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Metal-mediated synthesis of pyrrolines

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The five-membered, nitrogen-containing pyrroline ring is a privileged structure. This ring is present in many bioactive compounds from natural sources. Pyrrolines—the dihydro derivatives of pyrroles—have three structural isomer classes, depending on the location of the double bond: 1-pyrrolines (3,4-dihydro-2*H*-pyrroles), 2-pyrrolines (2,3-dihydro-1*H*-pyrroles) and 3-pyrrolines (2,5-dihydro-1*H*-pyrroles). This review aims to describe the latest advances for the synthesis of pyrrolines by transition metal-catalyzed cyclizations. Only reactions in which the pyrroline ring is formed by metal promotion are described. Transformations of the pyrroline ring in other heterocycles, and the structural manipulations of the pyrroline itself are not discussed. The review is organized into three parts, each covering the metal-mediated synthesis of the three pyrroline isomers. Each part is subdivided according to the metal involved, and concludes with a brief description of notable biological activities within the class.

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1. Introduction

Heterocyclic ring systems are the fundamental building blocks in the vast majority of drugs used to treat animal and human diseases. Among these heterocyclic rings, those containing nitrogen are the most significant. Pyrrolines—the dihydro derivatives of pyrroles—have received considerable attention lately since they exhibit a variety of biological activities. Pyrrolines have three structural isomer classes (Fig. 1), depending on the location of the double bond: 1-pyrrolines (3,4-dihydro-2*H*-pyrroles), 2-pyrrolines (2,3-dihydro-1*H*-pyrroles) and 3-pyrrolines (2,5-dihydro-1*H*-pyrroles).

Pyrrolines are considered privileged structures as reflected by their presence in many bioactive compounds from natural sources[1–9] such as hemes,[10] chlorophyll,[10] and alkaloids;[11,12] as well as in bioactive synthetic molecules.[13–19]

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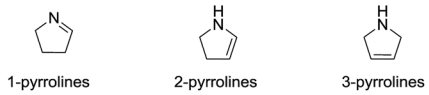

Fig. 1 Structural isomers of the pyrrolines.

1-Pyrrolines are cyclic imines whose reactivity allows synthetic manipulation through nucleophilic attack on the prochiral endocyclic imine. Accordingly, stereoselective transformations can occur.[20] 2-Pyrrolines possess an enamine moiety that allows the further functionalization of the ring system. 2-Pyrrolines are found frequently in the literature under the name "2,3-dihydropyrroles" since the monohydrogenation of pyrroles leads directly to 2,3-dihydropyrroles. In contrast, the cyclic amine and alkene functional groups of the 3-pyrrolines react separately. When this cyclic core is used as precursor, further modifications often involve the double bond, which can be easily transformed *e.g.* by hydrogenation, (di)halogenation, and dihydroxylation. Thus the 1-, 2- and 3-pyrrolines represent appealing intermediates to obtain pyrroles and pyrrolidines through oxidation[21] and reduction,[22,23] respectively. Due to the remarkable breadth of their reactivity, pyrrolines are useful intermediates in the preparation of more complex heterocycles.[24–37]

A variety of well-established methods of pyrrolines synthesis are available.[38,39] These methods include intramolecular cyclizations of bifunctional compounds and multi-component cyclizations,[39–45] 1,3-dipolar cycloadditions,[46–51] photo- and thermoinduced reactions,[52–54] and ring expansion of aziridines,[55,56] among others. However, metal-mediated syntheses have emerged as a valuable complement to these methods[20,57,58] due to their high atom economy, their mild reaction conditions, and the high functional group tolerance of the transition metal-catalyzed reactions. This review discusses the latest advances[24,38,39,59] (from 2011 to December 2018) for the synthesis of pyrrolines by transition metal-catalyzed cyclizations. Only reactions in which the pyrroline ring is formed by metal promotion are described. Transformations of the pyrroline ring in other heterocycles, and the structural manipulations of the pyrroline itself are not discussed. The review is organized into three parts, each covering the metal-mediated synthesis of the three pyrroline isomers. Each part is subdivided according to the metal involved, and concludes with a brief description of notable biological activities within the class and a synthetic sequence which involve a metal-mediated synthesis of pyrrolines as intermediate towards a more complex heterocycle.

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2. Synthesis of pyrrolines

2.1. Synthesis of 1-pyrrolines

The 1-pyrroline core is exemplified by numerous compounds with biological activity (Fig. 2). Examples include the iminosugar nectrisine (**1**),[60] discovered as an immunomodulator; the iminosaccharide **2** that has glycosidase inhibitory activity;[15,61] and the 1-pyrroline **3** that has antihypertensive properties.[14] β-Trifluoromethylated 1-pyrrolines (**4–6**)[62] are nitric oxide synthase inhibitors[63] and as such possess anti-infective,[64–66] anti-tumor,[67] and anti-inflammatory activities.[65,68] The steroidal alkaloid plakinamine A (**7**) shows antimicrobial activity against

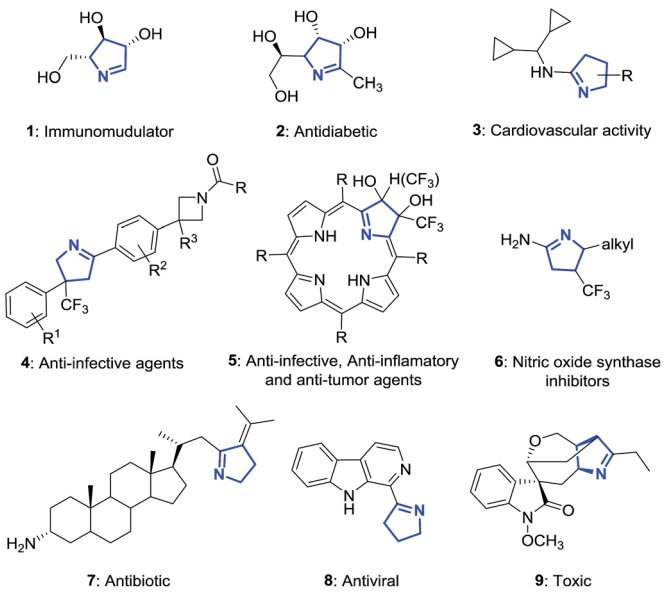
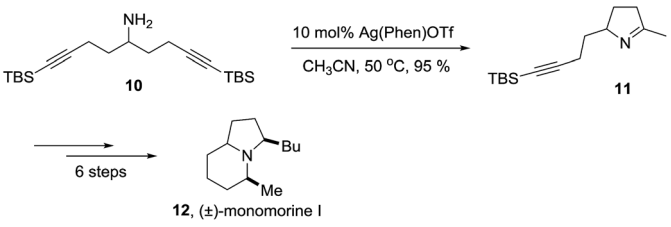
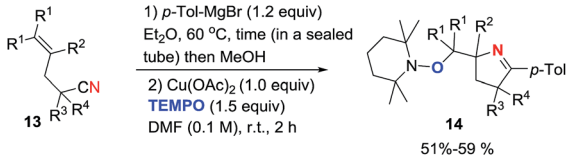


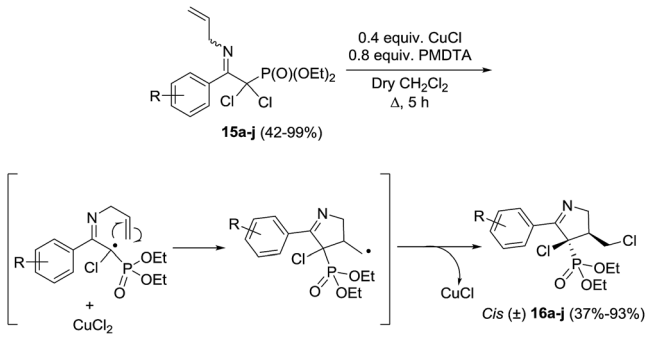
Fig. 2 Selected examples of biologically active 1-pyrrolines.



Scheme 1 Synthesis of the alkaloid (±)-monomorine I through the 1-pyrroline **11**.



Scheme 2 Cu(II)-mediated intramolecular aminooxygenation of alkenylimines towards 1-pyrrolines.



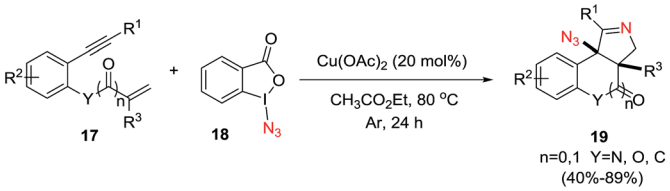
Scheme 3 Copper-catalyzed heteroatom transfer radical cyclization (HATRC) towards 1-pyrrolines.

S. aureus and *C. albicans*,[69] whereas eudistomin (**8**) has antiviral activity.[2] The alkaloid gelsenicine (**9**) is recognized for its high toxicity.[70]

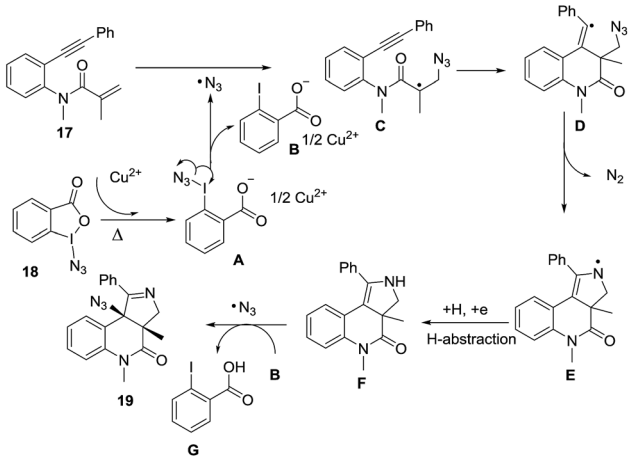
A selected example of 1-pyrroline used as an intermediate towards a more complex heterocycle is described in the Scheme 1. Helquist *et al.* reported a silver-catalyzed hydroamination of the aminoalkyne **10** that led to 1-pyrroline **11** which was applied to a seven step synthesis of the alkaloid (±)-monomorine I in 26% overall yield.[27]

2.1.1. Synthesis of 1-pyrrolines by copper catalysis. Chiba *et al.*[71] developed a method for the synthesis of oxymethyl-substituted pyrrolines employing $Cu(OAc)_2$-mediated intramolecular aminooxygenation of alkenylimines with TEMPO (Scheme 2). The addition of a Grignard reagent (such as *p*-tolylmagnesium bromide) to a range of alkenyl carbonitriles **13** was performed in a sealed tube at 60 °C. MeOH was used to protonate the products, and DMF was added to reach a concentration of 0.1 M. Immediately, 1 equivalent of $Cu(OAc)_2$ and 1.5 equivalents of TEMPO were added. The aminooxygenation proceeded smoothly at room temperature affording (after 2 h) diverse oxymethyl pyrrolines **14** in moderate yields (typically 50%). Various other Grignard reagents were equally successful.

Stevens *et al.*[72] synthesized a library of ten 1-pyrrolines **16a–j** from the α,α-dichlorinated imines **15a–j** using a heteroatom transfer radical cyclization (HATRC) (Scheme 3). The free-radical ring closure reaction was performed with CuCl in presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) as a ligand. Other ligands such as *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) proved equally efficient. The addition of the ligands modifies the solubility and the redox potential of the copper catalyst, thus improving its activity. Formation of the five-membered ring proceeds through a radical 5-*exo*-*trig* cyclization. Two stereogenic centers are generated during the ring closure. The reaction displays an excellent *cis*/*trans* diastereoselectivity (diastereoisomeric ratios are all in the range of 90/10). The authors attribute this diastereoselectivity to the steric hindrance caused by the ethoxy substituents of the phosphonate.

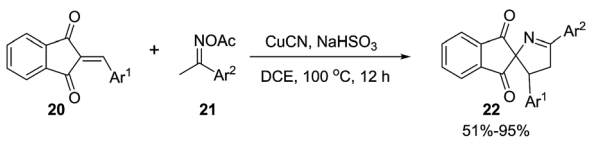


Scheme 4 [2 + 2 + 1] Annulation/azidation of 1,*n*-enynes as an entry to fused 1-pyrrolines.

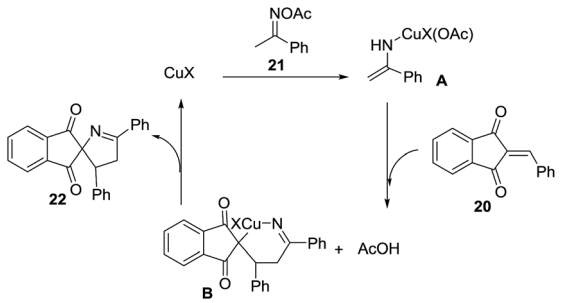


Scheme 5 Proposed mechanism of [2 + 2 + 1] annulation/azidation of 1,*n*-enynes.

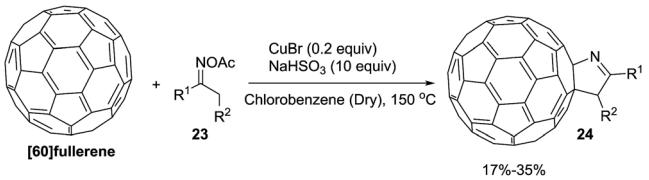
Li *et al.*[73] developed a novel selective copper-catalyzed, azide radical-mediated, [2 + 2 + 1] annulation of benzene-linked 1,*n*-enynes (n = 6, 7) to give fused pyrrolines **19** (Scheme 4). Azidobenziodoxolone **18** was the source of the azide radical. Other azide reagents such as $TMSN_3$ and NaN_3 failed to produce the fused pyrrolines. This one-step synthesis of fused pyrrolines proceeds *via* the generation of the azide radical from azidobenziodoxolone **18** with the aid of the Cu^{2+} species as catalyst (Scheme 5). Addition of the azide radical to the alkene moiety of enyne **17** affords an alkyl radical intermediate which undergoes intramolecular addition to the alkyne moiety to give fused pyrroline **F** as an intermediate. Finally, a second azide radical is incorporated to furnish the final fused pyrroline structures. Internal alkenes with $R_1 \neq$ aliphatic are suitable substrates.



Scheme 6 Copper-catalyzed heteroannulation reaction between aryl ketone-derived ketoxime acetates and 2-arylideneindane-1,3-dione.



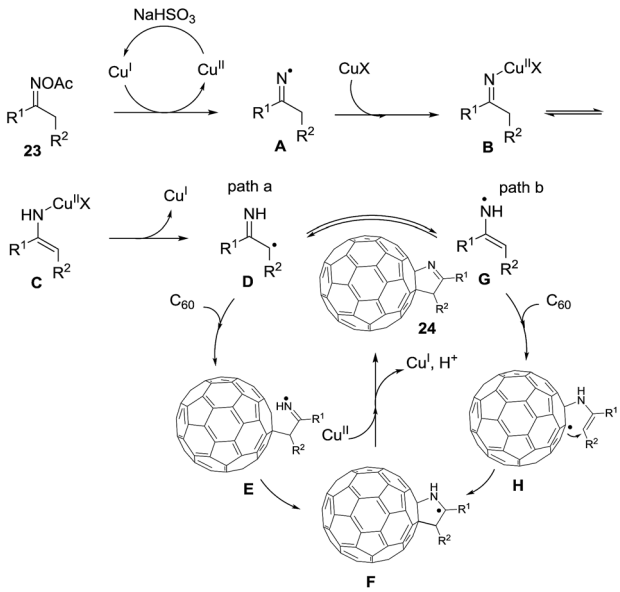
Scheme 7 Proposed mechanism for the copper-catalyzed heteroannulation reaction between ketoxime acetates and 2-arylideneindane-1,3-dione.



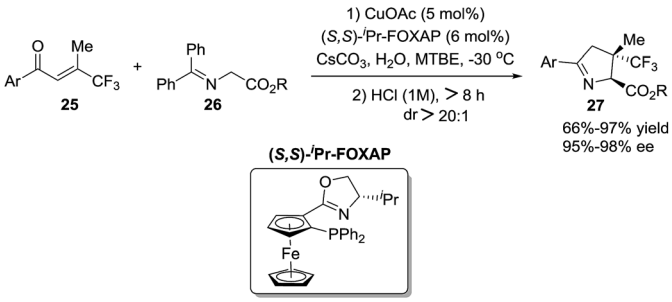
Scheme 8 Copper(I)-catalyzed heteroannulation of [60]fullerene with ketoxime acetates.

Li *et al.*[74] developed an efficient copper-catalyzed heteroannulation reaction between 2-arylideneindane-1,3-diones (**20**) and ketoxime acetates (**21**) for the straightforward synthesis of spiro[indane-1,3-dione-1-pyrrolines] **22** (Scheme 6). The methodology shows broad substrate scope and tolerates a wide range of functionalities in both the 2-arylideneindane-1,3-diones and aromatic ketoxime acetates. Alkyl ketoxime acetates failed to deliver the spiro compounds.

The proposed mechanism for this transformation begins with the cleavage of the N–O bond in the ketoxime acetate **21** by



Scheme 9 Proposed mechanism of the heteroannulation of [60] fullerene with ketoxime acetates.

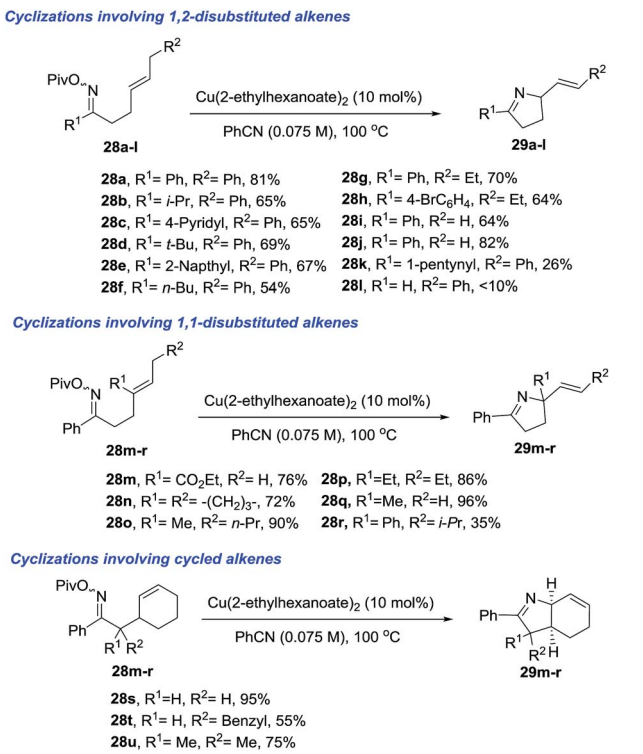


Scheme 10 Cu(I)-catalyzed Michael addition of ketiminoesters to β-trifluoromethyl β,β-disubstituted enones.

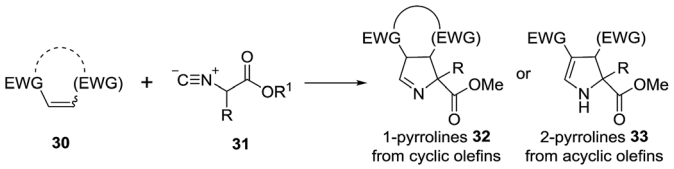
cuprous cyanide, through an oxidative addition (Scheme 7). As a result, the copper enamide **A** intermediate is formed, which reacts with the 2-arylideneindane-1,3-diones **20** to give intermediate **B**. The product **22** is formed, and the catalyst regenerated, by an intramolecular redox heteroannulation of **B**.

Wang *et al.*[75] constructed novel 1-fulleropyrrolines **24** using a cuprous bromide-catalyzed heteroannulation reaction of [60] fullerene with ketoxime acetates **23** (Scheme 8). The proposed mechanism begins with ketoxime N–O cleavage by Cu(I) to give an imino radical with formation of the C–C and C–N bonds (Scheme 9).

Zhang *et al.*[76] reported a straightforward one-pot synthesis of 1-pyrrolines bearing two contiguous stereocenters exemplified by structure **27**, where one is a trifluoromethyl-substituted quaternary carbon (Scheme 10). The copper-catalytic process



Scheme 11 Copper(I) catalyzed Heck-like cyclizations of oxime esters towards 1-pyrrolines.



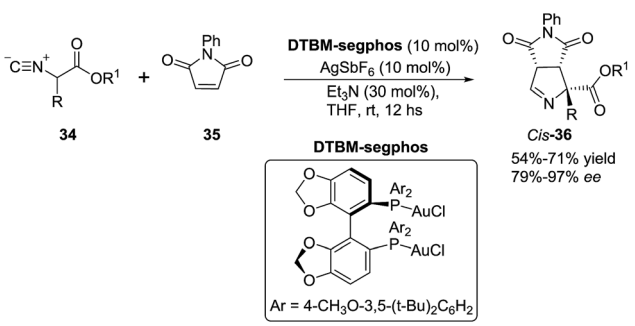
Scheme 12 [3 + 2] Cycloaddition of isocyanoacetates with electron-deficient alkenes.

relies on an asymmetric Michael addition of ketiminoesters **26** to β-trifluoromethyl β,β-disubstituted enones **25** and subsequent hydrolytic cyclization. The optimized asymmetric conditions employed CuOAc as the catalyst and (*S*,*S*)-^{i}Pr-FOXAP as a chiral ligand in the presence of water (6 equiv.) to achieve this highly chemo-, diastereo-, and enantioselective reaction.

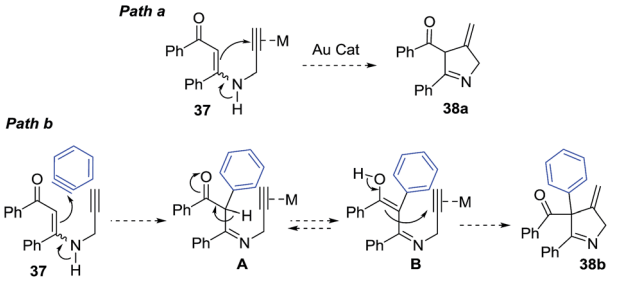
Bower *et al.*[77] developed a copper(I)-catalyzed Heck-like cyclization of oxime esters as an effective alternative to Pd-based protocols (Scheme 11). One advantage of this methodology is that it works with less activated oxime esters such as pivaloyl oxime (**28**) as the starting material, instead of the more expensive *O*-pentafluorobenzoyl oximes that are required for the Pd protocol. The range of substrates which delivers 1-pyrrolines (**29**) includes pivaloyl oxime esters **28a–l** that possess pendant 1,2-disubstituted alkenes, the more heavily substituted 1,1-disubstituted alkenes **28m–r**, and the cyclohexenes **28s–u**. The proposed mechanism involves an intermediate that has iminyl radical character that triggers cyclization to form a C–N bond.

2.1.2. Synthesis of 1-pyrrolines by gold catalysis. A convergent preparation of pyrrolines consists of the formal [3 + 2] cycloaddition of isocyanoacetates **31** with electron-deficient alkenes **30** (Scheme 12). Base, or a metal complex accelerate significantly the reaction.[78] With cyclic alkenes the cycloaddition gives the 1-pyrroline (**32**), whereas with acyclic alkenes the acyclic 2-pyrroline (**33**) is obtained.

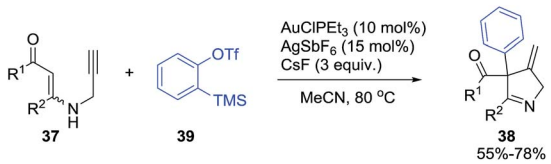
In 2012, Carretero *et al.* reported[79] a highly diastereoselective and enantioselective synthesis of 1-pyrrolines **36** by reaction of isocyanoacetates **34** with phenylmaleimide (**35**) using an Au(I) catalyst with a chiral DTBM-segphos ligand. The use of substituted isocyanoacetates led to 1-pyrrolines bearing a quaternary stereocenter at C-5 (Scheme 13). The reaction of α-aryl-substituted and α-alkyl-substituted isocyanoacetates gave



Scheme 13 Au-catalyzed asymmetric formal [3 + 2] cycloaddition of isocyanoacetates with maleimides.



Scheme 14 Strategies for the conversion of *N*-propargylic β-enaminone **37** to 1-pyrroline **38b** *via* gold catalysis.

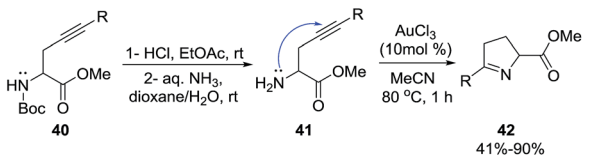


Scheme 15 Gold-catalyzed cyclization of *N*-propargylic β-enaminones **37** towards 1-pyrrolines **38b** in presence of aryne precursor **39**.

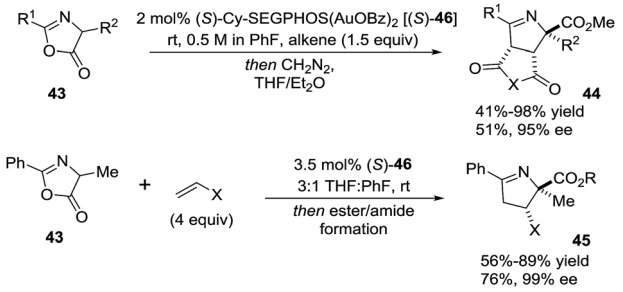
the 1-pyrroline adduct as a single diastereomer and with high enantiocontrol. This methodology afforded 1-pyrrolines containing a quaternary stereocenter with complete *cis* diastereoselectivity (both carbonyl substituent oriented in the same direction of the pyrroline ring) and high enantioselectivity (up to 97% ee).

Karunakar *et al.*[80] envisaged a route to 3-methylene-1-pyrrolines from *N*-propargylic β-enaminones and arynes using gold catalysis. However, only recovered starting material was obtained from the attempted reaction of enaminone **37** and various gold catalysts (Scheme 14, path a). The failure of the reaction was attributed to the poor nucleophilicity of the enaminone or the weak electrophilic character of the propargylic functionality. Then, they had the innovative idea to use an external aryne to enable cyclization (path b). Using benzyne generated *in situ* and $AuCl_3/AgSbF_6$ as catalysts, they observed the formation of the 3-methylene-1-pyrroline **38b** (Scheme 14). After a rigorous catalyst screening, they found that the combination of $AuCl\cdot PEt_3$ (10 mol%) and $AgSbF_6$ (15 mol%) in presence of the aryne precursor **39** in CH_3CN at 80 °C gave the best yields (Scheme 15). Evaluation of the scope of the reaction using different *N*-propargylic β-enaminones demonstrated that enaminone with electron-donating groups increased the yield of the cyclisation products.

Our group[81] developed a versatile strategy to obtain a variety of disubstituted 1-pyrrolines **42** through a gold-catalyzed *N*-



Scheme 16 Gold-catalyzed C–N functionalization of alkynyl amino acids derivatives.



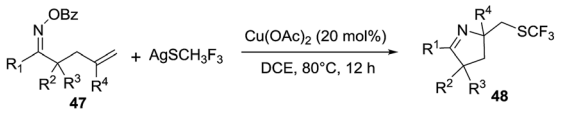
Scheme 17 Enantioselective gold(I)-catalyzed reactions of azlactones.

cycloisomerization from alkyne-containing amino acids **40** (Scheme 16). Of the gold catalysts examined, the most effective for this C–N functionalization was $AuCl_3$.

Although this transformation can be performed with other transition metals and with Brønsted acids, $AuCl_3$ is the superior catalyst as it provides a broader scope and better yields. This cycloisomerization of aryl-substituted alkynyl-containing amino acids proceeds exclusively *via* Au(III)-catalyzed 5-*endo-dig* *N*-cyclization. Aryl-substituted alkynyl amino acids bearing electron withdrawing groups provide excellent yields (typically 90%) of the C–N functionalized product whilst derivatives carrying electron-donating groups furnish lower yields (typically 55%). Terminal alkynes fail to afford the pyrroline, they are unreactive under these conditions.

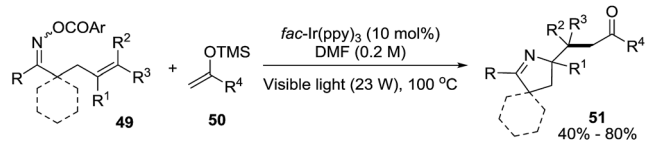
Toste *et al.*[82] evaluated the gold-catalyzed reactions between azlactones **43** and electron-deficient alkenes (such as maleimide and maleic anhydrides, or monosubstituted alkenes) to give stereoselectively the products (**44** and **45**, respectively) of 1,3-dipolar cycloaddition (Scheme 17). The use of C_2-symmetric bis(phosphinegold(I) carboxylate) complexes (*S*-**46**) provided good to excellent diastereo- and enantioselectivity to afford 1-pyrrolines **44** and **45**. The authors proposed a mechanism in which the gold complexes activate pro-nucleophiles to catalyze the cycloaddition, rather than the more typical mechanism of activation of the carbon–carbon π-bond toward nucleophilic addition.

Zhu *et al.* reported a copper-catalyzed domino cyclization/trifluoromethylthiolation of monosubstituted or 1,1 disubstituted olefins **47** leading to SCF_3-substituted 1-pyrrolines **48** in 60–90% yields (Scheme 18).[83] $AgSCF_3$ is the reagent of choice as SCF_3 source. Benzoyloxy group and $Cu(OAc)_2$ proved to be the best oxime leaving group and catalyst for this transformation. This

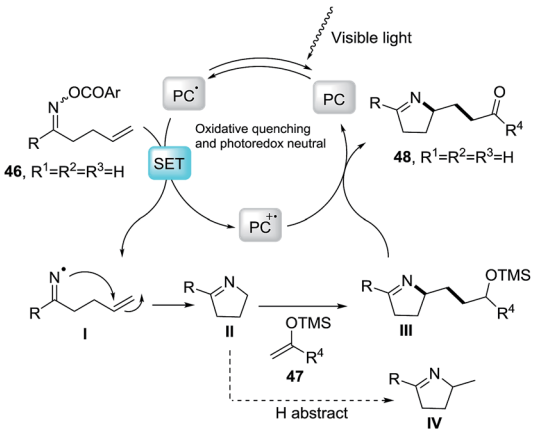


48a, R^1=Ph; R^2=H; R^3=H; R^4=H; 81%
48b, R^1=4-MeOC_6H_4; R^2=H; R^3=H; R^4=H; 75%
48c, R^1=4-MeC_6H_4; R^2=H; R^3=H; R^4=H; 71%
48d, R^1=4-ClC_6H_4; R^2=H; R^3=H; R^4=H; 70%
48e, R^1=3-MeOC_6H_4; R^2=H; R^3=H; R^4=H; 65%
48f, R^1=3-ClC_6H_4; R^2=H; R^3=H; R^4=H; 89%.
48g, R^1=2-ClC_6H_4; R^2=H; R^3=H; R^4=H; 74%
48h, R^1=3,4-MeOC_6H_4; R^2=H; R^3=H; R^4=H; 67%
48i, R^1=2-naphthyl; R^2=H; R^3=H; R^4=H; 65%
48j, R^1=2-thienyl; R^2=H; R^3=H; R^4=H; 60%
48k, R^1=Ph; R^2=H; R^3=H; R^4=Me; 70%
48l, R^1=Ph; R^2=Me; R^3=Me; R^4=H; 73%
48m, R^1=Ph; R^2;R^3=cyclohexyl; R^4=H; 75%
48n, R^1=Ph; R^2=Me; R^3=Me; R^4=Me; 63%
48o, R^1=$CH_2CH_2C_6H_4$; R^2=H; R^3=H; R^4=H; 61%

Scheme 18 Copper-catalyzed synthesis of SCF_3-containing 1-pyrrolines **48**.



