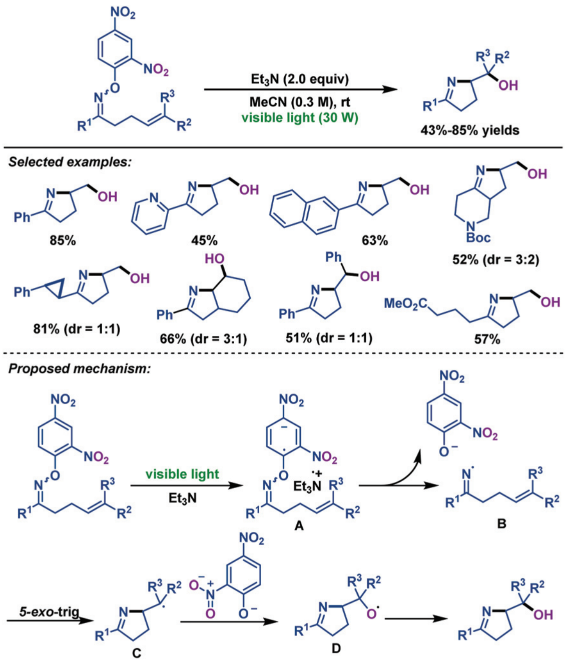
Meanwhile, the reaction conditions for visible-light-mediated iminohydroxylation of γ,δ-unsaturated oxime ethers were identified by the Leonori group (Scheme 23).[55] Utilizing the visible-light-mediated triethylamine triggered iminohydroxylation process, various iminoalcohols were synthesized. It is worth mentioning that the dinitrophenyl of oxime ether plays two roles in the reaction. Aside from the role of reducing the bond energy of the N–O bond to facilitate homolytic scission, it can also afford the oxygen atom to the final product. A mechanism involving visible-light-mediated SET from triethylamine to the substrate and the oxygen atom of the product originated from the nitro groups of the aromatic unit was proposed by the authors.



Scheme 21 Iminyl radical generations from γ,δ-unsaturated oxime esters (ethers) *via* visible light irradiation.



Scheme 22 Leonori's visible-light mediated hydroimination of γ,δ-unsaturated oxime ethers with CHD.



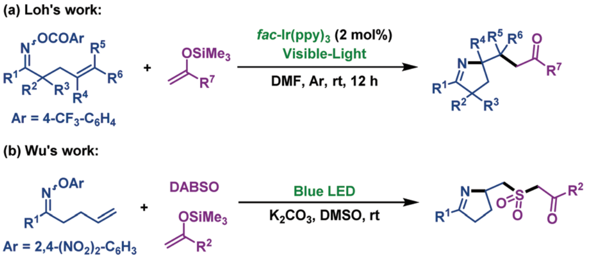
Scheme 23 Leonori's visible-light mediated imino-hydroxylation of γ,δ-unsaturated oxime ethers.

Since 2016, two research groups[56,57] have reported the visible light-promoted imino-functionalization of γ,δ-unsaturated oxime esters with silyl enol ethers independently. First, Feng and Loh[56] realized the synthesis of pyrroline derivatives using *fac*-[Ir-(ppy)$_3$] as the photoredox catalyst (Scheme 24a). The group of Wu[57] expanded the scope of this reaction, and they achieved the imino-sulfonylation of γ,δ-unsaturated oxime esters with silyl enol ethers and DABSO. This tandem radical process involved iminyl radical-mediated cyclization and insertion of sulfur dioxide, which was trapped by silyl enol ethers, and afforded a variety of sulfonated pyrrolines (Scheme 24b).

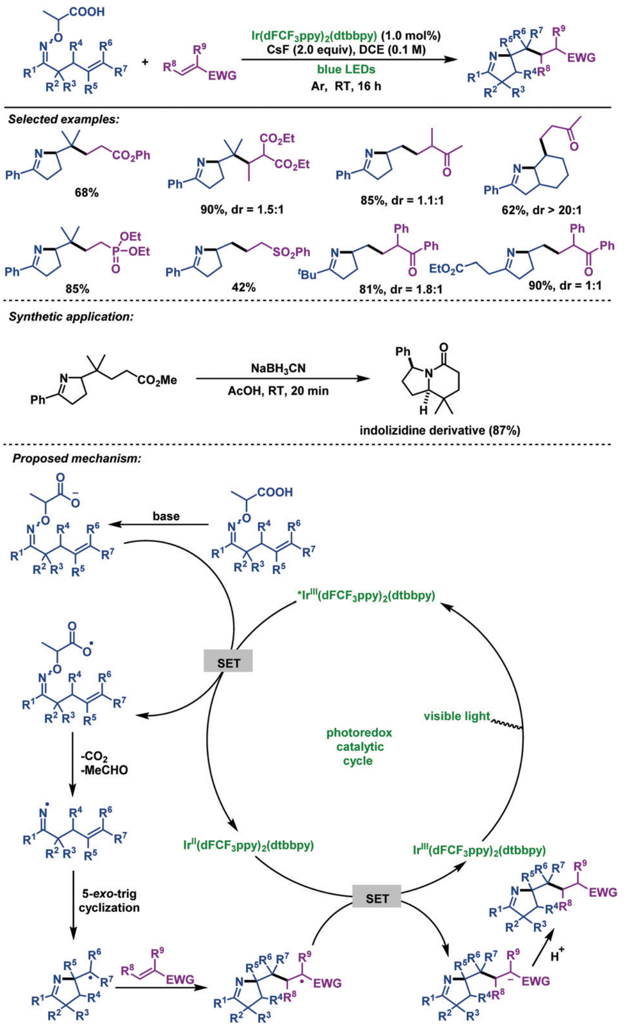
In 2017, Studer *et al.*[58] described the visible-light-promoted carboimination of γ,δ-unsaturated oxime ethers with Michael acceptors to afford pyrroline derivatives in good yields. A wide range of Michael acceptors, such as phenyl vinyl ketone, methyl vinyl ketone, α,β-unsaturated amides and phosphonates, are compatible with this reaction. Furthermore, the indolizidine skeleton could be easily synthesized from a prepared pyrroline derivative by this method. More remarkably, they applied α-imino-oxy propionic acids as a new type of efficient precursor to generate iminyl radicals upon SET oxidation (Scheme 25).

In the same year, Leonori and co-workers[59] described visible-light-mediated decarboxylation radical cascade cyclization of γ,δ-unsaturated oxime ethers with a variety of SOMOphiles, which include ArSSAr, NCS, NIS, diethyl-bromomalonate, NFSI, DEAD, ArSO$_2$N$_3$, Michael acceptor, IBX reagents *etc.* A variety of polyfunctionalized pyrrolines were obtained in favourable yields. The addition of two methyl groups at the methylenic position of oxime ethers unit could increase the electron density of carboxylate and decrease its $E^{\text{ox}}_{1/2}$ (1.65 V). Notably, by using this protocol, a molecule with a complex structure, such as the functionalized morphane derivative thevinone, was successfully involved in the formation of functionalized pyrroline products *via* imino-amination, imino-azidation and imino-selenation of γ,δ-unsaturated oxime ethers (Scheme 26).

Recently, Liu and co-workers[60] reported a novel radical cyclization of γ,δ-unsaturated oxime ethers *via* synergistic photoredox organocatalysis and cobalt catalysis. Diverse γ,δ-unsaturated oxime ethers, bearing different substituents, smoothly underwent radical cyclization reactions, and delivered a range of alkene-containing pyrrolines. The reaction was initiated by oxidative decarboxylation of oxime ethers, generating iminyl radical intermediate **A** with loss of acetone and CO$_2$. Next, intermediate **A** underwent 5-*exo-trig* cyclization to deliver alkyl radical intermediate **B**. Subsequently, **B** reacted with Co(II) species to form Co(III) intermediate **C**, which is followed by β-H elimination to furnish alkene-containing pyrrolines (Scheme 27).



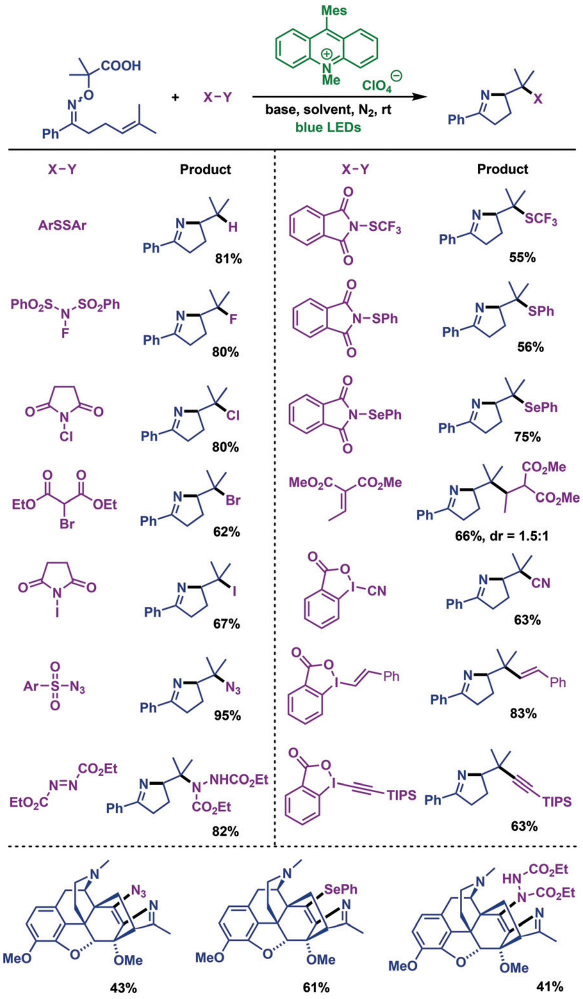
Scheme 24 Visible light-promoted imino-functionalization of γ,δ-unsaturated oxime esters (ethers) with silyl enol ethers.



