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Metal-catalyzed synthesis of cyclic imines: a versatile scaffold in organic synthesis

Debasmita Saha[1], Sourav Bagchi[1], Anuj Sharma[1]*

[1] *Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee 247667, India; e-mail: anujsfcy@iitr.ac.in, anujsharma.mcl@gmail.com*

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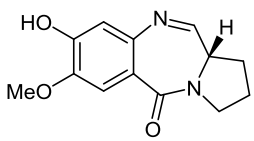
This review decisively focuses on the metal-catalyzed techniques for the synthesis of various five-, six-, and seven-membered cyclic imines. It provides a critical analysis of the catalytic aptitudes of transition metal catalysts in the synthesis of cyclic imines. Enhancement of the existing methodologies in terms of broadened scope, environmentally benign methods, new techniques, and entirely novel catalytic methods is emphasized. The review covers the original literature from 2002 to 2017.

Keywords: cyclic imines, marine toxins, metal-catalyzed synthesis, pharmaceutical industry, versatile scaffolds.

Cyclic imines are an important class of nitrogen-containing heterocycles found in several pharmacologically important alkaloids.[1] Although no standard textbook definition of cyclic imines exists in the literature, any cyclic imine without a residual aromaticity may fall under the category of this class of compounds. This definition would then encompass a huge ensemble of molecules having various applications. For example, this class of compounds constitute a huge family of structurally related marine neurotoxins.[2] These toxins pose a risk to human health with simultaneous contribution toward life-changing medicines. The known marine biotoxins, namely, pirolides, gymnodimines, pinnatoxins, pteriatoxins, prorocentrolides, and spiro-prorocentrimine belong to the class of cyclic imines.[3] Cyclic imines are considered to be useful building blocks in the synthesis of compounds with appropriate structural motifs, including pharmaceutically relevant substances.

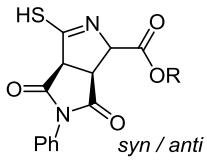
Likewise, cyclic imines retain application in various fields of materials and medicines.[4] Examples of such applications are shown in Figure 1.

Antitumor



(11a*S*)-8-Hydroxy-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]-benzodiazepin-5-one

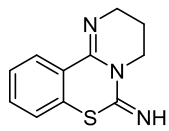
Antioxidant



syn / *anti*

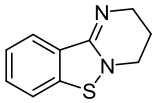
(3a*S*,6a*S*)-4,6-Dioxo-5-phenyl-3-sulfanyl-1,3a,4,5,6,6a-hexahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate derivatives

Antiviral



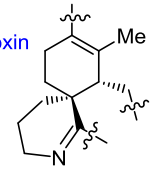
3,4-Dihydro-2*H*-pyrimido-[1,2-*c*][1,3]benzothiazin-6-imine

AntiHIV



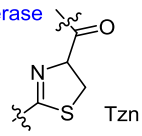
3,4-Dihydro-2*H*-pyrimido-[1,2-*b*][1,2]benzothiazole

Marine toxin



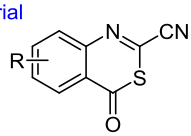
Gymnodimine A

RNA polymerase inhibitor



Cyclothiazomycin B1

Antibacterial



4-Oxo-4*H*-3,1-benzothiazine-2-carbonitrile derivatives

Figure 1. Application of cyclic imines.

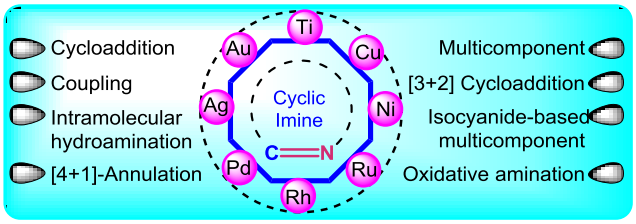


Figure 2. Metal-catalyzed synthetic methods for cyclic imines.

Versatile synthetic protocols have been proposed for the synthesis of cyclic C=N electrophiles such as pyrazolines, oxazolines, imidazolines, benzodiazepines, and benzothiazepines, etc.[5–8] New strategies for the use of cyclic imines as scaffold templates in asymmetric synthesis have paved way to the new prospects in the synthesis of enantio-enriched motifs.[9,10]

Past years have witnessed an upsurge in the research of cyclic imines and their application including progress in chemical synthesis and analytical methods to characterize them.[11] Some excellent reviews have been published on cyclic imine derivatives in context of their natural origin, toxicity, and mechanism of action.[3,12] However, till date, there does not exist a comprehensive review on the synthetic aspects of cyclic imines and present article is expected to fill this void. This review specifically summarizes the synthetic journey of various classes of cyclic imine moieties such as pyrrolines, thiazolines, oxazines, and benzothiazepines, etc. There is an insurmountable amount of literature available on the synthetic paradigm of the above-mentioned heterocyclic structures.[13] Consequently, this review article covers selective metal-catalyzed synthetic procedures adopted till now as a part of cyclic imine synthetic tactics.

As mentioned, the synthesis of cyclic imines covers a vast array of synthetic methodologies like cycloaddition, coupling, multicomponent reaction, [4+1]-annulation, intramolecular hydroamination, etc (Fig. 2). Transition metals are the prime candidates for catalyzing various organic reactions as they contribute to the essential properties for a catalyst, such as bonding ability, variability of oxidation state, and coordination number. For convenience, this article is divided into sections according to the heterocycle size (5-, 6-, or 7-membered cyclic imines) and, further, according to the transition metal used for catalysis.

1. SYNTHESIS OF FIVE-MEMBERED CYCLIC IMINES

Amidst all ring sizes, five-membered cyclic imines are the most prevalent and advantageous.[14] Depending on the type of the heteroatom, they can be classified as pyrrolines, pyrazolines, thiazolines, imidazolines, oxindolines, etc. For example, 2-acetyl-1-pyrroline is an aroma compound with a white bread-like smell and 1-pyrroline-5-carboxylic acid is a biosynthetic metabolite.[4] Whereas, Δ^1-pyrroline, 5-methyl-Δ^1-pyrroline, and 5,5-dimethyl-Δ^1-pyrroline have been identified as substances metabolized to γ-amino-butyric acid (GABA), 4-aminopentanoic acid (methyl-GABA), and 4-amino-4-methylpentanoic acid (dimethyl-GABA), respectively.[15] It has been verified that pyrrolines may represent a chemical class of brain-penetrating precursors of pharmacologically active analogs of GABA.[16]

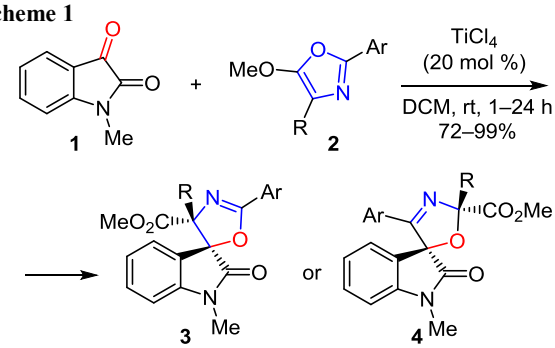
On the other hand, pyrazoles and oxazolines possess a broad spectrum of biological activities such as anti-inflammatory, antimicrobial, antianxiolytic, herbicidal, insecticidal, antimalarial, antitumor, antiviral (including antiHIV), CNS stimulant, etc.[17a–d] For example, celecoxib is a pyrazole derivative used as an analgesic.[17c,d]

1.1. 1st Transition metal series catalyzed synthesis

1.1.1. Titanium-catalyzed synthesis

Starting with the first transiton metal series, Ti was found to be an effective catalyst for synthesis of five-membered oxazolines. Franz's group developed the synthesis of spirocyclic oxindoleoxazolines **3** or **4** by the addition of 5-alkoxy-2-aryloxazoles to isatin **1**.[18] This method provided excellent regiocontrol depending on the substitution at the C-4 atom of 5-alkoxy-2-aryloxazole **2** to obtain either 2-oxazolines **3** or 3-oxazolines **4** in excellent yields (72–99%) (Scheme 1).