Scheme 19 Visible-light-promoted carboimination of unactivated alkenes towards 1-pyrrolines.

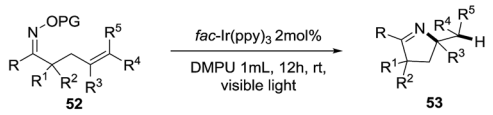


Scheme 20 Proposed reaction mechanism.

reaction involves the N–O cleavage of benzoyl oximes and subsequent alkene difunctionalization and tolerates electron-donating and electron-withdrawing groups on the aryl-substituted *O*-acyl oximes (R^1 = Ar, **48a–h**) as well as alkyl-substituted *O*-acyl oxime. R^1 = naphthyl and thienyl delivered the SCF_3-containing 1-pyrrolines in good yields. The reaction is also compatible with alkyl moieties as the substituents R^2 and R^3.

2.1.3. Synthesis of 1-pyrrolines by iridium catalysis. Loh *et al.*[84] developed a strategy based on the iminyl-radical formation for the creation of the C–N bond of the pyrroline (Scheme 19). The iminyl-radical is generated from the *O*-acyl oxime derivatives **49** in presence of a photocatalyst such as *fac*-[Ir(ppy)$_3$] and visible light. The cascade reaction takes place through an intramolecular 5-*exo* cyclization followed by intermolecular carbon radical trapping with silyl enol ether derivatives **50** (Scheme 20). The procedure allows easy access to densely functionalized pyrroline derivatives **51**. The use of silyl enol ethers as coupling partners regenerate the photocatalyst without necessity of an external reductant, while introducing the synthetically useful ketone functionalities. The procedure shows tolerance to a broad range of functionalities and enables diverse substitution patterns with respect to both the starting oxime derivative and the silyl enol ether. Different densely functionalized pyrrolines are obtained in moderate to good yields (typically 40–80%).

Then, the same group reported a modification of previous protocol adding *N*,*N*′-dimethylpropylene urea (DMPU) as solvent, reductant and H donor.[85] As result, a visible-light-promoted hydroimination of unactivated alkenes **52** catalyzed by iridium towards the synthesis of 1-pyrrolines **53** was accomplished (Scheme 21). As in the previous report, the procedure shows



52 53

53a,R=Ph; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 72%
53b,R=4-MeC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 77%
53c,R=2-MeC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 64%
53d,R=4-MeOC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 90%
53e,R=4-FC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 77%
53f,R=3-FC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 89%
53g,R=4-ClC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 96%
53h,R=3-ClC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 87%
53i,R=2-ClC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 96%
53j,R=4-BrC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 81%
53k,R=4-$CF_3C_6H_4$; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 66%
53l,R=3,5-di$CF_3C_6H_4$; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 69%
53m,R=4-BocNHC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 86%
53n,R=4-Me$CO_2C_6H_4$; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 98%
53o,R=4-PhNHCOC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 90%
53p,R=4-CNC_6H_4; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 86%
53q,R=2-Thienyl; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 56%[a], 59%[b]
53r,R=2-naphthyl; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 48%
53s,R=Ph; R^1=Me; R^2=Me; R^3=H; R^4=H; R^5=H; 80%
53t,R=Ph; R^1=Me; R^2=Me; R^3=Me; R^4=H; R^5=H; 90%
53u,R=Ph; R^1=Me; R^2=Me; R^3=H; R^4=Me; R^5=Me; 78%
53v,R=$C_6H_4OCH_2$-; R^1=H; R^2=H; R^3=H; R^4=H; R^5=H; 40%

53w, 95%
53x, 83%
53y, 34%
53z, 14%
53aa, 39%

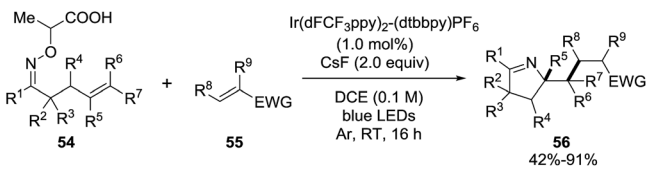
[a]:*Z*-configuration substrate.
[b]:*E*-configuration substrate.

Scheme 21 Intramolecular cycloaddition of **52** by iridium catalyst.

a broad scope of functionalities and tolerates diverse substitution patterns of the aryl *O*-acyl oximes to afford 1-pyrrolines XX in good to excellent yields (64–98%). However, a diminished yield was observed when alkyl, naphthyl, alkenyl and alkynyl derived *O*-acyl oximes (R) were employed as substrates (14–48%).

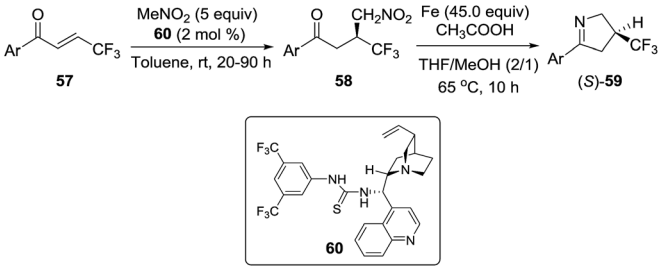
Studer *et al.* applied visible light to promote the generation of iminyl-radicals by a photoredox decarboxylation of α-imino-oxy propionic acids **54** towards the synthesis of 1-pyrrolines **56** (Scheme 22).[86] The reaction mixture between α-imino-oxy propionic acids **54** and olefins with electron withdrawing groups **55** in the presence of 1 mol% of $Ir(dFCF_3ppy)_2$-(dtbbpy)PF_6 – a photoredox catalyst – and K_3PO_4 in 1,2-dichloroethane is irradiated with blue LED light to produce 1-pyrrolines **56** in good to excellent yields (typically 42–91%). The reaction takes place without any control of the diasteroselectivity. Different α,β-unsaturated esters with substituents at the α and β position, α,β-unsaturated amides, phosphonate and ketones were efficient Michael acceptors (**55**). Regarding the iminyl radical precursor **54**, phenyl groups with electron-rich or electron-poor substituents, 2-thienyl, 2-naphthyl and alkyl groups at R^1 position were well tolerated. α-Iminyl-oxy acids with substituents at R^2, R^3, R^5 and R^6 positions were good substrates.

Messerle *et al.*[87] reported the synthesis of 1-pyrrolines *via* an intramolecular hydroamination of a series of alkynamines catalyzed by both iridium and rhodium complexes with bidentate N–N′ donor ligands (see Fig. 3, Schemes 44 and 45 in Subsection 2.1.7.: Synthesis of 1-pyrrolines by rhodium catalysis).



54 55 56

Scheme 22 Synthesis of 1-pyrrolines **56** using blue LEDs.



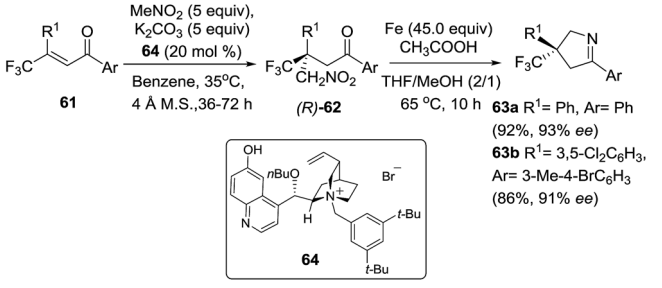
57 58 (*S*)-59 60

Scheme 23 One-pot enantioselective synthesis of 3-trifluoromethylated 1-pyrrolines (*S*)-**59**.

2.1.4. Synthesis of 1-pyrrolines by iron catalysis. In 2012, Shibata *et al.*[88] described the one-pot enantioselective synthesis of β-trifluoromethyl-substituted pyrrolines **59** by an asymmetric conjugate addition of nitromethane to β-trifluoromethylenones **57** catalyzed by a cinchona alkaloid-derived/thiourea (**60**), followed by an iron-mediated reduction/cyclization/dehydration sequence of the intermediate **58**. Excellent yields and high enantioselectivities (up to 98% ee) were obtained (Scheme 23).

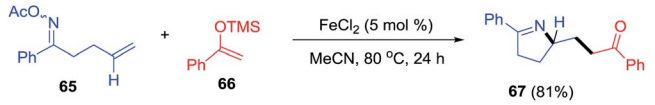
Trifluoromethylated 3,5-diaryl-pyrrolines (**63**) have attracted much attention because of their promising agrochemical activity as antiparasitics. Since this finding in 2005, more than 7000 variants have been described across numerous patents. In related work Shibata *et al.*[89] disclosed the asymmetric synthesis of 3-trifluoromethyl 3,5-diaryl-pyrrolines **63** using excess Fe(0) for the cyclization step (Scheme 24). The chiral starting materials for this reaction were made by the enantioselective conjugate addition (using a phase-transfer organocatalyst **64**) of nitromethane with a variety of β,β-disubstituted enones (**61**). A family of eighteen 1,4 adducts **62** were obtained in excellent yields and enantioselectivities. Conversion of **62** into the trifluoromethylated 3,5-diaryl-pyrrolines **63** was carried out using excess iron in the presence of acetic acid for the nitro reduction/cyclization/dehydration sequence, and without any loss of the enantiopurity. Transformation to the biologically important trifluoromethylated arylpyrrolines **63** were achieved from the nitromethane adduct **62** with high to excellent yields (typically 90%) in a single step.

Yang *et al.*[90] envisaged oxime esters as electrophilic partners for iron catalysis (Scheme 25). Reductive cleavage of the oxime N–O bond by iron generates useful iminyl radicals.[91] Coupling

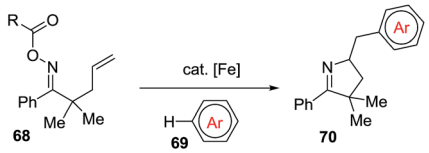


61 (*R*)-62 64

Scheme 24 Enantioselective conjugate addition of nitromethane to β,β-disubstituted enones **61**, followed by an iron-mediated reduction/cyclization/dehydration sequence to 1-pyrrolines **63**.



Scheme 25 Iron-catalyzed coupling of *O*-acyloximes with silyl enol ethers.



Scheme 26 Synthesis of 1-pyrrolines **70**.

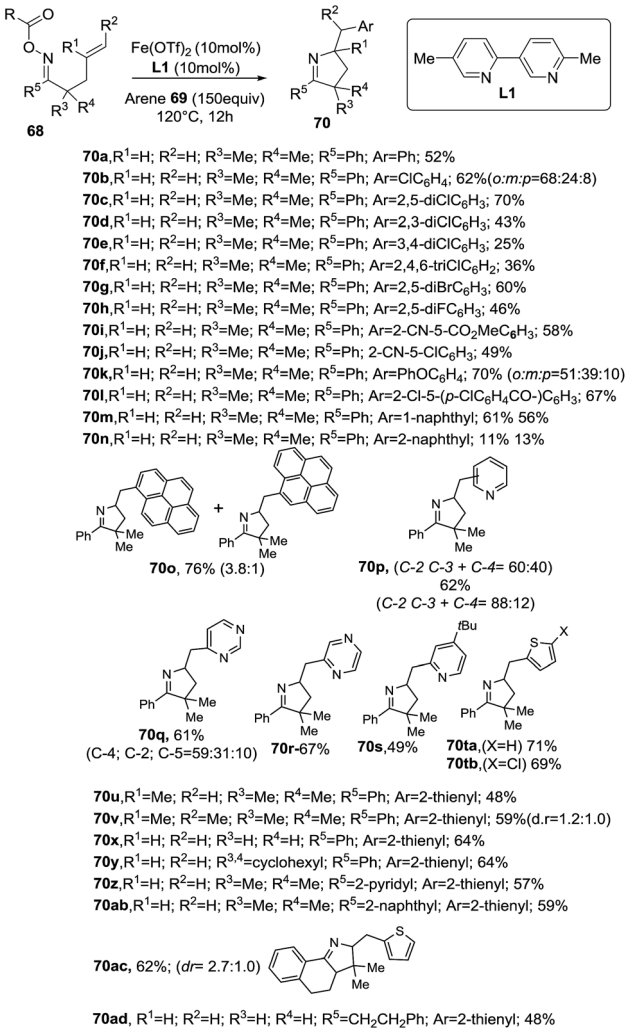
of iminyl radical derivatives of γ,δ-unsaturated oxime (**65**) with silyl enol ether (**66**) lead to pyrroline **67** through an intramolecular C–N bond formation.

The Oche and the Okamoto group disclosed an iron-catalyzed methodology to achieve 1-pyrrolines **70** that involved the formation of iminyl radicals from alkene-tethered oxime esters **68** and subsequent aminative cyclization and intermolecular homolytic aromatic substitution (Scheme 26).[92]

The optimized conditions use 10 mol% of $Fe(OTf)_2$ and ligand **L1** in presence of a great excess of arenes (150 equiv.). The mixture is heated a 120 °C for 12 h.

The reaction tolerates different arenes **69** with electron-rich and electron-poor substituent, polycyclic aromatic compounds as well as nitrogen- or sulfur-containing heteroarenes. Regarding the scope of alkene-tethered oxime ester **68**, R = picolinoyl ester (**68a**-2-Py) and R = pivaloyl ester (**68a**-*t*Bu) can be used with the picolinoyl ester giving better yields with substituted arenes. Oxime esters with substituted alkenes ($R^1 \neq H$ and/or $R^2 \neq H$) provided 1-pyrrolines in good yields. The reaction is applicable to oxime esters **68** with R^3 and R^4 = H or alkyl groups and R^5 = heteroaryl, naphthyl or alkyl groups (Scheme 27). This transformation involving radical intermediates affords 1-pyrrolines **70** with moderate to good yields (36–71%).

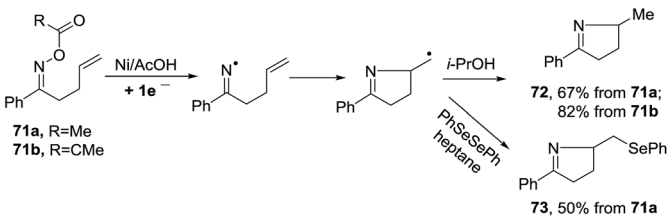
2.1.5. Synthesis of 1-pyrrolines by nickel catalysis. Zard *et al.*[93] conceived of a method for the generation of iminyl radicals based on the reduction of oxime esters (**71**) with a combination of nickel powder and acetic acid (Scheme 28). The radical center on the nitrogen is intercepted intramolecularly by the well-positioned terminal alkene. Subsequent quenching by isopropanol gives pyrroline **72**. The authors proved this radical mechanism with addition of diphenyldiselenide (PhSeSePh), which led to selenide **73**. On the other hand, when they replaced the unsubstituted terminal alkene of **71a/b** by a trisubstituted alkene of **74a/b**, they obtained the isopropenyl alkene **76a** and the tertiary acetate **75a** in the case of **74a**. When starting from **74b**, they observed only formation of **75b** (Scheme 29). The authors determined that this mechanism is ionic, and not radical, with the following experiment. Reaction of the oxime acetates **74a** and **74b** containing an isopropylidene group with $Cu(OAc)_2$/AcOH in refluxing *t*-butanol



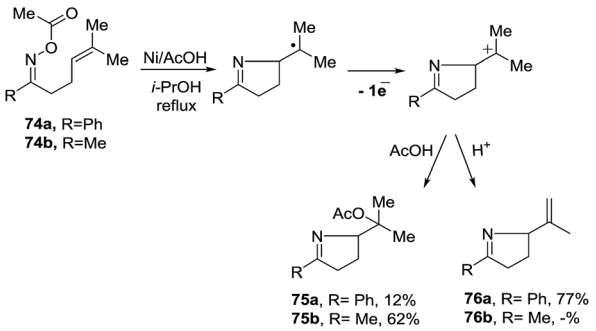
Scheme 27 Aminative cyclization/intermolecular homolytic aromatic substitution involving iminyl radicals towards 1-pyrrolines **70**.

gave the 1-pyrrolines **77a** and **77b** with an isopropenyl side-chain with very good yields (Scheme 30). Evaluation of other metallic salts for this reaction showed that from **74a** $FeCl_3$/AcOH in *t*-butanol at room temperature gave the acetate **75a** and the alcohol **78**. When they treated oxime **71a** with $FeCl_3$ in *t*-butanol in the absence of acetic acid (also at room temperature) they obtained the chloride **79** (64% yield) and a small amount of the alcohol **80** (8% yield) as the products.

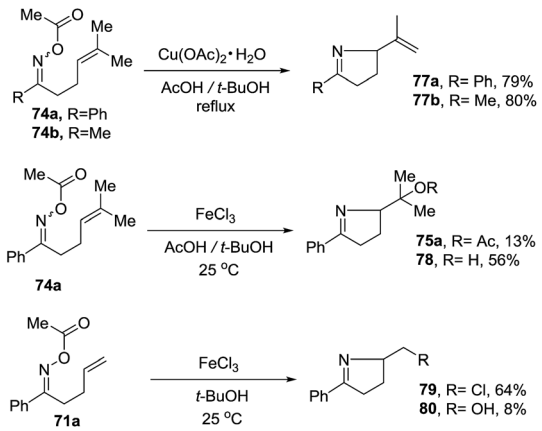
The scope of this $FeCl_3$-promoted ionic transformation in *t*-butanol was examined with and without the presence of acetic



Scheme 28 Dissolving nickel metal mediated generation of iminyls from oxime esters.



Scheme 29 Unexpected transformations of an unsaturated oxime acetate.



Scheme 30 Cupric and ferric ion-mediated cyclizations of unsaturated oxime acetates.

acid (Table 1). While several substitution patterns on the alkene were well tolerated, only the oxime acetate derived from aromatic ketones gave the 1-pyrrolines. The case of oxime acetate **90** derived from a methyl ketone is an exception since other oxime acetate derived from aliphatic ketones produced complex mixtures.

A possible mechanism is given in Scheme 31. The nitrogen from the oxime and the oxygen of ester form an intermediate complex with the metal ion, probably in equilibrium with the enamine that reacts *via* transition state **101** wherein acetate leaves as the weak N–O bond is broken by nucleophilic attack of the alkene. Electron-rich alkenes are therefore better nucleophiles and improve the reaction. With Cu(II), an alkene is formed by abstraction of a proton (path a). With the Fe(III) of $FeCl_3$, chloride anion competes as a nucleophile to give the chloride as a final product (path b).

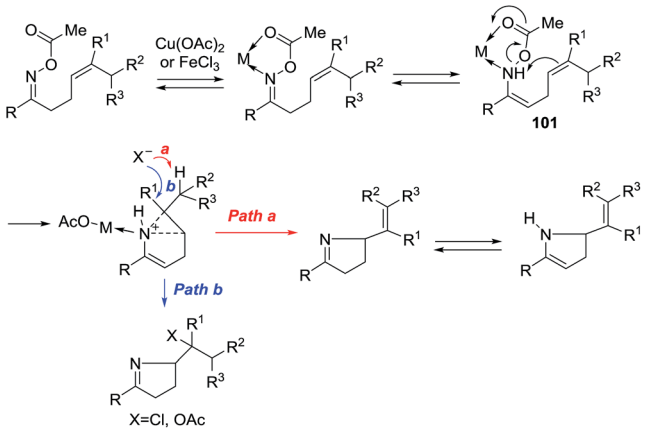
Unlike palladium catalyzed cross-coupling reactions that suffer from β-H-elimination, cross-coupling reactions catalyzed with Ni are not susceptible to β-H-elimination. This feature was exploited by Selander *et al.* to developed a Nickel-catalyzed 1,2-aminoarylation of oxime ester-tethered alkenes with boronic acids (Scheme 32).[94] By reacting γ,δ-unsaturated oxime esters **102** with boronic acids **103** in presence of $NiBr_2$ (20 mol%), Et_3N (10 equiv.) and ligands **L2** or **L3** (20 mol%) in dioxane at 90 °C, 1-pyrrolines **104** were obtained with moderate to good yields (31–

Table 1 Formation of chloroalkyl-1-pyrrolines **90–100** from unsaturated oxime acetates **81–90** mediated by $FeCl_3$

Oxime Acetate	1-Pyrroline
81	**91**, 52%
82	**92**, 70%
83	**93**, 77%
84	**94**, 80%
85	**95**, 83%
86	**96**, 72%
87	**97**,43%
88	**98**, 56%
89	**99**, 55%
90	**100**, 65%

82%). The reaction tolerates well several substituted arylboronic acids with electron withdrawing groups or electron donor groups and fused aromatic, heteroaromatic and vinylic boronic acids (R^4 = Ar, hetAr, vinyl). Aryl and heteroaryl oxime esters proceed well to 1-pyrrolines (R^1 = Ar, HetAr). The reaction is also suitable for non-terminal and cyclic alkenes. This nickel-catalyzed protocol is an excellent alternative to palladium catalyzed cross-coupling reactions (see Subsection 2.1.6.: Synthesis of 1-pyrrolines by palladium catalysis).

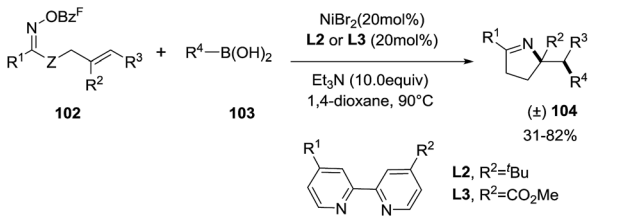
Recently, Wang *et al.* disclosure a Ni-biquinoline-catalyzed synthesis of multisubstituted 1-pyrrolines **107** through a reductive 1,2-iminoacylation of alkenes (Scheme 33).[95] Oxime esters incorporating a pendant terminal olefinic unit **105** were reacted with electrophilic acylating reagents like acid chlorides (**106b**) or anhydrides (**106a**) and zinc as a reductive agent to generate 1-pyrrolines **107** in yields ranging from 46 to 98%. Aromatic and heteroaromatic groups in position R^1 are well tolerated. Also,



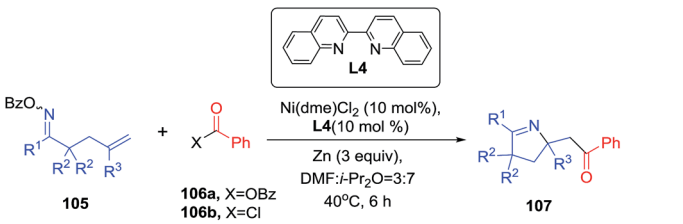
Scheme 31 Possible mechanism.

oxime esters with $R^2 = H$ and monosubstituted alkenes ($R^3 = H$) were suitable substrates. Internal alkenes fail to deliver the product. The iminoacylation reaction can be performed with carboxylic acids in presence of $(Boc)_2O$ instead of the acid chlorides or anhydrides. This procedure is an alternative to Bower's Pd catalyzed 1,2-iminoacylation of oxime esters-tethered alkenes with carbon monoxide and organoborons[96] (see Subsection 2.1.6.: Synthesis of 1-pyrrolines by palladium catalysis).

2.1.6. Synthesis of 1-pyrrolines by palladium catalysis. Bower *et al.*[96] developed an extraordinary umpolung approach to obtain a great variety of 1-pyrrolines (Scheme 34). Their methodology is based on the oxidative addition of Pd(0) into the

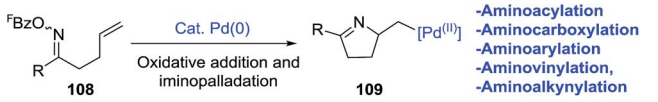


Scheme 32 Synthesis of 1-pyrrolines **104** by $NiBr_2$.



107a, R^1= Ph, R^2= Me, R^3= Me, 90%
107b, R^1= 3-ClC_6H_4, R^2= Me, R^3= Me, 68%
107c, R^1= 4-FC_6H_4, R^2= Me, R^3= Me, 73%
107d, R^1= 4-MeOC_6H_4, R^2= Me, R^3= Me, 93%
107e, R^1= 2-naphthyl, R^2= Me, R^3= Me, 76%
107f, R^1= 2-furyl, R^2= Me, R^3= Me, 88%
107g, R^1= Ph, R^2=cyclobutyl, R^3= Me, 83%
107h, R^1= Ph, R^2= cyclopentyl, R^3= Me, 98%
107i, R^1= Ph, R^2= Me, R^3= Ph, 81%
107j, R^1= 4-FC_6H_4, R^2= H, R^3= Me, 60%
107k, R^1= 2-furyl, R^2= H, R^3= Me, 61%
107l, R^1= Ph R^2= Me, R^3= H, 81%

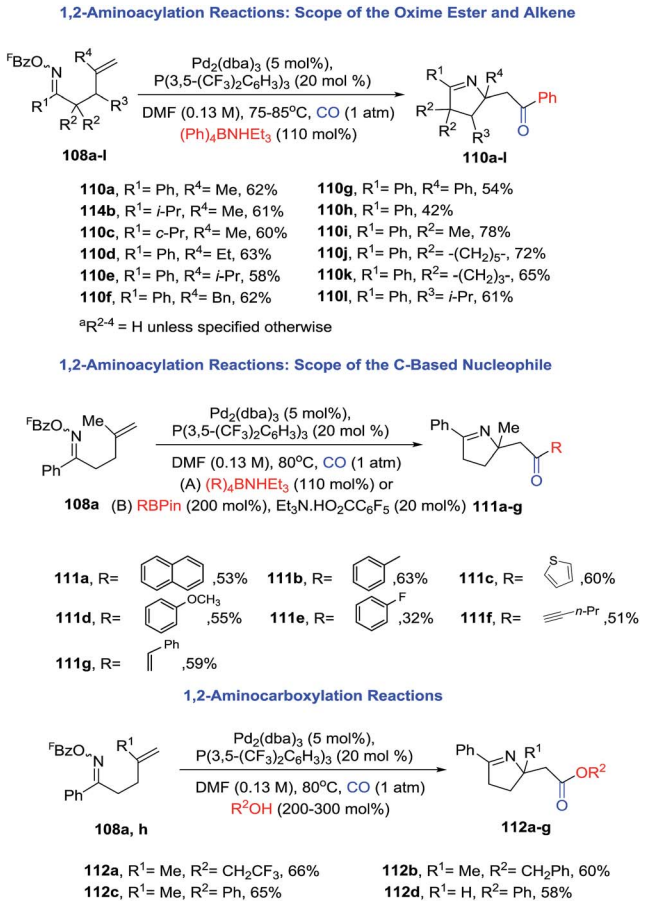
Scheme 33 Ni-catalyzed 1,2-iminoacylation of alkenes towards 1-pyrrolines.



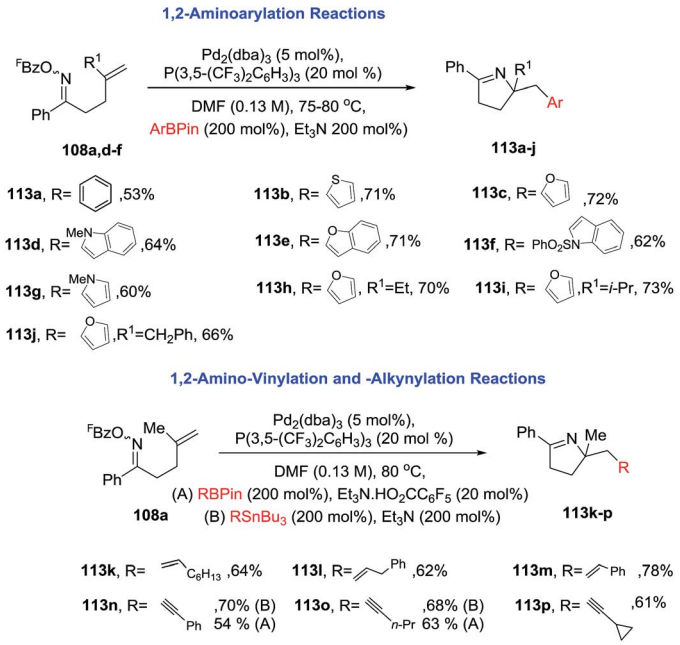
Scheme 34 Oxidative addition in the oxime ester N–O bond.

N–O bond of *O*-pentafluorobenzoyl oxime esters (**108**) to generate an imino-Pd(II) intermediate **109**. This intermediate undergoes an 5-*exo* cyclization with sterically diverse alkenes to form alkyl-Pd(II) pyrroline intermediates. These intermediates can be decorated by subsequent reaction with organometallic or alcohol nucleophiles (Scheme 35). Moreover, the procedure can be carried out in presence of CO (carbonylative) or absence of CO (non-carbonylative) conditions. Under carbonylative conditions, 1,2-aminoacylation reactions are achieved by using triethylammonium tetraarylborates or pinacol organoboronates as the nucleophiles (products are **110** and **111**). With alcohol nucleophiles under carbonylative conditions, a 1,2-aminocarboxylation occurs (product is **112**).

Under noncarbonylative conditions 1,2-aminoarylation is achieved employing a variety of pinacol arylboronates as nucleophiles (Scheme 36, products **113a–j**). 1,2-Aminovinylation and 1,2-aminoalkynylation products are obtained using vinyl boronates or alkynyl-stannanes, respectively (products are **113k–p**). For alkynylation, less toxic pinacol



Scheme 35 Pd-catalyzed 1,2-carboamination of alkenes.