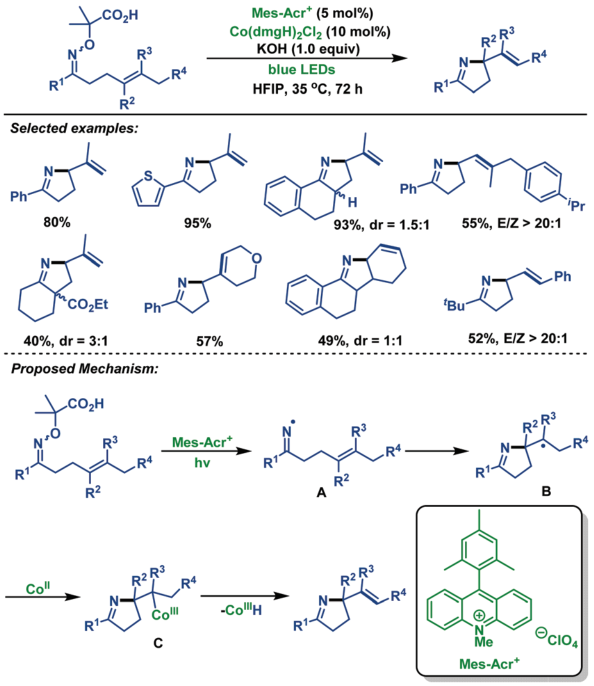
Scheme 25 Studer's visible-light-promoted carboimination of γ,δ-unsaturated oxime ethers with Michael acceptors.

In addition, the Liu group[60] investigated the cascade radical cyclization of γ,δ-unsaturated oxime ethers with terminal alkenes (Scheme 28). A series of *E*-selective alkene-functionalized pyrrolines were obtained in acceptable yields. Notably, the site-selective β-H elimination process of Co(III) intermediates led to the thermodynamically stable internal alkenes as products, and the terminal alkene products were not observed in the reaction.

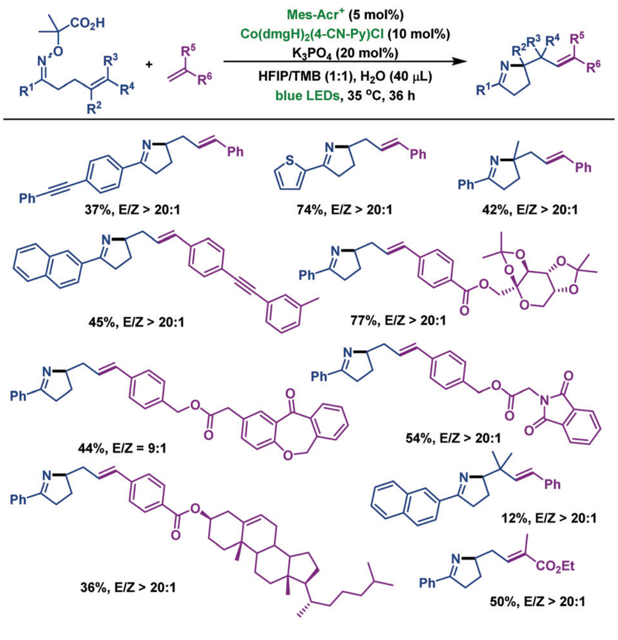
In the abovementioned methods, iminyl radicals were formed *via* the N–O bond cleavage of γ,δ-unsaturated oxime ethers under photoredox conditions. However, the re-oxidation reagents were required to regenerate the photocatalyst in most of the cases. Itoh *et al.*[61] developed an economical and novel iminyl radical evolution method using *O*-PMB oxime ether in 2018. They realized visible-light-mediated hydroimination of



Scheme 26 Leonori's visible-light mediated imino-functionalization of γ,δ-unsaturated oxime ethers.



Scheme 27 Liu's radical cyclization of γ,δ-unsaturated oxime ethers *via* synergistic photoredox organocatalysis and cobalt catalysis.



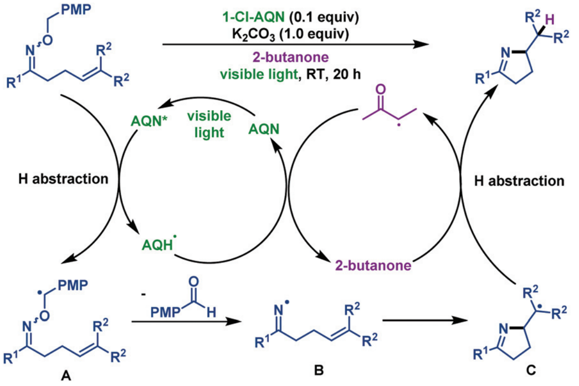
Scheme 28 Liu's cascade radical cyclization of γ,δ-unsaturated oxime ethers with terminal alkenes.

γ,δ-unsaturated oxime ethers with 2-butanone. No additional reagent was used in this transformation because of the hydrogen atom being circulated between 2-butanone and 1-Cl-AQN, which was abstracted from the benzylic position of γ,δ-unsaturated oxime ethers. The author assumed the mechanism as follows: first, benzyl radical intermediate **A** was formed *via* hydrogen atom abstraction of excited 1-Cl-AQN from benzyl oxime ether. Then, **A** immediately underwent β-scission to produce iminyl radical intermediate **B** and *p*-anisaldehyde. Subsequently, formation of intermediate **C** was noted *via* 5-*exo-trig* cyclization of **B**. Next, intermediate **C** trapped the hydrogen atom from 2-butanone, and delivered the final pyrroline derivatives. 2-Butanone was regenerated by the hydrogen abstraction from AQH$^\bullet$, thus regenerating AQN to complete the catalytic cycle (Scheme 29).

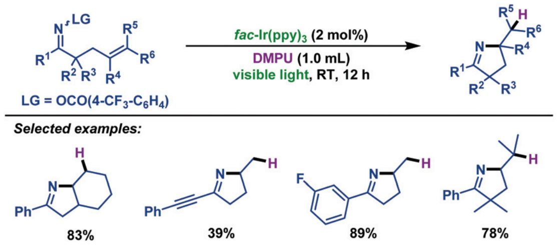
In addition, Loh and co-workers[62] realized the visible-light-promoted hydroimination of γ,δ-unsaturated oxime ethers with DMPU (*N*,*N*′-dimethylpropylene urea) to synthesize pyrroline derivatives (Scheme 30). Different substrates exhibited an outstanding performance, producing the desired products in moderate to good yields. It is noteworthy that DMPU revealed triple roles in this transformation, including catalyst regeneration reagent, H-donor for the formation of products and solvent.

2.1.4 Generation of iminyl radicals *via* SmI$_2$ irradiation.

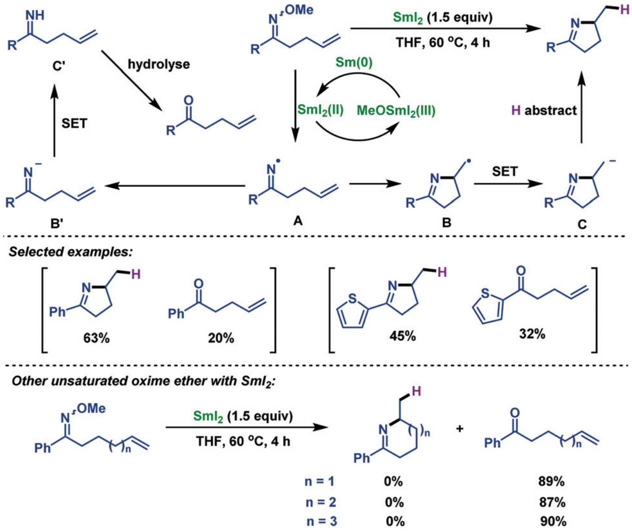
Recently, another effective strategy for the generation of iminyl



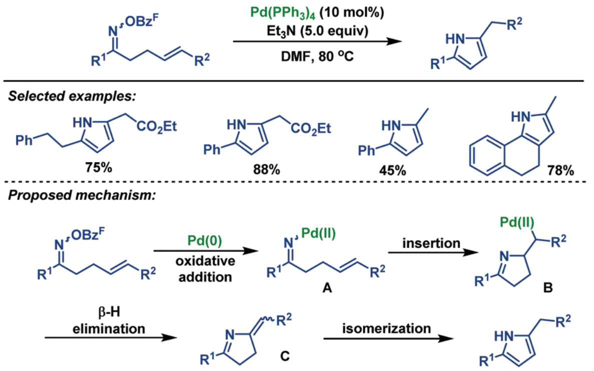
Scheme 29 Itoh's visible-light-mediated hydroimination of γ,δ-unsaturated oxime ethers with 2-butanone.



Scheme 30 Loh's visible-light-promoted hydroimination of γ,δ-unsaturated oxime esters with DMPU.



Scheme 31 Zhang's SmI_2 promoted hydroimination of γ,δ-unsaturated oxime ethers.



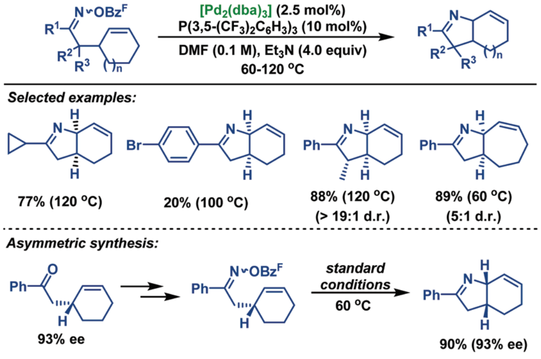
Scheme 32 Narasaka's palladium-catalyzed Heck-type cyclization of γ,δ-unsaturated oxime: synthesis of pyrrole derivatives.

radicals was developed by the Zhang group.[63] They reported a new method to generate iminyl radicals by SmI_2-promoted reductive cleavage of the N–O bond of γ,δ-unsaturated oxime ethers in 2019 (Scheme 31). Various hydroimination products were obtained in moderate yields. The result of this transformation highly depended on the concentration of SmI_2. With a low concentration of SmI_2, the hydroimination products were obtained. With a high concentration of SmI_2, the corresponding ketones were obtained by hydrolysis. Other unsaturated oxime ethers were also tested under optimal conditions and the corresponding ketones were obtained instead of hydroimination products.

