Chapter

Access to *N*-Heterocyclic Molecules *via* Ru(II)-Catalyzed Oxidative Alkyne Annulation Reactions

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Abstract

In last few decades, the transition metal-catalyzed C-H bond activation and alkyne annulation reactions have turned out to be effective methods for the construction of highly important heterocycles. In particular, the Ru(II) catalysts have been used for the oxidative coupling between an internal alkynes and readily available nitrogen directed compounds in a rapid and sustainable manner. The Ru (II) catalysts are very much beneficial due to their stability in both air and water, ease of preparation, inexpensive than those of Rh(III) and designer Co(III) catalysts usually used for alkyne annulation reactions, requirement of mild reaction conditions, and compatible with various oxidants. Owing to these advantages of Ru(II) catalysts herein, we attempt to highlight the recent development in C-H activation and annulation reactions, which lead to the formation of several important *N*-heterocycles.

Keywords: Ru(II)-catalysts, C-H activation, alkyne annulation, *N*-heterocycles

1. Introduction

The development of highly efficient methods for the synthesis of *N*-heterocyclic skeletons is one of the important targets in organic synthesis. This is because, the nitrogen-containing heterocycles represents a significant class of organic substances, which are particularly found in various biologically active compounds, natural products, drugs, and other medicinally related compounds [1–10]. The *N*-heterocycles especially, pyrroles [2], pyridines/pyridinos [3, 4], indoles [5], isoquinolines [6], quinozalines/quinolizines [7, 8] are useful building blocks of many biologically as well as pharmaceutically active molecules, constitute the core motif of many natural products, and also found wide application in the field of materials science. Due to photo and electrochemical properties highly substituted π-conjugated fused polycyclic *N*-heterocyclic compounds are extensively used as organic semiconductors or luminescent materials [9]. Furthermore, some of these polycyclic *N*-heteroarenes derivatives are versatile building blocks for various natural products [10]. Consequently, in the light of their importance, a large number of efficient methods have been developed, among which the transition metal [Rh(III), Co(III), Ru(II), Pd(II), Ni(II)/Ni(0)]-catalyzed C-H bond activation and oxidative

alkyne annulation reactions are serving as most attractive methodologies, for the construction of *N*-heterocycles [11–16]. The *ortho*-C-H bond activation *via* the use of coordinative functional group followed by cyclization with internal alkynes, commonly known as annulation reaction is extremely motivating as it allows the formation of highly important heterocycles in an atom economical fashion. In this context, the Ru(II) catalysts have been used extensively for the catalytic activation of unreactive C-H bonds and oxidative annulation reactions, particularly with internal alkynes. This is due to several advantages of Ru(II) catalyst such as both air and water stability, easy to prepare, mild reaction conditions, compatible with various oxidants, relatively cheaper and provides excellent chemo- and regio-selective functionalizations than those of Rh(III) and Co(III) catalysts. In this chapter, we attempt to highlight the progresses in the field of C-H bond activation catalyzed by Ru(II) complexes leading to the construction of various *N*-heterocycles via oxidative alkyne annulation reactions.

2. The ruthenium(II) catalyst

For C-H bond activation and oxidative alkyne annulation reactions, the commonly used ruthenium(II) catalyst is dichloro(*p*-cymene)ruthenium(II) dimer, $[Ru(p\text{-cymene})Cl_2]_2$. This dimeric Ru(II) catalyst in combination with acetate/carbonate bases or acetate containing oxidants $Cu(OAC)_2 \cdot H_2O$ generates the active species *via* ligand exchange which is responsible for the deprotonative C-H or C-H/N-H activation. In the presence of other oxidants such as $AgSbF_6$ or KPF_6, the dimeric Ru(II) complex forms an active cationic species either in the absence or presence of $Cu(OAC)_2 \cdot H_2O$. Again, the oxidants are necessary to reoxidize the Ru (0) to Ru(II) after the reductive elimination to regenerate the active catalyst. The various combination of reagents with Ru(II) dimeric complex for the *in situ* generation of active Ru(II) catalyst in the C-H bond activation and oxidative alkyne annulation processes are shown in **Figure 1**.