Scheme 1



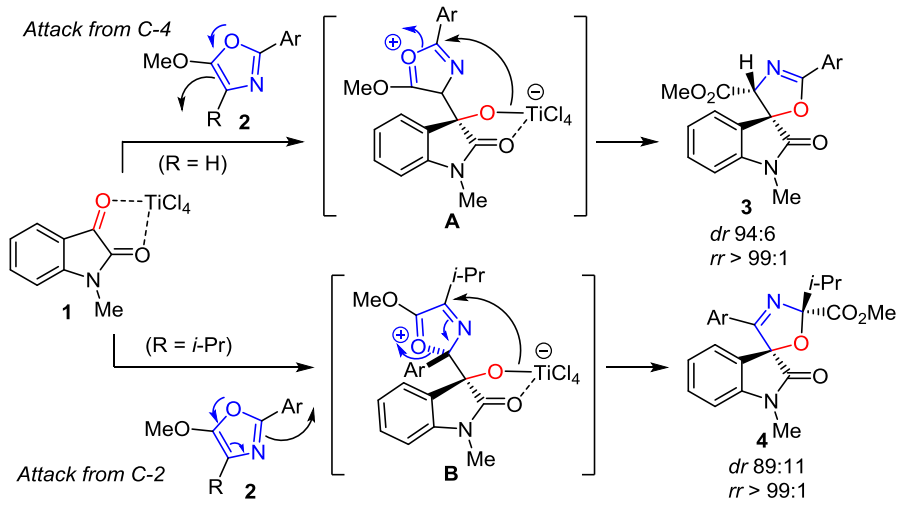
R = H, Me, *i*-Pr
Ar = Ph, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 3,4,5-(MeO)$_3$C$_6$H$_2$

Mechanistically, titanium(IV) activates isatin dicarbonyl to cause nucleophilic attack by oxazole forming zwitterionic intermediate which cyclizes through an intramolecular acyl transfer to afford the *cis*-oxazoline selectively. When R is H or Me on the oxazole ring, initial attack takes place at the C-4 position of the oxazole ring to afford 2-oxazolines **3** selectively *via* the intermediate **A**. Whereas if R = *i*-Pr, steric interactions divert the initial bond formation at the C-2 position *via* intermediate **B** to exclusively form 3-oxazolines **4** (Scheme 2).

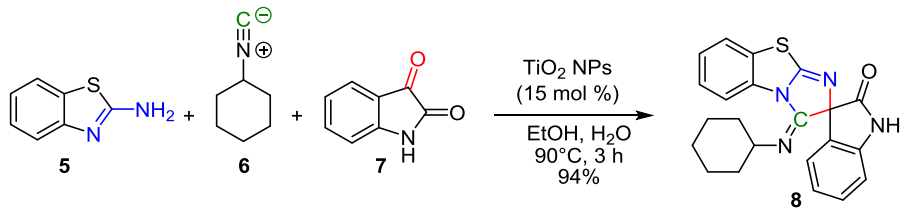
Improving the catalytic system, Tailor et al.[19] devised recyclable and reusable TiO_2 nanoparticles (NPs) to accomplish an isocyanide-based domino protocol for the synthesis of structurally diverse spiroheterocycles spiro-annulated with imidazothiazole or imidazothiadiazole. Three-component reaction involving 2-aminobenzothiazole (**5**), cyclohexyl isocyanide (**6**), and isatin (**7**) gave spiro compound **8** in 94% yield (Scheme 3). This protocol could easily afford diverse spiroheterocycles in excellent yields.

According to the proposed mechanism, the first step is nucleophilic attack of amino group of 2-aminobenzothiazole (**5**) on carbonyl carbon by coordination of TiO_2 NPs with carbonyl oxygen of isatin (**7**) with the formation of imine intermediate. Then nucleophilic attack of endo-

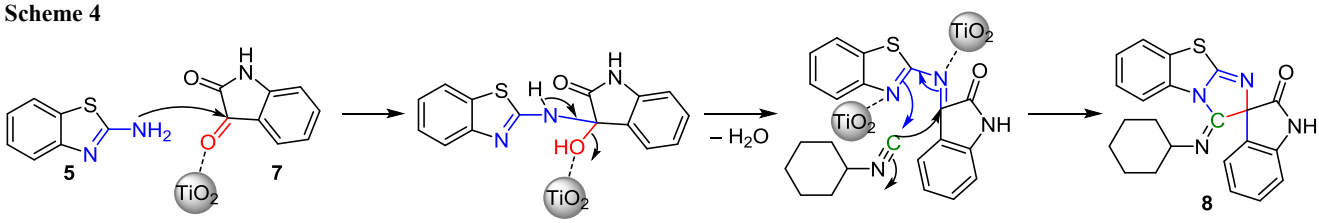
Scheme 2



Scheme 3



Scheme 4

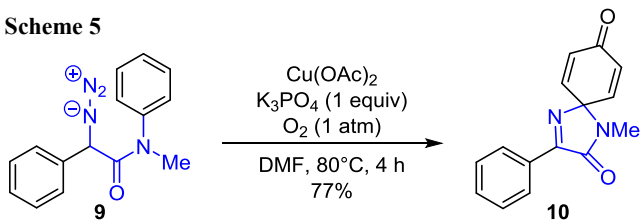


cyclic nitrogen of benzothiazole moiety on carbon of cyclohexylnitrile group and simultaneous attack of cyclohexyl nitrile carbon on imino carbon of imine intermediate provides product **8** through [4+1] cycloaddition (Scheme 4).

1.1.2. Copper-catalyzed synthesis

Copper being the next important metal in transition series is accountable for many intramolecular cyclization reactions. In this milieu, Chiba's group in 2010 developed a copper-catalyzed reaction of *N*-phenyl amide **9** to provide azaspirocyclohexadienone **10** under oxygen atmosphere using K_3PO_4 as an efficient base (Scheme 5).[20a] Azaspirocyclohexadienones are characterized as pivotal intermediates in preparation of biologically active molecules. Azaspiranes are also known antivirals and have inhibitory action for KB cells and human mammary cancer cells.[20b–d] Control reactions and radioisotopic experiments were performed to determine if the reaction is possible in the absence of oxygen and the resulting carbonyl group of the azaspirodienone is from O_2 and plays an important role in C–N bond formation. Electron-donating substituents on the cyclohexadienone ring in azaspirodienones provided good yields, while sterically hindered group in the phenyl moiety of the reactants afforded lower yields. Interestingly, the *N*-phenyl group substituted by a chlorine atom limited the formation of azaspirodienones.

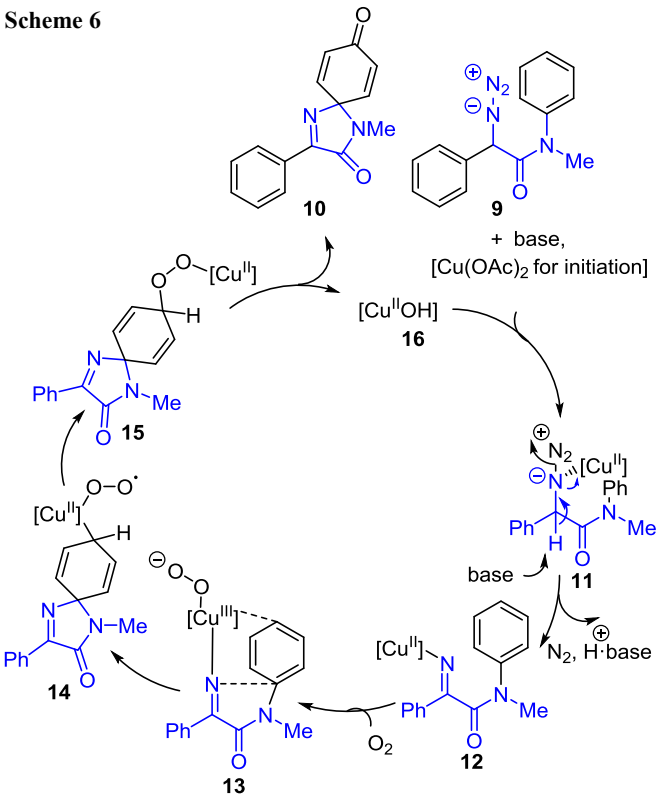
Scheme 5



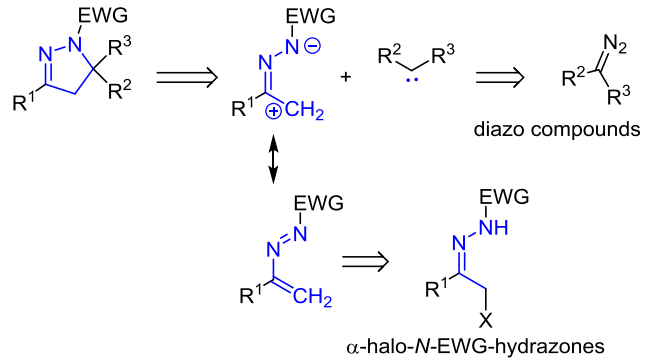
According to the mechanism of the reaction, the first step is denitrogenative formation of iminyl copper **12** *via* intermediate **11**, followed by its oxidation with O_2 to form peroxycopper(III) **13**. Further intramolecular imino-cupration of compound **13** gives C–N and C–Cu bonds simultaneously at the *ipso* and *para* positions of the benzene ring, respectively, affording intermediate **14**. Next, isomerization of intermediate **14** to peroxydiene **15** followed by elimination of [Cu(II)–OH] species **16** forms azaspirodienones **10** (Scheme 6).