2.2. Cyclization reactions of γ,δ-unsaturated oxime esters *via* N–O bond oxidative addition

2.2.1 Palladium-catalyzed reactions. As early as 1999, Narasaka and co-workers[64] realized the first palladium-catalyzed Heck-type cyclization of γ,δ-unsaturated oxime esters to synthesize pyrrole derivatives (Scheme 32). Numerous γ,δ-unsaturated oxime esters were employed and furnished the corresponding products in moderate yields. The reaction pathway is described in Scheme 32; the first step involves the oxidative addition of Pd(0) to the N–O bond of γ,δ-unsaturated oxime esters to form Pd(II) intermediate **A**. Then intermediate **A** undergoes the intramolecular Heck insertion to form alkyl palladium intermediate **B**. Subsequently, β-hydride elimination of intermediate **B** generates intermediate **C**, followed by isomerization to form functionalized pyrrole derivatives.

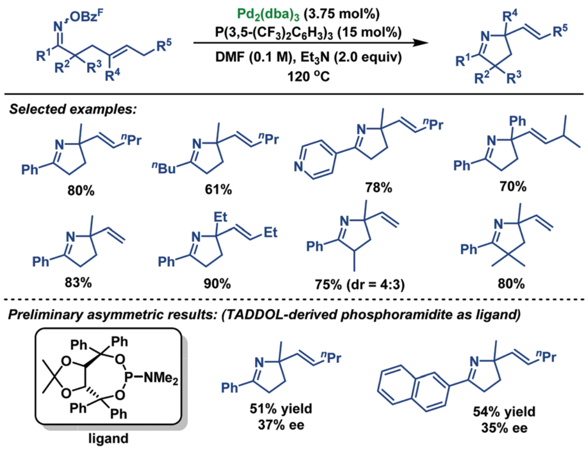
In 2012, Bower and co-workers[39] reported a palladium-catalyzed Heck type cyclization of γ,δ-unsaturated oxime esters with cyclic olefins (Scheme 33). This transformation is reliant upon the use of electron-deficient phosphine ligands $P(3,5\text{-}(CF_3)_2C_6H_3)_3$, probably due to three factors: (1) it makes the Pd center more electron-deficient and increases the stability of the putative imino-Pd^{II} intermediate; (2) the imine moiety gives greater σ donation and makes the imino-Pd bond stronger, which reduces protodepalladation and avoids the formation of ketone hydrolysis byproducts; and (3) the electron-deficient imino-Pd^{II} intermediate may accelerate the rate of the iminopalladation process. A variety of perhydroindoles and related scaffolds were obtained in moderate yields by using $P(3,5\text{-}(CF_3)_2C_6H_3)_3$ as the ligand. However, the corresponding products were not detected from aldoxime ester substrates probably because the Beckmann rearrangement predominated



Scheme 33 Bower's Narasaka–Heck cyclizations of oxime esters with cyclic alkenes.

to deliver the corresponding nitriles, which were observed as byproducts. It should be stressed that this methodology is readily translated to asymmetric synthesis. When the enantioenriched substrate (93% ee) was subjected to the standard conditions, no loss of the enantiomeric excesses was observed in the products.

In 2013, the Bower group[40] achieved an efficient palladium-catalyzed cyclization of oxime esters with 1,1-disubstituted alkenes to synthesize a range of α,α-disubstituted pyrrolines in moderate to good yields (Scheme 34). For C–N bond formation to occur, the N–Pd^{II} bond of the imino-Pd^{II} intermediate must be oriented towards the alkene. Thus, substrates bearing smaller R^1 groups show lower efficiency, probably because the steric factor is less effective at enforcing this configuration. Moreover, they also demonstrated the catalytic asymmetric variants of this chemistry. By using TADDOL-derived phosphoramidite as the chiral ligand, the desired pyrrolines were effectively generated in moderate yields, albeit with low ee values. More importantly, the TADDOL scaffold could be readily modified, which gives an opportunity to tune steric and electronic properties to find a more suitable chiral ligand.

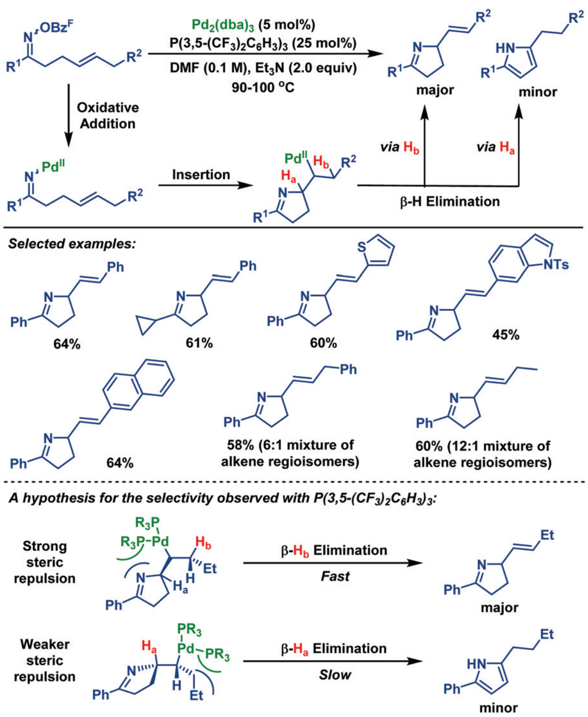


Scheme 34 Bower's palladium-catalyzed Narasaka–Heck cyclizations of oxime esters with 1,1-disubstituted alkenes.

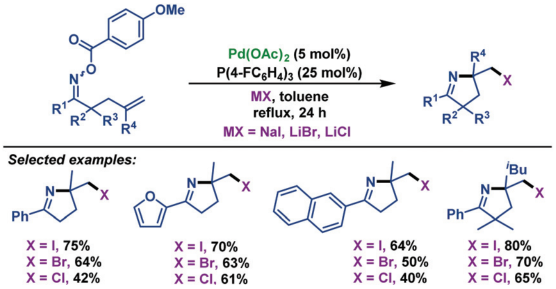
In the same year, Bower *et al.*[41] demonstrated a substrate and catalyst-controlled strategy for selective pyrroline formation (*vs.* pyrrole) of oxime esters with 1,2-dialkylated alkenes (Scheme 35). Notably, in the cases where C–H$_b$ is not benzylic, the corresponding pyrrolidine products were obtained with good selectivity over the undesired pyrroles. The authors proposed that selective β-hydride elimination could be facilitated by the interplay of the sterically demanding ligand system. The electronic and steric properties of P(3,5-(CF$_3$)$_2$C$_6$H$_3$)$_3$ were crucial for both efficient cyclization and selective pyrroline formation. By using this protocol, a wide range of pyrrolidine derivatives were obtained in moderate yields with good selectivity.

In 2015, Tong and co-workers[65] described a palladium(0)-catalyzed imino-halogenation of γ,δ-unsaturated oxime esters with the assistance of different halide salts. A variety of synthetically useful 2-halomethyl pyrrolines were obtained in moderate to good yields (Scheme 36). The use of an excess amount of electron-poor phosphine ligands (P(4-F-C$_6$H$_4$)$_3$) proved to be crucial to facilitate C$_{alkyl}$–Pd(II)–halide reductive elimination. Compared to Bower's work,[39–41,66] the pentafluorobenzoate leaving group was not necessary for this transformation. Moreover, the radical scavenger (TEMPO) did not have an adverse effect on the reaction, which indicated that the radical process was not involved in these transformations.

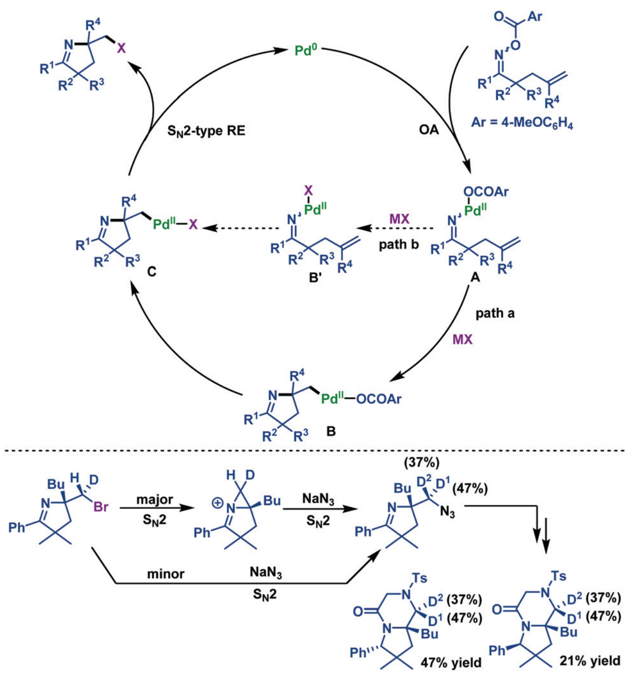
A classical transition-metal-catalyzed pathway is documented in Scheme 37. First, the oxidative addition of γ,δ-unsaturated oxime esters to the Pd(0) catalyst affords imino-Pd(II) intermediate **A**, which is followed by alkene inser-



Scheme 35 Bower's palladium-catalyzed cyclizations of oxime esters with 1,2-disubstituted alkenes.



Scheme 36 Tong's palladium-catalyzed imino-halogenation of γ,δ-unsaturated oxime esters with halide salts.



Scheme 37 Proposed mechanism.

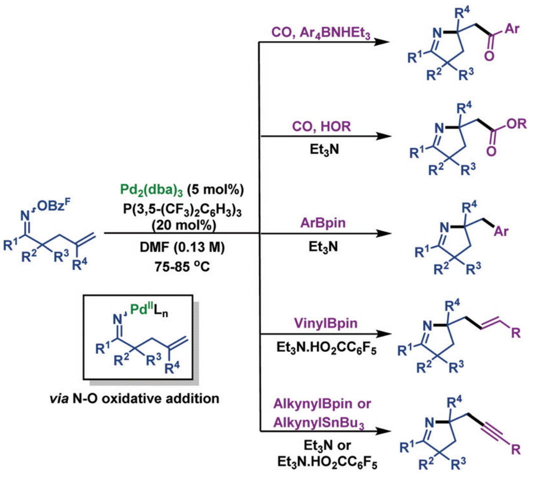
tion to generate C$_{\text{alkyl}}$–Pd(II) intermediate **B** (Scheme 37, path a). After ligand exchange with halide salts, **B** is converted into the C$_{\text{alkyl}}$–Pd(II)–halide intermediate **C**. Alternatively, ligand exchange of intermediate **A** occurs before the alkene insertion (Scheme 37, path b). Finally, **C** undergoes C$_{\text{alkyl}}$–Pd(II)–halide reductive elimination to deliver 2-halomethyl pyrrolines. Although path a is proved to be more reasonable, path b cannot be completely ruled out.