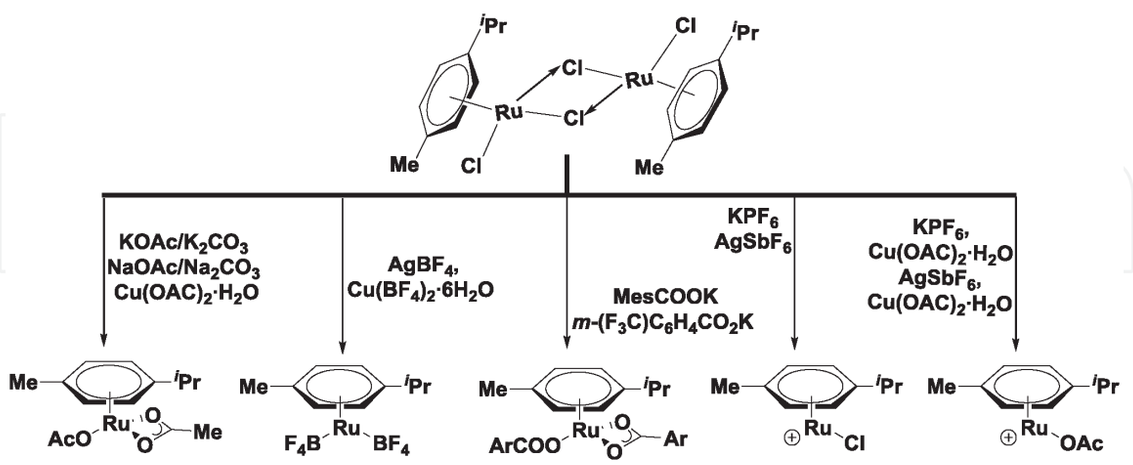

Figure 1.
In Situ *generated active Ru(II) complex.*

3. Ruthenium(II)-catalyzed C-H bond activation

In the past few decades, Ru(II)-catalyzed C-H bond activation has become much popular for the C-C cross coupling reactions. In particular, the directing group assisted (chelation-assisted) C–H bond activation using coordinative functional

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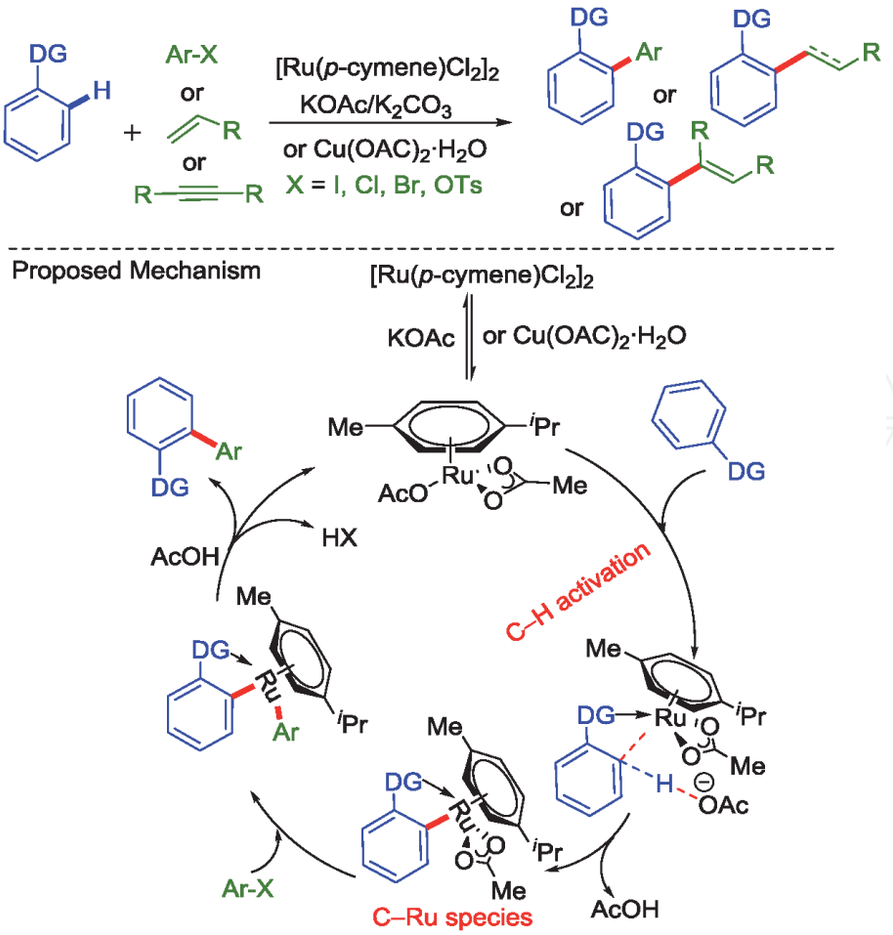