Another Cu-catalyzed reaction was developed by Attanasi et al. to assemble pyrazoline structures by [4+1]-annulation reaction involving *in situ* generated C_1 and C_2N_2 partners.[21] For this reason, α-halo-*N*-electron-withdrawing-group-hydrazones were used as 1,4-dipoles to react with diazocarbonyl compounds which acted as 1,1-dipole one-carbon synthons (Scheme 7).

Scheme 6

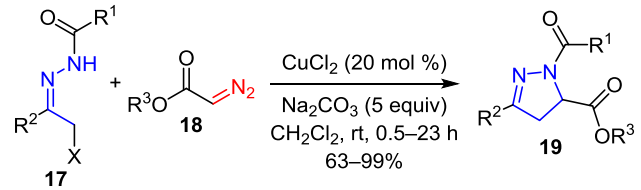


Scheme 7



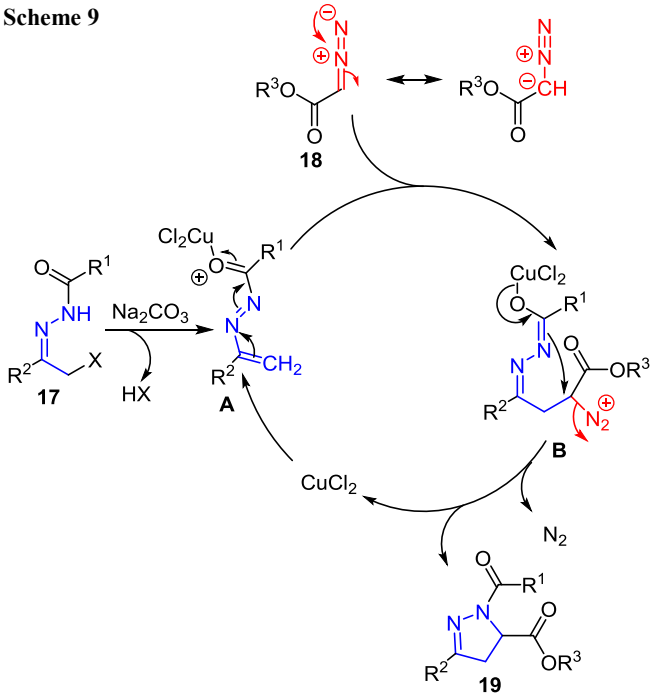
The optimized conditions for this transformation required stirring the mixture of α-halohydrazones **17** and diazocarbonyl compounds **18** at room temperature in the presence of Na_2CO_3 as base and $CuCl_2$ as catalyst (Scheme 8).[21] The versatility of the established method was explored in four aspects: a) protective groups for hydrazone nitrogen atom; b) various electron-donating and -withdrawing substituents on the phenyl ring of acyl hydrazone; c) different ester substituents; d) cyclic *N*-acyl-α-halohydrazone compatibility with the reaction conditions. Overall both electron-withdrawing and -donating groups on the phenyl ring were well tolerated and various alkyl, aryl, acyl, aminocarbonyl, and alkoxycarbonyl groups were found compatible with this methodology (yields 63–99%). In addition, a range of cyclic hydrazones, including five-, six-, and seven-membered rings were synthesized as well. The plausible mechanism for this [4+1]-annulation is described in Scheme 9.

Scheme 8



X = Br, Cl; R^1 = *n*-Bu, OMe, OEt, Ph, Bn, NHPh, 2-Fur; R^2 = Me, CO_2Et, Ph, 4-$O_2NC_6H_4$, 3-$MeOC_6H_4$; R^3 = Et, Bn

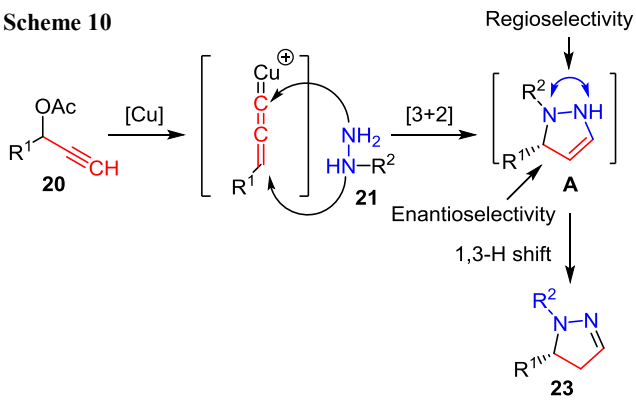
Scheme 9



Initially, *N*-acyl-α-halohydrazone **17** reacts with a base (Na_2CO_3) to generate the short-living azoene species **A** followed by 1,4-conjugated addition of diazoester ylide **18** to hydrazone **A** producing hydrazine intermediate **B**. Subsequent intramolecular cyclization with displacement of N_2 occurs to form the desired dihydropyrazole **19**.

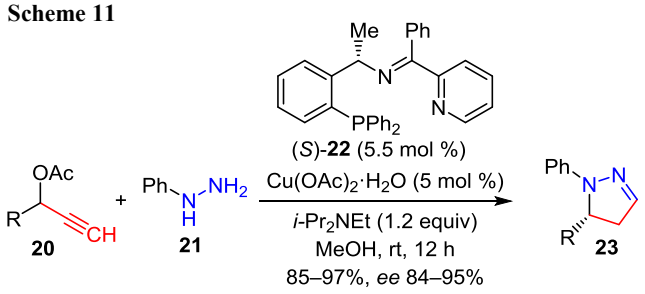
An enantioselective version of 2-pyrazoline synthesis has also been developed involving a catalytic asymmetric [3+2] cycloaddition of hydrazines **21** to biselectrophiles generated from propargylic acetates **20** followed by an 1,3-H migration *via* intermediate **A** to afford 2-pyrazolines **23** (Scheme 10).

Scheme 10



Zhang et al.[22] recently applied this methodology under ambient conditions of stirring for 12 h with $Cu(OAc)_2·H_2O$ catalyst in combination with *P*,*N*,*N*-tridentate chiral ligand **22** (Scheme 11).

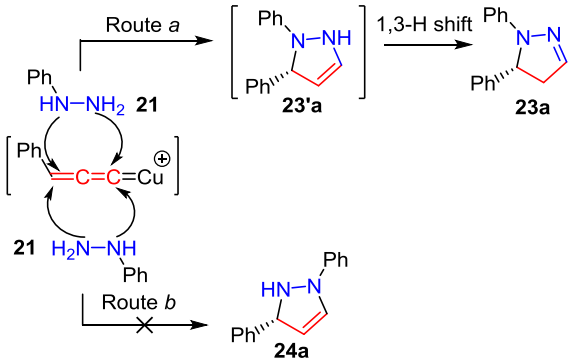
Scheme 11



R = Me, Bn, Ph, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-naphthyl, 2-thienyl

The beauty of this reaction lies in a selective formation of the appropriate regioisomer **23a** with excellent enantioselectivity (Scheme 12, route *a*) in spite of the equally competitive route *b* resulting in compound **24a**. According to the proposed mechanism, the reaction proceeds *via* formation of a Cu-allenylidene complex with hydrazine **21** giving intermediate **23'a**, which in a result of an intramolecular 1,3-H migration leads to chiral 2-pyrazoline **23a**.

Scheme 12



Examining the substrate scope, the functionality on phenyl rings of propargylic acetates has a negligible effect on this cycloaddition reaction, as all electron-donating and -withdrawing groups provided good yields and excellent enantioselectivities. In terms of hydrazines, *ortho*-substituted phenylhydrazines provided lower yields in comparison to *para*- and *meta*-substituted ones.