To get more insight into the unprecedented nature of C$_{\text{alkyl}}$–Pd(II)–Br reductive elimination, the authors conducted further studies regarding the stereochemical nature of the C–Br bond forming step (Scheme 37). After a four-step synthetic transformation, two separable diastereomers were obtained and analyzed by NOE experiments. The NOE experiment results clearly indicated that C$_{\text{alkyl}}$–Pd(II)–Br reductive elimination occurred *via* an S$_N$2-type pathway, which was consistent with microscopic reversibility in the oxidative addition of alkyl halide to Pd(0) species.

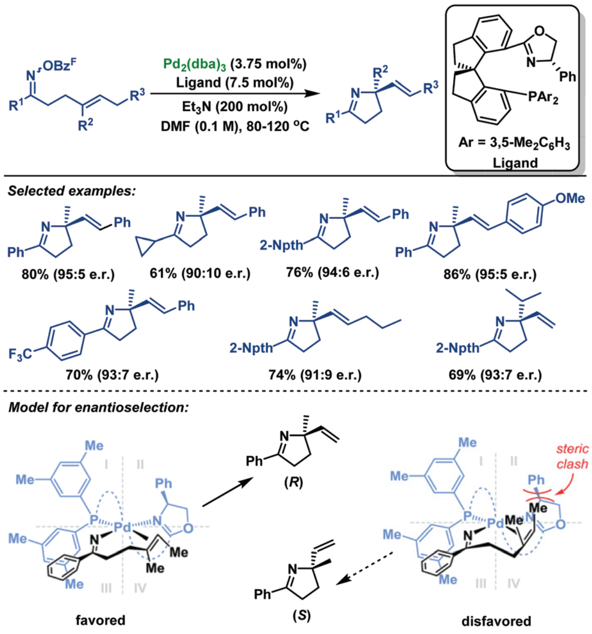
Shortly after, the Bower group[66] illustrated palladium-catalyzed imino-acylation, imino-arylation, imino-carboxylation, imino-alkynylation and imino-vinylation of γ,δ-unsaturated oxime esters with various nucleophiles (Scheme 38). The pentafluorobenzoate leaving group was found to be crucial for efficient cyclization. The reaction mechanism may involve the following steps: oxidative addition of Pd^0 into the N–O bond of γ,δ-unsaturated oxime esters generates N–Pd$^{\text{II}}$ intermediates, which undergo 5-*exo-trig* cyclization to form C$_{\text{alkyl}}$–Pd$^{\text{II}}$ intermediates. Then, C$_{\text{alkyl}}$–Pd$^{\text{II}}$ intermediates are intercepted by various nucleophiles under carbonylative or noncarbonylative conditions to provide diversiform functionalized pyrrolines.

In 2017, Bower and co-workers[67] realized the first example of highly enantioselective Narasaka–Heck cyclizations of γ,δ-unsaturated oxime esters (Scheme 39). The use of the SPINOL-derived P,N-ligand promotes Pd-catalyzed 5-*exo-trig* cyclization of a range of γ,δ-unsaturated oxime esters to generate pyrrolines containing tetrasubstituted nitrogen-bearing stereocenters in 56%–86% yields and 90 : 10–95 : 5 er. The structural features of the ligand backbone play a key role in enantioinduction. Besides, the key factor in the chemical efficiency of this ligand likely lies in the weak donor ability of the N atom of oxazoline, which enhances σ-donation from the *trans*-imino group. This lowers the basicity of the imino moiety, thus suppressing protodepalladation and the cyclization efficiency is enhanced.

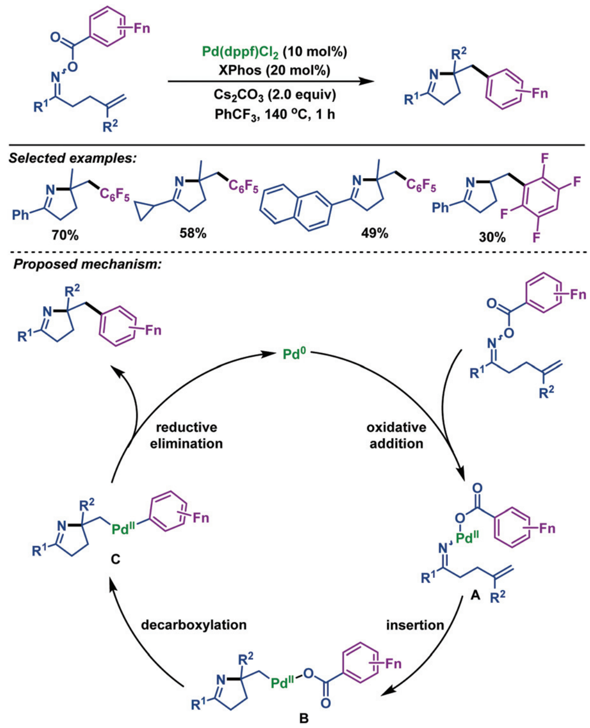
In 2019, the Liang group[68] developed a palladium-catalyzed imino-polyfluorophenylation of γ,δ-unsaturated polyfluorobenzoyl oxime esters, which proceeds through iminopalladation and polyfluorobenzoyloxy decarboxylation cascade reaction, thus delivering various polyfluorophenylated pyrrolines (Scheme 40). This reaction effectively utilized the polyfluorobenzoyloxy leaving group as the polyfluorophenylated source



Scheme 38 Bower's palladium-catalyzed imino-acylation, imino-arylation, imino-carboxylation, imino-alkynylation and imino-vinylation of γ,δ-unsaturated oxime esters with various nucleophiles.



Scheme 39 Bower's enantioselective Narasaka–Heck cyclizations of γ,δ-unsaturated oxime esters.

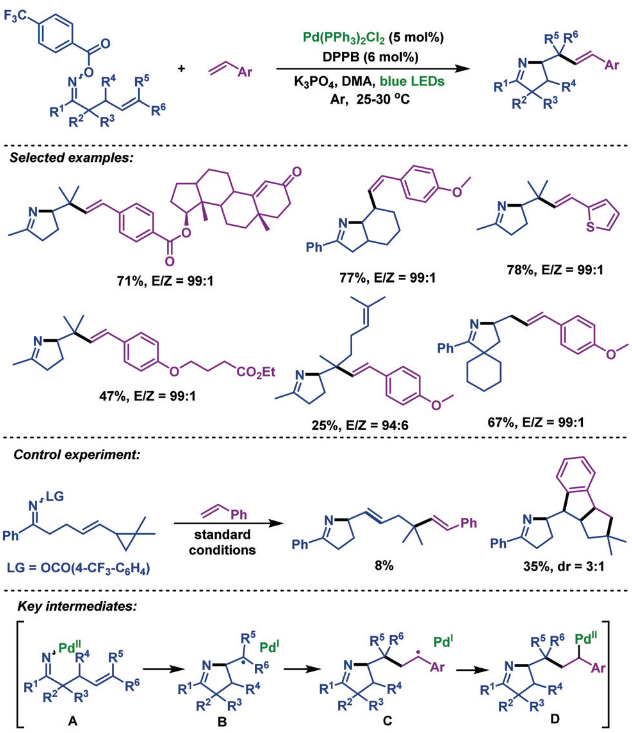


Scheme 40 Liang's palladium-catalyzed imino-polyfluorophenylation of γ,δ-unsaturated polyfluorobenzoyl oxime esters.

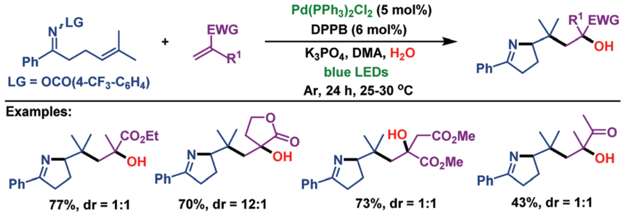
instead of the use of additional polyfluoroarene, which provided a new atom-economic strategy to synthesize polyfluorophenylated pyrrolines. A plausible mechanism to account for the formation of polyfluorophenylated pyrrolines was proposed by the authors. The reaction is initiated by the oxidative addition of Pd^0 to γ,δ-unsaturated oxime esters to afford Pd^{II} intermediate **A**, which is followed by alkene insertion to generate the C$_{alkyl}$–Pd^{II} intermediate **B**. Subsequently, intermediate **B** could release a molecule of CO$_2$ to form intermediate **C** by the decarboxylation of the pentafluorobenzoyloxy. Finally, intermediate **C** undergoes C–Pd^{II}–C reductive elimination to deliver polyfluorophenylated pyrrolines.

Very recently, Zhou and Xia[69] described a palladium-catalyzed domino cross-coupling reaction of γ,δ-unsaturated oxime esters with aromatic alkenes (Scheme 41). This reaction was different from the previous palladium catalyzed reactions, in which the N–O bond was activated by photoexcited-state Pd(0). A wide range of functional groups were well tolerated in the reaction to afford the corresponding products in excellent yields. Control experiments demonstrated that both the SET pathway and oxidative addition were involved. The mechanism was proposed by the authors: first, oxidative addition of Pd(0) to the N–O bond of γ,δ-unsaturated oxime esters generates Pd(II) intermediate **A**, which is followed by 5-*exo-trig* cyclization to give alkyl radical intermediate **B** and Pd(I) species through a SET process. After radical addition to aromatic alkenes, conversion of **B** into radical intermediate **C** occurs. Subsequently, **C** coordinates with the palladium complex to deliver Pd(II) intermediate **D**, and then followed by β-H elimination to give the desired products.

Moreover, the palladium-catalyzed domino cross-coupling reaction of γ,δ-unsaturated oxime esters with α,β-unsaturated



Scheme 41 Zhou and Xia's palladium-catalyzed domino cross-coupling reaction of γ,δ-unsaturated oxime esters with aromatic alkenes under blue LED irradiation.