Figure 2.
Ru(II)-catalyzed C-H bond activation for the construction of C-C bond.

group has offered several advantages [17]. Actually this activation strategy uses the proximate effect by coordination of a functional group in a given substrate to the ruthenium centre of the catalyst that brings about regioselective C-H bond activation and functionalization. In the processes of C-H bond activation reactions, the active Ru(II) catalysts facilitates the deprotonation of C-H bonds, before any oxidative addition and the process occur via the assistance of Ru(II) site and *in situ* coordinated carbonate [18] or carboxylate [19]. Alternatively, an intermolecular deprotonation of C-H bonds by carboxylate activates the Ru(II) [20] thereby forming a C – Ru species, which is the key intermediate in the coupling reactions (**Figure 2**).

4. Ru(II)-catalyzed oxidative alkyne annulation reactions

The chelating group assisted ruthenium(II)-catalyzed insertion of an internal alkynes into the *ortho*-C_{Sp2}-H bond, followed by an intramolecular cyclization with the directing heteroatom (particularly O and N atom) or insertion of the alkynes into the C_{Sp2}-H/heteroatom-H bonds is commonly known as oxidative alkyne annulation reaction. These oxidative alkyne annulation reactions provide an environmentally friendly approach and are popular for the synthesis of a verity of useful heterocyclic compounds via the formation of C-C and C-heteroatom bonds in a step economical fashion (**Figure 3**) [21]. The ruthenium(II)-catalyzed alkyne annulation reaction proceeds mainly via insertion of the *in situ generated* active ruthenium(II) complex into the *ortho*-C_{Sp2}-H bond thereby forming a ruthenacycle complex,