1.1.3. Nickel-catalyzed synthesis

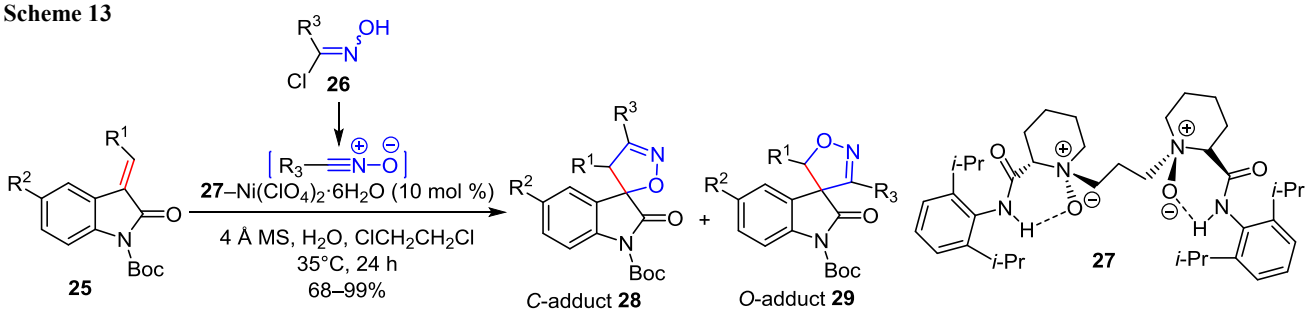
Lian and coworkers[23] designed a highly enantioselective 1,3-dipolar cycloaddition of nitrile oxides **26** to 3-arylideneoxindoles **25** effected by a chiral *N*,*N*'-dioxide-nickel(II) complex to afford a new class of spirooxindoles **28**, **29** (Scheme 13). Here 3-arylideneoxindole derivatives **25** are employed as the dipolarophiles whereas nitrile oxides **26** are used as dipoles. Construction of a spiroindoline structure is associated with several challenges of selectivity *viz.* the reaction regioselectively yields the favored *C*-adduct or the disfavored *O*-adduct. In the search of a new chiral Lewis acid catalyst, various catalytic systems were screened, and 10 mol % of **27**–$Ni(ClO_4)_2·6H_2O$, 1:1, with a small amount of H_2O in DCE at 35°C for 24 h was found to be the optimal conditions affording the product in 43% yield, 97:3 regioselectivity, and 99% *ee*. The method scored well in terms of regioselectivity and enantioselectivity (87–97%), as well as versatility, being compatible with various substituted 3-arylideneoxindoles and nitrile oxides. As an exception 1,3-dipolar cycloaddition reaction of 3-bromo-substituted arylideneoxindoles generated the desired product in 68:32 regioselectivity and 65% yield. The reduced regioselectivity might mainly be influenced by the steric factors due to important differences in terminal nitrile oxide atoms involved in bond formation.

1.2. 2nd Transition metal series catalyzed synthesis

1.2.1. Ruthenium-catalyzed synthesis

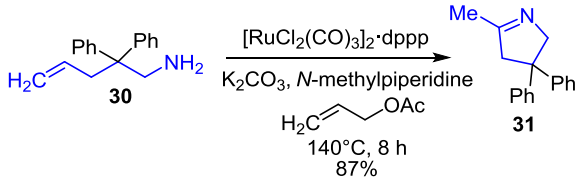
Among 2nd row transition metals, ruthenium is an eminent metal for a catalytic composition to accomplish a wide variety of coupling and amination reactions. One such important method to form 1-pyrrolines is intramolecular cyclization of unsaturated amines or nitriles catalyzed by 2nd row transition metal, e.g., ruthenium. For example, Kondo et al. devised a direct synthesis of 1-pyrroline derivative **31** by a ruthenium-catalyzed oxidative amination[24] of aminoalkene **30** in presence of K_2CO_3 and allyl acetate in *N*-methylpiperidine (Scheme 14). The novel catalyst developed for this purpose is $[RuCl_2(CO)_3]_2$·dppp

Scheme 13



R^1 = Ph, 3-FC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 2,6-Cl$_2$C$_6$H$_3$, 2-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-PhOC$_6$H$_4$, 2-napthyl; R^2 = H, F, Br, MeO; R^3 = Ph, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-CF$_3$C$_6$H$_4$, 4-MeOC$_6$H$_4$

Scheme 14

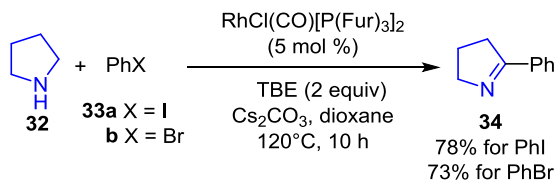


(dppp = 1,3-bis(diphenylphosphino)propane). This protocol can regioselectively give five- and six-membered cyclic imines with its rate of formation being dependent of substitution at the C-2 atom of the aminoalkenes. For example, *gem*-disubstituted at the C-2 atom aminoalkenes showed a dramatic rate enhancement whereas 5-phenyl-4-pentenyl-1-amine having no substituent at the C-2 atom did not yield the product due to significant nonbonding interactions in the acyclic form relative to the cyclic form. Apart from the substituents, product formation was also biased for the ring size as the yield followed an order 5-membered > 6-membered > 7-membered. This dependence was primarily controlled by ring-forming transition states. Interestingly that regiochemistry of olefinic moieties in aminoalkenes (*E* and *Z*) did not affect the reaction.

1.2.2. Rhodium-catalyzed synthesis

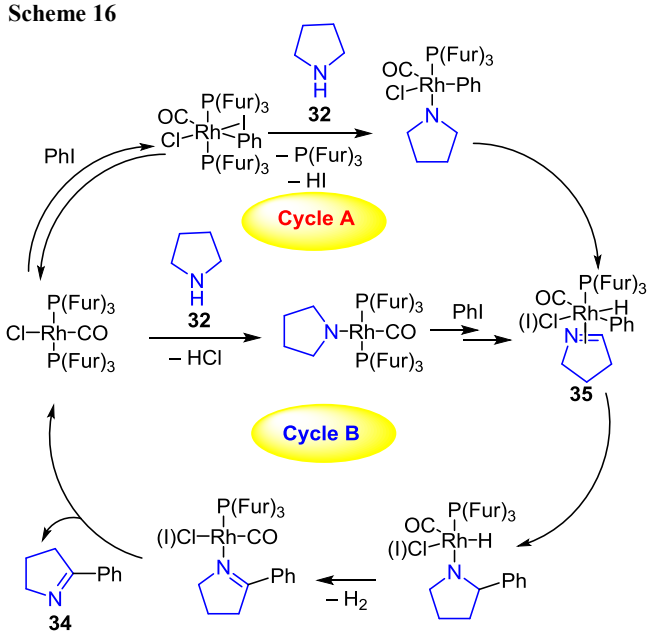
Next, Sezen et al. used saturated 1-pyrroline analogs as substrates *viz.* saturated NH-heterocycle **32** for the synthesis of 1-pyrroline **34**. This method deals with *C*-arylation of saturated NH-heterocycles with haloarene donors **33** by disfavoring *N*-arylation over C–H functionalization.[25] Pyrrolidine (**32**) and iodobenzene (**33a**) were employed as the precursors to examine the feasibility of the cross-coupling reaction in which $RhCl(CO)[P(Fur)_3]_2$ as catalyst, TBE (*tert*-butylethylene) as hydrogen acceptor, Cs_2CO_3 as a base, and dioxane as a solvent at 120°C provided the best yields (Scheme 15). Reaction scope was evaluated in terms of heteroarene donors, size and character of the ring, and chiral NH-heterocyclic substrates. The degree of success of the reaction relied upon three important factors, i.e., nonproductive reduction of haloarene donors present, haloarene degradation pathways due to temperature changes, and catalyst decomposition factor at higher reaction temperature reframe.