Scheme 42 Zhou and Xia's palladium-catalyzed domino cross-coupling reaction of γ,δ-unsaturated oxime esters with α,β-unsaturated esters (ketones) under blue LED irradiation.

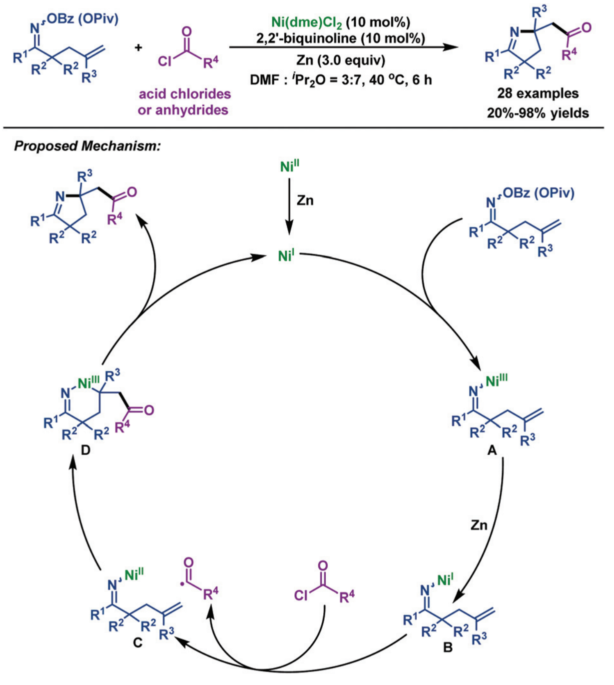
esters (ketones) was also investigated by Zhou and Xia (Scheme 42).[69] The α,β-unsaturated esters (ketones) underwent 1,4-addition, which is followed by hydroxylation to form the corresponding α-OH esters (ketones).

2.2.2 Nickel-catalyzed reactions. In 2018, a nickel-catalyzed imino-acylation of γ,δ-unsaturated oxime esters with acid chlorides or anhydrides was demonstrated by the Wang group (Scheme 43).[52] Under the Ni-biquinoline catalytic system, various γ,δ-unsaturated oxime esters reacted with acid chlorides or anhydrides in the presence of Zn as a reductant, furnishing a series of acylated pyrrolines in moderate to good yields. This protocol avoids the use of pregenerated organometallics, CO gas and strong basic additives, which makes this methodology desirable for practical use from the viewpoint of step-economy and safety. The authors also proposed a plausible mechanism for this transformation: firstly, oxidative addition of oxime esters to Ni^I leads to the imino-Ni^{III} intermediate **A**, which is reduced by Zn to provide a Ni^I complex **B**. Subsequently, acid chloride or anhydride reacts with the generated Ni^I complex **B** to give a Ni^{II} intermediate and an acyl radical, which can recombine with each other *via* radical addition to give intermediate **D**. Finally, **D** undergoes reductive elimination to deliver the acylated pyrrolines.

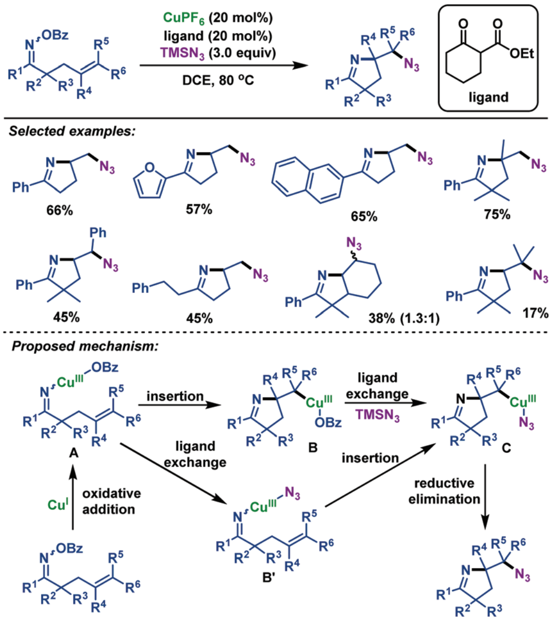
2.2.3 Copper-catalyzed reactions. In the same year, Yu and co-workers[70] reported a copper-catalyzed imino-azidation of γ,δ-unsaturated oxime esters with $TMSN_3$ (Scheme 44). Different kinds of γ,δ-unsaturated oxime esters were investigated in this reaction, affording the desired azide-containing pyrrolines in good yields with good group tolerance. The addition of the radical scavenger (TEMPO) did not inhibit the reaction which demonstrated that the radical intermediates were not involved in the cyclization step. The classical transition-metal-catalyzed pathway was proposed: first, the oxidative addition of oxime esters to the Cu^I leads to the imino-Cu^{III} intermediate **A**, which is followed by alkene insertion to generate alkyl-Cu^{III}-intermediate **B**. After ligand exchange from OBz to N_3, **B** is converted into the alkyl-Cu^{III}–N_3 intermediate **C** which might also be generated *via* intermediate **B′**. Finally, **C** undergoes reductive elimination to deliver the azide functionalized pyrrolines.

2.3 Concurrence of N–O bond oxidative addition and N–O bond homolytic cleavage in cyclization reactions

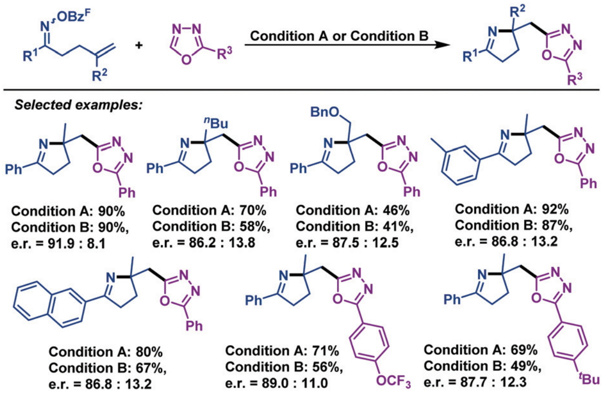
A palladium-catalyzed enantioselective imino-arylation of γ,δ-unsaturated oxime esters with oxadiazoles was achieved by Zhu and colleagues in 2017 (Scheme 45).[71] More importantly, in the presence of a chiral phosphine ligand (Synphos), the enantioselective version of this unprecedented transformation was subsequently realized. The corresponding pyrrolines were obtained in good yields with good enantioselectivity. Control experiments indicated the possible concurrence of single elec-



Scheme 43 Wang's nickel-catalyzed imino-acylation of γ,δ-unsaturated oxime esters with acid chlorides or anhydrides.

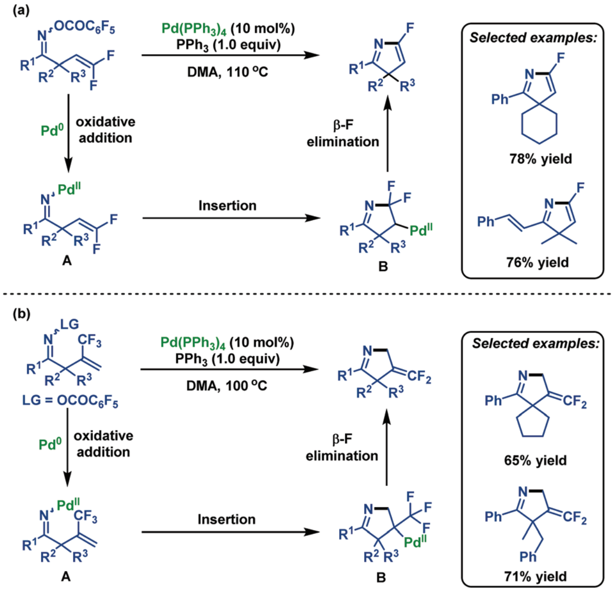


Scheme 44 Yu's copper-catalyzed imino-azidation of γ,δ-unsaturated oxime esters with $TMSN_3$.

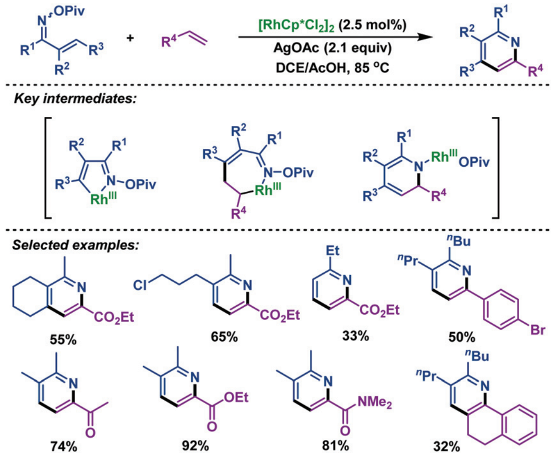


Scheme 45 Zhu's palladium-catalyzed enantioselective imino-arylation of γ,δ-unsaturated oxime esters with oxadiazoles. Condition A: $Pd(OAc)_2$ (10 mol%) BINAP (20 mol%), Cs_2CO_3 (3.0 equiv.), $^iPr_2NEt$ (4.0 equiv.), DMSO, 120 °C, 8 h. Condition B: $Pd(OAc)_2$ (10 mol%), (*S*)-Synphos (20 mol%), K_2CO_3 (3.0 equiv.), DMSO, 100 °C, 8 h.

tron transfer and the two electron process in this Pd-catalyzed transformation.



Scheme 46 Ichikawa's palladium-catalyzed intramolecular Heck-type 5-*endo-trig* cyclization of β,γ-unsaturated oxime esters.



Scheme 47 Rovis' rhodium-catalyzed coupling of α,β-unsaturated oxime esters with alkenes to synthesize pyridines.