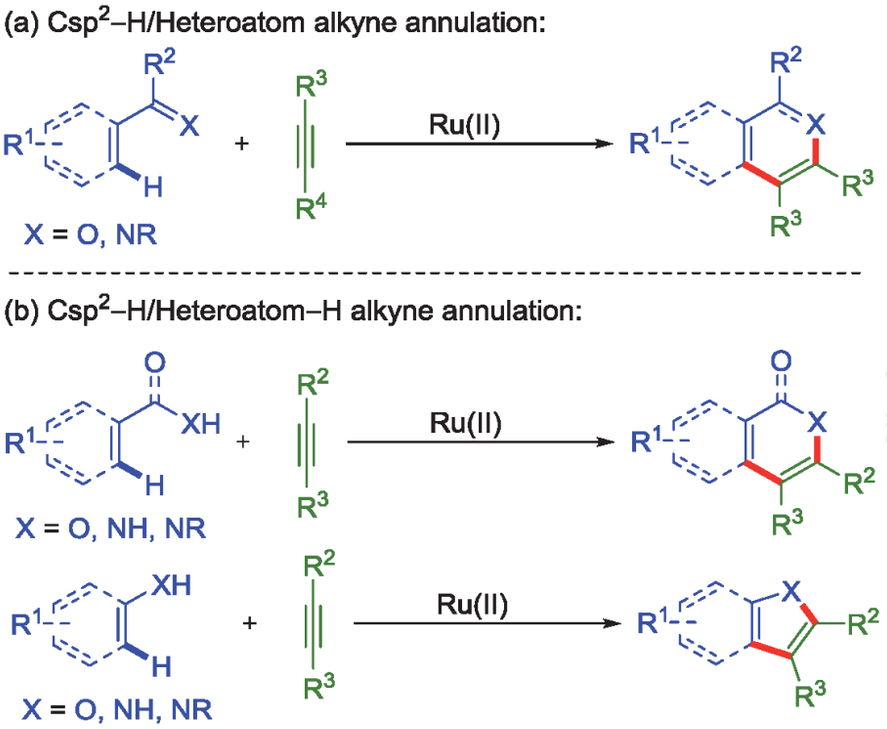

Figure 3.
Ru(II)-catalyzed oxidative alkyne annulation reactions.

insertion of an internal alkyne partner and finally reductive elimination of the active ruthenium complex. Herein, the applications of the ruthenium(II)-catalyzed C_{Sp2}-H/N and C_{Sp2}-H/N-H oxidative alkyne annulation reactions leading to the construction of various *N*-heterocyclic molecules is highlighted.

5. Mechanisetic aspect of Ru(II)-catalyzed C-H/N & C-H/N-H alkyne annulation reactions

5.1 Nature of the C-H bond activation

Ruthenium(II)-catalyzed alkyne annulation reaction started via the activation of the C-H bond *ortho* to the nitrogen atom of the directing group thereby forming a C-Ru species. In this C-H bond activation, whether the C-H ruthenation step is reversible or irreversible can be confirmed by a deuterium-scrambling experiment (**Figure 4**) [22]. If the deuterium exchange on a specific substrate in the absence or presence of alkyne under the standard reaction condition in a deuterated solvent (ionisable) did not afford any H/D exchange or undergoes a minor exchange at the *ortho*-C-H position, suggest an irreversible C-Ru bond formation. On the other hand, if the H atom of the *ortho*-C-H undergoes a significant H/D exchange then the ruthenation step might be reversible.

5.2 Kinetic Isotop effect (KIE) study

In Ru(II)-catalyzed oxidative alkyne annulation reactions the rate-determining step can be explained on the basis of kinetic isotop effect [23]. This can be done by an intermolecular competitive experiment between a non-deuterated and corresponding deuterated substrates with an internal alkyne under the standard reaction condition (**Figure 5a**) or from two parallel reaction involving non-deuterated and corresponding deuterated substrates individually (**Figure 5b**).

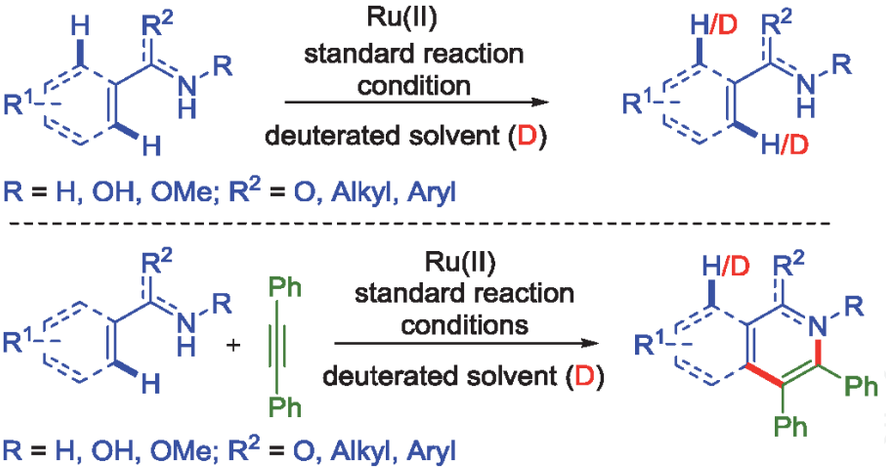

Figure 4.
Deuterium-scrambling experiment.