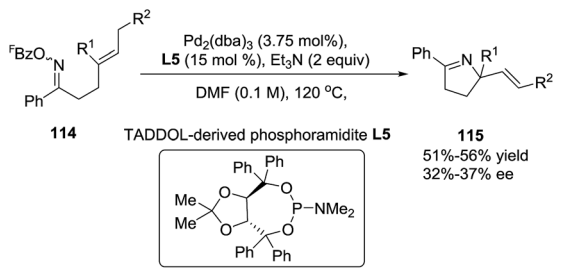


Scheme 36 Pd-catalyzed 1,2-carboamination of alkenes.

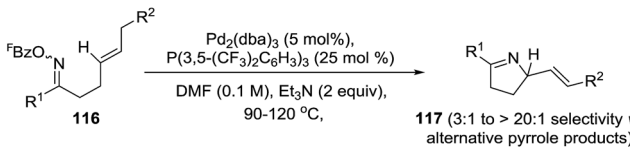
alkynylboronates can be used instead of alkynyl-stannanes. This approach provides an unified strategy for achieving alkene 1,2-aminoacylation, -carboxylation, -arylation, -vinylation, and -alkynylation.

Previously Bower *et al.* reported[97] the Pd-catalyzed cyclization of *O*-pentafluorobenzoyl oxime esters with 1,1-disubstituted alkenes as a general entry to chiral α,α-disubstituted pyrrolines (**115**). In this study the key ligand P(3,5-$(CF_3)_2C_6H_3)_3$ used in the achiral catalytic systems was replaced by the TADDOL-derived phosphoramidite **L5**. With **114** as the starting material, modest enantioselectivities (typically 32–37% ee) were achieved (Scheme 37). Nonetheless, these results establish the feasibility of asymmetric Narasaka–Heck cyclizations.

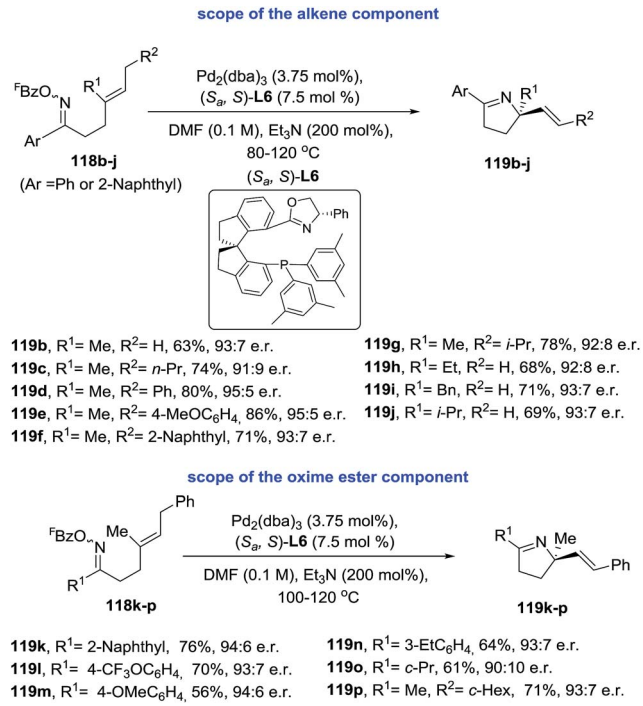
The same group performed Pd-catalyzed cyclizations of oxime esters with 1,2-dialkylated alkenes (**116**) as a general entry to chiral dihydropyrroles (**117**) and avoiding the formation of the undesired pyrrole (Scheme 38).[98] In the previous case where 1,1-disubstituted alkenes were used, the nature of the alkene acceptor controlled the direction of β-hydride elimination and the pyrrole formation was bypassed. The selectivity in favor of the pyrroline, and against the pyrrole, derives from the



Scheme 37 Asymmetric Pd-catalyzed cyclization of oxime esters with 1,1-disubstituted alkenes.



Scheme 38 Pd-catalyzed cyclization of oxime esters with 1,2-disubstituted alkenes.

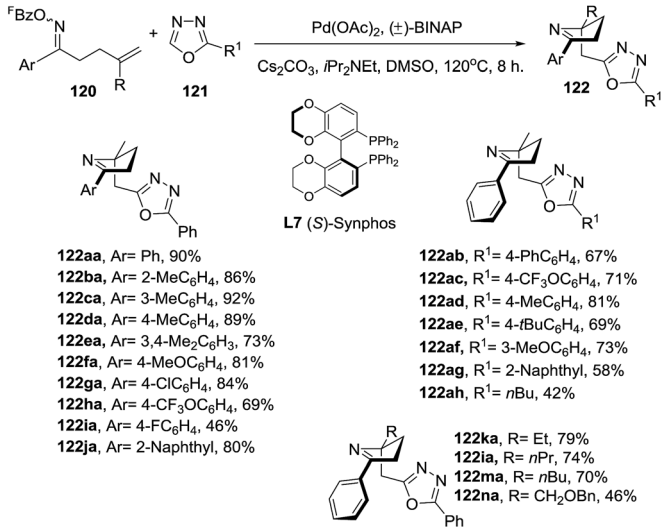


Scheme 39 Enantioselective Narasaka–Heck cyclizations.

aryl moiety (R^2 = aryl). This moiety weakens the benzylic C–H bond and so increases the propensity for β-hydride elimination. Where $R^2 \neq$ aryl, the pyrroline/pyrrole selectivity is lower.

Very recently, Bower and coworkers[99] identified a SPINOL-derived P–N ligand system [(S_a,*S*)-**L6**] that promoted the first examples of highly enantioselective Narasaka–Heck cyclizations (Scheme 39). This Pd-catalyzed 5-*exo* cyclization tolerates a range of oxime esters and diverse sterically trisubstituted alkenes (**118**) and generates otherwise challenging pyrrolidine derivatives containing tetrasubstituted nitrogen-bearing stereocenters (**119**). Cycled products are obtained in moderate to excellent yields (56–86%) and high enantioselectivity (91 : 9 to 95 : 5 e.r.).

Almost simultaneously with the report of Bower, Bao *et al.*[100] reported a domino processes that involved a palladium-catalyzed Narasaka–Heck reaction followed by direct arene C–H alkylation leading to 2,5,5-trisubstituted dihydropyrroles (**122**) (Scheme 40). In this process two new bonds were formed: one N(sp^2)–C(sp^3) bond and one C(sp^3)–C(sp^2) bond and a quaternary center was generated. The optimized conditions of $Pd(OAc)_2$ (0.1 equiv.), (±)-BINAP (0.2 equiv.), $^iPr_2NEt$ (4.0 equiv.), Cs_2CO_3 (3.0 equiv.) in DMSO at 120 °C were applied to substrates with a range of substituted on the aryl (Ar) group of

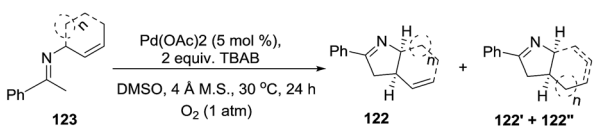


Scheme 40 Domino Narasaka–Heck reaction/direct arene C–H alkylation.

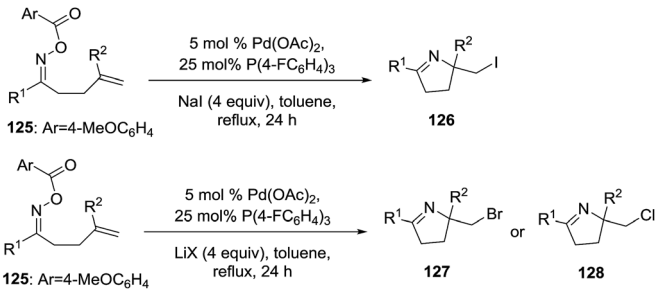
the oxime ester (**120**), exploring both the electronic nature and position of the substituent. In most of cases, the 1-pyrrolines **122aa–122ja** were obtained in very good yields. A variety of substituents on the oxadiazole (**121**), and different alkyl groups attached to the alkene, were well tolerated. An enantioselective version of this cascade process was developed using (*S*)-Synphos (**L7**) as chiral ligand, isolating the 2,5,5-trisubstituted pyrroline **122** in good yields with good to high enantioselectivity.

The Glorius group[101] developed an entry to 1-pyrrolines (**124**, **124′**, **124″**) starting from the imines **123** derived from acetophenone and cyclic *N*-allylamines (Scheme 41). The procedure employs a mild oxidative palladium-catalyzed cyclization using O_2 as the terminal oxidant. Besides cyclic *N*-allylamines, *N*-allylamines containing γ-substituents on the allyl group also deliver the 1-pyrrolines in good yields (61–87%). This atom-economical procedure relies on an intramolecular C–H dehydrogenative 5-*exo* cyclization.

Tong *et al.*[102] developed a methodology to synthesize 2-halomethyl 1-pyrrolines **126** from the oxime ester **125** using a Pd(0)-catalyzed intramolecular iminohalogenations of 1,1-disubstituted alkenes assisted with halide salts (Scheme 42). The use of electron-poor phosphine as ligands proved to be essential to obtain alkyl halogenated dihydropyrroles under reductive elimination. Iminochlorination (**128**) is less efficient compared to iminobromination (**127**) and iminoiodination (**126**). For example, when R^1 = Ph and R^2 = Me the yields for the iminohalogenation are 75% for iodination, 64% for bromination and 42% for chlorination.



Scheme 41 Palladium(II)-catalyzed cyclization of imines to 1-pyrrolines.



Scheme 42 Palladium(0)-catalyzed iminohalogenation of alkenes.

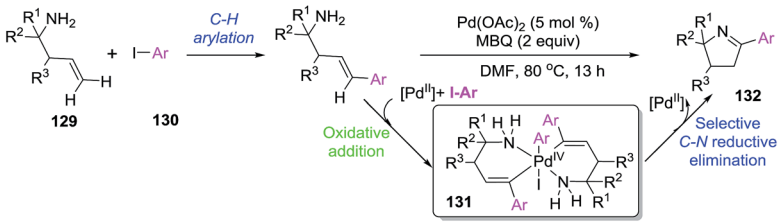
Homoallylic primary amines **129** reacted with aryl iodides **130** in the presence of a Pd catalyst to provide 2-aryl-1-pyrrolines **132** *via* a cascade C–H arylation/C–H amination sequence (Scheme 43).[103] The transformation proceeds thorough a Pd-promoted Heck coupling followed by a C–H amination cocatalyzed by Pd and the aryl iodide, and final tautomarization from 2-pyrrolines to the isolated 1-pyrrolines. Interestingly, this report represents the first example of aryl iodide acting as both coupling reagent and cocatalyst involved in the generation of the active bivalent aryl palladium catalyst **131** capable of promoting the formation of new N–C bond. The optimized protocol involved the use of 2 eq. of aryl iodide **130**, $Pd(OAc)_2$ (10 mol%), MBQ (2-methylbenzoquinone, 20 mol%) as oxidant in DMF at 80 °C, leading to a small collection of the final heterocycles **132** with poor to good yields (26–74%). The presence of an oxidant was essential to achieve complete annulation step.

2.1.7. Synthesis of 1-pyrrolines by rhodium catalysis. The hydroamination of alkynes is a highly atom-efficient approach to the synthesis of imines and consist of the N–H addition to a C–C triple bond. If the reaction is intramolecular, the results are cycled imines as 1-pyrrolines. Late transition metal complexes of Ru, Rh, Ir, Pd, Pt, and Cu are effective catalysts for the hydroamination reaction.[104,105]

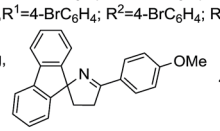
In 2012, Messerle and coworkers[87] reported a series of cationic rhodium (**133**, **135**) and iridium complexes (**134**, **136**) with bidentate *N*,*N*′-pyrazolyl–triazolyl ligands (Fig. 3). These complexes were evaluated as catalysts for the intramolecular hydroamination of a series of alkynylamines. In the case of the cyclization of the terminal alkyne as 4-pentyn-1-amine (**137**) to 2-methyl-1-pyrroline (**138**) at 60 °C (Scheme 44), the iridium complexes $[Ir(N–N)(CO)_2]$–$BArF_4$ (**136c,d**) were the most active catalysts giving 5-*exo*-cyclization exclusively (>98% yield).

The rhodium complexes generally were less active as catalysts than their iridium analogues. In the case of intermolecular hydroamination of internal alkynes, such as with 4-phenyl-3-butyn-1-amine (**139a**) and 5-phenyl-4-pentyn-1-amine (**139b**), the reaction required a higher temperature (110 °C) to reach complete conversion (>98%) towards pyrrolines **140a,b** (Scheme 45).

Rhodium(I) catalysts with ligands such as $(Cy_2P)_2NMe$ and PNP(Cy) are efficient reagents to perform the union of S-chelating aldehydes **141** (aldehydes with a methyl sulfide group in β position) and allylic amines **142** to deliver linear

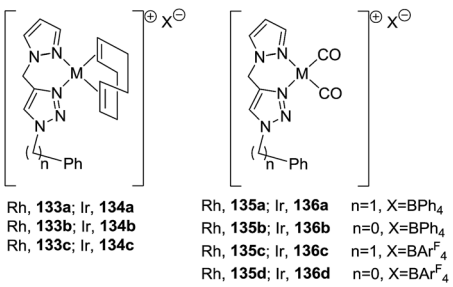


132a,R^1=Ph; R^2=Ph; R^3=H; Ar=4-$MeOC_6H_4$; 72%
132b,R^1=4-MeC_6H_4; R^2=4-MeC_6H_4; R^3=H; Ar=4-$MeOC_6H_4$; 77%
132c,R^1=4-$MeOC_6H_4$; R^2=4-$MeOC_6H_4$; R^3=H; Ar=4-$MeOC_6H_4$; 54%
132d,R^1=4-FC_6H_4; R^2=4-FC_6H_4; R^3=H; Ar=4-$MeOC_6H_4$; 58%
132e,R^1=4-ClC_6H_4; R^2=4-ClC_6H_4; R^3=H; Ar=4-$MeOC_6H_4$; 53%
132f,R^1=4-BrC_6H_4; R^2=4-BrC_6H_4; R^3=H; Ar=4-$MeOC_6H_4$; 55%

132g,  47%

132h,R^1=Ph; R^2=4-MeC_6H_4; R^3=H; Ar=4-$MeOC_6H_4$; 70%
132i,R^1=Ph; R^2=2-naphthyl; R^3=H; Ar=4-$MeOC_6H_4$; 58%
132j,R^1=Ph; R^2=2-thienyl; R^3=H; Ar=4-$MeOC_6H_4$; 45%
132k,R^1=Ph; R^2=cyclohexyl; R^3=H; Ar=4-$MeOC_6H_4$; 74%
132l,R^1=Ph; R^2=Me; R^3=H; Ar=4-$MeOC_6H_4$; 26%
132m,R^1=*n*-Bu; R^2=*n*-Bu; R^3=H; Ar=4-$MeOC_6H_4$; traces
132n,R^1=Ph; R^2=Ph; R^3=Me; Ar=4-$MeOC_6H_4$; 67%
132o,R^1=Ph; R^2=Ph; R^3=H; Ar=Ph; 67%
132p,R^1=Ph; R^2=Ph; R^3=H; Ar=4-MeC_6H_4; 58%
132q,R^1=Ph; R^2=Ph; R^3=H; Ar=4-*t*-BuC_6H_4; 62%
132r,R^1=Ph; R^2=Ph; R^3=H; Ar=4-FC_6H_4; 65%
132s,R^1=Ph; R^2=Ph; R^3=H; Ar=4-ClC_6H_4; 52%
132t,R^1=Ph; R^2=Ph; R^3=H; Ar=4-BrC_6H_4; 50%
132u,R^1=Ph; R^2=Ph; R^3=H; Ar=5-MeC_6H_4; 55%
132v,R^1=Ph; R^2=Ph; R^3=H; Ar=5-$MeOC_6H_4$; 63%
132w,R^1=Ph; R^2=Ph; R^3=H; Ar=5-FC_6H_4; 55%
132x,R^1=Ph; R^2=Ph; R^3=H; Ar=6-MeC_6H_4; 70%
132u,R^1=Ph; R^2=Ph; R^3=H; Ar=2-thienyl; 46%

Scheme 43 Synthesis of 2-aryl-1-pyrrolines **132** *via* a cascade C–H arylation/C–H amination sequence.



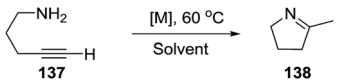
Rh, **133a**; Ir, **134a**
Rh, **133b**; Ir, **134b**
Rh, **133c**; Ir, **134c**

Rh, **135a**; Ir, **136a** n=1, X=BPh_4
Rh, **135b**; Ir, **136b** n=0, X=BPh_4
Rh, **135c**; Ir, **136c** n=1, X=BAr^F_4
Rh, **135d**; Ir, **136d** n=0, X=BAr^F_4

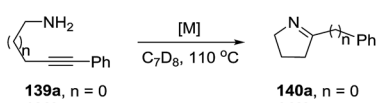
Fig. 3 Pyrazolyl–triazolyl bidentate ligands and their rhodium(I) and iridium(I) complexes.

hydroacylation adducts **143.** These adducts are treated *in situ* with *p*-TsOH to provide the pyrrolines **144** through a dehydrative cyclization (Scheme 46).[23] The pyrroline products (**144**) are formed in good-to-excellent yields (48–90%).

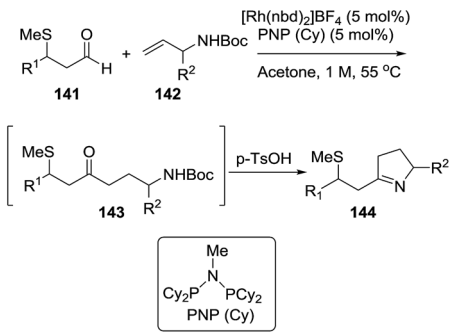
A variety of alkyl, aryl and heteroaryl substituents (R^2 = Ar, HetAr, alkyl) were well tolerated at the allylic position of the alkenes. Also, different aryl or heteroaryl (R^1 = Ar, HetAr) S-chelated aldehydes provided the pyrrolines. Aldehydes featuring a chelating group in β-position other than methylthio



Scheme 44 Catalyzed cyclization of 4-pentyn-1-amine.



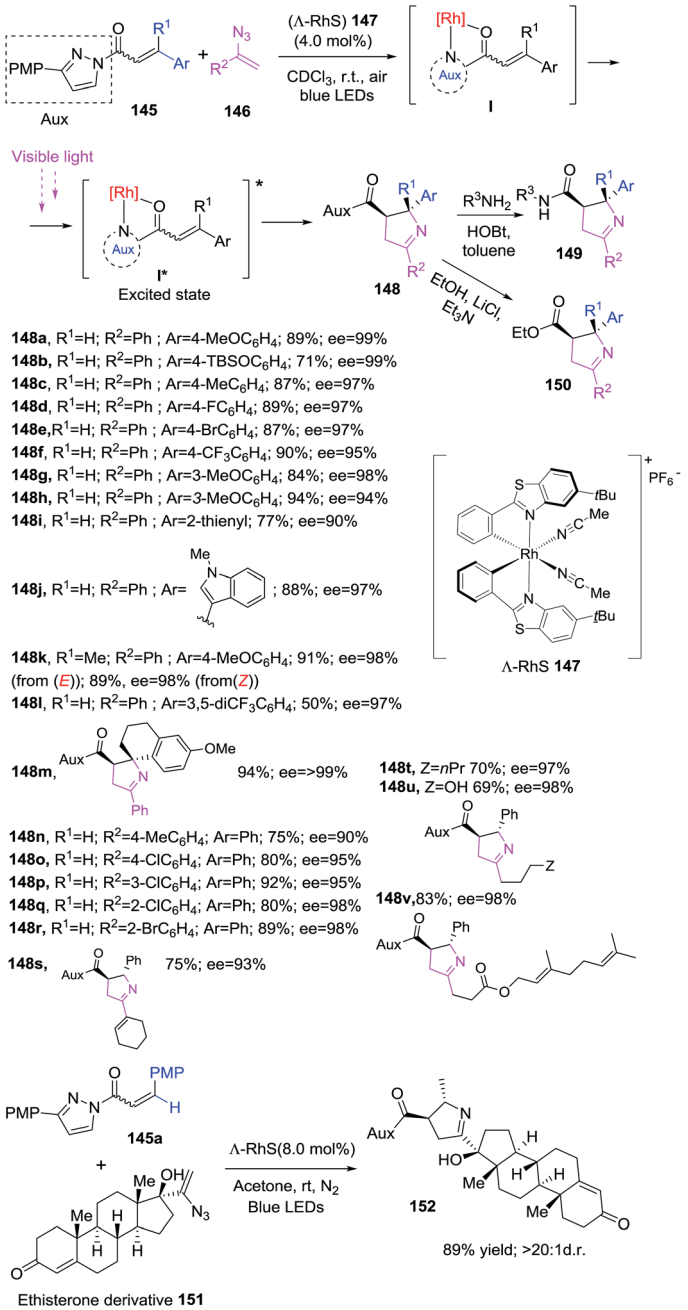
Scheme 45 Catalyzed cyclization of non-terminal alkynamines.



Scheme 46 Pyrroline synthesis from the combination of S-chelating aldehydes and allylic amines.

and disubstituted alkenes were not reactive under these conditions.

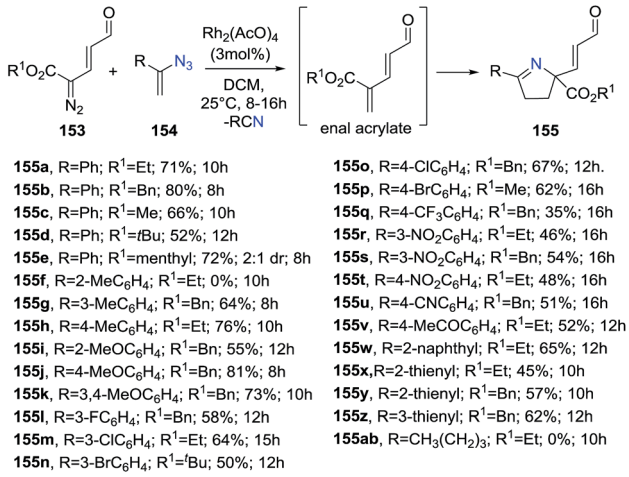
The Meggers group reported for first time a visible-light-induced [2 + 3] photocycloaddition of alkenes **145** with vinyl azides **146** using a chiral rhodium catalyst **147** to obtain enantiomeric pure 1-pyrrolines **148** (Scheme 47).[106] The protocol makes use of α,β-unsaturated *N*-acylpyrazole **145** in combination with vinyl azides **146** in presence of catalyst (Λ-RhS) **147** (4 mol%) using chloroform as solvent under irradiation of blue LEDs. As a result, 1-pyrrolines **148** were obtained in good to excellent yields (69–94%) with complete diastereoselectivity and enantioselectivities of up to >99% ee. The pyrazole auxiliary have a major impact on the reaction result, the best performance is achieved with 3-(*p*-methoxyphenyl)pyrazole (PMP). The chiral rhodium catalyst **147**, developed in Megger's group, coordinates with substrates **145** through the carbonyl oxygen and the pyrazole auxiliary. This complex **I** generates an excited intermediate **I*** upon visible-light irradiation which subsequently reacts with a vinyl azides to afford a 1-pyrrolines (Scheme 47). The methodology tolerates various β-aryl



Scheme 47 Synthesis of 1-pyrrolines using a chiral rhodium catalyst.

substituent on *N*-acylpyrazole **145** regardless the electronic nature or position as well as heteroaryl moieties and is able to provide 1-pyrrolines with quaternary stereocenter (R ≠ H). α,β-Unsaturated *N*-acylpyrazoles with *E* or *Z* configuration produce the same result. Aryl, vinyl and alkyl azides **146** successfully afforded the desired 1-pyrrolines. The good functional group tolerance was tested with a complex steroid vinyl azide derivative **151** proving the utility of the protocol in late stage synthesis. Finally, the *N*-acylpyrazole can be easily converted in other functionalities such as amide **149** or ester **150**.

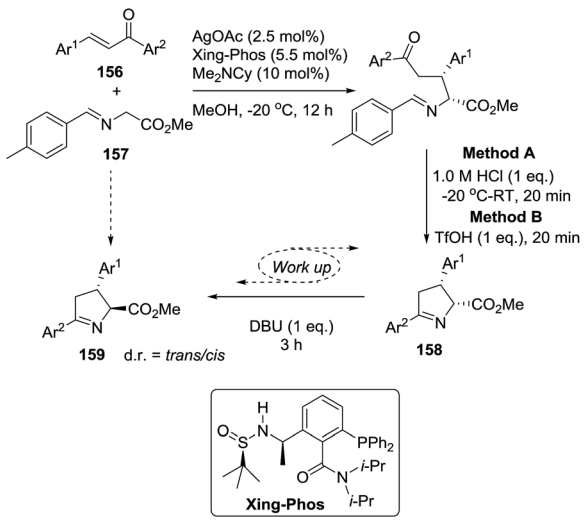
Katukojvala *et al.* discovered a new rhodium-catalyzed [1 + 1 + 3] annulation reaction of diazoenals **153** and vinyl azides **154** to generate enal-functionalized 1-pyrroline derivatives **155**



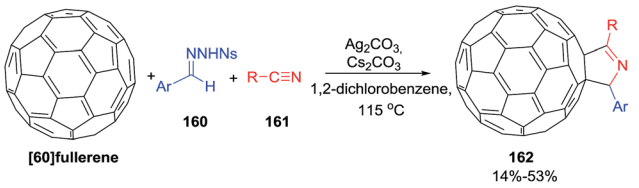
Scheme 48 Rhodium-catalyzed [1 + 1 + 3] annulation reaction to generate enal-functionalized 1-pyrrolines **155**.

(Scheme 48).[107] These functionalized 1-pyrrolines can be synthetically modified to provide further structural diversity. The reaction occurs through a rhodium-catalyzed olefination of diazoenals with vinyl azides to produce the enal acrylate and subsequent annulation to access to 1-pyrrolines. The optimized conditions involve the use of $Rh_2(OAc)_4$ as the catalyst, and of 2.5 equiv. of vinyl azides in dichloromethane at room temperature. Ethyl, benzyl, and methyl ester diazoenals **153** delivered the 1-pyrrolines in very good yields (66–80%). Regarding vinyl azides **154**, neutral and electron-rich styryl azides afforded very good yields of functionalized 1-pyrrolines (64–81%) but the used of electron-deficient styryl azides resulted in lower yields (35–54%). Thienyl azides were also compatible with the reactions conditions but aliphatic vinyl azide failed to deliver the 1-pyrrolines **155**.

2.1.8. Synthesis of 1-pyrrolines by silver catalysis. Bai *et al.*[22] reported a one-pot asymmetric Michael-type conjugate



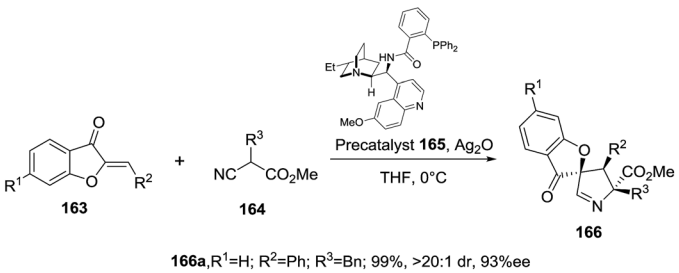
Scheme 49 Stereodivergent synthesis of *cis*- and *trans*-1-pyrrolines (**158** and **159**).

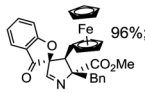
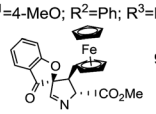


Scheme 50 Silver(I)-mediated three-component annulation reaction for the synthesis of [60]fullerene-fused 1-pyrrolines.

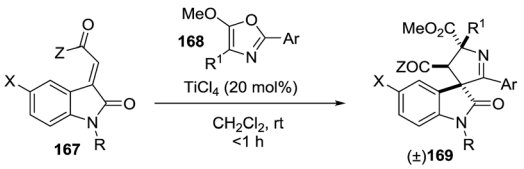
addition of glycine imino esters (**157**) to chalcones (**156**) using a Ag/Xing-Phos-catalyzed [3 + 2] cycloaddition reaction to afford stereoselectively the 1-pyrrolines **158** (Method A, Scheme 49). The combination of Ag/Xing-Phos catalyst with Me_2NCy as a base gave the best performance in term of yield (81–98%), diastereoselectivity, and enantioselectivity (up to 98% ee).

Moreover, *trans*-pyrrolines could be obtained using the same catalytic system but incorporating an epimerization protocol into the work-up conditions. Method A (HCl) gave the *cis*-pyrrolines **158** whereas the use of TfOH and DBU (Method B) led to the *trans*-pyrrolines **159** which were obtained with yields ranging from moderate to excellent (60–95%). The *trans* isomers **159** were obtained with diastereoselectivities (d.r. = *trans*/*cis* ratio) ranging from 83 : 17 d.r. −92 : 8 d.r. and enantioselectivities from 81% ee to 98% ee. This stereodivergent synthesis offers the possibility to obtain the *cis* and *trans* pyrrolines **158** and **159** as single enantiomers.