Scheme 15



Mechanistically, the first step is oxidative addition of iodobenzene to the rhodium(I) complex followed by α-hydride elimination and formation of imine rhodium hydride, which on a sequential carbometalation and second α-hydride elimination forms 2-phenyl-1-pyrroline coordinated to the rhodium metal. The intermediate rhodium(I)

Scheme 16

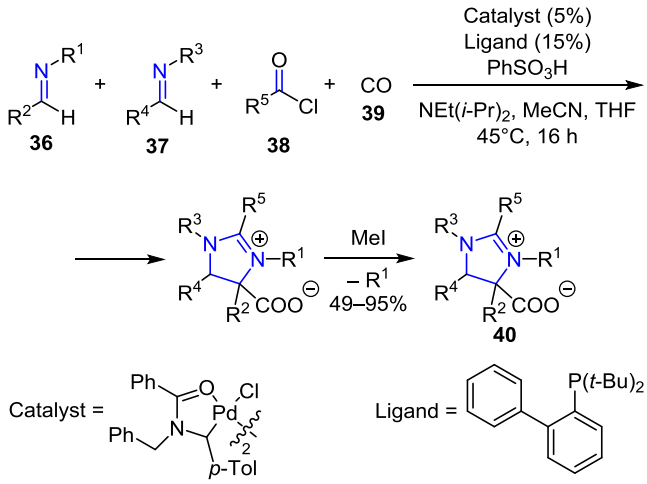


complex **35** can be formed along either cycle A or cycle B, as shown in Scheme 16. Replacement of the organic product by the phosphine ligand at the metal center would form the final product **34** (Scheme 16).

1.2.3. Palladium-catalyzed synthesis

Palladium-catalyzed multicomponent reaction of pharmaceutically relevant imidazolines **40** was proposed by Worrall et al.[26] It includes simultaneous coupling of two imines **36** and **37**, acid chloride **38**, and carbon monoxide **39** within 16 h under mild conditions (45°C, 4 atm of CO) (Scheme 17). 2-Imidazoline, being part of various natural products and pharmaceuticals, is the most important heterocycle among all imidazoline isomers. Some of the generic names of the drugs bearing this ring include oxymetazoline, xylometazoline, and tetrahydrozoline.

Scheme 17

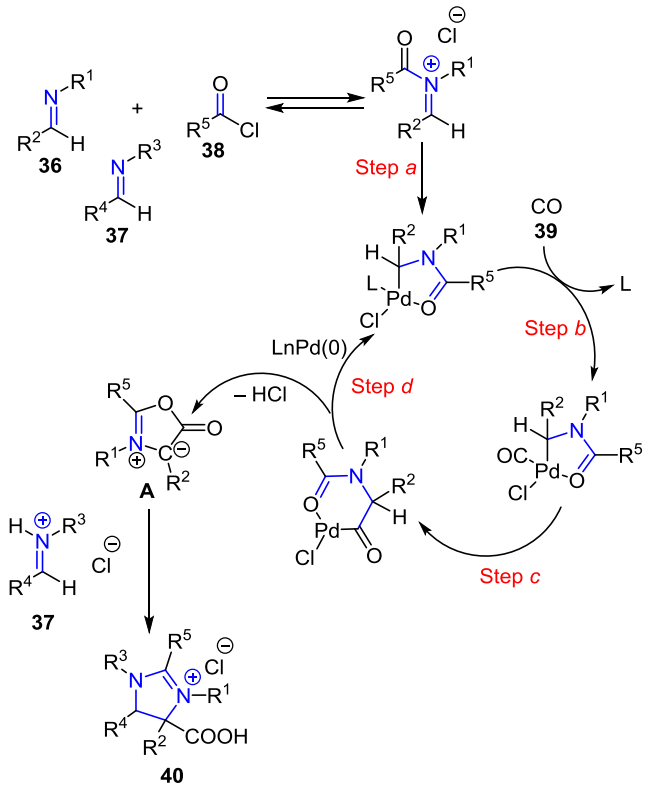


$R^1 = R^3$ = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4
$R^2 = R^4$ = CH_2Ph, furan-2-ylmethyl
R^5 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-thienyl

In their previous reports,[26] the authors described this reaction to be sluggish and of limited substrate scope. These issues have been well addressed in the recent method *via* modification of reaction conditions, allowing access to a diverse range of substituted imidazolinium salts and imidazolines. The main theme of the report by Worrall[26] is in the development of a more active palladium catalyst. From a survey of various triaryl-, dialkyl-, trialkylphosphine ligands used, di(*tert*-butyl)-2-biphenylphosphine produces the greatest rate enhancement with reaction proceeding to completion within hours at 45°C. A range of aromatic imines with halo, thioether, ether, and even furanyl substituents were also compatible with the reaction except for enolizable imines and imines with bulky nitrogen substituents providing diverse imidazolines.

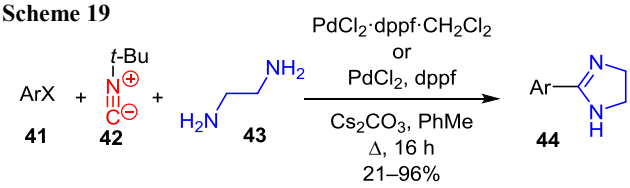
The reaction proceeds through a series of palladium-mediated steps (step *a*: oxidative addition; step *b*: CO coordination; step *c*: CO insertion into Pd–C bond; step *d*: reductive elimination) to form münchnone intermediate **A**. Protonated imine **37** then undergoes rapid cycloaddition to intermediate **A** to form the imidazoline core (Scheme 18).

Scheme 18



Geden et al. synthesized a series of 2-aryl-2-imidazolines[27a] by a palladium-catalyzed isocyanide-based multicomponent synthesis (Scheme 19). This three-component reaction combines aryl halides **41**, isocyanide **42**, and ethane-1,2-diamine (**43**) to provide diverse 2-aryl-2-imidazolines **44** in excellent yields (up to 96%). Motivated by the idea of Whitby et al.,[27b] authors replaced compound **43** by other substituted 1,2-diamines, which provided entry into a wide array of imidazolines.

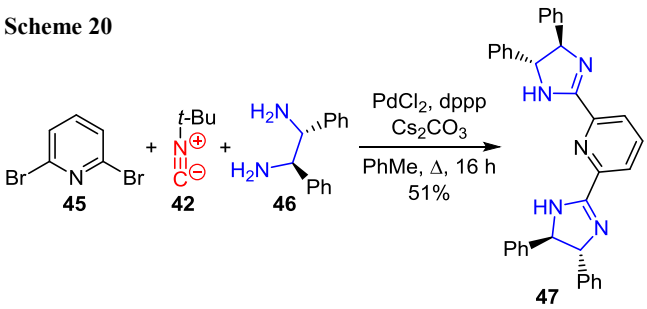
Scheme 19



X = I, Br, OTf; Ar = Ph, 4-ClC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-PhC$_6$H$_4$, 2-Py, 3-Py, 2-thienyl, 2-naphthyl

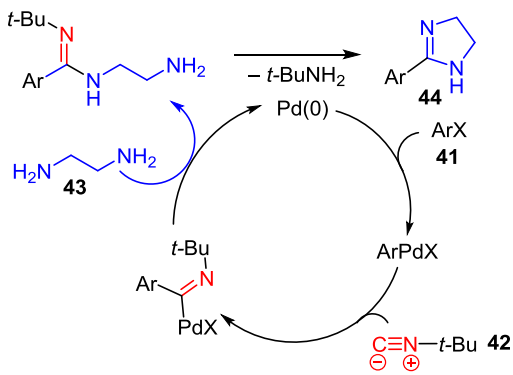
Optimization of the reaction conditions specified the importance of both the phosphine ligand and the inorganic base in achieving higher yields. A broad range of aryl and heteroaromatic halides and aryl triflates performed well under reaction conditions except for nonaromatic halides. Among the diamine alternatives, 1,3-diaminopropane and *N*-alkylated ethylenediamine, with both carbons of the ethylenediamine unit substituted, were found to react successfully. 1,2-Diaminobenzenes provided lower yields of benzimidazoles.

Scheme 20



The significance of this approach was also demonstrated by a one-pot synthesis of chiral pybim ligand **47**, which has applications in ruthenium-catalyzed asymmetric transfer hydrogenation and epoxidation reactions, from dibromide **45** and diamine **46** (Scheme 20). The mechanism is similar to any typical palladium-catalyzed reaction with initial formation of amidine and subsequent cyclization with loss of *tert*-butylamine to form the desired 2-arylimidazolines (Scheme 21).