3. Cyclization reactions of other unsaturated oxime esters

3.1 Palladium-catalyzed reactions

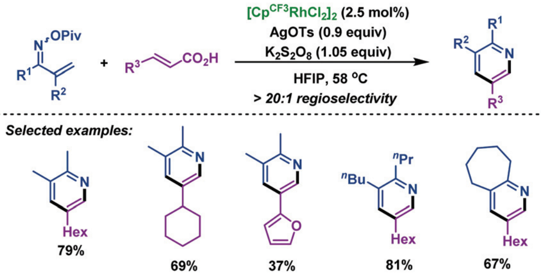
In 2005, Ichikawa and co-workers[72] realized an intramolecular Heck-type 5-*endo-trig* cyclization of β,γ-unsaturated oxime esters. A range of substituted 5-fluoro-3*H*-pyrroles can be generated in good yields using PPh_3 as a ligand for Pd(0). This transformation started from the oxidative addition of N–O bonds, followed by 5-*endo-trig* cyclization and β-fluorine elimination (Scheme 46a). Moreover, in 2006 this group[73] expanded the scope of substrates to 2-(trifluoromethyl)allyl ketone *O*-pentafluorobenzoyloximes, which underwent the similar 5-*endo-trig* cyclization, followed by β-F elimination to afford various 4-difluoro-methylene-1-pyrrolines (Scheme 46b).

3.2 Rhodium-catalyzed reactions

The first Rh(III)-catalyzed coupling of α,β-unsaturated oxime esters with alkenes was developed by Rovis and co-workers. In 2013, they reported[74] a novel strategy to synthesize substituted pyridines from α,β-unsaturated oxime esters and activated alkenes in good yields and high regioselectivity. The oxime ester moieties were used as internal oxidants to complete the catalytic cycle. Mechanism investigations indicated that the substituted pyridines were formed *via* reversible C–H activation, alkene insertion, C–N bond formation and N–O bond cleavage processes. It is worth noting that the regioselectivity depends on the nature of alkenes and only activated alkenes react with exquisite regioselectivity (Scheme 47).

In order to remove this restriction, the same group[75] reported a Rh(III)-catalyzed decarboxylative coupling of α,β-unsaturated oxime esters with acrylic acids in 2014. In this transformation, the COOH moiety of acrylic acid served as a traceless activating group, which imparted the regioselectivity in the C–H activation process. Subsequently, the carboxylic acid moiety of acrylic acid derivatives can be removed by decarboxylation. Under the optimized conditions, diversiform substituted pyridines with good regioselectivity were obtained in good yields. Mechanistic studies indicated that the 6π-electrocyclization process can be ruled out (Scheme 48).

In 2015, the Rovis group[76] developed an efficient Rh(III)-catalyzed coupling of α,β-unsaturated oxime esters with 1,1-disubstituted alkenes for the synthesis of 2,3-dihydropyridines. The electron-deficient trifluoromethyl-substituted Cp^*CF_3 was found to be optimal to promote this transformation. Notably, catalytic reduction of the 2,3-dihydropyridines in one pot deli-

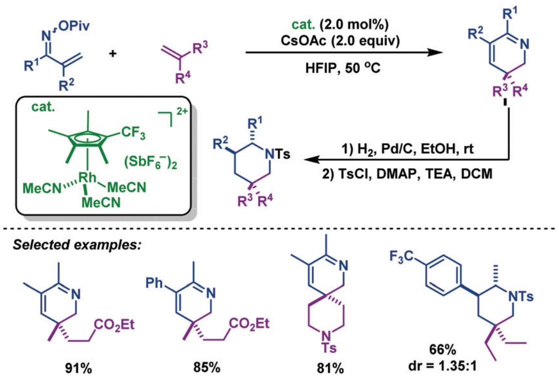


Scheme 48 Rovis's rhodium-catalyzed decarboxylative coupling of acrylic acids with α,β-unsaturated oxime esters.

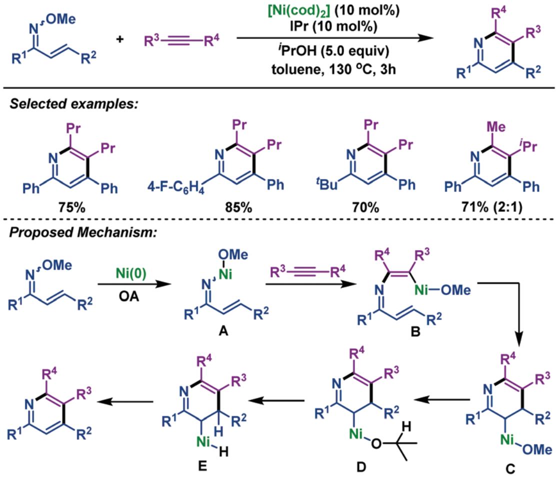
vered piperidine derivatives with good diastereocontrol (Scheme 49).

3.3 Nickel-catalyzed reactions

In 2012, Kurahashi and Matsubara[77] described a nickel-catalyzed cyclization of α,β-unsaturated oxime ethers with alkynes to synthesize 2,3,4,6-tetrasubstituted pyridines (Scheme 50).



Scheme 49 Rovis' Rh(III)-catalyzed coupling of α,β-unsaturated oxime esters with 1,1-disubstituted alkenes for the synthesis of 2,3-dihydropyridines.



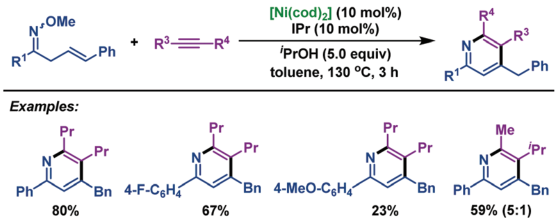
Scheme 50 Kurahashi and Matsubara's nickel-catalyzed cyclization of α,β-unsaturated oxime ethers with alkynes to synthesize pyridines.

Different from the previous Rh-catalyzed cyclization reactions,[74–76] this reaction was initiated by oxidative addition of Ni(0) to the N–O bond of α,β-unsaturated oxime ethers to afford intermediate **A**. Then, internal alkynes inserted into the N–Ni bond to afford intermediate **B**, followed by intramolecular insertion of the alkene to afford **C**. Subsequently, ligand exchange reaction of **C** with ^{i}PrOH afforded intermediate **D**, which is followed by two β-H elimination processes to give the final pyridine products.

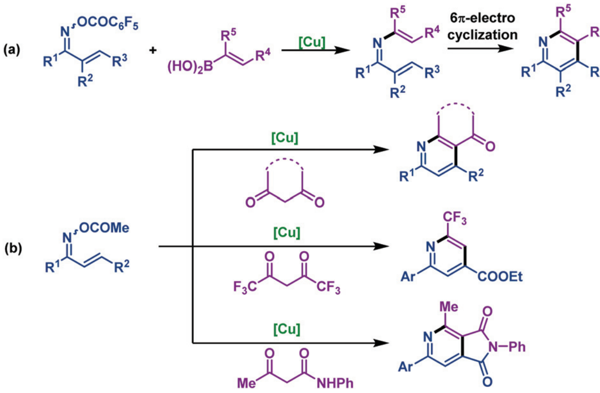
It is noteworthy that the present nickel-catalyzed cyclization can be applied not only to α,β-unsaturated oxime ethers but also to β,γ-unsaturated oxime ethers for the synthesis of pyridines (Scheme 51).[77] Diverse β,γ-unsaturated oxime ethers, bearing either electron-donating groups or electron-withdrawing groups, smoothly received cycloaddition with internal alkynes, delivering diversiform pyridines in good yields. Functional groups such as fluoro and methoxyl which are useful in further synthetic transformations were all well tolerated under the optimal conditions.

3.4 Copper-catalyzed reactions

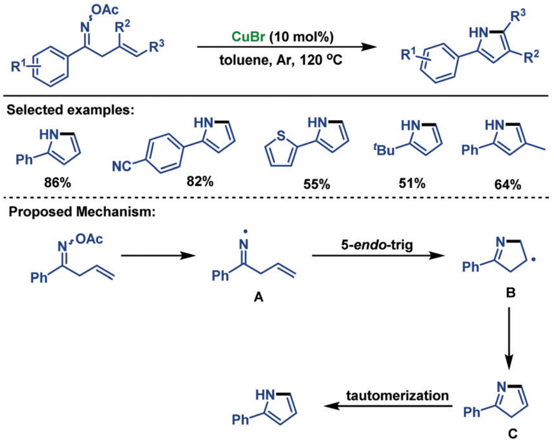
In 2008, Liebeskind and colleagues[78] disclosed a copper-catalyzed annulation of α,β-unsaturated oxime esters with alkenylboronic acids, which underwent oxidative addition, transmetallation and 6π-electrocyclization to synthesize various substituted pyridines (Scheme 52a). Recently, Guo and co-workers[79] realized the copper-catalyzed [4 + 2] cycloaddition reaction of



Scheme 51 Kurahashi and Matsubara's nickel-catalyzed cyclization of β,γ-unsaturated oxime ethers with alkynes to synthesize pyridines.



Scheme 52 Copper-catalyzed annulation of α,β-unsaturated oxime esters.



Scheme 53 Guan's copper-catalyzed 5-*endo-trig* cyclization of β,γ-unsaturated oxime esters for the synthesis of pyrroles.

α,β-unsaturated oxime esters with 1,3-dicarbonyl compounds for the synthesis of three types of structurally diverse multisubstituted pyridines. The addition of the radical scavenger did not inhibit the reaction and the corresponding radical captured intermediate was not detected, which demonstrated the reaction proceeded through an ionic pathway rather than the radical process (Scheme 52b).

Although the cyclization of unsaturated oxime esters mostly occurs *via* 5-*exo* processes, in 2014, the Guan group[80] established a copper-catalyzed 5-*endo-trig* cyclization of β,γ-unsaturated oxime esters for the rapid construction of 2-arylpyrroles in moderate to good yields. This cyclization reaction features broad functional group tolerance. The authors proposed an anti-Baldwin 5-*endo-trig* radical cyclization pathway, and the iminyl radical intermediate was involved in the catalytic cycle (Scheme 53).

4. Summary and outlook

We have summarized the cascade cyclization reactions of unsaturated oxime esters with various nucleophiles in the last decade. Related cyclizations as well as enantioselective Narasaka–Heck cyclizations are also included in this review. By using this protocol, a variety of functionalized pyrrolines and related scaffolds, including biologically significant N-heterocycles, have been efficiently accessed in moderate to good yields.

Despite the huge progress made in this field, some challenges and opportunities still remain. For instance, is it possible to develop asymmetric reactions based on the radical species? Also further research on the synthesis of more diverse functionalized nitrogen-containing scaffolds should be expected. Moreover, some cascade reactions could be employed in this strategy for the synthesis of complex organic structures.