166a,R^1=H; R^2=Ph; R^3=Bn; 99%, >20:1 dr, 93%ee
166b,R^1=OMe; R^2=Ph; R^3=Bn; 99%, >20:1 dr, 93%ee
166c,R^1=Br; R^2=Ph; R^3=Bn; 95%, >20:1 dr, 94%ee
166d,R^1=H; R^2=2-ClC_6H_4; R^3=Bn; 99%, 20:1 dr, 97%ee
166e,R^1=H; R^2=2-MeC_6H_4; R^3=Bn; 99%, 20:1 dr, 94%ee
166f,R^1=H; R^2=3-ClC_6H_4; R^3=Bn; 98%, 18:1 dr, 88%ee
166g,R^1=H; R^2=3-MeOC_6H_4; R^3=Bn; 98%, >20:1 dr, 93%ee
166h,R^1=H; R^2=4-BrC_6H_4; R^3=Bn; 99%, >20:1 dr, 83%ee
166i,R^1=H; R^2=4-MeOC_6H_4; R^3=Bn; 99%, >20:1 dr, 94%ee
166j,R^1=H; R^2=1-naphthyl; R^3=Bn; 98%, >20:1 dr, 93%ee
166k,R^1=H; R^2=3-indolyl; R^3=Bn; 98%, 8:1 dr, 94%ee
166l,R^1=H; R^2=3-pyridyl; R^3=Bn; 99%, 16:1 dr, 88%ee
166m,R^1=H; R^2=2-furyl; R^3=Bn; 99%, >20:1 dr, 96%ee
166n,R^1=H; R^2=2-thienyl; R^3=Bn; 99%, >20:1 dr, 94%ee
166o,  96%; 8:1dr, 97%ee
166p,R^1=H; R^2=Ph; R^3=Me; 99%, >20:1 dr, 94%ee
166q,R^1=H; R^2=Ph; R^3=^{i}Pr; 99%, 16:1 dr, 94%ee
166r,R^1=H; R^2=Ph; R^3=^{n}Bu; 99%, >20:1 dr, 97%ee.
166s,R^1=H; R^2=Ph; R^3=$CH_2CH_2CO_2Me$; 98%, >20:1 dr, 96%ee
166t,R^1=H; R^2=Ph; R^3=cyclohexyl; 96%, 17:1 dr, 97%ee
166u,R^1=H; R^2=Ph; R^3=allyl; 99%, >20:1 dr, 94%ee
166v,R^1=H; R^2=Ph; R^3=4-MeOC_6H_4; 90%, 5:1 dr, 85%ee
166w,R^1=H; R^2=4-BrC_6H_4; R^3=4-MeOC_6H_4; 78%, 5:1 dr, 90%ee
166x,R^1=H; R^2=Ph; R^3=H; 83%, 7:1 dr, 95%ee
166y,R^1=H; R^2=4-MeOC_6H_4; R^3=H; 88%, 9:1 dr, 98%ee
166z,R^1=H; R^2=4-BrC_6H_4; R^3=H; 82%, 9:1 dr, 99%ee
166aa,R^1=H; R^2=2-furyl; R^3=H; 87%, 5:1 dr, >99%ee
166ab,R^1=4-MeO; R^2=Ph; R^3=H; 85%, 3:1 dr, >90%ee
166ac,  90%, 5:1 dr, >99%ee

Scheme 51 Synthesis of spiro-1-pyrrolines **166** catalyzed by chiral silver complexes.



Scheme 52 Titanium(IV)-catalyzed stereoselective synthesis of spirooxindole-1-pyrrolines.

Zang and coworkers[108] used a novel three-component annulation reaction between [60]fullerene, sulfonylhydrazones **160** and nitriles **161** mediated by Ag(I) as a general entry to disubstituted [60]fullerene-fused pyrrolines **162** (Scheme 50). The reaction exhibits a broad substrate scope and excellent functional-group tolerance. As such it represents a general synthesis of fullerene-bound macromolecules.

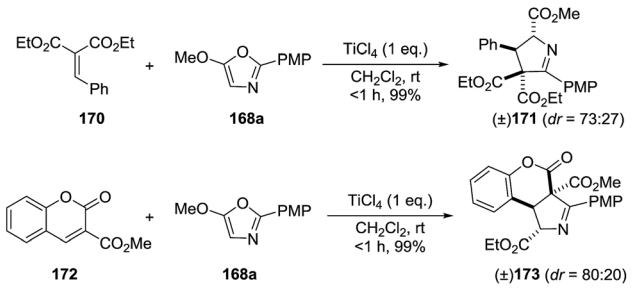
He, Shao and coworkers have recently developed the first enantioselective formal [3 + 2] cycloaddition between isocyanoacetates **164** and aurone anologues **163** catalyzed by chiral silver complexes (Scheme 51).[109] Several chiral precatalysts were tested in combination with Ag_2O under different reaction conditions to define the optimal procedure which required the use of silver oxide (10 mol%) and precatalyst **165** (20 mol%) in THF at 0 °C. The protocol is robust and simple, tolerating air and moisture. This efficient and atom-economical synthetic methodology provided a set of spiro-1-pyrrolines **166** bearing three stereocenters, with excellent yields (72–99%), and high diastero- and enantioselectivities (up to >20 : 1 and >99% ee, respectively). Interestingly, this protocol was successfully escalated up to a gram-reaction without a significant loss in yield or stereoselectivity. The mechanism is still under investigation.

Mukhopadhyay *et al.*[110] reported the silver-promoted regioselective synthesis of spiro-1-pyrrolines and spiro-2-pyrrolines (see Subsection 2.2.12.: Synthesis of 2-pyrrolines by silver catalysis, Scheme 113).

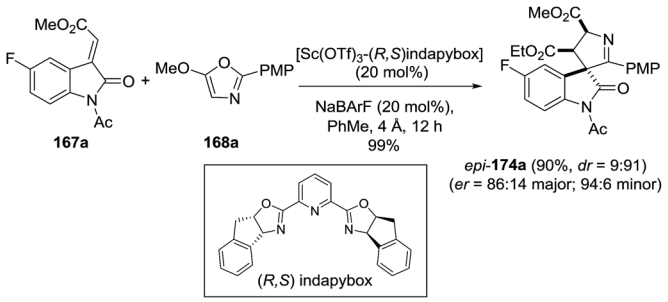
2.1.9. Synthesis of 1-pyrrolines by titanium catalysis. Franz *et al.*[111] devised access to spirocyclic oxindole 1-pyrrolines **169** in excellent yield and diastereoselectivity using a $TiCl_4$-catalyzed formal [3 + 2] cycloaddition between alkylidene oxindoles **167** and 5-alkoxy-2-aryloxazoles **168** (Scheme 52). A chelating group on the nitrogen of the indole is essential for selectivity (R = Ac, Cbz). Substitution at the 4-position of the oxazole afforded a spiro-1-pyrroline (X = F; Z = OEt; R^1 = Me; R = Ac; Ar = PMP), containing two stereogenic quaternary centers, with high diastereoselectivity (dr = 94 : 6)

They extended this methodology to the synthesis of the highly functionalized pyrrolines **171** and **173** from ethyl benzylidene malonate (**170**) and coumarin (**172**) derivatives, respectively (Scheme 53).

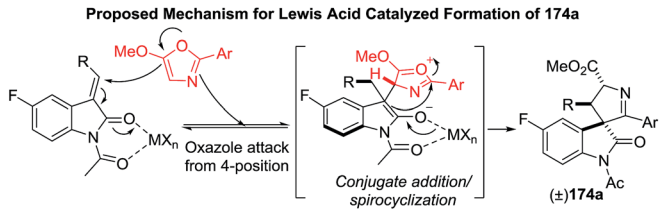
The use of a chiral scandium(III)–indapybox/BArF complex provided the enantioenriched spirooxindole-1-pyrroline **174a**



Scheme 53 Cyclization with malonate alkylidene and coumarin electrophiles.



Scheme 54 Synthesis of enantioenriched pyrroline *epi*-**174a**.



Scheme 55 Proposed mechanism for Lewis acid catalyzed spirooxindole-1-pyrrolines.

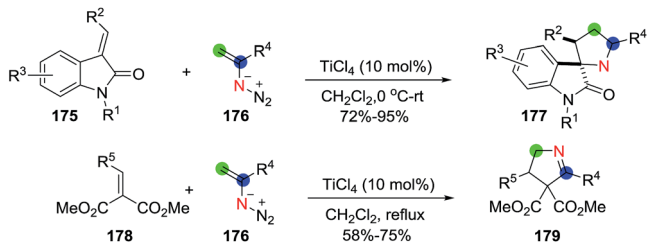
(86 : 14 er), and a ligand-induced reversal of diastereoselectivity was observed (Scheme 54).

The proposed mechanism is depicted in the Scheme 55.

Chiba *et al.*[112] carried out a $TiCl_4$-catalyzed addition of vinyl azides (**176**) onto α,β-unsaturated carbonyl compounds to construct the 1-pyrroline (Scheme 56). Employing 3-alkylidene-2-oxoindoline (**175**) as the α,β unsaturated carbonyl and $TiCl_4$ (10 mol%), the 1-pyrroline-containing spiro structures **177** were obtained in excellent yields (72–95%). When a 2-alkylidenemalonate (**178**) was used, a series of 1-pyrrolines with various aryl, alkenyl and alkyl motifs (**179**) were obtained in satisfactory yields (58–75%). The proposed mechanism involves titanium-catalyzed conjugate addition of vinyl azides to the α,β unsaturated carbonyl and subsequent denitrogenative ring-expansion of the transient azidocyclobutane intermediates formed to obtain the 1-pyrroline ring.

2.2. Synthesis of 2-pyrrolines

The 2-pyrrolines ring is found in many biologically-active compounds (Fig. 4). Notable examples include the cytotoxin



Scheme 56 Titanium-catalyzed construction of 1-pyrrolines using vinyl azides.

spirotryprostatin B (**180**, showing complete inhibition of the cell cycle progression of tsFT210 cells in the G2/M phase and growth inhibition toward leukemia K562 and HL-60 cells);[7] the antibiotic and cytotoxin anthramycin (**181**, produced by *Streptomyces refuineus*);[8] and the synthetic, highly substituted racemic 2-pyrroline **182** demonstrated to have antiproliferative activity.[16]

An example of 2-pyrroline used as an intermediate towards a more complex heterocycle was described by Knolker *et al.*[30] The antibiotics pentabromopseudilin **187a** and pentachloropseudilin **187b** were synthesized in seven steps from the benzaldehydes **183a** and **183b** respectively (Scheme 57). Both syntheses made use of a silver(I)-catalyzed cyclization of *N*-tosylhomopropargylamines **184a** and **184b** that led to 2-pyrrolines **185a** and **185b**. These pyrrolines were oxidized to the pyrroles **186a** and **186b** which were finally transformed in pentabromo- (**187a**) and pentachloropseudilin (**187b**) in 23% and 19% overall yield, respectively.

2.2.1. Synthesis of 2-pyrrolines by copper catalysis. Zhu *et al.* described the copper-catalyzed oxidative cyclization of

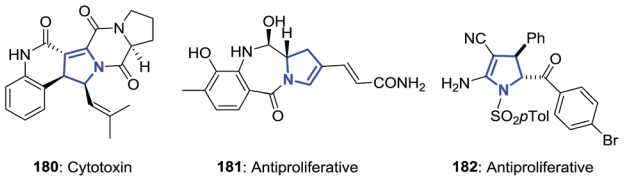
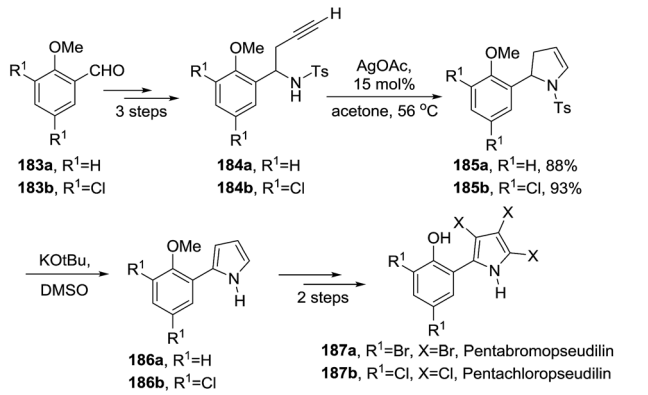
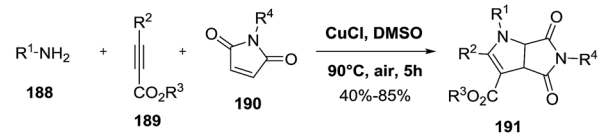


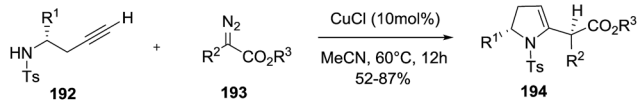
Fig. 4 Selected examples of biologically active 2-pyrrolines.



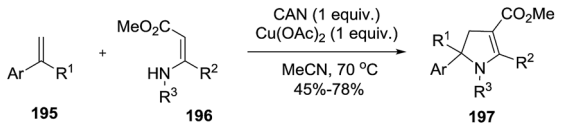
Scheme 57 Synthesis of pentabromopseudilin **187a** and pentachloropseudilin **187b** through the 2-pyrrolines **186a** and **186b**, respectively.



Scheme 58 Cu-catalyzed synthesis of fully substituted 2-pyrrolines.



Scheme 59 Copper-catalyzed tandem annulation towards 2-pyrrolines.

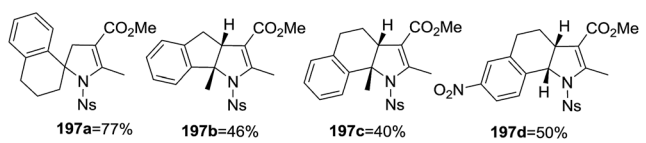


Scheme 60 Oxidative radical cyclization of *N*-sulfonyl β-enamino esters with alkenes towards 2-pyrrolines.

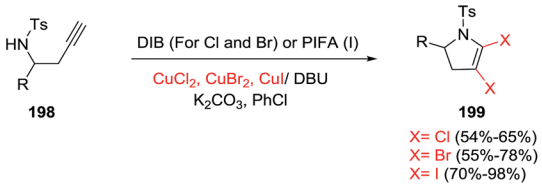
maleimides **190** with different amines **188** and alkynyl esters **189** to give a variety of 2-pyrrolines **191** (Scheme 58).[113] CuCl in dimethylsulfoxide (DMSO) at 90 °C in presence of air were the most effective conditions. The presence of oxygen in the reaction medium was necessary to effect the transformation. The reaction has a good tolerance towards different functional groups, allowing both N-protected and free NH maleimide, amines containing electron-donating and electron-withdrawing substituents, and alkyl- as well as aryl-substituted alkynyl esters. In all cases, the desired product was obtained in good to moderate yield (40–85%). A radical mechanism was proposed.

Sun *et al.* reported the copper-catalyzed 5-*exo-dig* hydroamination of homopropargyl sulfonamides **192** with diazo compounds **193** to give 2-pyrrolines **194** (Scheme 59).[114] The possible first step involves formation of allenoate intermediates by metal-catalyzed cross-coupling of an alkyne with diazo compounds which then undergo a 5-*exo-dig* intramolecular hydroamination.

When chiral homopropargyl sulfonamides with a variety of substituent adjacent to the N-atom are subjected to the optimal reaction conditions (10 mol% CuCl in acetonitrile), 2,5 disubstituted 2-pyrrolines are obtained with good yields (52–87%) and good diasteroselectivity (dr typically 4 : 1). A library of twenty-four 2,5-disubstituted 2-pyrrolines **194** was synthesized.



Scheme 61 Spirocyclic and tricyclic dihydropyrrole obtained by the reaction with cyclic alkenes.

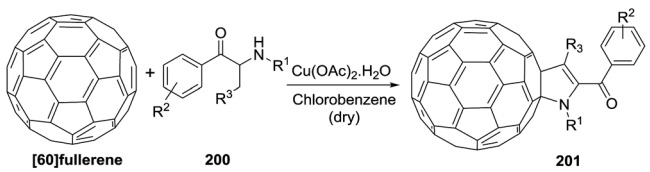


Scheme 62 Transformation of homopropargyl sulfonamides into dihalo-2-pyrrolines.

An alternative synthesis of multi-substituted 2-pyrrolines **197** was described by Yoshida *et al.* in 2016 (Scheme 60).[115] They reported the oxidative radical cyclization of *N*-sulfonyl β-enamino esters **196** with different aryl-substituted alkenes **195**. When cyclic alkenes are used, spirocyclic and tricyclic dihydropyrroles like **197a**, **197b**, **197c**, and **197d** were obtained (Scheme 61). Under optimal conditions with ceric ammonium nitrate and $Cu(OAc)_2$ as oxidants, the desired products were obtained in moderate to high yields (45–78%).

In 2017, the Xiang research group reported the synthesis of 4,5-dihalo-substituted 2,3-dihydropyrroles **199** from a variety of homopropargyl sulfonamides **198** (Scheme 62).[116] This transformation uses two equivalents of copper halides and one equivalent of a hypervalent iodine compound, in the presence of an organic base (such as DBU) and an inorganic base (such as K_2CO_3) in chlorobenzene as the solvent. The combination of CuI and PIFA gives the 2,3-dihydro-4,5-diiodopyrroline products. The dibromopyrrolines (dichloropyrrolines) are obtained using $CuBr_2$ ($CuCl_2$) and oxidant DIB [$PhI(OAc)_2$]. A breadth of different aromatic, heteroaromatic, and alkyl-substituted alkynyl amines under the former conditions give the diiodopyrrolines in very good to excellent yields, defining a broad scope to the reaction. In general, the diiodopyrrolines were obtained in higher yields than the dibromopyrroline, with the dichloropyrroline obtained in the lowest yield.

Wang *et al.* reported a copper-catalyzed synthesis of 2-fulleropyrrolines **201** bearing a trisubstituted or a tetrasubstituted C=C bond promoted by copper from α-amino ketones **200** and



201a,R^1=Ph; R^2=H; R^3=H; 5h; 34%
201b,R^1=2-MeC_6H_4; R^2=H; R^3=H; 5h; 34%
201c,R^1=3-MeC_6H_4; R^2=H; R^3=H; 5h; 33
201d,R^1=4-MeC_6H_4; R^2=H; R^3=H; 5h; 31%
201e,R^1=4-$MeOC_6H_4$; R^2=H; R^3=H; 3h; 34%
201f,R^1=4-ClC_6H_4; R^2=H; R^3=H; 5h; 31%
201g,R^1=3,5-*di*-MeC_6H_3; R^2=H; R^3=H; 3h; 40%
201h,R^1=3,5-*di*-MeC_6H_3; R^2=4-Me; R^3=H; 3h; 37%
201i,R^1=*i*Pr; R^2=H; R^3=H; 3h; 17%
201j,R^1=Ph; R^2=H; R^3=Me; 3h; 18%
201k,R^1=3,5-*di*-MeC_6H_3; R^2=H; R^3=Me; 3h; 22%
201l,R^1=Ph; R^2=H; R^3=Ph; 3h; 40%
201m,R^1=3,5-*di*-MeC_6H_3; R^2=H; R^3=Ph; 3h; 43%

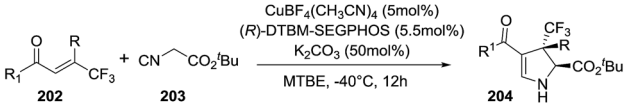
Scheme 63 Synthesis of 2-fulleropyrrolines **201**.

[60]fullerene (Scheme 63).[117] This is the first synthesis of a 2-fulleropyrrolines with $R^3 = H$. The yields are in the range of 17% to 43%.

Recently, Zhang *et al.* disclosed an enantioselective [3 + 2] cycloaddition synthesis of 2-pyrrolines **204** bearing a trifluoromethylated all-carbon quaternary stereocenter from α-*tert*-butyl isocyanoacetates **203** and β-trifluoromethyl β,β-disubstituted enones **202** in the presence of a copper catalysis (Scheme 64).[118] The combination of $Cu(CH_3CN)_4BF_4$ and the chiral ligand (*R*)-DTBM-SEGPHOS provided high diastereoselectivities (>20 : 1) and enantioselectivities (50–96% ee) along with very good yields (57–99%). The protocol tolerates a variety of enones **202** bearing electron-rich or -poor substituted aryl groups (R^1) but good diasteroselectivities are only obtained when R = Me. The presence of the β-trifluoromethyl group in the enone **202** is necessary for attaining high reactivity and stereocontrol.

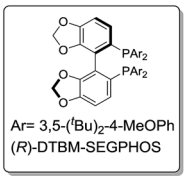
Fan *et al.* reported a copper-catalyzed cascade reaction synthesis of 3-acyl-2-pyrrolines **207** from pyrrolidines **205** and 2-oxo-2-arylacetic acids **206** (Scheme 65).[119] The reaction is believed to occur through a $C(sp^3)$–H bond dehydrogenation of the pyrrolidine to give an enamine intermediate which is subsequently cross-coupled with the acyl species coming from the decarboxylation of 2-oxo-2-arylacetic acid **206**. It is postulated that the copper catalyst plays an essential role in the dehydrogenation, decarboxylation and cross coupling steps. *N*-Aryl substituted pyrrolidines **205** and various 2-oxo-2-arylacetic acids **206** deliver the 3-acyl-2-pyrrolines **207** in good yields (58–68%). *N*-Alkyl substituted pyrrolidines give pyrroles instead of 3-acyl-2-pyrrolines.

2.2.2. Synthesis of 2-pyrrolines by gold catalysis. The Rutjes group developed an enantioselective gold-catalyzed 5-*endo-dig* cyclization into the 2,3-dihydro-3-hydroxy-substituted 2-pyrrolines **209** using the alkynyl-substituted amino alcohols **208** as

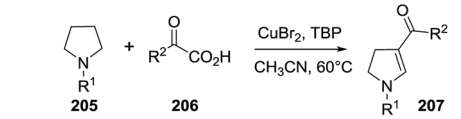


202 203 204

204a, R=Me; R^1=4-ClC_6H_4; >20:1; *ee*=93%; 94%
204b, R=Me; R^1=4-BrC_6H_4; >20:1; *ee*=94%; 80%
204c, R=Me; R^1=4-FC_6H_4; >20:1; *ee*=90%; 85%
204d, R=Me; R^1=4-$NO_2C_6H_4$; >20:1; *ee*=90%; 99%
204e, R=Me; R^1=4-CNC_6H_4; >20:1; *ee*=94%; 91%
204f, R=Me; R^1=4-$CF_3C_6H_4$; >20:1; *ee*=94%; 89%
204g, R=Me; R^1=4-$MeO_2CC_6H_4$; >20:1; *ee*=93%; 85%
204h, R=Me; R^1=4-$CH_3C_6H_4$; >20:1; *ee*=91%; 79%
204i, R=Me; R^1=4-$MeOC_6H_4$; >20:1; *ee*=93%; 68%
204j, R=Me; R^1=4-PhC_6H_4; >20:1; *ee*=96%; 87%
204k, R=Me; R^1=C_6H_4; >20:1; *ee*=90%; 70%
204l, R=Me; R^1=3,4-$Cl_2C_6H_4$; >20:1; *ee*=93%; 85%
204m, R=Me; R^1=2-naphthyl; >20:1; *ee*=90%; 71%
204n, R=Me; R^1=2-furyl; >20:1; *ee*=90%; 76%
204o, R=Et; R^1=4-ClC_6H_4; 6:1; *ee*=90%; 98%
204p, R=Bu; R^1=4-ClC_6H_4; 6:1; *ee*=90%; 76%
204q, R=Ph; R^1=4-ClC_6H_4; 7:1; *ee*=94%; 76%
204r, R=4-ClC_6H_4; R^1=4-ClC_6H_4; 6:1; *ee*=93%; 74%
204s, R=4-FC_6H_4; R^1=4-ClC_6H_4; 7:1; *ee*=95%; 75%
204t, R=4-$CF_3C_6H_4$; R^1=4-ClC_6H_4; 7:1; *ee*=95%; 70%
204u, R=4-$MeOC_6H_4$; R^1=4-ClC_6H_4; >20:1; *ee*=82%; 57%
204v, R=Me; R^1=cyclohexyl; 6:1; *ee*=61%; 77%
204w, R=Me; R^1=$PhCH_2CH_2$; 5:1; *ee*=50%; 67%



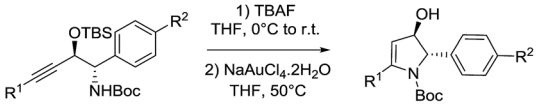
Scheme 64 Synthesis of 2-pyrrolines **204** by enantioselective [3 + 2] cycloaddition.



205 206 207

207a, R^1=Ph; R^2=Ph; 68%
207b, R^1=4-ClC_6H_4; R^2=Ph; 67%
207c, R^1=3,5-*di*-MeC_6H_3; R^2=Ph; 61%
207d, R^1=Ph; R^2=3-MeC_6H_4; 58%
207e, R^1=Ph; R^2=3-BrC_6H_4; 64%
207f, R^1=Ph; R^2=4-MeC_6H_4; 62%
207g, R^1=Ph; R^2=4-ClC_6H_4; 58%
207h, R^1=Ph; R^2=4-BrC_6H_4; 60%.

Scheme 65 Copper-catalyzed synthesis of 3-acyl-2-pyrrolines **207**.



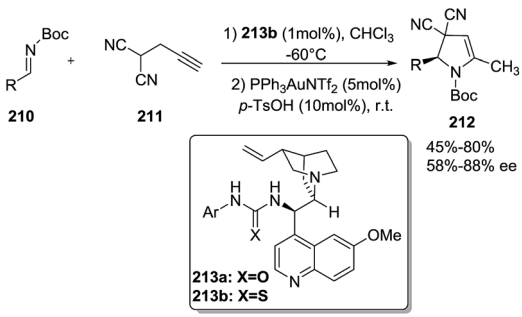
208 209

209a, R^1=Ph; R^2=H; *R,S* (87%)
209b, R^1=Ph; R^2=F; *R,S* (80%)
209c, R^1=4-$MeOC_6H_4$; R^2=F; *S,R* (91%)
209d, R^1=3-$MeOC_6H_4$; R^2=H; *S,R* (81%)
209e, R^1=3-$MeOC_6H_4$; R^2=F; *S,R* (82%)
209f, R^1=3-$MeOC_6H_4$; R^2=Cl; *S,R* (79%)
209g, R^1=4-FC_6H_4; R^2=Cl; S,R (76%)
209h, R^1=3-piperonyl; R^2=H; *S,R* (83%)

Scheme 66 Gold-catalyzed cyclization of substituted alkyne-containing amino alcohols towards 2-pyrrolines.

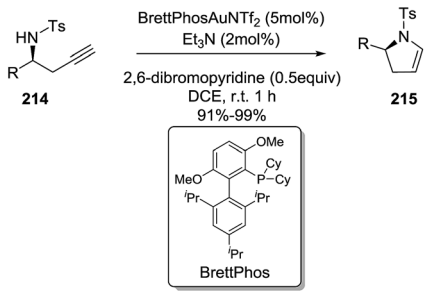
the starting material (Scheme 66).[120] This starting material originated through enzyme-catalyzed hydrocyanation of the α,β-acetylenic aldehydes. Deprotection of the hydroxyl group with TBAF followed by reaction with $NaAuCl_4 \cdot 2H_2O$ (10 mol%) in THF at 50 °C gave the 4-hydroxy-2-pyrrolines **209** in good yields over the two steps.

Jørgensen reported[121] an enantioselective synthesis of 2-pyrrolines **212** from propargyl malononitrile (**211**) and *N*-Boc-protected imines **210** through an organocatalytic Manich-type reaction followed by gold-catalyzed alkyne hydroamination and subsequent isomerization (Scheme 67). This one-pot sequential protocol that combine transition-metal catalysis with organocatalysis furnished the 2-pyrrolines **212** in good yields (up to 80%), high selectivities *endo*/*exo* (10 > 1), and enantioselectivities up to 88%. The protocol works only for terminal alkynes. Once the organocatalyst **213b** forms the Mannich product, the latter is protonated by the excess of *p*-TsOH, and in this way deactivation of the gold catalyst is prevented. The two catalytic systems are compatible with one-pot operation.



210 211 212

Scheme 67 Asymmetric one-pot sequential organo- and gold catalysis for the enantioselective synthesis of 2-pyrrolines **212**.

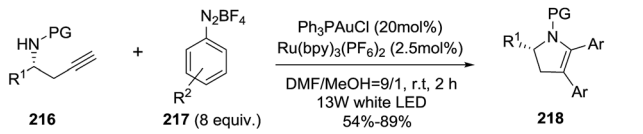


Scheme 68 Enantioselective synthesis of 2-pyrrolines *via* gold-catalyzed cycloisomerization of chiral homopropargyl sulfonamides.

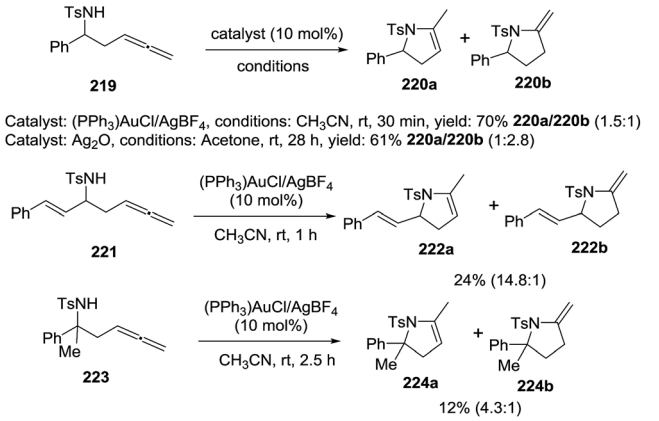
Ye *et al.* reported an enantioselective gold-catalyzed synthesis of 2-pyrrolines **215** from chiral homopropargyl sulfonamides **214** using a combination of bases as catalytic additives.[122] The intramolecular hydroamination occurs *via* a 5-*endo-dig* cyclization, through an anti-Markovnikov addition. The optimal reaction conditions use BrettPhos·$AuNTf_2$ (5 mol%), a combination of Et_3N (2 mol%) and 2,6-dibromopyridine (0.5 equivalent) as the basic additives, in 1,2-dichloroethane at room temperature (Scheme 68). The 2,3-dihydropyrroles **215** are isolated in excellent yields and without epimerization of the stereocenter. This practical procedure offers a route to both 2-pyrrolines enantiomers, simply by selecting the starting chiral homopropargyl sulphonamides (*R* or *S*) **214**. The reaction showed wide generality. Diversely substituted homopropargyl sulfonamides produced the 2-pyrrolines in excellent yields (91–99%).

Later, the same group reported an enantioenriched access to multisubstituted 2-pyrrolines **218** by a combination of gold catalysis and visible-light photoredox catalysis.[123] Using different chiral homopropargyl sulfonamides **216** and a variety of aryldiazonium salts **217** in the presence of Ph_3P·AuCl and a visible light photocatalysts such $Ru(bpy)_3(PF6)_2$, and irradiating with 13 W white LEDs, a bis-arylative 5-*endo-dig* cyclization led to enantioenriched 2,3-dihydropyrroles with high enantiomeric excesses (96–99% ee) and moderate yields (54–89%) (Scheme 69). The proposed mechanism is an Au(I)/Au(III) redox cycle accomplished by visible-light photoredox catalysis, without using a strong oxidant, and accomplished in a mild and selective manner.