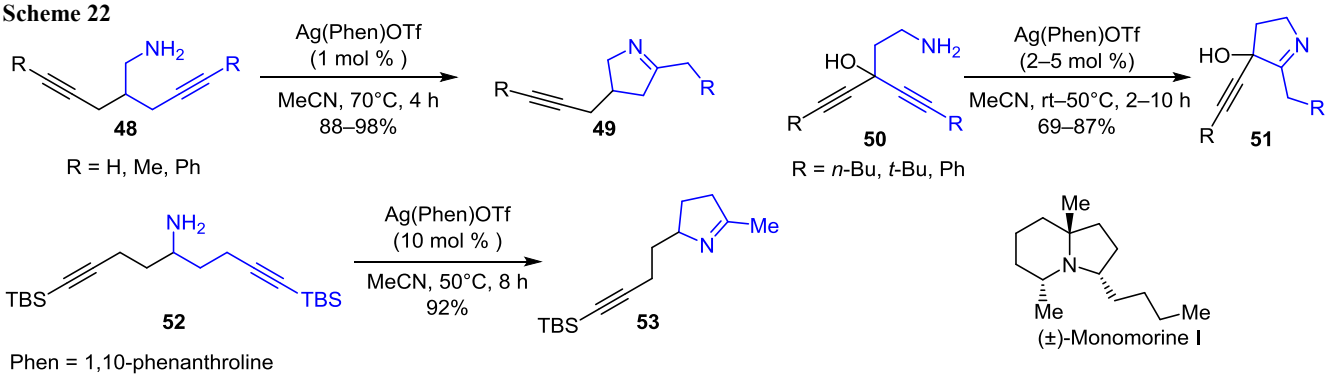
Scheme 21



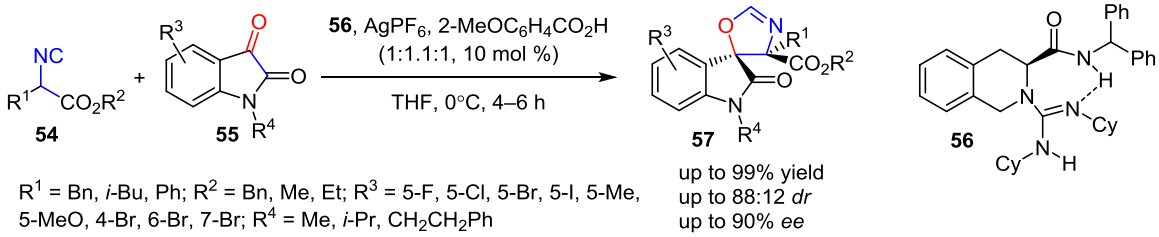
1.2.4. Silver-catalyzed synthesis

Iska et al. described desymmetrization of diynes **48** by the means of silver-catalyzed intramolecular hydroamination to produce functionalized 1-pyrroline derivatives **49** in good to excellent yields.[28] This method is compatible

Scheme 22



Scheme 23



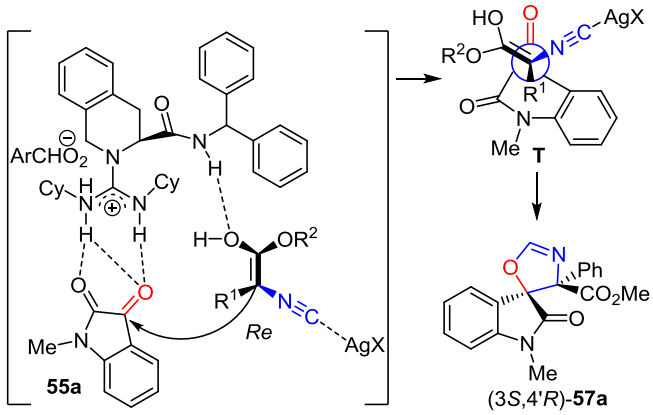
with an interfering functional group, e.g., hydroxyaminodiynes **50** were used as the starting substrates to generate 1-pyrrolines **51** with modified substitution pattern in excellent yields (69–87%) (Scheme 22). Silylated alkyne groups in compound **52** were also found to be compatible with this methodology (92% yield). DFT studies showed that enantioselective desymmetrization could not be achieved because of the silver square-planar coordination. Application of this method has been well demonstrated by the synthesis of indolizidine alkaloid (±)-monomorine I.

Following earlier reports, asymmetric aldol reaction of isocyanoacetate was found to be a well-investigated synthetic area. For example, Ito et al.[29] used a chiral ferrocenylphosphine–gold(I) complex for the asymmetric aldol reaction of aldehydes in 1986. Zhao et al. developed a cooperative combination of chiral aminophosphines and Ag_2O in the addition reactions of aldehydes and unactivated ketones.[30] Escolano performed [3+2] cycloaddition of isocyanoacetate to α,β-unsaturated carbonyl compounds.[31] Recently, Shi et al. reported a bifunctional cinchona alkaloid-derived thiourea-catalyzed asymmetric aldol addition of isocyanoacetates to isatins.[32] Since this reaction was not compatible with aliphatic isocyanoacetates, Lu and coworkers[33] utilized cooperative catalysis of silver salt with chiral guanidine amide **56** to perform the asymmetric aldol reaction between isocyanoacetates **54** and isatins **55**. The corresponding chiral spiro[oxazoline-5,3'-oxindoles] **57** were obtained in good yields (up to 99%), moderate diastereoselectivities (up to 88:12 *dr*) and good enantioselectivities (up to 90% *ee*) (Scheme 23).

Considering the scope of the reaction, phenyl- and alkyl-substituted isocyanoacetates afforded moderate yields. Isatins bearing electron-withdrawing substituents at the C-5 position provided lower yields in comparison to those with electron-donating substituents.

The proposed mechanism suggests that the reaction of $AgPF_6$ with the terminal carbon of isocyanoacetate forms a silver complex, which would increase the acidity of its α-proton. On the other hand, isatin **55a** is activated by the guanidinium unit of the chiral catalyst. The transition state **T** (Scheme 24) enables much easier interaction from the *Si*-face of the isatin and *Re*-face of the isocyanoacetate, leading to the formation of two newly generated stereocenters. Subsequent cyclization would occur by an intramolecular reaction between the hydroxyl group and isocyano group to afford the observed cyclic product (3*S*,4'*R*)-**57a**.

Scheme 24



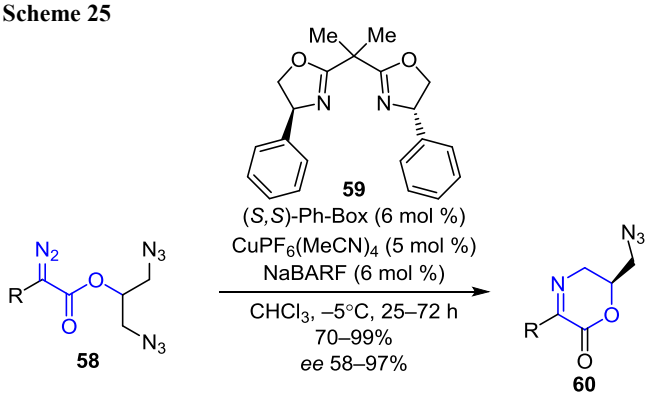
2. SYNTHESIS OF SIX-MEMBERED CYCLIC IMINES

2.1. Copper-catalyzed synthesis

Dihydropyridines are potent blockers of L-type Ca^{2+} channels and have been used as specific probes in the study of dihydropyridine-sensitive Ca^{2+} channels.[34] Encouraged by its pharmaceutical relevance, Wu et al. synthesized dihydroxazolines **60** by catalytic enantioselective

desymmetrization of 1,3-diazido-2-propanol *via* an intramolecular interception of alkyl azides **58** by Cu-carbenoids.[35] The optimized conditions at –5°C in $CHCl_3$ for several days yielded the desired products (Scheme 25).

Scheme 25



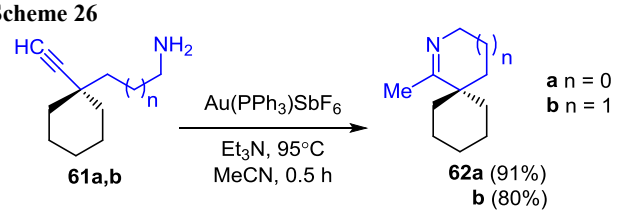
R = Ph, 4-FC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 3-BrC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 1-Naphth, 2-Naphth

Electron-withdrawing substituents on the aryl ring of diazoarylacetates improved the conversion in comparison to electron-donating substituents. Also *ortho* substituents in the aryl ring had an impact on enantioselectivity, for example, chlorine-containing compound showed 97% *ee*, while *ee* of methoxy group-containing compound was 58%.