We hope this brief review will serve as a handy reference for organic chemists who are interested in the cascade cyclization of unsaturated oxime esters and for those who wish to utilize this important strategy for the synthesis of drug candidates and natural products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We express our gratitude to the National Natural Science Foundation of China (No.: 21901184; 21572160; 21702091); the Science & Technology Development Fund of Tianjin Education Commission for Higher Education (No.: 2018KJ159), the Doctoral Program Foundation of Tianjin Normal University (No.: 043135202-XB1703) and the Program for Innovative Research Team in University of Tianjin (No.: TD13-5074) for generous financial support.

Notes and references

1 E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the structural diversity, substitution patterns, and frequency of nitrogen heterocycles among U.S. FDA approved pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257.

2 R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in drugs, *J. Med. Chem.*, 2014, **57**, 5845.

3 http://njardarson.lab.arizona.edu/sites/njardarson.lab.arizona.edu/fies/TopUSPharmaceuticalProductsof2013.pdf, accessed on 28th March 2017.

4 I. V. Magedov, G. Luchetti, N. M. Evdokimov, M. Manpadi, W. F. A. Steelant, S. V. Slambrouck, P. Tongwa, M. Y. Antipin and A. Kornienko, Novel three-component synthesis and antiproliferative properties of diversely functionalized pyrrolines, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1392.

5 M. Biava, G. C. Porretta, G. Poce, S. Supino, D. Deidda, R. Pompei, P. Molicotti, F. Manetti and M. Botta, Antimycobacterial agents. Novel diarylpyrrole derivatives of BM212 endowed with high activity toward mycobacterium, tuberculosis and low cytotoxicity, *J. Med. Chem.*, 2006, **49**, 4946.

6 C. Marti and E. M. Carreira, Total synthesis of (−)-spirotryprostatin B: synthesis and related studies, *J. Am. Chem. Soc.*, 2005, **127**, 11505.

7 J. Boivin, A.-M. Schiano and S. Z. Zard, Iminyl radicals by stannane mediated cleavage of oxime esters, *Tetrahedron Lett.*, 1994, **35**, 249.

8 J. Boivin, A.-C. Callier-Dublanchet, B. Quiclet-Sire, A.-M. Schiano and S. Z. Zard, Iminyl, amidyl, and carbamyl radicals from O-benzoyl oximes and O-benzoyl hydroxamic acid derivatives, *Tetrahedron*, 1995, **51**, 6517.

9 M. M. Jackman, Y. Cai and S. L. Castle, Recent advances in iminyl radical cyclizations, *Synthesis*, 2017, **49**, 1785.

10 M. Kitamura and K. Narasaka, Catalytic radical cyclization of oximes induced by one-electron transfer, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 539.

11 N. J. Race, I. R. Hazelden, A. Faulkner and J. F. Bower, Recent developments in the use of aza-Heck cyclizations for the synthesis of chiral N-heterocycles, *Chem. Sci.*, 2017, **8**, 5248.

12 J. Davies, S. P. Morcillo, J. J. Douglas and D. Leonori, Hydroxylamine derivatives as nitrogen-radical precursors in visible-light photochemistry, *Chem. – Eur. J.*, 2018, **24**, 12154.

13 J. Li, Y. Hu, D. Zhang, Q. Liu, Y. Dong and H. Liu, Transition metal-catalyzed reactions involving oximes, *Adv. Synth. Catal.*, 2017, **359**, 710.

14 H. Huang, J. Cai and G.-J. Deng, O-Acyl oximes: versatile building blocks for N-heterocycle formation in recent transition metal catalysis, *Org. Biomol. Chem.*, 2016, **14**, 1519.

15 M. Kitamura and K. Narasaka, Synthesis of aza-heterocycles from oximes by amino-heck reaction, *Chem. Rec.*, 2002, **2**, 268.

16 K. Narasaka and M. Kitamura, Amination with oximes, *Eur. J. Org. Chem.*, 2005, 4505.

17 J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, Visible light photoredox-controlled reactions of N-radicals and radical ions, *Chem. Soc. Rev.*, 2016, **45**, 2044.

18 T. Xiong and Q. Zhang, New amination strategies based on nitrogen-centered radical chemistry, *Chem. Soc. Rev.*, 2016, **45**, 3069.

19 Y. Zhao and W. Xia, Recent advances in radical-based C–N bond formation via photo-/electrochemistry, *Chem. Soc. Rev.*, 2018, **47**, 2591.

20 J.-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, Exploration of visible-light photocatalysis in heterocycle synthesis and functionalization: reaction design and beyond, *Acc. Chem. Res.*, 2016, **49**, 1911.

21 P. Xiong and H.-C. Xu, Chemistry with electrochemically generated N-centered radicals, *Acc. Chem. Res.*, 2019, **52**, 3339.

22 W. Yin and X. Wang, Recent advances in iminyl radical-mediated catalytic cyclizations and ring-opening reactions, *New J. Chem.*, 2019, **43**, 3254.

23 T. Xiao, H. Huang, D. Anand and L. Zhou, Iminyl-radical-triggered C–C bond cleavage of cycloketone oxime derivatives: generation of distal cyano-substituted alkyl radicals and their functionalization, *Synthesis*, 2020, **52**, 1585.

24 C. Song, X. Shen, F. Yu, Y.-P. He and S. Yu, Generation and application of iminyl radicals from oxime derivatives enabled by visible light photoredox catalysis, *Chin. J. Org. Chem.*, 2020, **40**, DOI: 10.6023/cjoc202004008.

25 X.-Y. Yu, J.-R. Chen, P.-Z. Wang, M.-N. Yang, D. Liang and W.-J. Xiao, A visible-light-driven iminyl radical-mediated C-C single bond cleavage/radical addition cascade of oxime esters, *Angew. Chem., Int. Ed.*, 2018, **57**, 738.

26 X.-Y. Yu, Q.-Q. Zhao, J. Chen, J.-R. Chen and W.-J. Xiao, Copper-catalyzed radical cross-coupling of redox-active oxime esters, styrenes, and boronic acids, *Angew. Chem., Int. Ed.*, 2018, **57**, 15505.

27 X.-Y. Yu, J. Chen, H.-W. Chen, W.-J. Xiao and J.-R. Chen, Visible-light-driven copper-catalyzed C(sp^3)–O cross-coupling of benzylic radicals with phenols, *Org. Lett.*, 2020, **22**, 2333.

28 X.-Y. Yu, Q.-Q. Zhao, J. Chen, W.-J. Xiao and J.-R. Chen, When light meets nitrogen-centered radicals: from reagents to catalysts, *Acc. Chem. Res.*, 2020, **53**, 1066.

29 Z. Mirjafary, M. Abdoli, H. Saeidian, A. Kakanejadifard and S. M. F. Farnia, Review of the synthesis of acyclic and cyclic oxime ethers, *RSC Adv.*, 2016, **6**, 17740.

30 Z. Mirjafary, M. Abdoli, H. Saeidian, S. Boroon and A. Kakanejadifard, Oxime ethers as versatile precursors in organic synthesis: a review, *RSC Adv.*, 2015, **5**, 79361.

31 H. Huang, X. Ji, W. Wua and H. Jiang, Transition metal-catalyzed C–H functionalization of N-oxyenamine internal oxidants, *Chem. Soc. Rev.*, 2015, **44**, 1155.

32 J. A. Blake, D. A. Pratt, S. Lin, J. C. Walton, P. Mulder and K. U. Ingold, Thermolyses of O-phenyl oxime ethers. A new source of iminyl radicals and a new source of aryloxyl radicals, *J. Org. Chem.*, 2004, **69**, 3112.

33 J. C. Walton, The oxime portmanteau motif: released heteroradicals undergo incisive EPR interrogation and deliver diverse heterocycles, *Acc. Chem. Res.*, 2014, **47**, 1406.

34 F. Portela-Cubillo, J. S. Scottb and J. C. Walton, Microwave-assisted preparations of dihydropyrroles from alkenone O-phenyl oximes, *Chem. Commun.*, 2007, **39**, 4041.

35 F. Portela-Cubillo, J. S. Scott and J. C. Walton, Microwave-assisted syntheses of N-heterocycles using alkenone-, alkynone- and aryl-carbonyl O-phenyl oximes: formal synthesis of neocryptolepine, *J. Org. Chem.*, 2008, **73**, 5558.

36 Y. Cai, A. Jalan, A. R. Kubosumi and S. L. Castle, Microwave-promoted tin-free iminyl radical cyclization with TEMPO trapping: a practical synthesis of 2-acylpyrroles, *Org. Lett.*, 2015, **17**, 488.

37 Y. Koganemaru, M. Kitamura and K. Narasaka, Synthesis of dihydropyrrole derivatives by copper-catalyzed cyclization of γ,δ-unsaturated ketone O-methoxycarbonyloximes, *Chem. Lett.*, 2002, **31**, 784.

38 A. Faulkner, N. J. Race, J. S. Scott and J. F. Bower, Copper catalyzed Heck-like cyclizations of oxime esters, *Chem. Sci.*, 2014, **5**, 2416.

39 A. Faulkner and J. F. Bower, Highly efficient narasaka–heck cyclizations mediated by $P(3,5\text{-}(CF_3)_2C_6H_3)_3$: facile access to N-heterobicyclic scaffolds, *Angew. Chem., Int. Ed.*, 2012, **51**, 1675.

40 A. Faulkner, J. S. Scott and J. F. Bower, Palladium catalyzed cyclizations of oxime esters with 1, 1-disubstituted alkenes: synthesis of α, α-disubstituted dihydropyrroles and studies towards an asymmetric protocol, *Chem. Commun.*, 2013, **49**, 1521.

41 N. J. Race and J. F. Bower, Palladium catalyzed cyclizations of oxime esters with 1,2-disubstituted alkenes: synthesis of dihydropyrroles, *Org. Lett.*, 2013, **15**, 4616.

42 K. Guo, H. Zhang, S. Cao, C. Gu, H. Zhou, J. Li and Y. Zhu, Copper-catalyzed domino cyclization/trifluoromethylthiolation of unactivated alkenes: access to SCF_3-containing pyrrolines, *Org. Lett.*, 2018, **20**, 2261.