Pyne *et al.* reported the cyclization of β-amino allenes **219** by gold and silver catalysis to afford the pirrolines **220a** *via* a 5-*endo-dig* cyclization to **220b** and subsequent isomerization to the more stable isomer **220a** (Scheme 70).[124] Under gold catalysis, the optimal conditions consist of using 10 mol% of $(PPh_3)AuCl/AgBF_4$ in acetonitrile at room temperature. β-amino allenes **219** provided the pyrroline **220a** and the pyrrolidine **220b** with 70% isolated yield in a ratio (**220a**/**220b** = 1.5 : 1). Treating the same allene with Ag_2O in acetone a room temperature generated a mixture **220a**/**220b** = 1 : 1.28 in 61% overall yield. The β-amino allene **221**, substituted with the conjugated cinnamyl group, was subjected to the optimized gold catalyzed conditions obtaining a mixture between the pyrroline **222a** and pirrolidine **222b** in low yield but favoring the



Scheme 69 Dual photoredox/gold catalysis towards enantioenriched 2-pyrrolines.



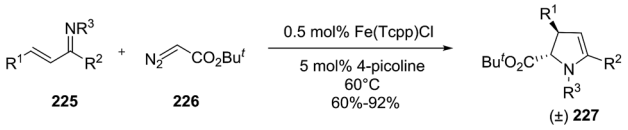
Scheme 70 Gold- and silver-catalysed cyclisation reactions of β-amino allenes.

formation of **222a**. Under optimized conditions, the β,β-disubstituted allene **223** produced the pyrroline **224a** and the isomer **224b** in low yield (12%) in a ratio **224a**/**224b** = 4.3 : 1.

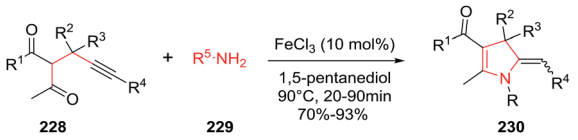
Hou *et al.*[125] have studied the gold and palladium catalyzed intramolecular hydroamination of *N*-(3-butynyl) sulfonamides leading to 2,3-dihydropyrroles (see Scheme 83, Subsection 2.2.7.: Synthesis of 2-pyrrolines by palladium catalysis).

2.2.3. Synthesis of 2-pyrrolines by iron catalysis. Tang *et al.* reported the diastereoselective synthesis of *trans*-2,3-disubstituted 2-pyrrolines **227** from α,β-unsaturated imines **225** and alkyl diazoacetate **226** in presence of catalytic tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(Tcpp)Cl) and 4-picoline (Scheme 71).[126] The formal [4 + 1] annulations occur *via* an iron carbenoid intermediate, which is readily available from alkyl diazo acetate. The yields are ranging from 60% to 92% with diastereoselectivities higher than 50 : 1.

The development of iron-catalyzed organic reactions is attractive since iron is an abundant, cheap, environmentally friendly, and efficient catalyst. In 2014, Bi *et al.* described the $FeCl_3$ catalyzed stereoselective synthesis of 5-(aryl)alkylidene-4,5-dihydropyrroles **230** through a [4C + 1N] cyclization of 4-alkynyl ketones **228** with primary amines **229** (Scheme 72).[127]



Scheme 71 Diastereoselective synthesis of 2-pyrrolines *via* a catalytic formal [4 + 1] annulations.



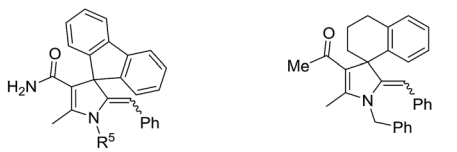
228 229 230

Scheme 72 Iron-catalyzed [4C + 1N] cyclization of 4-acetylenic ketones with primary amines.

The optimized conditions used $FeCl_3$ (10 mol%) in 1,5-pentanediol at 90 °C. The protocol tolerates a wide range of 4-alkynyl ketones to give the multisubstituted 2-pyrroline **230** in very good to excellent yields (70–93%) and high stereoselectivities (*Z*/*E* ratio typically 1 : 0.05). The *Z*-isomer of the exocyclic alkene dominates the product mixture. The procedure is also useful to obtain 3-spirodihydropyrroles **230a** and **230b** from the cyclization of 4-alkynyl ketones containing a cyclic quaternary carbon center, again using primary amines to initiate the cyclization (Scheme 73).

Recently, the Rueping group reported an intramolecular hydroamination of α-allenic amines **231** to 2-pyrrolines **233** catalyzed by an air- and moisture-stable iron cyclopentadienone complex (Scheme 74).[128] The protocol consists in adding 5 mol% of iron complex **232** and 6 mol% of trimethylamine *N*-oxide to Cbz-allenic amines **231** in THF at 70 °C for 24 h. The yields obtained varied from 57% to 86% of the 2-pyrrolines **233**.

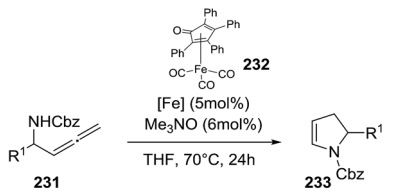
2.2.4. Synthesis of 2-pyrrolines by iridium catalysis. Zhang *et al.* described an iridium-catalyzed synthesis of 2-pyrrolines **236** from vinylaziridines **234** and α-unsubstituted 1,3-dicarbonyls **235** through a domino-ring-opening cyclization in good



230a
R^5=Bn, 86% (*Z*/*E*=1:0.12)
R^5=cyclopropyl, 75% (*Z*/*E*=1:0.08)

230b
78% (*Z*/*E*=1:0.08)

Scheme 73 Synthesis of 3-spiro 2-pyrrolines by Fe-catalyzed [4C + 1N] cyclization.



231 232 233

233a, R^1=Ph; 82%
233b, R^1=*p*-ClC_6H_4; 78%
233c, R^1=*p*-FC_6H_4; 86%
233d, R^1=*p*-$CF_3C_6H_4$; 81%
233e, R^1=*p*-BrC_6H_4; 60%
233f, R^1=*o*-ClC_6H_4; 74%
233g, R^1=*p*-MeC_6H_4; 69%
233h, R^1=Naphthyl; 81%
233i, R^1=$(CH_2)_4CH_3$; 57%
233j, R^1=$(CH_2)_2Ph$; 82%
233k, R^1=ciclohexyl; 67%
233l, R^1=CH_2OBn; 60%

Scheme 74 Iron-catalyzed hydroamination of α-allenic amines **231** towards 2-pyrrolines **233**.

234 235 236

236a, R^1=Ts; R^2= Me; R^3=H; R^4=Me; 85%
236b, R^1=Ts; R^2= CF_3; R^3=H; R^4=Me; 60%
236c, R^1=Ts; R^2= *n*-Bu; R^3=H; R^4=Me; 84%
236d, R^1=Ts; R^2= *i*-Pr; R^3=H; R^4=Me; 82%
236e, R^1=Ts; R^2=C_6H_5; R^3=H; R^4=Me; 89%
236f, R^1=Ts; R^2=4-ClC_6H_4; R^3=H; R^4=Me; 72%
236g, R^1=Ts; R^2=H; R^3=H; R^4=Me; 66%
236h, R^1=Ts; R^2=4-$MeOC_6H_4$; R^3=H; R^4=Me; 88%
236i, R^1=Ns; R^2=H; R^3=H; R^4=Me; 62%
236j, R^1=Ms; R^2=H; R^3=H; R^4=Me; 55%
236k, R^1=Ts; R^2=Me; R^3=Me; R^4=Et; 61%
236l, R^1=Ts; R^2=Me; R^3=H; R^4=Et; 71%
236m, R^1=Ts; R^2=Me; R^3=H; R^4=*i*-Bu; 65%
236n, R^1=Ts; R^2=Me; R^3=H; R^4=Cpr; 49%
236o, R^1=Ts; R^2=Me; R^3=H; R^4=OEt; 54%

Scheme 75 Reaction between vinylaziridines **234** and 1,3-dicarbonyls **235** towards 2-pyrrolines **235**.

yields (49–89%)(Scheme 75).[129] The reaction conditions involve the use of 5 mol% of $[Ir(COD)Cl]_2$, 10 mol% of $AgSbF_6$ as additive in dichloroethane at room temperature for 2 h. Alkyl or aryl substituents on the vinylaziridine (R^2) are well tolerated. Regarding the N-protecting group (R^1), tosyl, nosyl and mesyl provide the 2-pyrrolines with similar yields. Symmetrical and unsymmetrical 1,3 diketones produced the corresponding 2-pyrrolines with excellent regioselectivity. β-ketoesters are suitable substrates.

2.2.5. Synthesis of 2-pyrrolines promoted by manganese. Zheng *et al.* disclosed the first oxidative cyclization promoted by $Mn(OAc)_3$ to access to polysubstituted 2-pyrrolines **240** from anilines **237**, alkynes esters **238** and alkenes **239** (Scheme 76).[130] This free radical multi-component reaction consists in adding 2 equiv. of $Mn(OAc)_3$ to the three substrates in DMSO at 80 °C. The reaction accepts a broad scope of anilines furnishing 2-pyrrolines in good to excellent yields irrespective of the electronic nature or position of substituent. Regarding the alkenes **239**, the methodology displays a broad scope for terminal olefins with yields ranging from 60% to 91%. Alkyl amines and 1,2 disubstituted alkenes fails to delivers the 2-pyrrolines.

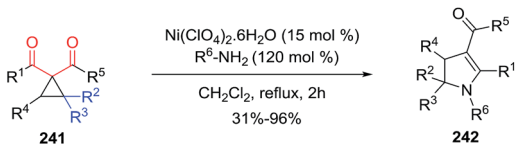
2.2.6. Synthesis of 2-pyrrolines by nickel catalysis. France *et al.*[131] developed a general synthetic approach to 4-carboxy- and 4-keto-2,3-dihydropyrroles **242** using $Ni(ClO_4)_2 \cdot 6H_2O$ as

237 238 239 240

240a, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=Ph; 85%
240b, R^1=4-Me; R^2=Et; R^3=H; R^4=H; R^5=Ph; 85%
240c, R^1=4-MeO; R^2=Et; R^3=H; R^4=H; R^5=Ph; 79%
240d, R^1=4-Cl; R^2=Et; R^3=H; R^4=H; R^5=Ph; 78%
240e, R^1=4-Br; R^2=Et; R^3=H; R^4=H; R^5=Ph; 76%
240f, R^1=3-Me; R^2=Et; R^3=H; R^4=H; R^5=Ph; 84%
240g, R^1=3-NO_2; R^2=Et; R^3=H; R^4=H; R^5=Ph; 60%
240h, R^1=2-Me; R^2=Et; R^3=H; R^4=H; R^5=Ph; 82%
240i, R^1=H; R^2=Me; R^3=H; R^4=H; R^5=Ph; 84%.
240j, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=4-MeC_6H_4; 84%
240k, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=4-*t*-BuC_6H_4; 79%
240l, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=4-FC_6H_4; 80%
240m, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=4-ClC_6H_4; 83%
240n, R^1=H; R^2=Et; R^3=H; R^4=H; R^5=4-BrC_6H_4; 75%
240o, R^1=H; R^2=Et; R^3=H; R^4=Me; R^5=Ph; 87%

240p, 88%
240q, 91%
240r, 0%
240s, 80%

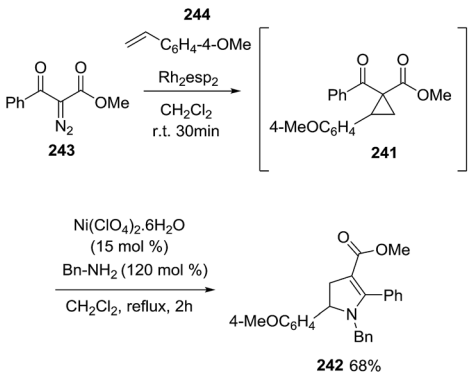
Scheme 76 Synthesis of polysubstituted 2-pyrrolines **240**.



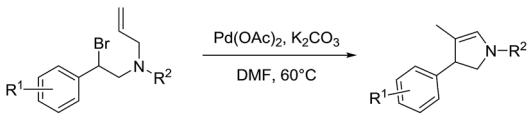
Scheme 77 Amine ring-opening cyclizations of cyclopropanes to form 2-pyrolines. Donor moiety in blue, acceptor moiety in red.

a Lewis acid catalyst *via* nucleophilic primary amine ring-opening cyclizations of donor–acceptor (D–A) cyclopropanes **241** (Scheme 77). The optimized conditions were 15 mol% of $Ni(ClO_4)_2 \cdot 6H_2O$ with 1.2 equiv. of the primary amine in refluxing CH_2Cl_2 or 1,2-dichloroethane. In this way, several primary amine nucleophiles and different substituted D–A cyclopropanes **241** provided highly substituted 2,3-dihydropyrroles **242** with an electron-withdrawing group in position four in good to excellent yields (31–96%). The particularity of 2,3 dihydropyrroles bearing an electron-withdrawing group at position four is the extended conjugation with the enamine that makes possible vinylogous reactivity.

Taking advantage of the fact that the synthesis of the D–A cyclopropanes **241** from alkenes **244** and α-diazo carbonyls **243** and the subsequent pyrroline formation are both carried out in CH_2Cl_2, the authors performed the tandem one-pot cyclopropanation/amine ring-opening cyclization to obtain the desired vinylogous 2,3-dihydropyrroles **242** in very good yield for the two steps (Scheme 78).

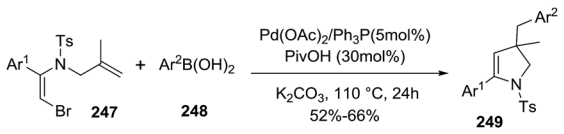


Scheme 78 One-pot tandem cyclopropanation/amine ring-opening cyclization.

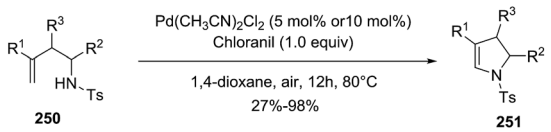


246a, R^1= H; R^2= Ts 86%
246b, R^1= *p*-Cl; R^2= Ts 83%
246c, R^1= *m*-Cl; R^2= Ts 63%
246d, R^1= *o*-Cl; R^2= Ts 43%
246e, R^1= *p*-Me; R^2= Ts 67%
246f, R^1= *p*-AcO; R^2= Ts 52%
246g, R^1= *p*-t-Bu; R^2= Ts 76%
246h, R^1= *p*-CN; R^2= Ts, 91%
246i, R^1= H; R^2= SO_2Ph 76%
246j, R^1= *p*-t-Bu; R^2= SO_2Ph, 95%

Scheme 79 Palladium-catalyzed intramolecular Heck reaction towards 2-pyrrolines.



Scheme 80 Palladium-catalyzed tandem synthesis of 2-pyrrolines.



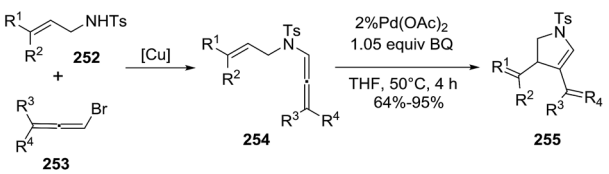
R^1= Aryl, COOR
R^2= (Hetero)Aryl, Alkyl, Alkenyl
R^3= H, Me

Scheme 81 Pd-promoted intramolecular oxidative amination towards 2-pyrrolines.

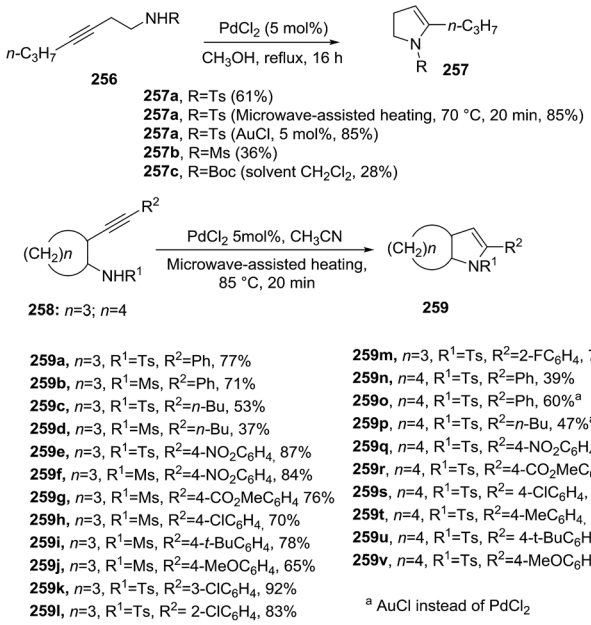
2.2.7. Synthesis of 2-pyrrolines by palladium catalysis. A broad variety of approaches towards the synthesis of 2-pyrrolines using palladium catalysts has been developed. Several of these involve the cyclization of alkenyl-substituted amines. In particular, bromoalkenyl amines provide the 2-pyrroline *via* Pd-catalysis of the intramolecular Heck reaction. For instance, Pan *et al.*[132] described a ligand-free palladium catalyst for the cyclization of secondary benzylic bromides bearing β-hydrogens **245** (Scheme 79). The optimal reaction conditions were $Pd(OAc)_2$ (1 mol%) and K_2CO_3 in DMF at 60 °C for 24 h. The desired 2-pyrrolines **246** were obtained with moderate to excellent yields and with high regioselectivities. Suitable substrates included different aromatic substituents, as well as various *N*-sulfonyl amines.

A variety of 2-pyrrolines **249** derivatives were synthesized from the reaction of vinyl bromide **247** with arylboronic acids **248** by a palladium-catalyzed tandem intramolecular Heck/intermolecular Suzuki cross-coupling reaction (Scheme 80).[133] The optimized conditions were 5 mol% of $Pd(OAc)_2$, 5 mol% of PPh_3, 2 equiv. K_2CO_3 and 30 mol% of pivalic acid in *N*,*N*-dimethylacetamide at 110 °C for 24 hours. The 2-pyrrolines **249** were obtained in moderate to good yields (typically 52–66%).

Loh *et al.*[134] described the use of *N*-homoallyl-*N*-tosyl amines **250** to generate multisubstituted dihydropyrroles **251** *via* direct amination of the alkene (Scheme 81). The optimal reaction conditions of this oxidative amination used $Pd(CH_3CN)_2Cl_2$ (10 mol%) and chloranil (1 equiv.) as the oxidant in 1,4-dioxane, at 80 °C for 24 h under air atmosphere. Different derivatizations at several positions (R^1–R^3) achieved the pyrroline with



Scheme 82 Carbocyclization of aza-enallenes **254** promoted by [Pd].

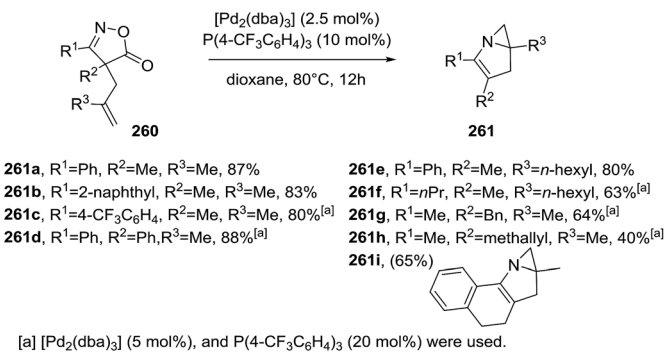


Scheme 83 Pd-catalyzed intramolecular hydroamination of *N*-(3-butynyl) sulfonamides towards mono and bicyclic 2-pyrrolines.

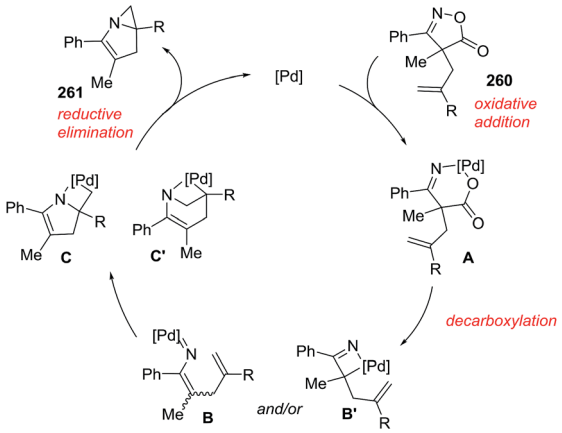
moderate to high yield (27–98%), proving the versatility of the reaction. Notably, the 5-*endo-trig* cyclization proceeded efficiently when the alkenes were substituted with electron-withdrawing groups at R^1 position. On the contrary, when R^1 is a long alkyl chain the annulations did not take place.

Bäckvall reported the carbocyclization of aza-enallenes **254** in the presence of catalytic $Pd(OAc)_2$ to give the 2-pyrrolines **255** (Scheme 82).[135] Several substitution patterns on both the alkene **252** and allene **253** were well tolerated, providing moderate to high yields of the final pyrrolines (64–95%) (Scheme 82).

Hou *et al.*[125] studied the Pd-catalyzed intramolecular hydroamination of *N*-(3-butynyl) sulfonamides leading to 2,3-dihydropyrroles (Scheme 83). Both *N*-substituted 3-heptynamines **256** and the cyclopentanamine (and cyclohexanamine) analogues **258** underwent 5-*endo-dig* cyclization providing 5-propyl-2,3-dihydro-1*H*-pyrroles **257a–c** and **259a–v**, respectively, with good yields (up to 92%). The optimal reaction conditions for **256** used $PdCl_2$ (5 mol%) in anhydrous methanol at reflux for



Scheme 84 Pd-catalyzed intramolecular aziridination of 4*H*-isoxazol-5-ones 1 leading to N-fused bicyclic aziridines **261**.

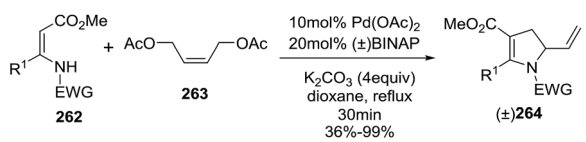


Scheme 85 Proposed mechanism for the intramolecular aziridination transformation.

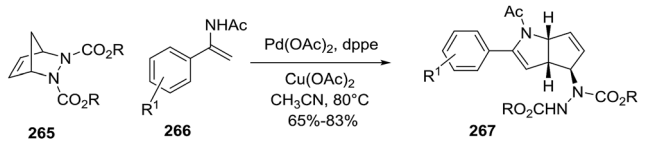
16 hours. In contrast, the amines **258** required microwave heating in acetonitrile for 20 minutes to achieve the bicyclic-2-pyrrolines **259** with higher yields. Optimum results were obtained with aryl-alkynes substituted with electron-withdrawing groups on the aromatic ring (R^2 = 4-NO_2–Ph, 3-Cl–Ph). Interestingly, the annulation of **256** into **257** and **258** into **259** proceeded efficiently in presence of AuCl catalyst.

Okamoto *et al.* developed the Pd-catalyzed intramolecular aziridination of 4*H*-isoxazol-5-ones **260** leading to *N*-fused bicyclic aziridines **261a–i** (Scheme 84) as a different approach.[136] The optimal reaction conditions used $Pd_2(dba)_3$ (2.5 mol%) and $(4\text{-}CF_3C_6H_4)_3P$ (10 mol%) in dioxane at 80 °C for 12 hours, affording the fused bicyclic structures in good yields (63–88%). Aromatic substituents at R^1 position proved to be very reactive substrates. Furthermore, the tetracyclic product **261i** was obtained in 65% yield. The proposed mechanism starts with an oxidative addition of isoxazolone **260** leading to a six-membered palladacycle **A**, which readily undergoes decarboxylation towards vinylnitrene/palladium complex **B** and/or four-membered azapalladacyclobutene intermediate **B′** (Scheme 85). Subsequent cycloaddition of these alkenes provides two possible azapalladacycles **C** and **C′**, which can undergo the reductive elimination to produce bicyclic aziridine **261**.

Palladium-mediated intermolecular strategies affording 2-pyrrolines were developed as well. As an example, Yoshida *et al.* prepared the 2-vinyl-2,3-dihydropyrroles **264** from reaction of the β-enaminocarbonyls **262** with 1,4-diacetoxy-2-butene **263**, using $Pd(OAc)_2$ as catalyst and BINAP as an additive (Scheme 86).[137] The reaction tolerates a variety of sulfonyl groups as the EWG moiety on nitrogen, and as well different alkyl and aryl



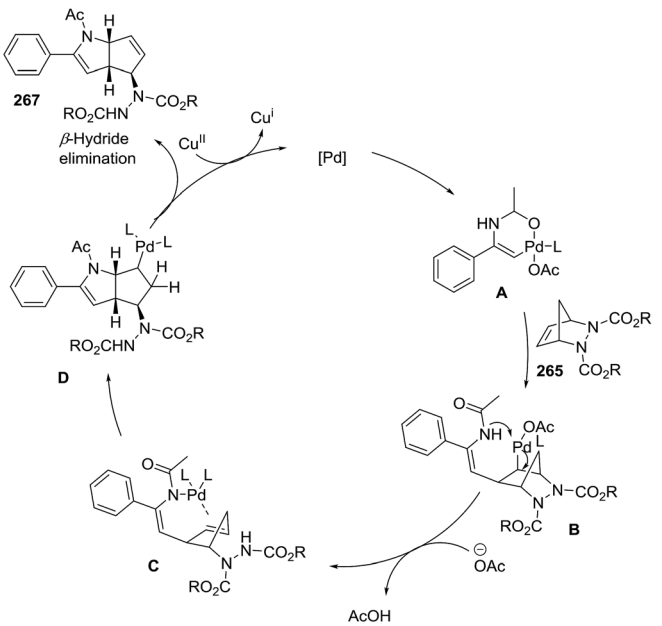
Scheme 86 Synthesis of functionalized 2-pyrrolines by oxidative radical cyclization of *N*-sulfonyl β-enamino esters with alkenes.



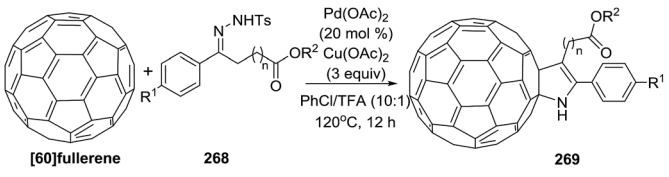
Scheme 87 Pd-catalyzed CH activation/oxidative coupling towards cyclopentene fused 2-pyrrolines.

substituents on the β-enamino ester. In addition, both *E* or *Z* 2-butene-1,4-diol bisacetates can be used to obtain 2-vinyl-2,3-dihydropyrroles **264**.

A second example of Pd-catalyzed C–H activation/oxidative is the coupling of enamides **266** with diazabicyclic olefins **265**, leading to the cyclopentane-fused N-protected 2-pyrrolines **267** (Scheme 87).[138] The optimal reaction conditions (using **265** with enamide **266**) were $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.0 equiv.), and dppe (10 mol%) in acetonitrile at 80 °C for 12 hours. In general, aryl enamides with electron-withdrawing substituents on the aromatic ring afforded the highest yields (65–83%). A plausible mechanism would include two stages (Scheme 88).

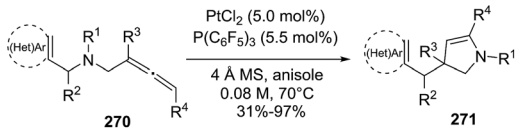


Scheme 88 Proposed mechanism for the Pd-catalyzed CH activation/oxidative coupling.



269a,R^1=H; R^2=Me; n=2; 28%
269b,R^1=H; R^2=Et; n=2; 30%
269c,R^1=H; R^2=*i*-Pr; n=2; 34%
269d,R^1=H; R^2=Me; n=1; 24%
269e,R^1=H; R^2=Et; n=1; 27%
269f,R^1=OMe; R^2=Me; n=2; 31%
269g,R^1=H; R^2=*sec*-Butyl; n=2; 43%
269h,R^1=H; R^2=Phenethyl; n=2; 37%
269i,R^1=H; R^2=Bu; n=2; 31%
269j,R^1=H; R^2=Pr; n=2; 28%
269k,R^1=F; R^2=Me; n=2; 21%
269l,R^1=F; R^2=Et; n=2; 24%

Scheme 89 Pd-catalyzed syntheses of the fulleropyrrolines **269**.



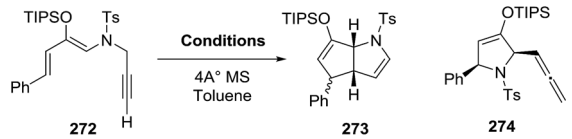
Scheme 90 Platinum-catalyzed intramolecular annulation of (hetero) aryl-allenes.

The first is C–H bond activation of the enamide **266** by $Pd(OAc)_2$ to form cyclic intermediate **A**. Coordination of the alkene **265** to **A** followed by carbopalladation would produce intermediate **B**. Aminopalladation and subsequent ring opening of **A** could generate intermediate **C**, which would furnish the bicyclic product **267** *via* a final β-hydride elimination. Reoxidation of palladium by the Cu(II) completes the catalytic cycle.

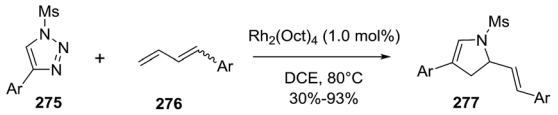
Peng *et al.* reported an efficient Pd-catalyzed synthesis of the scarce *N*-unsubstituted 2-fulleropyrrolines **269** employing [60] fullerene and benzoyl hydrazone esters **268** (Scheme 89).[139] The reaction involves the use of 20 mol% of $Pd(OAc)_2$ and 3 equivalent of $Cu(OAc)_2$ as oxidant in a solvent mixture of chlorobenzene/TFA (10 : 1) at 120 °C. The presence of TFA generates a highly electrophilic cationic Pd(II) species and provides better results. The reaction of benzoyl hydrazones esters **268** with electron-donating or electron-withdrawing substituent on the phenyl ring and a variety of esters proceeded efficiently in acceptable yields (21–43%).

2.2.8. Synthesis of 2-pyrrolines by platinum catalysis. A new synthesis of 2-pyrrolines was recently developed by Shi *et al.* *via* platinum-catalyzed cyclization of a variety of (hetero)aryl-allenes **270**, through the migration of the (hetero)aryl-methylene group (Scheme 90).[140] After screening several catalysts across a number of conditions, the use of $PtCl_2$ (5 mol%) with an electron-deficient phosphine ligand such as $P(C_6F_5)_3$ in anisole at 70 °C were identified as the optimal conditions. This Pt(II)-catalyzed migration protocol tolerates a wide range of (hetero)aryl-allenes **270**. The desired 2-pyrrolines **271** are obtained in yields up to 97%.