2.2. Gold-catalyzed synthesis

For the first time synthesis of α-quaternary cyclic imines **62a**,**b** *via* hydroamination of amino alkynes **61a**,**b** was reported by Zhang et al.[36] (Scheme 26). For this purpose, commonly used catalysts for alkyne hydroamination like $Ru_3(CO)_{12}$, phosphine, and *N*-heterocyclic carbene, and others (Fig. 3) have been examined. Amongst all, only $Au(PPh_3)SbF_6$, a convenient gold-phosphine catalyst, could facilitate the reaction. The final optimized conditions of heating amino alkynes **61a**,**b** in the presence of gold-phosphine catalyst and triethylamine in acetonitrile in a sealed tube could afford the respective five- and six-membered cyclic imines **62a**,**b** in 91 and 80% yields, respectively. Unfortunately, this reaction conditions did not afford the seven-membered cyclic imine.

Scheme 26



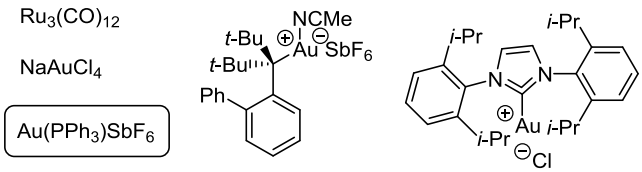


Figure 3. Commonly used catalysts for alkyne hydroamination.

3. SYNTHESIS OF SEVEN-MEMBERED CYCLIC IMINES

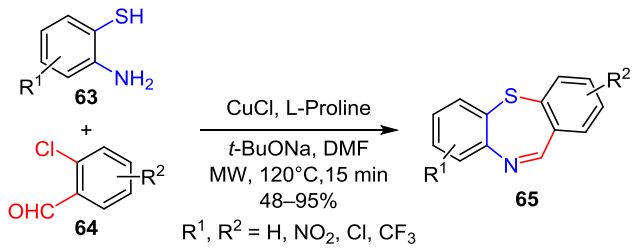
Seven-membered cyclic imines include various positional isomers of benzodiazepine, benzothiazepine, benzoxazepine, etc. These fused seven-membered cyclic imines are endowed with a large spectrum of biological and physiological activities.[37] For example, benzodiazepine scaffold is a vital part of a drug class used to treat anxiety and several other conditions. These are well-known sedatives, hypnotics, anxiolytics, anticonvulsants, and muscle relaxants.[38]

Also benzothiazepines are reported as potential Ca^{2+} channel blockers, anticoagulants, inhibitors of proteases, antihypertensive and antitumor agents. Moreover, this heterocycle is a part of well-known antipsychotics, e.g., clotiapine, quetiapine, tiazesim, diltiazem, etc.[39]

3.1. Copper-catalyzed synthesis

Being fascinated by the prominence of the seven-membered thiazepine rings, Saha et al. portrayed a one-pot copper-catalyzed reaction for the synthesis of dibenzothiazepines using *o*-aminothiophenol and *o*-chlorobenzaldehydes as the starting substrates[40] (Scheme 27).

Scheme 27

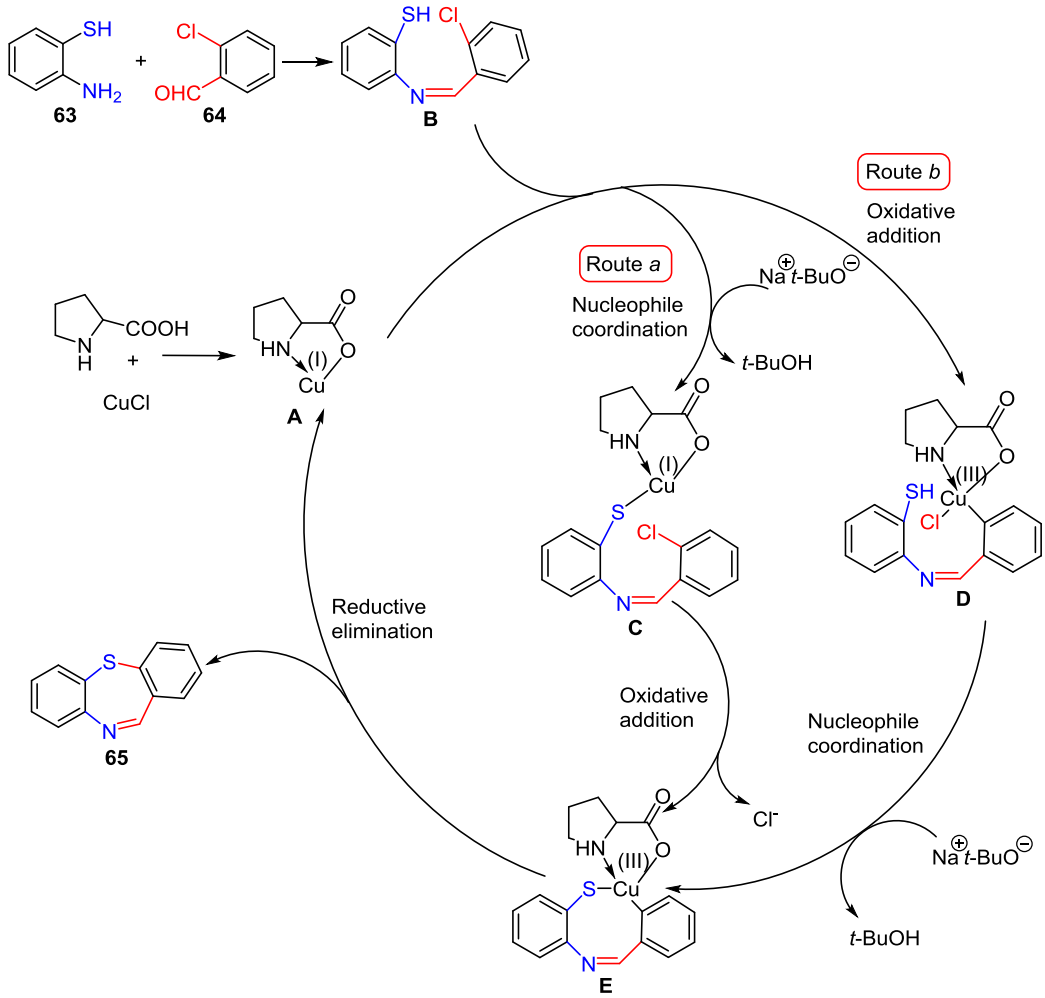


CuCl as a catalyst, L-proline as a ligand with Na^+*t*-BuO^- in DMF at 120°C, under microwave irradiation were declared as the best conditions, which afforded the desired products in 95% yield. Regarding the scope, unsubstituted as well as substituted dibenzothiazepines were obtained in good to moderate yields, indicating that steric rather than electronic effects were important in determining the course of this reaction.

The proposed mechanism might proceed *via* the formation of the Schiff base **B**, as confirmed during optimization reactions (Scheme 28). Here, L-proline acts as a promoter for the intramolecular S-nucleophilic coupling reaction. Proline-ligated Cu(I) complex **A** undergo Cu(I)/Cu(III) catalytic cycle *via* two plausible pathways based on the coordination of nucleophile. In the first case, the coordination of base-deprotonated thiolate ion to Cu(I) complex may occur before oxidative addition resulting in intermediate **C** (route *a*). On the contrary, this coordination may occur after oxidative addition and lead to intermediate **D** (route *b*). Finally, in both cases reductive elimination and removal of copper catalyst system in intermediate **E** may yield the target product **65**.