43 Y. Wang, J. Ding, J. Zhao, W. Sun, C. Lian, C. Chen and B. Zhu, Iminyl radical-promoted imino sulfonylation, imino cyanogenation and imino thiocyanation of γ,δ-unsaturated oxime esters: synthesis of versatile functionalized pyrrolines, *Org. Chem. Front.*, 2019, **6**, 2240.

44 C. Chen, J. Ding, Y. Wang, X. Shi, D. Jiao and B. Zhu, Copper-catalyzed iminohalogenation of γ,δ-unsaturated oxime esters with halide salts: synthesis of 2-halomethyl pyrrolines, *Tetrahedron Lett.*, 2019, **60**, 151000.

45 J. Zhao, Y. Bao, Y. Wang, C. Chen and B. Zhu, Copper-catalyzed group-transfer radical cyclization of γ,δ-unsaturated oxime esters: synthesis of ester-functionalized pyrrolines, *Asian J. Org. Chem.*, 2019, **8**, 1317.

46 L. Wang and C. Wang, Copper-catalyzed diamination of oxime ester-tethered unactivated alkenes with unprotected Amines, *J. Org. Chem.*, 2019, **84**, 6547.

47 H.-B. Yang and N. Selander, Divergent iron-catalyzed coupling of O-acyloximes with silyl enol ethers, *Chem. – Eur. J.*, 2017, **23**, 1779.

48 T. Shimbayashi, K. Okamoto and K. Ohe, Iron-catalyzed aminative cyclization/intermolecular homolytic aromatic substitution using oxime esters and simple arenes, *Chem. – Asian J.*, 2018, **13**, 395.

49 T. Shimbayashi, D. Nakamoto, K. Okamoto and K. Ohe, Facile construction of tetrahydropyrrolizines by iron-catalyzed double cyclization of alkene-tethered oxime esters with 1,2-disubstituted alkenes, *Org. Lett.*, 2018, **20**, 3044.

50 J. Boivin, A.-M. Schiano, S. Z. Zard and H. Zhang, A new method for the generation and capture of iminylradicals, *Tetrahedron Lett.*, 1999, **40**, 4531.

51 H.-B. Yang, S. R. Pathipati and N. Selander, Nickel-catalyzed 1,2-aminoarylation of oxime ester-tethered alkenes with boronic acids, *ACS Catal.*, 2017, **7**, 8441.

52 L. Wang and C. Wang, Ni-catalyzed 1,2-iminoacylation of alkenes via a reductive strategy, *Org. Chem. Front.*, 2018, **5**, 3476.

53 N. J. Race, A. Faulkner, M. H. Shaw and J. F. Bower, Dichotomous mechanistic behavior in Narasaka–Heck cyclizations: electron rich Pd-catalysts generate iminyl radicals, *Chem. Sci.*, 2016, **7**, 1508.

54 C. Chen, Y. Bao, J. Zhao and B. Zhu, Silver-promoted cascade radical cyclization of γ, δ-unsaturated oxime esters with P(O)H compounds: synthesis of phosphorylated pyrrolines, *Chem. Commun.*, 2019, **55**, 14697.

55 J. Davies, S. G. Booth, S. Essafi, R. A. W. Dryfe and D. Leonori, Visible-light-mediated generation of nitrogen-centered radicals: metal-free hydroimination and iminohydroxylation cyclization reactions, *Angew. Chem., Int. Ed.*, 2015, **54**, 14017.

56 S.-H. Cai, J.-H. Xie, S. Song, L. Ye, C. Feng and T.-P. Loh, Visible-light-promoted carboimination of unactivated alkenes for the synthesis of densely functionalized pyrroline derivatives, *ACS Catal.*, 2016, **6**, 5571.

57 R. Mao, Z. Yuan, Y. Li and J. Wu, N-Radical-initiated cyclization through insertion of sulfur dioxide under photoinduced catalyst-free conditions, *Chem. – Eur. J.*, 2017, **23**, 8176.

58 H. Jiang and A. Studer, Iminyl-radicals by oxidation of α-imino-oxy acids: photoredox-neutral alkene carboimination for the synthesis of pyrrolines, *Angew. Chem., Int. Ed.*, 2017, **56**, 12273.

59 J. Davies, N. S. Sheikh and D. Leonori, Photoredox imino functionalizations of olefins, *Angew. Chem., Int. Ed.*, 2017, **56**, 13361.

60 L. Tu, J.-L. Liu, W. Tang, M. Su and F. Liu, Radical aza-cyclization of α–imino-oxy acids for synthesis of alkene-containing N–heterocycles via dual cobaloxime and photoredox catalysis, *Org. Lett.*, 2020, **22**, 1222.

61 K. Usami, E. Yamaguchi, N. Tada and A. Itoh, Visible-light-mediated iminyl radical generation from benzyl oxime ether: synthesis of pyrroline via hydroimination cyclization, *Org. Lett.*, 2018, **20**, 5714.

62 S.-H. Cai, D.-X. Wang, L. Ye, Z.-Y. Liu, C. Feng and T.-P. Loh, Pyrroline synthesis via visible-light-promoted hydroimination of unactivated alkenes with N,N'-dimethylpropylene urea as *H*-donor, *Adv. Synth. Catal.*, 2018, **360**, 1262.

63 F. Huang and S. Zhang, Iminyl radicals by reductive cleavage of N–O bond in oxime ether promoted by SmI_2: a straightforward synthesis of five-membered cyclic imines, *Org. Lett.*, 2019, **21**, 7430.

64 H. Tsutsui and K. Narasaka, Synthesis of pyrrole derivatives by the Heck-type cyclization of γ,δ-unsaturated ketone O-pentafluorobenzoyloximes, *Chem. Lett.*, 1999, **28**, 45.

65 C. Chen, L. Hou, M. Cheng, J. Su and X. Tong, Palladium (0)-catalyzed iminohalogenation of alkenes: synthesis of 2-halomethyl dihydropyrroles and mechanistic insights into the alkyl halide bond formation, *Angew. Chem., Int. Ed.*, 2015, **54**, 3092.

66 A. Faulkner, J. S. Scott and J. F. Bower, An umpolung approach to alkene carboamination: palladium catalyzed 1, 2-amino-acylation, -carboxylation, -arylation, -vinylation, and -alkynylation, *J. Am. Chem. Soc.*, 2015, **137**, 7224.

67 N. J. Race, A. Faulkner, G. Fumagalli, T. Yamauchi, J. S. Scott, M. Rydén-Landergren, H. A. Sparkes and J. F. Bower, Enantioselective Narasaka–Heck cyclizations: synthesis of tetrasubstituted nitrogen-bearing stereocenters, *Chem. Sci.*, 2017, **8**, 1981.

68 W.-X. Wei, S. Chen, Y. Xia, M. Li, X.-S. Li, Y.-P. Han, C.-T. Wang and Y.-M. Liang, Palladium-catalyzed intramolecular self-alkylation of polyfluoroarene via heck and decarboxylation process, *ChemCatChem*, 2019, **11**, 5754.

69 L. Feng, L. Guo, C. Yang, J. Zhou and W. Xia, Visible-light-induced palladium-catalyzed intermolecular Narasaka–Heck reaction at room temperature, *Org. Lett.*, 2020, **22**, 3964.

70 H. Su, W. Li, Z. Xuan and W. Yu, Copper-catalyzed cyclization and azidation of γ,δ-unsaturated ketone O-benzoyl oximes, *Adv. Synth. Catal.*, 2015, **357**, 64.

71 X. Bao, Q. Wang and J. Zhu, Palladium-catalyzed enantioselective Narasaka–Heck reaction/direct C–H alkylation of arenes: iminoarylation of alkenes, *Angew. Chem., Int. Ed.*, 2017, **56**, 9577.

72 K. Sakoda, J. Mihara and J. Ichikawa, Heck-type 5-endo-trig-cyclization promoted by vinylic fluorines: synthesis of 5-fluoro-3H-pyrroles, *Chem. Commun.*, 2005, **37**, 4684.
73 J. Ichikawa, R. Nadano and N. Ito, 5-*endo* Heck-type cyclization of 2-(trifluoromethyl)allyl ketoneoximes: synthesis of 4-difluoromethylene-substituted 1-pyrrolines, *Chem. Commun.*, 2006, **42**, 4425.
74 J. M. Neely and T. Rovis, Rh(III)-Catalyzed regioselective synthesis of pyridines from alkenes and α,β-unsaturated oxime esters, *J. Am. Chem. Soc.*, 2013, **135**, 66.
75 J. M. Neely and T. Rovis, Rh(III)-Catalyzed decarboxylative coupling of acrylic acids with unsaturated oxime esters: carboxylic acids serve as traceless activators, *J. Am. Chem. Soc.*, 2014, **136**, 2735.
76 F. Romanov-Michailidis, K. F. Sedillo, J. M. Neely and T. Rovis, Expedient access to 2,3-dihydropyridines from unsaturated oximes by Rh(III)-catalyzed C–H activation, *J. Am. Chem. Soc.*, 2015, **137**, 8892.
77 Y. Yoshida, T. Kurahashi and S. Matsubara, Nickel-catalyzed cycloaddition of α,β-unsaturated oximes with alkynes: synthesis of highly substituted pyridine derivatives, *Chem. Lett.*, 2012, **41**, 1498.
78 S. Liu and L. S. Liebeskind, A simple, modular synthesis of substituted pyridines, *J. Am. Chem. Soc.*, 2008, **130**, 6918.
79 L. Zhang, J. Duan, G. Xu, X. Ding, Y. Mao, B. Rong, N. Zhu, Z. Fang, Z. Li and K. Guo, Copper-catalyzed N–O cleavage of α,β-unsaturated ketoxime acetates toward structurally diverse pyridines, *J. Org. Chem.*, 2020, **85**, 2532.
80 W. Du, M.-N. Zhao, Z.-H. Ren, Y.-Y. Wang and Z.-H. Guan, Copper-catalyzed 5-*endo*-trig cyclization of ketoxime carboxylates: a facile synthesis of 2-arylpyrroles, *Chem. Commun.*, 2014, **50**, 7437.