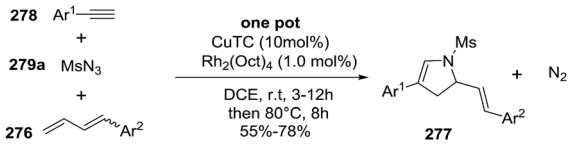
2.2.9. Synthesis of 2-pyrrolines by rhenium catalysis. Kusama *et al.*[141] reported the $[ReCl(CO)_5]$-catalyzed (10 mol%) synthesis of the 2-azabicyclo[3.3.0]octane **273** and the allenyl-substituted dihydropyrrole **274**, from the sulfonamide **272** (Scheme 91). This transformation can also be carried out by tungsten(0) catalysis. By evaluating different sulfonyl groups and alternative rhenium catalysts, the selective preparation of either **273** or **274** was possible. The optimal conditions for **273** used an *N*-nosyl amine and $[ReCl(CO)_4 \cdot PPh_3]$ as a neutral



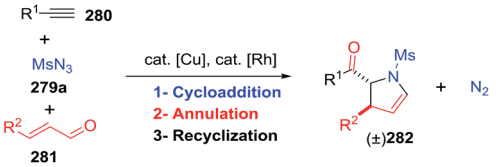
Scheme 91 Tungsten(0)- and rhenium(I)-catalyzed tandem cyclization of acetylenic dienol silyl ethers.



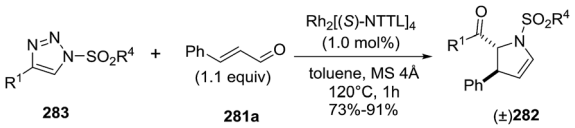
Scheme 92 Aza-[4 + 3] annulation through sequential [3 + 2]–[2 + 1] cycloadditions leading to 2-pyrrolines.



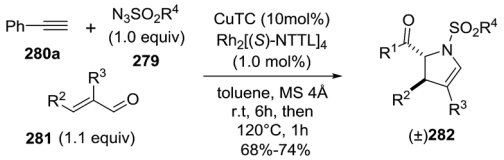
Scheme 93 One-pot synthesis of 2-pyrrolines starting from arylacetylenes, mesyl azide, and buta-1,3-dienylbenzenes.



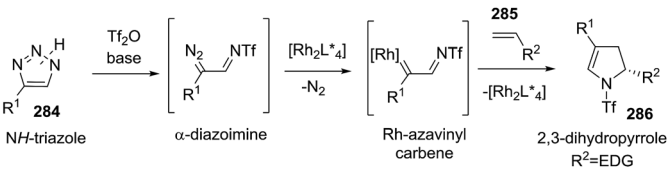
Scheme 94 Diastereoselective synthesis of *trans*-2-pyrrolines starting from terminal alkynes, *N*-sulfonyl azides, and α,β-enals.



Scheme 95 Rh(II)-catalyzed denitrogenative annulation of triazoles to synthesize racemic *trans*-2,3-disubstituted 2-pyrrolines.



Scheme 96 One-pot synthesis of 2-pyrrolines **282** starting from phenylacetylene.



Scheme 97 Reactions of *N*-triflyl-Rh-azavinyl carbenes with olefins.

catalyst. On the other hand, dihydropyrrole **274** was obtained as the major product with the *p*-methoxybenzenesulfonyl (Mbs) sulfonamide and the cationic rhenium catalyst prepared *in situ* from [ReCl(CO)$_5$] (1 mol%) and AgSbF$_6$ (10 mol%). These reactions demonstrate the high synthetic utility of geminal carbofunctionalization of alkynes and rhenium and tungsten complexes in pyrroline synthesis.

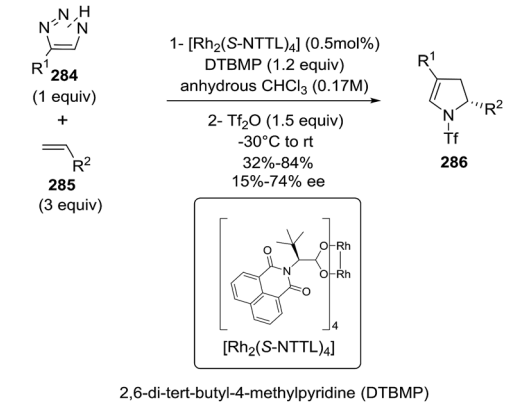
2.2.10. Synthesis of 2-pyrrolines by rhodium catalysis. Kim *et al.* reported the straightforward synthesis of 2-pyrrolines **277** from sulfonyl triazoles **275** and 1,3-dienes **276**, catalyzed by Rh$_2$(Oct)$_4$, under liberation of N$_2$ as the single byproduct (Scheme 92). This product results from sequential [3 + 2]–[2 + 1] cycloadditions giving a net [4 + 3] aza-annulation.[142] The sulfonyl group structure affected appreciably the yield of the reaction. The N^1-methanesulfonyl triazole was best, while a tosyl group was not tolerated. In contrast, different substituents at C-4 of the phenyl ring (Ar^1 of Scheme 88) of the triazole did not affect the yield. Both the *Z*- or *E*-1,3 diene gave similar yields of **277**. Finally, the authors applied this procedure starting from terminal alkynes **278**, mesyl azide, and 1,3-dienes **276** (Scheme 93). This one-pot, three-component synthesis of dihydropyrroles is a synthetically attractive annulation. In the first step, the mesyl triazole **275** is generated through a copper-catalyzed click reaction between the terminal alkyne **278** and the mesyl azide **279**. Rhodium-catalyzed annulation then leads to the 2-pyrrolines **277**. This result demonstrates that the copper does not interfere with this final annulation.

A rhodium(II)-catalyzed cycloaddition of 1-sulfonyl 1,2,3-triazoles **283** with α,β-unsaturated aldehydes **281** was disclosed in 2013 by the Murakami group.[143] The combination of terminal alkynes **280**, *N*-sulfonyl azides **279**, and α,β-unsaturated aldehydes **281** as starting materials resulted in the diasteroselective formation of the racemic *trans*-2,3-disubstituted 2-pyrroline **282** (Scheme 94).

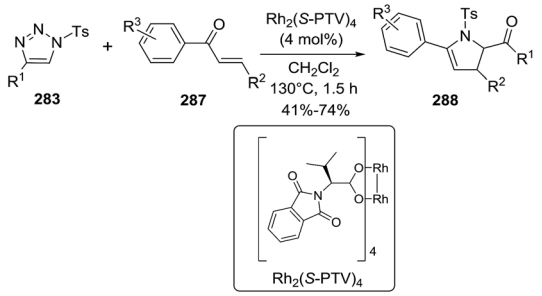
N-Sulfonyl-1,2,3-triazoles **283** are useful intermediates in the synthesis of heterocycles. In the presence of rhodium catalysts these triazoles generate α-imino rhodium carbene (azavinylcarbenes) which reacts with the α,β-unsaturated aldehydes **281** to give the 2-pyrrolines **282** (Scheme 95). With the chiral and bulky [Rh$_2$(S-NTTL)$_4$] as the catalyst, the exclusive formation of the racemic *trans*-2,3 disubstituted 2-pyrroline is observed. With less bulky Rh catalysts, an undesired 4,5-dihydro-1,4-oxazepine subproduct is observed. The production of the racemic dihydropyrroles even though the use of a chiral catalyst is explained by a non-stereospecific ionic mechanism. A screening of α,β-unsaturated aldehydes **281** revealed that a variety of (*E*) and (*Z*) β-monosubstituted enals and acyclic α,β-disubstituted enals were converted effectively into the 2-pyrrolines. Different groups at the 4-position of triazoles **283** and on the sulfonyl group all participated in the annulation reaction to give good yields (typically 80%).

The reaction was made more practical in the form of a one-pot synthesis starting from terminal alkynes **280a**, sulfonyl azides **279**, and α,β-unsaturated aldehydes **281**, using a mixture of CuTC (10 mol%) and Rh$_2$[(S)-NTTL]$_4$ (1.0 mol%) as co-catalysts (Scheme 96).

Using a similar strategy the Fokin group synthesized 2-pyrrolines **286** from *in situ* generated *N*-triflyl triazoles **284** and alkenes **285** (Scheme 97).[144] Azavinylcarbenes can be obtained directly from *N*-sulfonyl triazoles or *N*-triflyltriazoles in presence



Scheme 98 Catalytic asymmetric transannulation of NH-1,2,3-triazoles with alkenes.



Scheme 99 Carbenoid strategy to generate multisubstituted 2-pyrrolines.

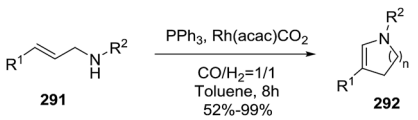
of a rhodium catalyst. These azavinyl carbenes react with 4-methoxystyrene to produce enantioenriched 2-pyrrolines **286** when a chiral rhodium catalyst is used. The highest enantioselectivity (72% ee) was achieved with $[Rh_2(S\text{-}NTTL)_4]$ (Scheme 98). The authors suggest that the moderate enantioselectivity arises from a rapid bond rotation that erodes the enantioselectivity during the mechanism. The protocol affords 2-pyrrolines when electron-rich olefins such as 4-methoxystyrene or 2-methoxystyrene are used as partners.

An efficient Rh-catalyzed annulation between α,β-unsaturated ketones **287** and *N*-sulfonyl-1,2,3-triazoles **283** have been developed leading to multisubstituted 2-pyrrolines **288** (Scheme 99).[145] In this methodology, the generated α-rhodium imino carbene species served as the electrophiles against the α,β-unsaturated ketones, which produced a nucleophilic attack through their oxygen atom. Interestingly, small structural differences in the ligands of the explored rhodium catalysts led to drastic changes in the outcome of the reaction. The optimized conditions for aryl enones (**287**) involved the use of $Rh_2(S\text{-}PTV)_4$ (4 mol%), using 2 equivalents of the triazole substrate in dry DCM, at 130 °C during 1.5 hours, under nitrogen atmosphere.

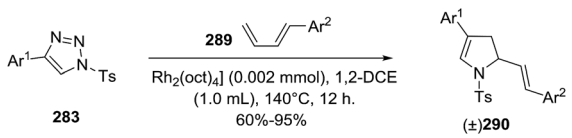
Tang *et al.* reported a rhodium(II)-catalyzed formal aza-[3 + 2] cycloadditions of 1-sulfonyl 1,2,3-triazoles **283** with (*E*)-1-aryl-1,3-butadienes **289** leading to 2-pyrrolines **290** (Scheme 100).[146] The key intermediaries, the α-imino rhodium carbenes (azavinyl carbenes), were readily prepared from *N*-sulfonyl-1,2,3-triazoles using $[Rh_2(oct)_4]$ as the rhodium catalyst (in 1,2-DCE at 140 °C for 12 h). The racemic 2-pyrrolines **290** are isolated as the sole products in very good yields (typically 60–95%). When (*Z*)-1-aryl-1,3-butadiene instead of the *E* analog are used, a [4 + 3] cycloaddition to give 2,5-dihydroazepine products was predominant. With 1,1-diphenyl-, 1-phenyl-2-methyl-, and 1-TBSO-substituted 1,3-dienes as the diene, 2-pyrrolines are the main product (typical yields of 23–90%).

Zhang reported the one-pot rhodium-catalyzed intramolecular hydroaminomethylation of substituted cinnamylamines **291** to generate the 4-aryl-2,3-dihydropyrroles **292** with moderate to excellent yields (typically 52–99%, Scheme 101).[147] The reaction is performed with H_2/CO in a 1/1 ratio at 20 bar pressure. Triphenylphosphine was the best phosphorous ligand for this reaction. Variations in the amine substituents with different R^2 alkyl group and electron-withdrawing substituents at the R^1 phenyl ring of the cinnamyl group all gave very good yields.

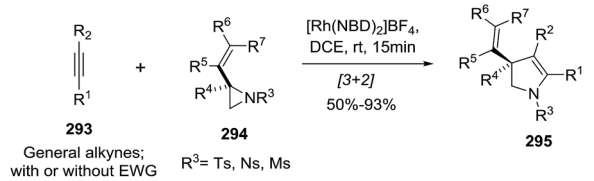
Zhang and co-workers[148] described a rhodium-catalyzed intermolecular [3 + 2] cycloaddition of chiral vinylaziridines **294** and alkynes **293** to give optically active 2-pyrrolines **295** (Scheme 102). The optimized conditions used 5 mol% of $[Rh(NBD)_2]BF_4$ in 1,2-dichloroethane (room temperature, 15 min). The procedure gives good to excellent yields of product for both internal and terminal alkynes **293** and for several substituted vinylaziridines **294**. In addition, a complete transfer



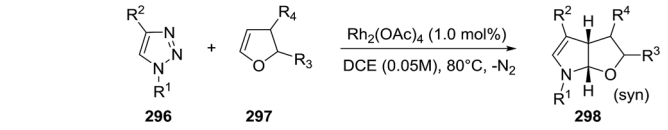
Scheme 101 Rh-catalyzed intramolecular hydroamino-methylation reaction leading to 2-pyrrolines.



Scheme 100 Rhodium(II)-catalyzed formal aza-[3 + 2] cycloadditions of 1-sulfonyl 1,2,3-triazoles with (*E*)-1-aryl-1,3-butadienes leading to 2-pyrrolines.

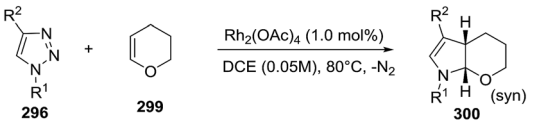


Scheme 102 Rhodium-catalyzed intermolecular [3 + 2] cycloaddition of chiral vinylaziridines and alkynes towards optically active 2-pyrrolines.



296 297 298

298a, R^1=Ts, R^2=Ph, R^3=H, R^4=H 88%(2.5 h)
298b, R^1=Ms, R^2=Ph, R^3=H, R^4=H 70%(3 h)
298c, R^1=SO_2*i*-Pr, R^2=Ph, R^3=H, R^4=H 56%(4 h)
298d, R^1=SO_2-4-$MeOC_6H_4$, R^2=Ph, R^3=H, R^4=H 63%(4.5 h)
298e, R^1=SO_2-4-ClC_6H_4, R^2=Ph, R^3=H, R^4=H 52%(1.5 h)
298f, R^1=SO_2-4-$CF_3C_6H_4$, R^2=Ph, R^3=H, R^4=H 70%(1 h)
298g, R^1=Ts, R^2=3-MeC_6H_4, R^3=H, R^4=H 68%(3 h)
298h, R^1=Ts, R^2=4-MeC_6H_4, R^3=H, R^4=H 71%(2 h)
298i, R^1=Ts, R^2=2-$MeOC_6H_4$, R^3=H, R^4=H 65%(3 h)
298j, R^1=Ts, R^2=4-$MeOC_6H_4$, R^3=H, R^4=H 71%(1 h)
298k, R^1=Ts, R^2=3-ClC_6H_4, R^3=H, R^4=H 60%[a](3.5 h)
298l, R^1=Ts, R^2=4-ClC_6H_4, R^3=H, R^4=H 60%[a](3.5 h)
298m, R^1=Ts, R^2=3-BrC_6H_4, R^3=H, R^4=H 59%[a](5 h)
298n, R^1=Ts, R^2=4-BrC_6H_4, R^3=H, R^4=H 55%[a](5 h)
298o, R^1=Ms, R^2=3-MeC_6H_4, R^3=H, R^4=H 70%(4 h)
298p, R^1=Ms, R^2=2-$MeOC_6H_4$, R^3=H, R^4=H 70%(3 h)
298q, R^1=Ms, R^2=4-$MeOC_6H_4$, R^3=H, R^4=H 75%(2 h)
298r, R^1=Ms, R^2=2-thienyl, R^3=H, R^4=H 55%(2.5 h)
298s, R^1=Ts, R^2=Ph, R^3=Ph, R^4=H 89%(1.5 h)
298t, R^1=Ts, R^2=Ph, R^3=4-MeC_6H_4, R^4=H 90%(4 h)
298u, R^1=Ts, R^2=Ph, R^3=4-ClC_6H_4, R^4=H 91%(4 h)
298v, R^1=Ts, R^2=Ph, R^3=H, R^4=Ph 84%(4 h)
298w, R^1=Ts, R^2=Ph, R^3=H, R^4=4-$MeOC_6H_4$ 78%(3 h)
298x, R^1=Ts, R^2=Ph, R^3=H, R^4=4-ClC_6H_4 77%(4 h)

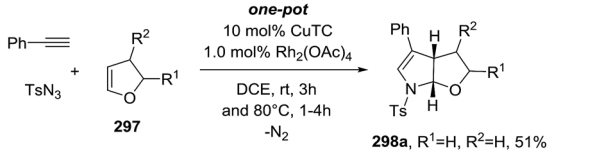


296 299 300

300a, R^1=Ts, R^2=Ph 60%(6 h)
300b, R^1=SO_2-4-$MeOC_6H_4$, R^2=Ph 55%(5 h)
300c, R^1=SO_2-4-ClC_6H_4, R^2=Ph 53%(5 h)
300d, R^1=Ts, R^2=4-$MeOC_6H_4$ 56%(6 h)
300e, R^1=Ts, R^2=3-ClC_6H_4 50%[a](6 h)
300f, R^1=Ts, R^2=4-ClC_6H_4 51%[a](6 h)

(a) $Rh_2(OAc)_4$ (2.0 mol%)

Scheme 103 Rhodium-catalyzed denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles with oxacycloalkenes.



297

298a, R^1=H, R^2=H, 51%
298s, R^1=Ph, R^2=H, 50%
298u, R^1=4-ClC_6H_4, R^2=H, 52%

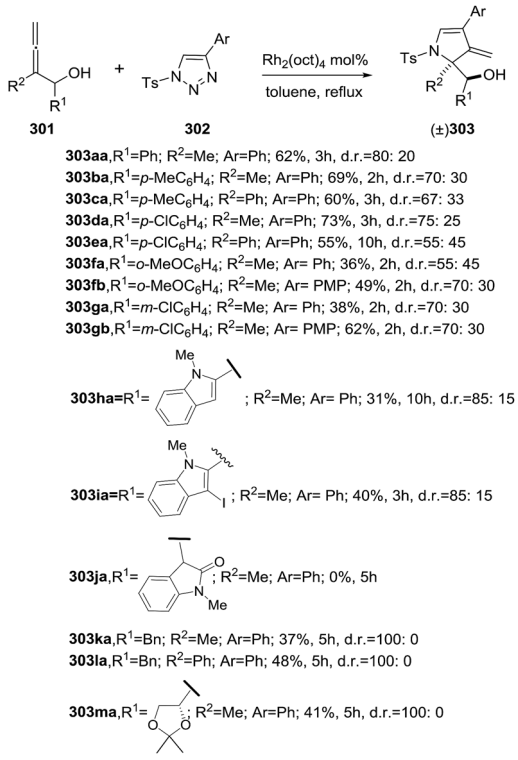
Scheme 104 Rh-catalyzed sequential transannulation.

of chirality from the vinylaziridine to the 2-pyrroline was observed with 90–99% ee. The use of aliphatic alkynes gave moderate to excellent NMR yields, but the cyclic enamines were unstable to purification since they are hydrolytically labile. With non-symmetric internal alkynes, the product of the reaction (in good yields) is a single regioisomer (R^1 = TMS, R^2 = Me, 64%, 96% ee; R^1 = 4-$MeOC_6H_4$, R^2 = CH_2OMe, 69%, 96% ee).

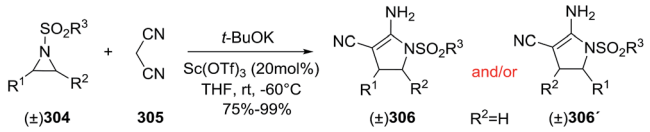
A diastereoselective methodology for the synthesis of tetrahydro-furanodihydropyrroles **298** and tetrahydropyranodihydropyrroles **300** containing *N*,*O*-acetal moieties was proposed by Lee *et al.* These bicyclic heterocyclic compounds were prepared by a rhodium-catalyzed denitrogenative transannulation of *N*-sulfonyl-1,2,3-triazoles **296** with oxacycloalkenes **297** and **299** (Scheme 103).[149] Optimal conditions for this transformation use $Rh_2(OAc)_4$ (1 mol%) as the catalyst, *N*-sulfonyl-1,2,3-triazoles, and oxacycloalkenes in dichloroethane solution (0.05 M) at 80 °C. Under this condition, different *N*-sulfonyl-1,2,3-triazoles **296** provided the transannulation product without significant variation of yields. The generality of the reaction was proven with the employment of different substituted dihydrofurans **297**. Variously substituted racemic 1,2,3-triazoles **296** were obtained as the single diastereomer in moderate to good yield. This protocol was evaluated using 2,3-dihydropyran **299**. The desired transannulated product was obtained in good yields (50–60%) (Scheme 103). Finally, the versatility of this rhodium-catalyzed [3 + 2] cycloaddition was demonstrated by the generation of the 1,2,3-triazoles *in situ* from terminal alkynes, tosyl azides in presence of 2,3-dihydrofuran and with a CuTC and $Rh_2(OAc)_4$ as co-catalysts. This three-component one-pot reaction gave the tetrahydrofuranodihydropyrroles in acceptable yields (typically 50–52%) and again proves compatibility between the copper and rhodium-carbenoid catalysts (Scheme 104).

Alcaide and Almendros group reported a rhodium-catalyzed synthesis of 2-pyrrolines **303** from 1-benzenesulfonyl-4-aryl-1,2,3-triazoles **302** with allenols **301** (Scheme 105).[150] The protocol makes use of 1 mol% of $Rh_2(oct)_4$ in toluene at reflux to obtain a separable mixture of 2-pyrrolines **303** (only the mayor diastereoisomer is shown) with yields in the range of 31–73% ($R^2 \neq H$). When R^1 is aromatic, the diastereoselectivities were modest (d.r. = 55 : 45 to d.r. = 85 : 15) but when R^1 is aliphatic only the *trans* diastereomer is observed. However, the yields obtained with R^1 = aliphatic are modest (typically 40%). The presence of the hydroxyl group in the allene is necessary for the success of the reaction. The mechanism involves the formation of azavinylcarbenes which suffer a nucleophilic addition of the allenol and subsequent azacyclization.

2.2.11. Synthesis of 2-pyrrolines by scandium catalysis. Ghorai *et al.*[151] disclosed a practical and enantioselective synthesis of the highly substituted 4,5-dihydropyrroles **306** and/or **306′** *via* a Domino Ring-Opening Cyclization (DROC) of *N*-activated aziridines **304** with malononitrile **305** using $Sc(OTf)_3$-catalysis (Scheme 106). The optimal reaction conditions used *t*-BuOK as a base. Initial screening with monosubstituted *N*-



Scheme 105 Rhodium-catalyzed synthesis of 2-pyrrolines **303**.

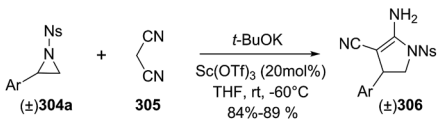


Scheme 106 Synthesis of 2-pyrrolines *via* an Sc(III)-catalyzed Domino Ring-Opening Cyclization (DROC) of N-activated aziridines with malononitrile.

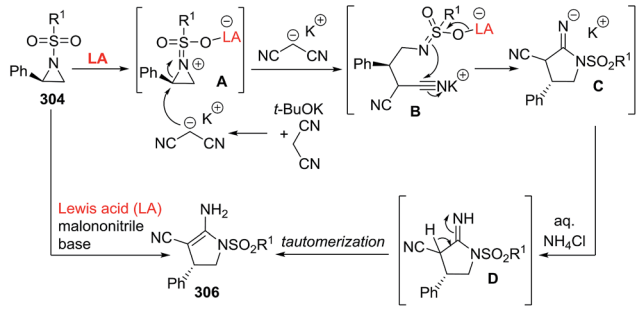
sulfonyl aziridines **304** gave satisfactory yields of the racemic 4,5-dihydropyrroles (typically 75–99%).

The aziridine having the more easily removable *N*-nosyl group gave excellent yields (84–89%) (Scheme 107).

Enantiomerically pure 4,5-dihydropyrroles **306** were obtained as a single regioisomer from enantiomerically pure alkyl monosubstituted and 2,3-disubstituted aziridines **304**. The proposed mechanism involves an S_N2 nucleophilic attack of the malononitrile anion on the Lewis activated aziridine to generate intermediate **B**, which undergoes intramolecular cyclization with subsequent protonation and tautomerization to deliver the product (Scheme 108).



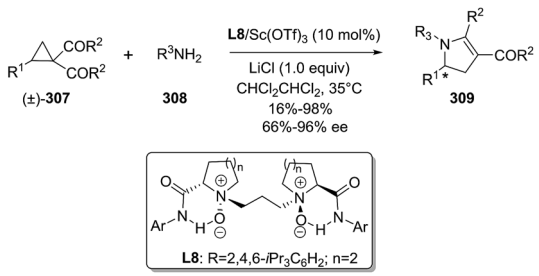
Scheme 107 Domino Ring-Opening Cyclization (DROC) with *N*-nosyl aziridines.



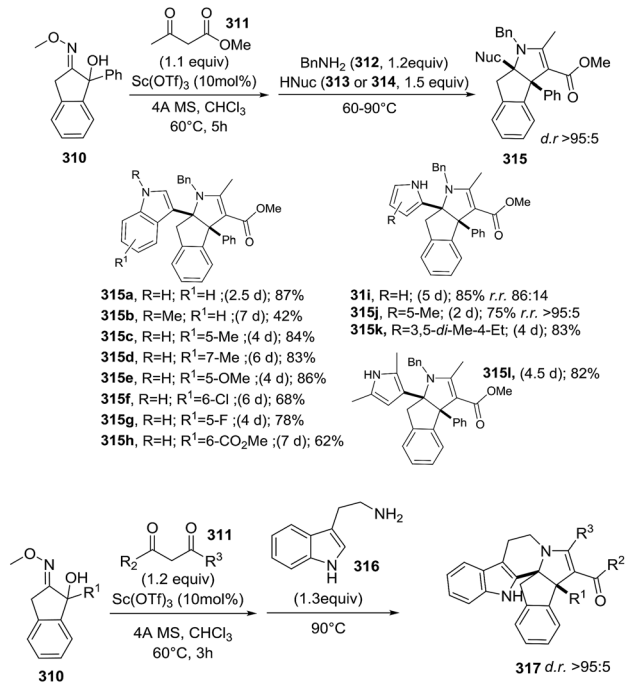
Scheme 108 Proposed mechanism for the Domino Ring-Opening Cyclization (DROC).

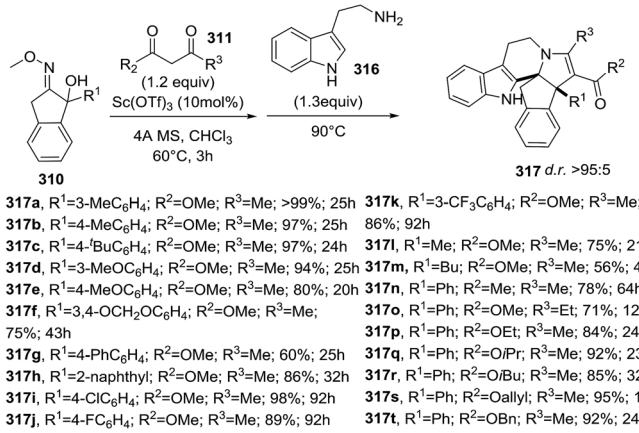
In 2015, Xia *et al.* reported the asymmetric scandium-catalyzed synthesis of chiral 2,4,5-trisubstituted 2-pyrrolines **309** through the ring-opening cyclization reaction of cyclopropyl ketones **307** with primary amines **308.**[152] The use of $Sc(OTf)_3$ with the chiral *N*,*N*′-dioxide ligand **L8** gave the best results (Scheme 109). The optimal reaction conditions used the Sc(III)/**L8** complex (10 mol%) as catalyst and LiCl as additive (in $CHCl_2CHCl_2$ at 35 °C for 96 h). The methodology tolerates a broad range of cyclopropyl ketones **307** and primary amines **308** with exception of aliphatic amines. In all cases (R^3 = Ar), the multisubstituted 2-pyrrolines **309** were obtained in good to excellent enantioselectivities (66–96% ee) and poor to excellent yields (16–98% yield). The origin of the enantioselectivity is caused by a kinetic resolution process.

Schneider *et al.* reported an $Sc(OTf)_3$-catalyzed multicomponent reaction towards multicyclic 2-pyrrolines **315** from 2-hydroxy oxime ethers **310**, 1,3-dicarbonyls **311**, primary amines **312** and indoles **313** or pyrroles **314** (Scheme 110).[153] This (2 + 2 + 1)-cycloannulation/aza-Friedel–Crafts alkylation sequence provide complex 2-pyrrolines with excellent yields (42–99%) and diasteroselectivities (d.r. >95 : 5). The procedure tolerates either electron-rich or electron-deficient indoles. However, the use of less nucleophilic *N*-methyl indole resulted in lower yields. Other than that, alkyl substituted pyrroles were sufficiently reactive to form the multicyclic 2-pyrrolines. An intramolecular version of this aza-Friedel–Crafts alkylation was achieved with the amine component tethered to the reactive π-nucleophile. This is exemplified with the use of 2-(heteroaryl)ethylamine as tryptamine **316.** Regarding the scope of 2-hydroxy oxime ethers **310**,



Scheme 109 Asymmetric scandium-catalyzed synthesis of chiral 2,4,5-trisubstituted 2-pyrrolines **309**.

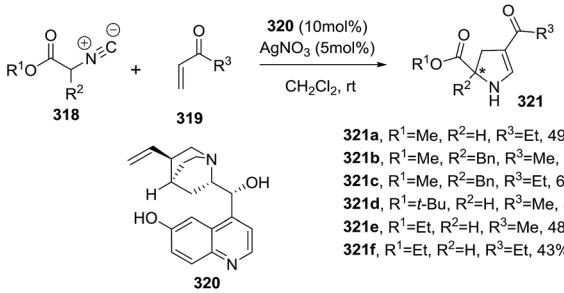




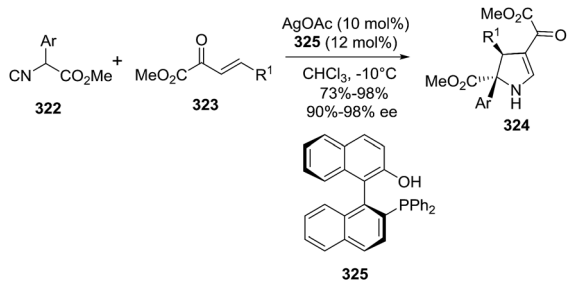
Scheme 110 $Sc(OTf)_3$-catalyzed multicomponent reaction towards multicyclic 2-pyrrolines **317**.

the protocol tolerates electron-rich or electron-deficient aryl groups, naphthyl and alkyl groups (R^1).