Also, further diversification of these privileged dibenzothiazepines was performed by synthesizing dihydrodibenzo-

Scheme 28

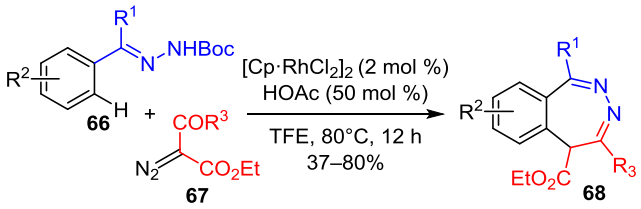


[*b*,*f*][1,4]thiazepine-11-carboxamides *via* the Ugi–Joullie sequence. A different series of potentially biologically active dibenzothiazepinyl and dibenzoxazepinyl phosphonates was obtained *via* solvent-free and catalyst-free Pudovik reaction.[40]

3.2. Rhodium-catalyzed synthesis

Recently Zhu et al. established a Rh(III)-catalyzed C−H activation protocol for the synthesis of 2,3-benzodiazepines **68** with use of *N*-Boc-hydrazones **66** and diazo keto esters **67** as starting substrates (Scheme 29).[41] This reaction undergoes a selective cleavage of *N*-Boc moiety and

Scheme 29



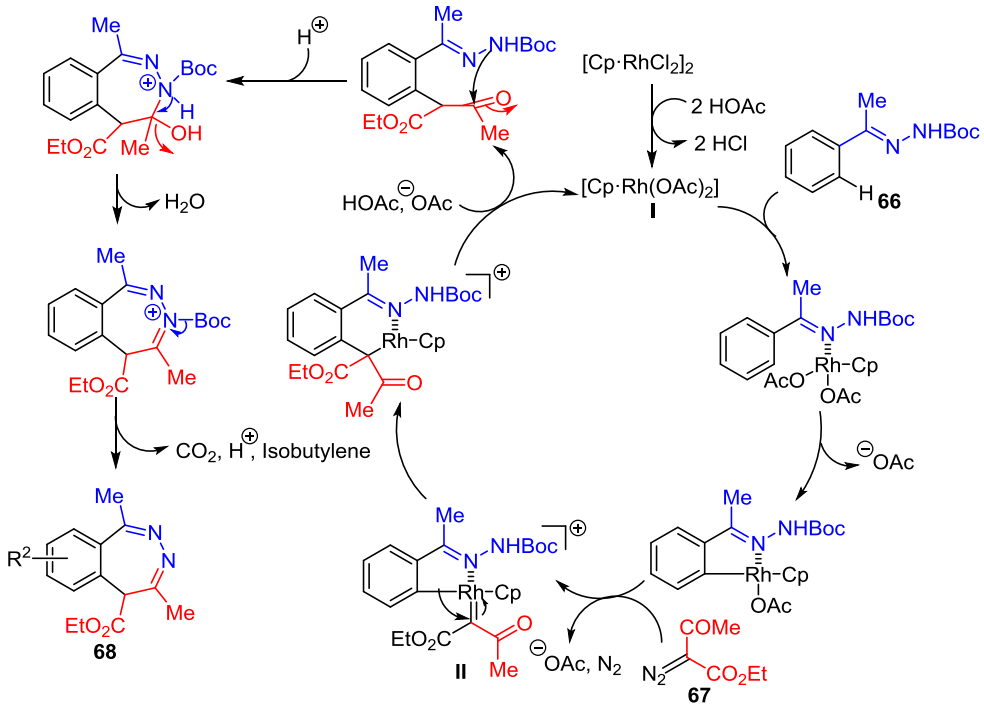
R^1 = Me, Et, *n*-Bu, *i*-Pr
R^2 = H, Me, Et, *t*-Bu, *i*-Pr, Br, Cl, F, CO_2Me, CN
R^3 = Me, *i*-Pr

retention of the C–N and N=N bonds. A wide substituent scope tolerance is the main highlight of this reaction. Here the bulkiness of the substituent on *N*-Boc-hydrazones (Me, Et to a bulkier *n*-Bu or *i*-Pr group) dictates the reactivity – as bulkiness increases reactivity diminishes. Also substrates bearing electronically diverse *ortho*, *meta*, and *para* substituents on the phenyl ring provide moderate yields of the product thereby offering plentiful opportunities for further synthetic expansion.

A combination of $[Cp·RhCl_2]_2$ (2 mol %) as catalyst with AcOH as additive (50 mol %) in triflouroethanol at 80°C afforded the required 2,3-benzodiazepine derivatives **68**.

Mechanistically, first the substrate *N*-Boc-hydrazone **66** coordinates with a reactive rhodium acetate species **I**, which comes from the rhodium catalyst dimer through a ligand exchange process (Scheme 30). This acts as the key step for subsequent C−H bond activation to form a rhodacycle complex. This generates a carbene species, which on further coordination with diazo ketone **67** forms intermediate **II**, followed by 1,1-migratory insertion and protoderhodation leading to the release of C−C coupling product and regeneration of active Rh(III) catalyst.

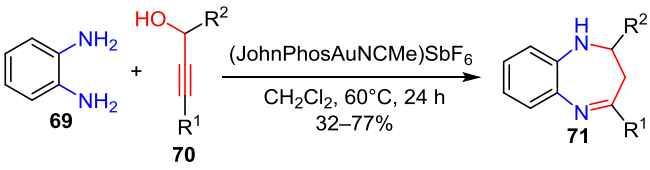
Scheme 30



3.3. Gold-catalyzed synthesis

A gold-catalyzed reaction was devised by Cacchi et al. using *o*-phenylenediamine (**69**) and propargylic alcohols **70** as the starting substrates to afford 1,5-benzodiazepines bearing different substituents on the C-2 and C-4 atoms.[42] This method allows the selective preparation of 2,4-substituted 1,5-benzodiazepine derivatives **71** (Scheme 31).

Scheme 31

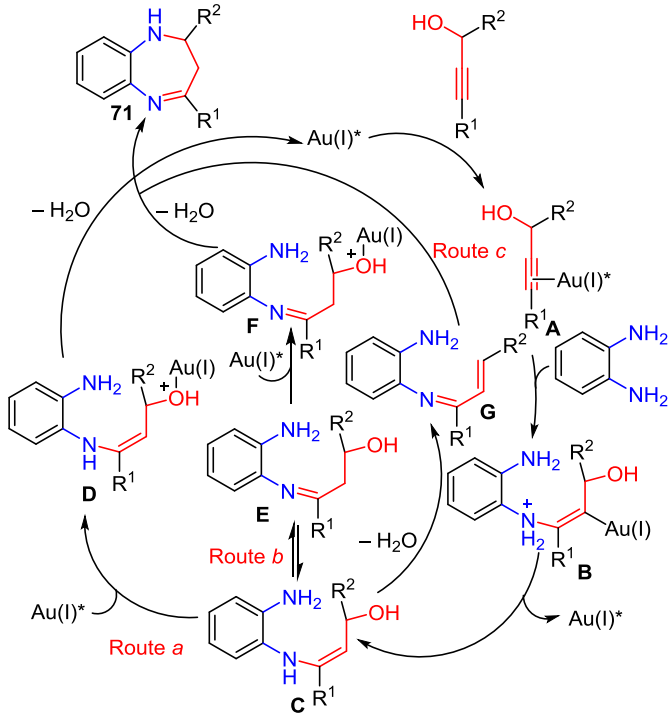


R^1, R^2 = Ph, 4-MeC_6H_4, 4-MeOC_6H_4, 4-NCC_6H_4, 3-MeOC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-EtO_2CC_6H_4

For the synthesis of 1,5-bezodiazepines **71**, 20 mol % of (JohnPhosAuNCMe)SbF_6 in CH_2Cl_2 at 60°C was employed as the standard conditions. Versatility of the method was explored with a range of substituents, and the respective 1,5-benzodiazepines were isolated in good to high yields. With R^1 = Ph, the presence of a strong electron-donating substituent on the propargylic carbon proved detrimental to the reaction yields, most probably affecting the cyclization step.

The reaction mechanism includes a domino hydroamination-substitution sequence involving basic steps shown in Scheme 32. Initially, cationic gold(I) interacts with the triple bond of a propargylic alcohol to form the intermediate **A**, which then reacts with *o*-phenylenediamine to provide intermediate **B**. Further, hydroamination reaction gives the intermediate **C** which *via* intramolecular substitution of the C–N bond for the activated C–O bond is

Scheme 32



converted into the desired product **71** (by route *a* through intermediate **D** or route *b* through intermediates **E**, **F**). Alternative way for compound **71** generation is from intermediate **G** through a conjugate addition reaction, possibly *via* the intervention of Au^+.

This review is a systematic analysis of the metal-catalyzed methods for the synthesis of five-, six-, and seven-membered cyclic imines and comparison of these methods

to the previously reported. The described protocols mostly include multicomponent reactions compatible with sustainable chemistry. The specified improvements of the existing synthetic protocols make them useful for natural product and novel drug compound total synthesis and their future application in the pharmaceutical industry.

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