2.2.12. Synthesis of 2-pyrrolines by silver. Amat *et al.*[154] disclosed the first example of an asymmetric cooperative multicatalytic cascade between isocyanoacetates **318** and α,β-unsaturated ketones **319** for the rapid construction of enantioenriched 2,3-dihydropyrroles **321**, employing the combination of a chiral cinchona alkaloid-derived organocatalyst and silver nitrate as the additive. The scope of the methodology was evaluated with respect to different substituted isocyanoacetates **318** and α,β-unsaturated ketones **319** which in combination



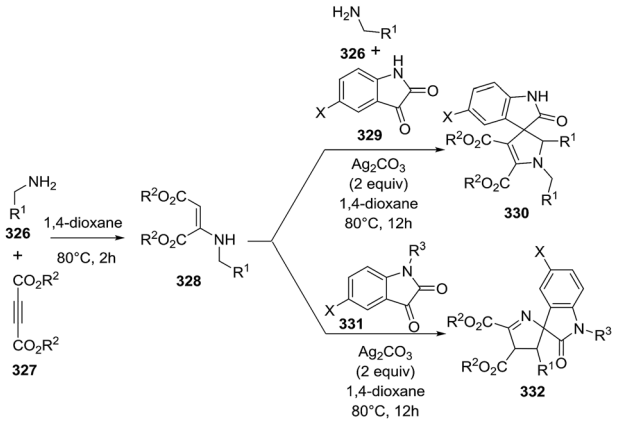
Scheme 111 Cooperative catalytic synthesis of enantioenriched pyrrolines **321**.



Scheme 112 Asymmetric formal [3 + 2] cycloaddition reaction towards chiral 2-pyrrolines.

with cupreine **320** as the chiral base, led to products in moderate enantiomeric excess (Scheme 111).

Simultaneously to the previous report, Gong *et al.*[155] published an analogous transformation towards optically active 2-pyrrolines **324** but using α,β-unsaturated esters **323** instead of α,β-unsaturated ketones as the starting materials (Scheme 112). This study represented the first example of a highly enantioselective [3 + 2] cycloaddition of isocyanoesters **322** to 2-oxobutenoate esters **323** catalyzed by the silver complex formed from silver acetate and (*S*)-(2′-hydroxy-1,1′-binaphthyl-2-yl) diphenylphosphine **325**. Different substituents present in both reactants were evaluated. In most of the cases 2,3-dihydropyrroles **324** were obtained with excellent yields (73–98%) and high enantioselectivity (90–98% ee).



330a, R1=Ph, R2=Et, R3=H, X=H, 90%
330b, R1=4-MeC6H4, R2=Et, R3=H, X=H, 92%
330c, R1=3-OMeC6H4, R2=Et, R3=H, X=H, 93%
330d, R1=4-FC6H4, R2=Et, R3=H, X=H, 80%
330e, R1=3-BrC6H4, R2=Et, R3=H, X=H, 78%
330f, R1=1-naphthyl, R2=Et, R3=H, X=H, 94%
330g, R1=Ph, R2=Et, R3=H, X=Cl, 92%
330h, R1=1-naphthyl, R2=Et, R3=H, X=Cl, 95%
330i, R1=4-MeC6H4, R2=Et, R3=H, X=I, 87%
330j, R1=Ph, R2=Me, R3=H, X=H, 93%
330k, R1=3-MeOC6H4, R2=Me, R3=H, X=H, 94%
330l, R1=4-FC6H4, R2=Me, R3=H, X=H, 85%
330m, R1=4-ClC6H4, R2=Me, R3=H, X=H, 85%
330n, R1=Ph, R2=Et, R3=H, X=OMe, 76%
332a, R1=Ph, R2=Et, R3=Bn, X=H, 90%
332b, R1=3-BrC6H4, R2=Et, R3=Bn, X=H, 86%
332c, R1=2-furane, R2=Et, R3=Bn, X=H, 72%
332d, R1=Ph, R2=Et, R3=Bn, X=Cl, 92%
332e, R1=Ph, R2=Et, R3=Bn, X=Br, 92%
332f, R1=4-MeOC6H4, R2=Et, R3=CH2CH=CH2, X=H, 91%
332g, R1=3-BrC6H4, R2=Et, R3=CH2CH=CH2, X=H, 80%
332h, R1=Ph, R2=Et, R3=CH2CH=CH2, X=Br, 85%
332i, R1=Ph, R2=Et, R3=CH2CH3, X=H, 87%
332j, R1=Ph, R2=Et, R3=(CH2)2CH3, X=H, 84%
332k, R1=Ph, R2=Et, R3=(CH2)3CH3, X=H, 82%
332l, R1=4-ClC6H4, R2=Et, R3=(CH2)3CH3, X=H ,75%
332m, R1=4-OMeC6H4, R2=Me, R3=Bn, X=H, 95%

Scheme 113 Regioselective synthesis of spiro-dihydropyrroles **330** and **332**.

Mukhopadhyay *et al.*[110] reported a multicomponent reaction promoted by Ag(I) through activation of the $C_\alpha(sp^3)$–H bond of the corresponding benzylamine **326** in presence of but-2-ynedioate **327** and isatin **329** (X = H). A regioselective [1,5]-rearrangement gave the spiro-2,3-dihydropyrroles **330** while an alternative [1,3]-rearrangement produced the spiro-1-dihydropyrroles **332**. The regioselective generation of each heterocyclic core (**330** *versus* **332**) was achieved under the same reaction conditions involving Ag(I) and depending on the nature of the group bond to the nitrogen of isatin (Scheme 113). When isatin or *N*-methylisatin is used, a [1,5] rearrangement occurs to afford 2-pyrrolines **330**. If the isatin is *N*-substituted with benzyl, allyl, ethyl, propyl, or an *n*-butyl group, a [1,3]-rearrangement occurs to give 1-pyrrolines **332**. NMR experiments are consistent with enamine **328** as the common intermediary to both products. The Ag(I) source of choice was Ag_2CO_3, one of the most available and least expensive sources of silver. In addition, the Ag_2CO_3 was recycled successfully. The scope of the reaction was evaluated using various derivatives of each starting material (R^1, R^2, R^3). A steric effect of the *N*-substituents is crucial for the fate of the reaction, for instance when R^3 = allyl or *n*-butyl produce lower yields compared with R^3 = benzyl. When R^3 = ethyl or propyl the reaction gives good yields (87% and 84% respectively).

2.3. Synthesis of 3-pyrrolines

Illustrative examples of the importance of the 3-pyrroline ring in natural products and bioactive compounds are displayed in Fig. 5. The 3-pyrroline scaffold is part of the polycyclic core of erysovine (**333**), a natural erythrinan alkaloid which presents chemotherapeutic properties.[9] The substituted 2,5-dihydropyrrole is the central ring of the kinesin spindle protein inhibitor **334** (ref. 19) and of compound **335**.[156] Both of these compounds exhibit antitumoral activity. Spirooxindol derivative **336** (ref. 157) has potent anti-microbial activity. The 2,5-dihydropyrrole formyl hydroxyamino derivatives **337** are peptide deformylase inhibitors achieving better *in vitro* antibacterial activities than existing drugs.[158] A set of synthetic *N*-3-pyrrolines amino arylacetamide derivatives **338** exhibited potent and high selectivity as kappa-agonists with potentially safer analgesic activity.[17]

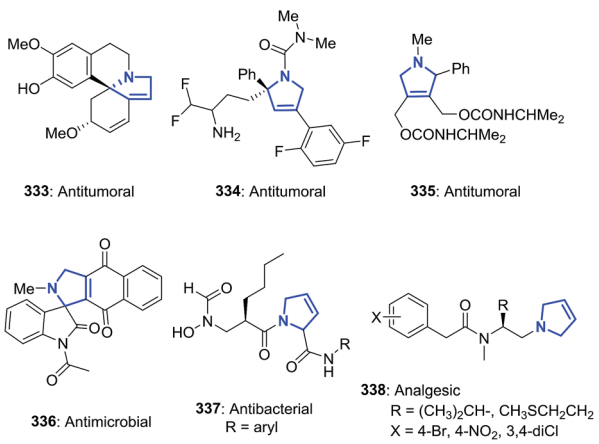
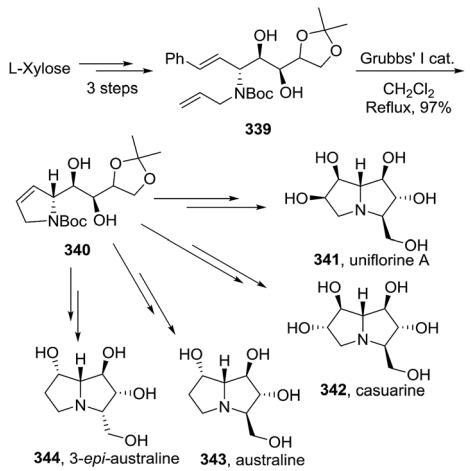
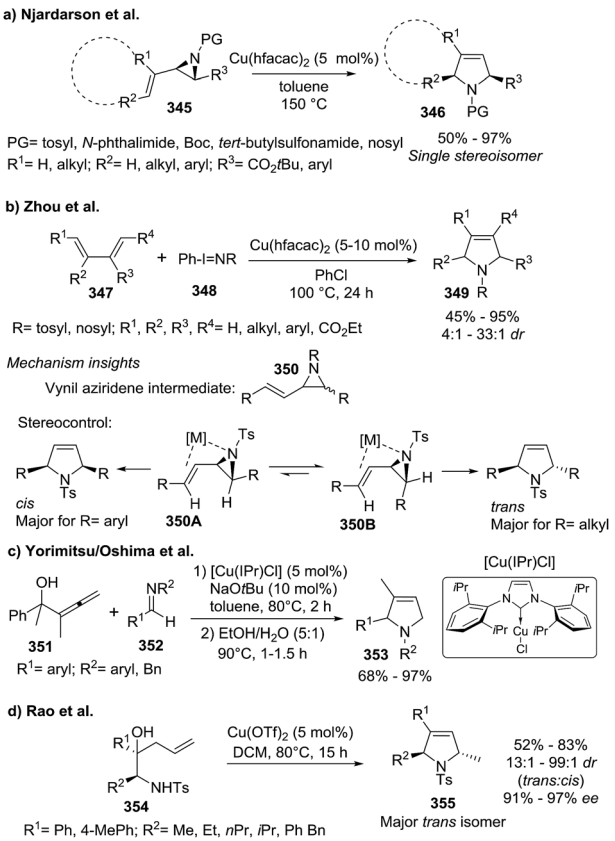


Fig. 5 Selected examples of biologically active 3-pyrrolines.



Scheme 114 Synthesis of pyrrolizidine alkaloids through the 3-pyrroline **340**.

Pyne *et al.* demonstrated the versatility of using 3-pyrrolines as intermediaries in their synthesis of complex alkaloids. The chiral 3-pyrroline **340** was used as an common intermediate towards the synthesis of the glycosidase inhibitors uniflorine A (**341**), casuarine (**342**), australine (**343**), and 3-*epi*-australine (**344**).[32] The chiral pyrroline **340** is available in gram scale starting from L-xylose and using a ring-closing metathesis of **339**

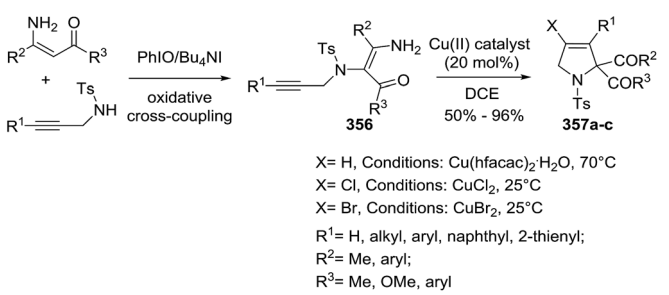


Scheme 115 Different synthetic approaches toward 3-pyrrolines *via* copper catalysis reported in 2010–2011.

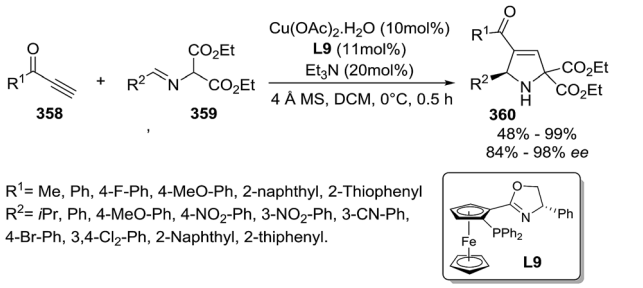
as a key step. The pyrrolizidine alkaloids **341–344** were obtained in satisfactory overall yields in several steps from **340** (Scheme 114).

2.3.1. Synthesis of 3-pyrrolines by copper catalysis. Between 2010 and 2011, several groups used known (but adapted) synthetic approaches to generate 3-pyrrolines under green, copper-catalyzed conditions. The Njardarson group[159] developed the $Cu(hfacac)_2$ (hfacac: hexafluoroacetylacetonate) catalyzed ring expansion of chiral vinyl aziridines **345** to produce a set of mono and fused 3-pyrroline products **346** (Scheme 115a). This transformation exhibited high stereocontrol, with each starting material produced a single stereoisomer. Using the same catalyst, Zhou and coworkers[160] generated the 3-pyrrolines **349** but *via* the different mechanism of overall intermolecular [4 + 1] cycloaddition of 1,3-dienes **347** and the nitrene precursors **348** (Scheme 115b). The more likely mechanism, however, involved [2 + 1] cycloaddition of a vinylaziridine intermediate (**350**), followed by ring expansion. This mechanism justifies the stereochemistry of the final pyrroline as determined exclusively by the geometry of the conjugated dienes (as inferred from the proposed metal-chelated vinylaziridines **350A**, **350B**.). In particular, the 1,4-disubstitued dienes were the best substrates to reach high diastereomeric ratio (*cis*-product with R^2 and R^3 substituents pointing towards the same side of the heterocycle compared to the *trans*-product with those substituents pointing to opposite faces of the ring). In the same year, a report described the synthesis of 3-pyrrolines **353** *via* tandem allenylation/cyclization reactions catalyzed by the NHC (*N*-heterocyclic carbene)-ligated copper complex [Cu(IPr)Cl] (Scheme 115c).[161] The proposed mechanism for this sequence of reactions invokes an amine allenyl intermediate that cyclizes in presence of the copper catalyst. Rao *et al.*[162] developed a synthetic route directed to trisubstituted 3-pyrrolines **355** *via* an intramolecular hydroamination of homoallylic amino alcohols **354** mediated by $Cu(OTf)_2$ (Scheme 115d). In this case, the use of enantioenriched aminoalcohols as starting materials produced chiral heterocycles with excellent dr [*trans* (R^2 and methyl group on the same side of the pyrroline): *cis* (R^2 and methyl group on opposite sides of the pyrrolines ring)] and ee values.

Wang and Fang[163] described subsequently the preparation of the highly substituted pyrrolines **357** from the alkynyl-substituted enamides **356** using Cu(II) catalysis. The key step in this synthesis is the preparation of the linear starting material **356** *via* a $PhIO/Bu_4NI$-mediated oxidative cross-coupling. Cyclization of such enamides **356** in presence of copper salts led to different halogenated final products **357a–c** (Scheme 116).



Scheme 116 Cu(II)-promoted cyclization of alkynyl-substituted enamides **356**.

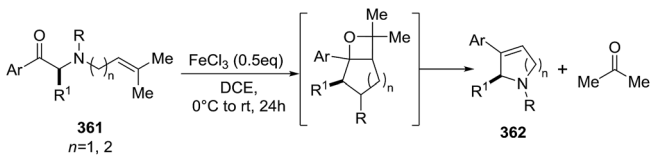


Scheme 117 Asymmetrical 1,3-dipolar cycloaddition of ethynyl ketone **358** to azomethine ylide **359** catalyzed by the complex $Cu(OAc)_2 \cdot H_2O$/FOXAP derivative **L9**.

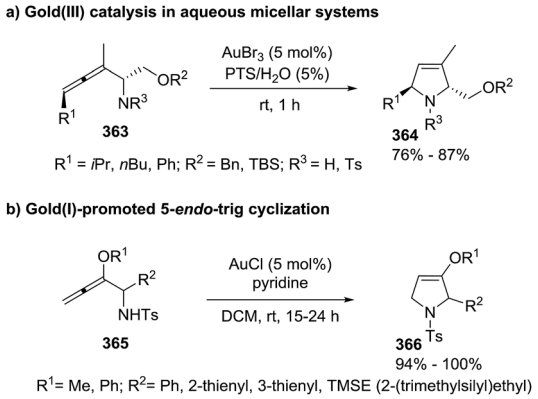
At the same time Tang *et al.*[164] reported the construction of enantioenriched and highly substituted 3-pyrrolines **360** *via* asymmetric 1,3-dipolar cycloaddition the ethynyl ketones **358** to the azomethine ylides **359** (Scheme 117). The optimized reaction conditions used $Cu(OAc)_2 \cdot H_2O$ with the FOXAP derivative **L9** as the ligand. The pyrrolines were obtained in acceptable to excellent yields (48–99%) and high enantiomeric excess (84–98%).

2.3.2. Synthesis of 3-pyrrolines by iron catalysis. Schindler's group described the synthesis of chiral 3-aryl-3-pyrrolines **362** using iron(III)-catalyzed carbonyl-olefin metathesis taking advantages of commercially available amino acids as chiral pool reagents to access metathesis substrates **361** (Scheme 118).[165] The optimized condition makes use of 0.5 equiv. of $FeCl_3$ in dichloroethane at 0 °C for 1 h and then warmed to rt. The best results were obtained with carbonyl-olefin metathesis substrates **361** bearing prenyl-derived alkenes and electron-deficient sulfonamide protecting groups (R). This strategy provided 34 aryl-3-pyrrolines in yields up to 99% with complete stereoretention (up to 98% ee).

2.3.3. Synthesis of 3-pyrrolines by gold catalysis. Lipshutz and Krause[166] reported in 2011 the first example of 3-pyrroline scaffolds obtained by gold catalysis in micellar systems using PTS or TPGS-750-M as amphiphiles. The heterocycles **364** were efficiently produced from the α-functionalized amino allenes **363** *via* a cycloisomerization promoted by the air-stable aqueous gold(III) solution (Scheme 119a). Interestingly, the reaction presents a broad scope of substrates, and tolerates the TBS ether, ester, and sulfonamide functional groups. More recently



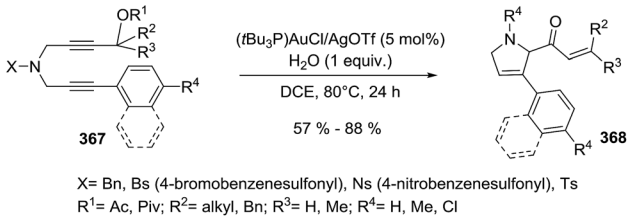
Scheme 118 3-Aryl-3-pyrrolines **362** *via* catalytic carbonyl-olefin metathesis.



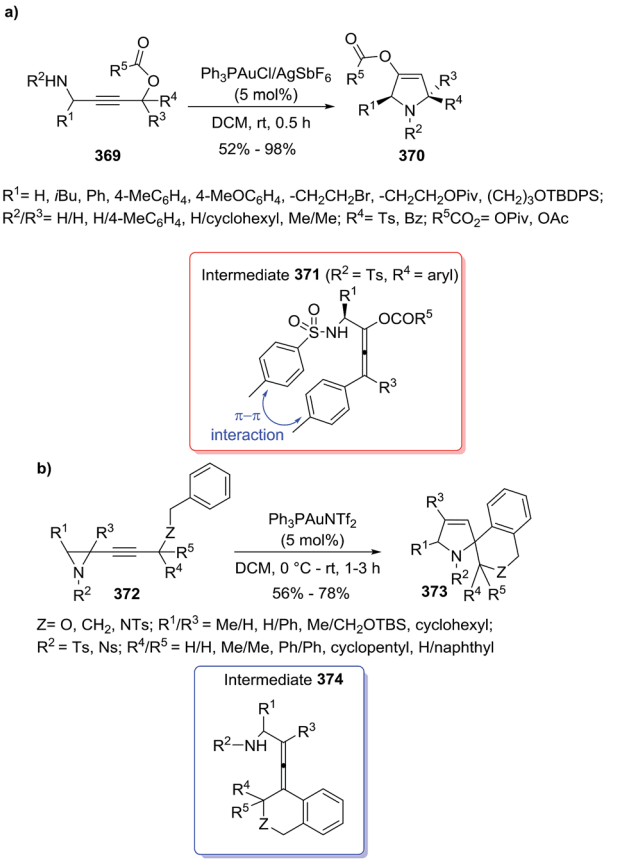
Scheme 119 Cyclization of allenyl amines and allenyl tosylamines.

Reissig *et al.*[167] published an analogous transformation but using Au(I) catalysis. Starting from allenyl *N*-tosylamines **365**, the 2,3-disubstituted pyrrolines **366** were obtained *via* 5-*endo-trig* cyclization (Scheme 119b). As previously discussed by the authors in preliminary results,[168] this annulation could be also achieved by either Ag(I) catalysis or the use of a base such as KO^{t}Bu. However, the auric catalyst gave higher yields (94–100%) under mild reaction conditions, and with a more convenient work up (except for the 2-pyrrolyl pyrrolines, which required strongly basic conditions). A similar cycloisomerization was described as part of an interesting multicomponent protocol based on sequential use of metals (Cu/Rh/Au).[169] This "three procedures/single work-up" methodology involved a final Au(I)-promoted cyclization of α-amino allenes analogous to those described above (see Subsection 2.3.11.: Synthesis of 3-pyrrolines by combined metal catalysis: Cu/Rh/Au, Scheme 138).

Several strategies toward the gold-promoted generation of 3-pyrroline scaffolds were based on initial gold-alkyne coordination, taking advantage of the high alkynophilicity of this metal. For instance, Shi *et al.*[59,170] developed a synthesis of 2,3-disubstituted 3-pyrrolines **368** by the gold(I)-promoted intramolecular cyclization of the functionalized 1,6-diynes **367** (Scheme 120). The use of the (tBu$_3$P)AuCl/AgOTf catalytic system in the presence of water (1 equiv.) was optimal, providing the final cycloadducts in up to 88% yield. A plausible mechanism for this annulation, implicating two Au(I) cationic complexes with the two alkynes in **367**, was proposed. Even though there is a broad scope of substrates, the terminal alkyne analogues compounds did not provide the pyrroline as a product, but instead the diketone "linear" products were produced.

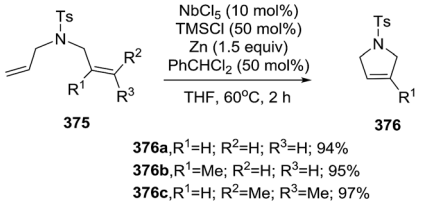


Scheme 120 Cyclization of 1,6-diynes **367** by Au(I) catalysis.

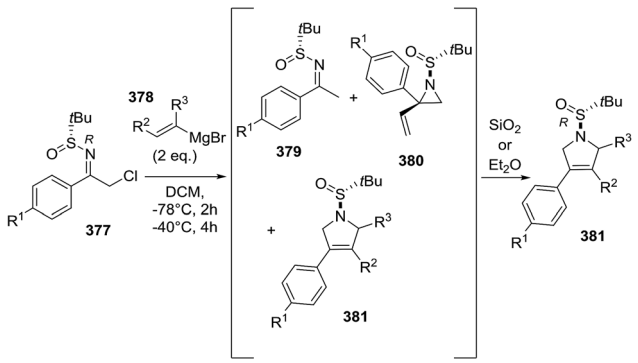


Scheme 121 Au(I)-catalyzed cascade reactions involving allenyl intermediates.

Xie, She *et al.*[171] applied gold-catalyzed tandem 1,3-acyloxy rearrangement/intramolecular azacyclization to provide the pyrrolines **370** from γ-amino substituted propargylic esters **369** (Scheme 121a). The authors screened the catalytic system, solvent, and time. The use of AuPh$_3$PCl/AgSbF$_6$ in DCM (room temperature, 30 min) gave the best results. The proposed mechanism started with gold–alkyne coordination to generate *via* a 3,3-rearrangement an allenyl intermediate **371**, on which an intramolecular S$_N$2-type reaction occurred, followed by a final gold elimination leading to the pyrroline, and regenerating the gold catalytic species. The π–π interaction present in intermediate **371** explained the *cis*-stereochemistry (sole products with R^1 and R^4 on the same side of the pyrroline ring) observed in the 2,5-disubstituted pyrrolines **370**. This cascade of transformations was applied efficiently to a total synthesis of natural alkaloid (±)-aphanorphine. Similarly, the Blanc and the Pale's groups[172] developed a novel gold salt methodology to obtain spiro[isochroman-4,2′-pyrrolines] **373** in high yields from aryl-containing alkynylaziridines **372** (Scheme 121b). Similar to the previous example, a cascade reaction through the aminoallenylidene isochromane intermediate **374** leads to the products. In this case, a dual σ and π gold activation by double gold-coordination to the aziridine and alkynyl moieties, respectively has been proposed.



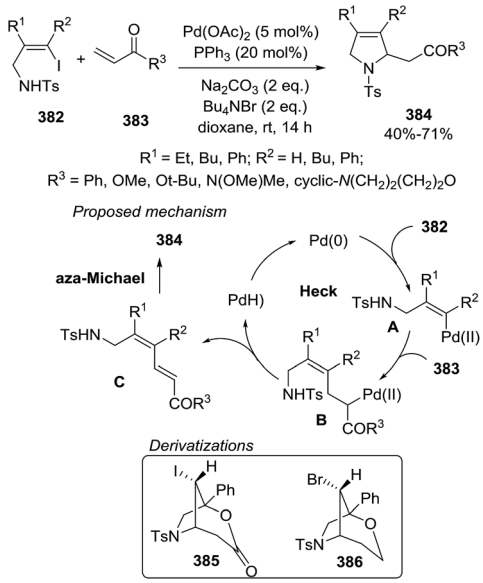
Scheme 122 Synthesis of 3-pyrrolines by *in situ*-generated niobium-based catalyst.



Scheme 123 : Synthesis of 3-aryl-3-pyrrolines **381** from vinyl-magnesium bromide (**378**) and chiral α-chloro *N-tert*-butanesulfinyl ketimines (**377**).

2.3.4. Synthesis of 3-pyrrolines by niobium catalyst. Obora *et al.* developed an active in situ-generated niobium catalyst formed by niobium pentachloride, trimethylsilyl chloride, zinc, benzyl dichloride and THF as solvent.[173] This Nb-based complex is an active ring-closing metathesis catalyst. 3-Pyrroline derivatives **376** were obtained in quantitative yields starting from *N*,*N*-diallyl-*p*-toluenesulfonamides **375** when heated at 60 °C for 2 h in presence of the Nb-based complex (Scheme 122).

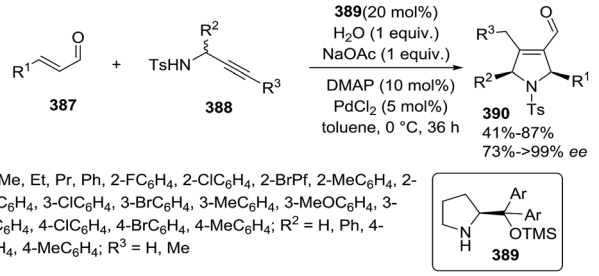
2.3.5. Synthesis of 3-pyrrolines promoted by magnesium. The rearrangement of vinylaziridines to pyrrolines is an exceptionally reliable methodology. The key for its success is the availability of the required highly substituted starting aziridine, and the selection of conditions to control reaction pathway. In this manner, De Kimpe's group[174] developed a mild and efficient addition of vinylmagnesium bromide **378** to chiral α-chloro *N-tert*-butanesulfinyl ketimines (**377**) to produce *in situ* the vinylaziridines **380**, leading exclusively to the 3-pyrrolines **381** *via* a S_N2' ring opening with C–N bond cleavage (Scheme 123). The crude reaction mixture contained a combination of dechlorinated imines (**378**), *N*-sulfinyl-2-aryl-2-vinylaziridenes intermediates (**380**), and final pyrrolines **381**. However, recrystallization from ether or purification by silica chromatography induced the 2-sulfinyl-2-aryl-2-vinylaziridines rearrangement to give the 3-aryl-3-pyrrolines **381** in good yields. Careful analysis gave insight into the effect of the substitution pattern on both the aziridine ring as well as the alkene moiety. In particular, when the R^2 substituent was different from hydrogen, the pyrroline was not obtained; the corresponding vinylaziridene was produced as the major product instead.



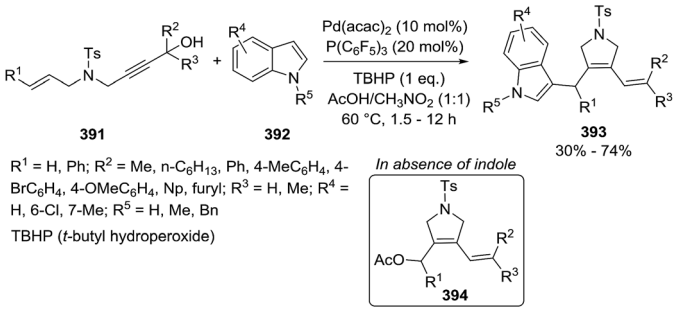
Scheme 124 Pd(0)-catalyzed domino Heck-aza-Michael reaction between (*Z*)-*N*-(3-iodoallyl)-tosylamides **382** and acrylic esters **383** and related.

2.3.6. Synthesis of 3-pyrrolines by palladium catalysis. By analysis of the Pd-catalyzed transformations of (*Z*)-vinyl iodides, Tong's group[175] discovered a domino process, combining Heck and aza-Michael reactions, to produce the 3-pyrroline. When tosylamide-substituted vinyl iodides **382** were used in combination with acrylic ester (and related structures **383**) in the presence of catalytic $Pd(OAc)_2/PPh_3$ and base (2 equiv.), the domino reaction gave the substituted 3-pyrrolines **384** in 40–71% yields (Scheme 124). Addition of Bu_4NBr increased the yield to 65%. Bridged derivatives (**385** and **386**) were obtained *via* synthetic modifications, initializing with ester hydrolysis and ester reduction. The proposed mechanism involves the oxidative addition of vinyl iodide **382** to Pd(0) to generate **A**, which undergo a Heck-type reaction with the acrylic ester leading to intermediate **C** (Scheme 124). Subsequently, spontaneous aza-Michael cyclization provides the desired *N*-tosyl pyrrolines.

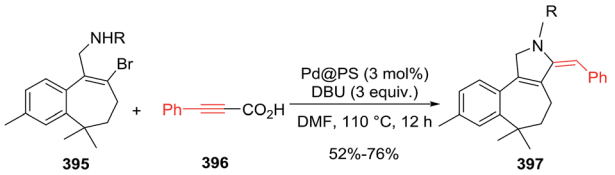
Another strategy to access 2,5-dihydropyrroles, also based on a Pd-promoted cascade reaction, was developed by Sun *et al.*[176]



Scheme 125 Asymmetric Pd/amine-catalyzed synthesis of tri- and tetrasubstituted 3-pyrrolines **390**.



Scheme 126 Pd-catalyzed addition of indoles to hydroxyl 1,6-enynes.

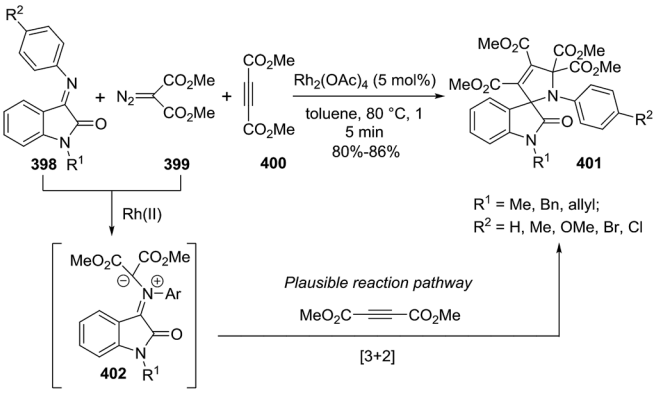


Scheme 127 Heterogeneous Pd-catalyzed tandem decarboxylative coupling-5-*exo* cyclization.

In this case the combination of metal and organic catalysis produced chiral 3-pyrrolines **390** from the readily available α,β-unsaturated aldehydes **387** and *N*-tosyl propargylamines **388** as the starting materials, *via* an iminium/enamide cascade (Scheme 125). The proposed mechanism integrates the two catalytic cycles. The overall cascade begins with the iminium activation of the aldehyde by the chiral amine **389**, followed by an aza-Michael addition and final Pd-promoted carbocyclization, in which the metal coordinates simultaneously the enamide and the alkyne moieties. This cascade organo-metal cooperative catalysis procedure facilitates the production of 3-pyrrolines in acceptable to good yields (41–87%) and with excellent diastereo- (>16 : 1 (*cis* : *trans*) dr, only the major *cis* diastereomer is shown) and enantioselectivities (73 to > 99% ee). Although limited to the use of terminal alkynes, diverse enantiomerically enriched tri- and tetrasubstituted pyrrolines were produced, presenting a wide scope of substituents at R^1 and R^2 positions.

The Pd-promoted cycloisomerization of enynes to 3-pyrrolines was exploited by Liang and coworkers (Scheme 126).[177] The starting *p*-toluensulfonamides 1,6-enynes (**391**) underwent cycloisomerization in the presence of $Pd(acac)_2$ to generate cyclopropylpalladium complexes, which were captured by the indoles **392** leading to the final 3-pyrrolines derivatives **393** with moderate yields (up to 74%). In the absence of the indole, an acetate anion from the reaction medium is incorporated, producing the truncated 3-pyrrolines **394**.

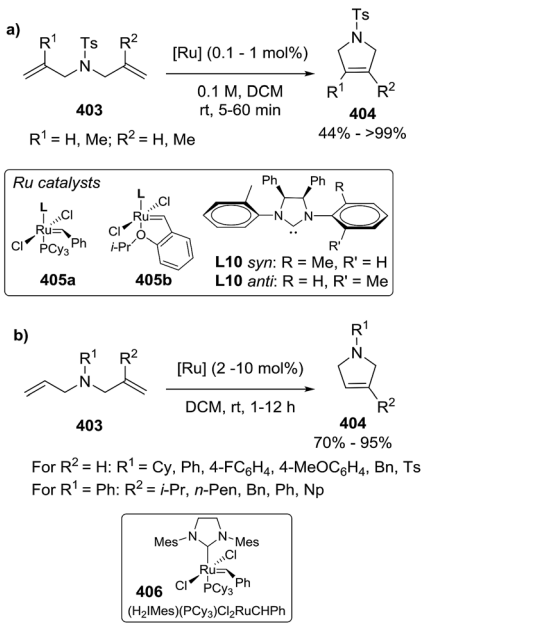
The use of polystyrene-supported palladium (Pd@PS) nanoparticles (NPs) has been applied for the generation of fused 3-pyrrolines.[178] This heterogeneous catalyst promotes a domino decarboxylative coupling-cyclization (DCC) from phenylpropiolic acid (**396**) and aminomethyl benzocycloheptene bromide **395**, leading to a new class of bioactive 3-pyrroline



Scheme 128 Multicomponent reactions towards spirooxindolyl pyrroline catalyzed by rhodium.

derivatives **397** with acceptable to good yields (52–76%) (Scheme 127). The catalytic species was proven to be Pd(0) in heterogeneous form. Furthermore, the catalyst could be used up to five times without significant decreased activity.

2.3.7. Synthesis of 3-pyrrolines by rhodium catalysis. A Rh-catalyzed multicomponent procedure was developed by Reddy *et al.*[179] to obtain highly functionalized spirooxindolyl pyrrolines **401**, which can be thought as hybrid drugs, as they present two active moeities (Scheme 128). The optimized multicomponent reaction required cyclic ketimines (**398**), dimethyl diazomalonate (**399**), and dimethyl acetylenedicarboxylate (**400**) in the presence of $Rh_2(OAc)_2$ (5 mol%) in benzene (80 °C, 15 min). The rhodium is proposed to catalyze the formation of azomethine ylides **402** from **398** and **399**, which are subsequently trapped by the alkyne derivatives **400** present in the reaction mixture through Huisgen's cycloaddition, to generate the pyrroline. This methodology results in the remarkably efficient,

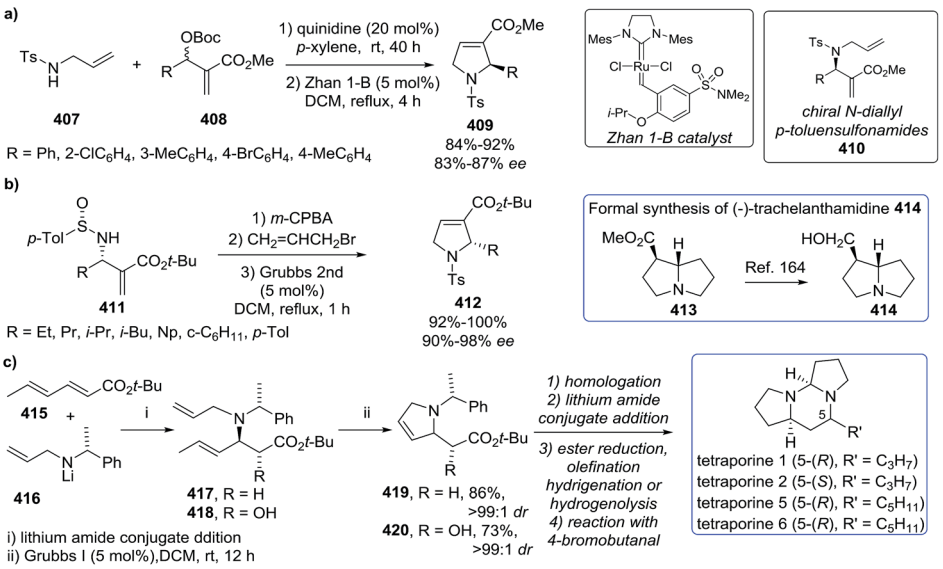


Scheme 129 RCM promoted by Ru catalysts towards 3-pyrrolines.

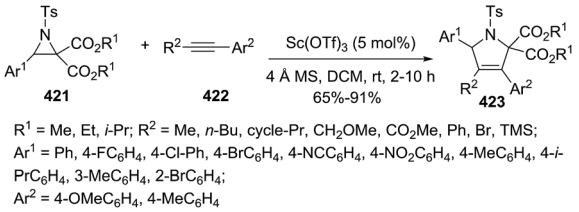
single-step production of the complex spirocycles **401** with good to excellent yields (80–86%).

2.3.8. Synthesis of 3-pyrrolines by ruthenium catalysis. Ru-catalyzed ring-closing metathesis (RCM) is one of the most efficient and broadly employed synthetic methods for the generation of various cyclic products.[180] The application of this methodology towards the generation of 3-pyrrolines has been broadly explored, encompassing different aspects such as mechanistic studies with different ruthenium catalysts,[181] an enyne version of the transformation,[182] and the evaluation of the catalyst loading.[183] Over the last years, this transformation has been improved and expanded. Most reports describe the Ru-promoted annulation of dialkenyl-substituted amines affording 3-pyrrolines whose substitution patterns were directly determined by the chemical structure achieved during the synthesis of such diolefinic starting materials. Diallyl sulfonamides are commonly used to study this RCM. For example, Perfetto *et al.*[181] described the performance of new ruthenium NHC ligand (**L10**) complexes **405** (Scheme 129a). Kinetics studies showed that the complex catalysts *syn*-**405a** and *syn*-**405b** are remarkably efficient for the RCM of hindered olefins. Samec *et al.*[184] expanded the substrate scope, as described by the synthesis of *N*-aryl, *N*-tosyl, and *N*-alkyl pyrrolines from diallylated amines **403**, derived from the Pd-catalyzed reaction between allylic alcohols and the corresponding amines (Scheme 129b, R^2 = H). The linear amine substrates **403** were transformed into the heterocycles **404** in good to excellent yields by RCM using $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (**406**). The sequence of reactions exhibited high atom economy, with only water and ethane as side products. A one-pot version of the transformation, with the co-presence of the Pd and Ru metals, was successful. Some years later, Samec's group[185] expanded the scope of this strategy towards unsymmetrical diallylated aromatic amines, which enabled RCM promoted by the same Ru catalyst to give 3-substituted 3-pyrrolines (Scheme 129b, R^2 ≠ H). The dialkenyl containing amines were obtained by a two-step coupling sequence between aniline and the two corresponding allylic alcohols in presence of *in situ*-generated Pd $[P(OPh)_3]_3$. An expansion of this methodology was achieved by adding Fe(III) (as $FeCl_3 \cdot 6H_2O$) during the cyclization step, leading *via* a two-step, one-pot procedure to the product of pyrroline oxidation, the pyrrole. In addition, Clayden *et al.*[186] explored the incorporation of urea functionality at R^1 position. Using *N*,*N*-diallylureas as suitable substrates for the RCM in presence of 5 mol% of Grubbs 1st generation catalyst, *N*-[(alkylamino)carbonyl]-2,5-dihydropyrroles were obtained.

Asymmetric syntheses of 3-pyrrolines *via* RCM promoted by ruthenium, in which the pyrroline stereochemistry is defined by the RCM substrates are also possible. For instance, Hong's and Wang's groups[187] collaborated to explore the used of Zhan 1-B Ru catalyst to obtain the 2-substituted 3-pyrroline **409** as a single enantiomer (83–87% ee) from chiral *N*-diallyl *p*-toluensulfonamides **410**, whose stereocenter was defined by the quinidine present in the previous reaction between **407** and **408** (Scheme 130a). Similarly, but with a different stereoselective approach, Kamimura's group[188] reported the preparation of optically active 2,5-dihydropyrroles (**412**) from enantiomerically-enriched aza-Baylis–Hillman adducts (**411**, Scheme 130b). These key substrates **411** were generated *via* an optimized domino-reaction procedure from chiral sulfinimines and *tert*-butyl acrylate. The annulation step promoted by Grubbs' second generation catalyst proceeded smoothly to provide the desired pyrrolines **412** in high yields (92–100%) and conserving the initial enantiomeric excess (90–98% ee). In addition, the formal synthesis of the natural pyrrolizidine alkaloid (−)-trachelanthamidine **414** was proposed based on this methodology, to afford the immediate precursor **413**.[189] Another interesting application of chiral pyrrolines as key intermediates in the synthesis of natural products was achieved by Davies and coworkers.[190] This group developed



Scheme 130 Asymmetric synthesis of 3-pyrrolines and their applications for the generation of natural products.



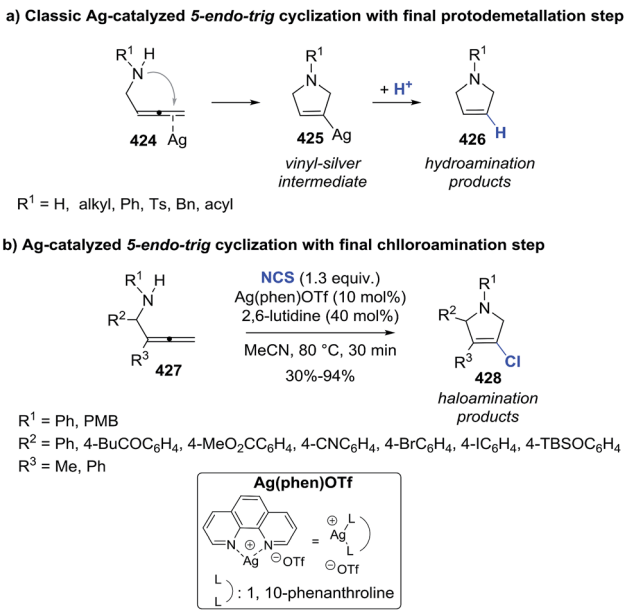
R^1 = Me, Et, *i*-Pr; R^2 = Me, *n*-Bu, cycle-Pr, CH_2OMe, CO_2Me, Ph, Br, TMS;
Ar^1 = Ph, 4-FC_6H_4, 4-Cl-Ph, 4-BrC_6H_4, 4-NCC_6H_4, 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 3-MeC_6H_4, 2-BrC_6H_4;
Ar^2 = 4-$OMeC_6H_4$, 4-MeC_6H_4

Scheme 131 Sc(III)-catalyzed synthesis of highly substituted 3-pyrrolines from *N*-tosylaziridines and alkynes.

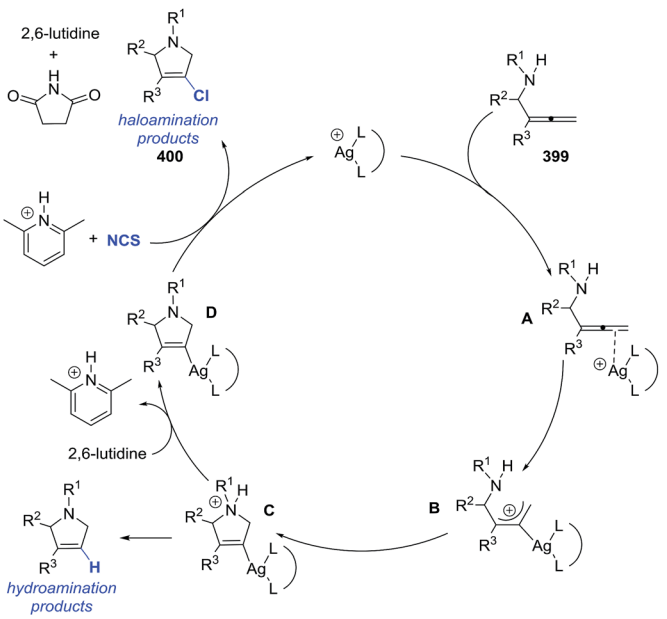
a diastereoselective lithium amide conjugation methodology that enabled the generation of enantiomerically pure β-amino esters **417** and **418**, from lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)-amides **416** and dienyl ester **415** (Scheme 130c). Subsequent ring closing metathesis of **417** and **418** promoted by Grubbs I catalyst provided the dihydropyrroles as the single diastereoisomers **419** and **420** (>99 : 1 dr). This lithium amide conjugate addition was applied as key stereodefining step during the synthesis of the natural alkaloids (+)-tetraponerine-1, -2, -5, and -6 (Scheme 130c).[37] The dehydroxy derivative **319** was used for access to the tricyclic core of the target molecules, which were isolated enantiomerically pure and in acceptable overall yields from commercial starting materials.

2.3.9. Synthesis of 3-pyrrolines by scandium catalysis. As previously mentioned, aziridines are convenient substrates for the generation of pyrrolines scaffolds. For instance, these ring-strained three-membered cyclic amines (**421**) produce azomethine ylides *via* selective C–C heterolysis under the mild reaction conditions involving $Sc(OTf)_3$ as the Lewis acid (Scheme 131).[191] These *in situ* generated dipoles underwent 1,3-dipolar cycloadditions with various electron-rich alkynes (**422**) to afford the highly substituted 3-pyrrolines **423**. This scandium-catalyzed [3 + 2] cycloaddition afforded the desired final heterocycles as a single regioisomer in good yields (65–91%) and with a diverse substitution pattern. Further synthetic modifications of the obtained 3-pyrroline core diversified the substitution, and allowed the transformation of these heterocycles into pyrroles, 1-pyrrolines, and pyrrolidines.

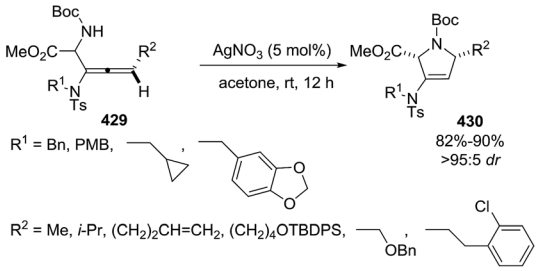
2.3.10. Synthesis of 3-pyrrolines by silver catalysis. The use of catalytic silver to produce 3-pyrrolines from amine-containing allenes has been broadly explored.[45,168,192,193] Usually in these cases, diversely *N*-protected allenic amines **424** underwent $AgNO_3$-catalyzed 5-*endo-trig* cyclization towards the 3-pyrrolines, involving a protodeargentation of the vinyl-silver intermediate **425** as the final step (hydroamination products **426**, Scheme 132a). A novel modification of this approach incorporated different electrophiles, instead of the proton.[194] This concept was probed successfully using *N*-chlorosuccinimide (NCS) as the electrophilic species to obtain the halogenated 3-pyrrolines **428** from allene **427** (Scheme 132b). The annulation was achieved with catalytic [Ag(phe)OTf], as a silver catyalyst with increased air and moisture stability, and lutidine as the base. The cyclic products of this chloroamination were isolated in up to 94% yield. The proposed mechanism is analogous to the previously indicated mechanism. Ag-allene coordination (**A**) leads to the cationic silver complex **B**, followed by nitrogen intramolecular attack with corresponding cyclization (**C**), but with final chlorination by NCS instead of a protodemetallation (Scheme 133). The presence of base is essential, as the base neutralizes the charged species **C** and prevents protonation as a side reaction. Unfortunately, all attempts to use *N*-bromosuccinimide (NBS) failed to give bromodihydropyrroles. Nonetheless, the chloropyrrolines were able to provide different pyrrolines by substitution of chloride, as well as the corresponding chloro-pyrrole cores after oxidative conditions.



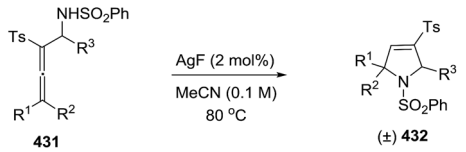
Scheme 132 Cyclization of allenic amines catalyzed by Ag(I).



Scheme 133 Proposed mechanism for the formation of chloro-3-pyrrolines **428**.



Scheme 134 $AgNO_3$-catalyzed synthesis of 2,5-disubstituted 3-pyrrolines **430**.



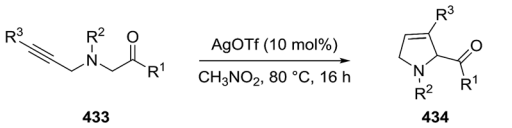
432a,R^1=Me; R^2=Me; R^3=Ph; 97%
432b,R^1=Me; R^2=Me; R^3= cyclohexyl; 97%
432c,R^1=Me; R^2=Me; R^3= isobutyl; 95%
432d,R^1=Me; R^2=Me; R^3= *p*-tolyl; 98%
432e,R^1=Me; R^2=Me; R^3= 4-ClC_6H_4; 78%
432f,R^1=Me; R^2=Me; R^3=4-$MeOC_6H_4$; 99%
432g,R^1=Me; R^2=Me; R^3=4-$NO_2C_6H_4$; 99%
432h,R^1=Me; R^2=Me; R^3= 2-furyl; 83%
432i,R^1=Me; R^2=Me; R^3=cinnamyl; 78%
432j,R^1, R^2= Cyclopentyl; R^3=Ph; 99%
432k,R^1, R^2= Cyclohexyl; R^3=Ph; 98%
432l,R^1, R^2= 4-*t*butylcyclohexyl; R^3= Ph; 99%

Scheme 135 Synthesis of 3-sulfonyl-2,5-disubstituted-3-pyrrolines **432** catalyzed by silver fluoride.

Based on the same strategy, the use of *N*-sulfonamide-substituted allenylamines **429** enabled the preparation of 2,5-disubstituted 3-pyrrolines **430** (Scheme 134).[195] This cyclization proceeded smoothly with $AgNO_3$ to afford the heterocycles in excellent yields (82–90%) and with high diastereoselectivity (>95 : 5 dr, only the major *cis*-diastereomer is shown).

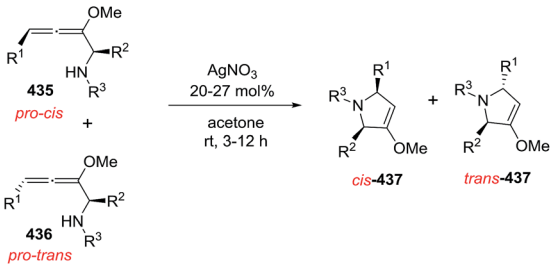
Harmata *et al.* treated a series of allenyl sulfonamides **431** with 2 mol% of AgF in acetonitrile at reflux to obtain the corresponding 3-sulfonyl-2,5-disubstituted-3-pyrrolines **432** with yields ranging from 78 to 99% (Scheme 135).[196] The 5-*endo-trig* cyclization catalyzed by silver tolerates phenyl rings with electron-withdrawing and electron-donating groups, heteroaromatic moieties and aliphatic chains in position R^3. Cyclic system like cyclopentyl and cyclohexyl groups in position R^1 and R^2 are rapidly transform in product indicating that there are no steric effects.

Wang *et al.*[197] reported a novel generation of 2,5-dihydropyrroles **434** from ketopropargylamines **433** *via* a 5-*endo-dig* cyclization promoted by Ag(I) through a Conia-ene-type reaction (Scheme 136). This report represents the first example of transition metal-catalysis of Conia-ene reactions employing monocarbonyl groups as starting materials. The reaction was compatible with a broad scope of functional groups, and with both terminal and internal alkynes. The reaction proceeded efficiently with tosyl and nosyl groups in R^2 position. However, the reaction failed if the *N*-substituent was alkyl, aryl, or acyl.



R^1 = Et, Ph, furyl, naphtyl, 2-$MeOC_6H_4$, 2-BrC_6H_4, 2-FC_6H_4, 3-BrC_6H_4, 3-IC_6H_4, 4-MeC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 3,4-diClC_6H_3; R^2 =Ts, Ns; R^3 = H, Me, Ph

Scheme 136 Silver(I)-catalyzed Conia-ene type reaction.

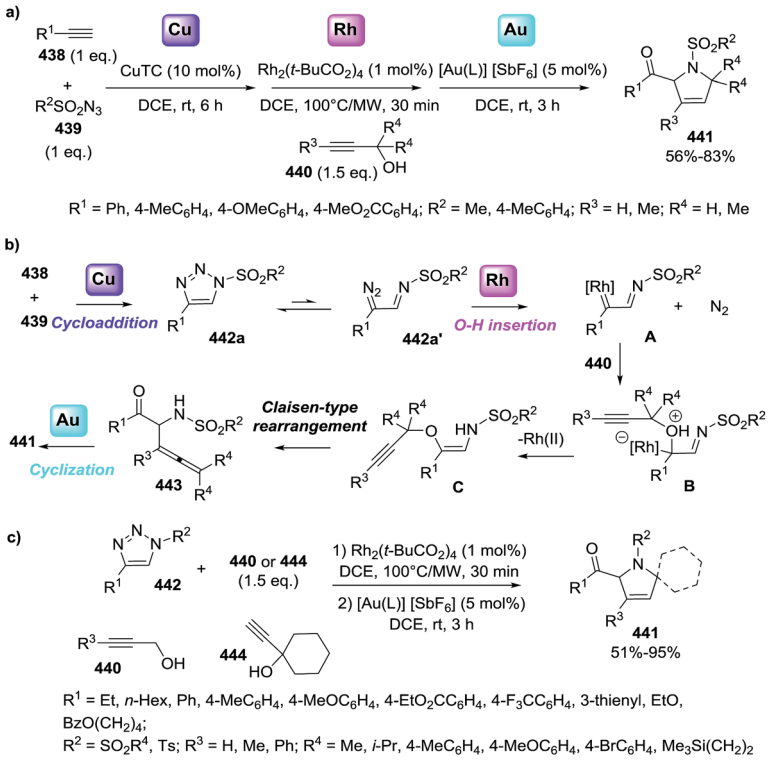


Scheme 137 Silver-catalyzed cyclization to give polysubstituted 3-pyrrolines **437**.

The final pyrrolines were obtained in acceptable to excellent yields (49–94%). Some of the pyrrolines were oxidized successfully to the corresponding pyrroles.

Reissig *et al.* published the synthesis of 1,2,3,5-tetrasubstituted 3-pyrrolines **437** from a mixture of pro-*cis* and pro-*trans* allenylamines (**435** and **436**) using silver nitrate as catalyst at room temperature (Scheme 137).[198] The *cis* and *trans* 3-pyrrolines (*cis*-**437** and *trans*-**437**) were obtained in good yields. However, the silver-catalyzed cyclization was not stereoespecific since silver nitrate would allow a configurational isomerization of axially chiral allenylamines **435** and **436**.

2.3.11. Synthesis of 3-pyrrolines by combined metal catalysis: Cu/Rh/Au. Miura, Murakami and coworkers[169] reported a one-pot, multistep-pathway to 3-pyrrolines **441** from terminal alkynes **438**, sulfonyl azides **439**, and propargyl alcohols **440**. The relay action of a set of three metals (copper, rhodium and gold: Scheme 138a) achieved three sequential reactions culminating with a single final work-up and purification. The plausible mechanism uses initial Cu(I)-catalyzed 1,3-dipolar cycloaddition between alkyne **438** and azide **439** to provide the triazole **442a**, which equilibrates with the α-diazo imine **442a′** (Scheme 138b). Intermediate **442a′** reacts with Rh(II) leading to the α-imine rhodium carbene complex **A**, which reacts with the propargyl alcohol **440** to generate the zwitterionic intermediate **B**. Rhodium release and a proton shift give the (*Z*)-isomer of **C**, which at 100 °C undergoes a spontaneous Claisen-type rearrangement to give the α-allenyl-α-aminoketone **443**. The final step is a gold-catalyzed cycloisomerization to the 3-pyrroline **441**, in a similar manner to the examples described previously in the gold subsection (see Subsection 2.3.3.: Synthesis of 3-pyrrolines by gold catalysis, Scheme 119). In addition, the application of sequential independent second Rh-catalyzed and third Au-catalyzed procedures (each step with its adequate work-up) was evaluated, using the corresponding triazoles **442**



Scheme 138 Sequential one-pot synthesis of 3-pyrrolines catalyzed by three different metals (Cu, Rh and Au). (a) Three transformations with a single, final work-up. (b) Plausible mechanism. (c) Evaluation of the sequential independent Rh-catalyzed and Au-catalyzed reactions.

as starting materials in combination with propargylic alcohols **440** or 1-ethynylcyclohexan-1-ol **444**.

3. Conclusions

In this review, we describe the latest advances in the transition metal-catalyzed or -mediated synthesis of the three classes of pyrrolines, illustrating the most important aspects of each synthetic method. These advances are classified according to the metal involved in the formation of the pyrroline ring. It is worth noting that a comprehensive and up-to-date compilation on the existing methodologies for the synthesis of the three classes of pyrrolines is missing in the literature. Transition metal-catalyzed reactions are no longer a niche of the organometallic chemist but have entered the mainstream synthesis of heterocycles and complex natural products. Efficiency, mild reaction conditions, and tolerance of a wide variety of functional groups are key characteristics of many of these metal-mediated syntheses. There are many articles encompassing a variety of methodologies that use metals in the synthesis of the pyrroline ring. The most common metals used are copper, gold, silver, palladium, rhodium and ruthenium. A popular methodology is the palladium-catalyzed synthesis of pyrrolines from alkene-tethered oxime esters, which allows decorating the pyrroline ring with different functional groups. Another methodology that we would like to highlight is the use of *N*-sulfonyl-1,2,3-triazoles as precursors of α-imino rhodium carbene (aza-vinylcarbenes), which can react with a variety of olefins to produce enantioenriched pyrrolines if chiral rhodium catalysts are used. The metal-catalyzed rearrangement of vinylaziridines to pyrrolines is another exceptionally reliable methodology. Metals such as scandium and nickel have been used lately with excellent results. For example, the scandium-catalyzed synthesis of multi-substituted pyrrolines through sequential reactions has generated complex heterocycles. Nickel catalysts have the advantage that they do not suffer β-H-elimination in cross-coupling reactions, which contrast with the situation met with those based on palladium.

The intention of this review is to inspire further development of the metal-catalyzed synthesis of nitrogen heterocycles, using the pyrrolines as a particular example. Future developments in the transition metal-catalyzed synthesis of pyrrolines will probably involve the adoption of greener reaction conditions, using easily-accessible and less expensive metal catalysts. An increased effort should be devoted to the design of new metal-catalyzed visible-light photo-induced reactions leading to pyrrolines and other nitrogen heterocycles. Apart from being conceptually appealing, these processes are usually efficient, enantioselective and green.

The presence of the pyrroline ring in many bioactive compounds and the remarkable breadth of their reactivity justified the development of new synthetic methods for their construction. Newer approaches to the synthesis of multi-substituted pyrrolines and catalytic asymmetric methodologies for the synthesis of pyrrolines, will be required in the future

to further develop these heterocycles for materials and for medicinal chemistry.

Conflicts of interest

There are no conflicts to declare.

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