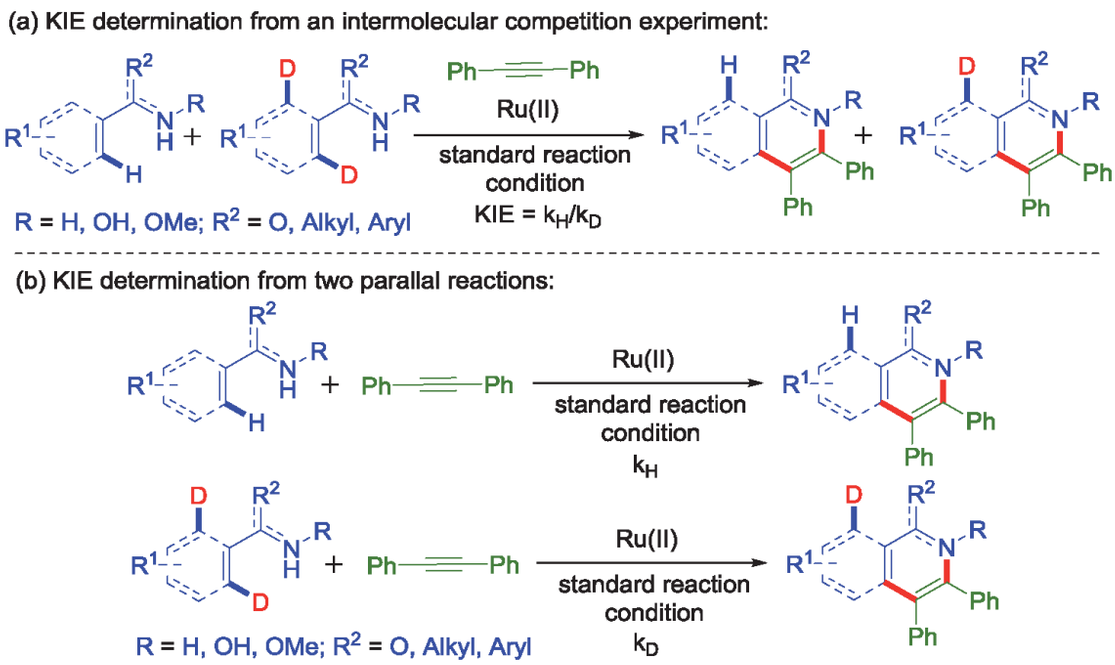

Figure 5.
KIE determination experiment.

If these experiments provide a $k_H/k_D > 1.0$ than it is suggests that the initial C-H bond cleavage, *i.e.*, the C-Ru (reversible or irreversible) bond formation is the rate determining step. The KIE is determined from the ratio between the kinetic constants for the non-deuterated (k_H) and deuterated (k_D) substrates. Nevertheless, it is also estimated indirectly by the measurement of the ratio of individual yield of the corresponding undeuterated product and deuterared analogues or from their ^{1}HNMR spectra in the case of a mixture of products on the basis of their integration ratio.

5.3 Regioselectivity of the alkyne annulation

The regioselectivity of these Ru(II)-catalyzed oxidative alkyne annulation can be determined by the reaction of an unsymmetrical internal alkyne having an alkyl and an aryl substituent such as 1-phenyl-1-propyne. It has been found that the internal

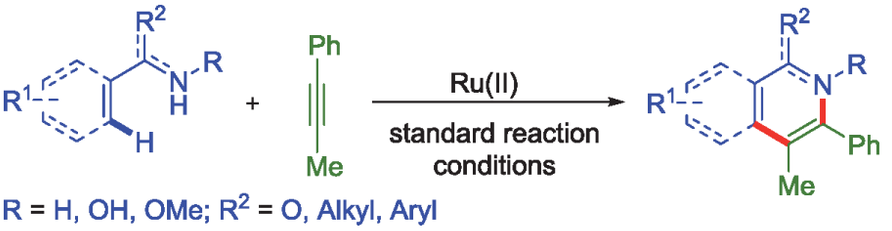

Figure 6.
Regioselectivity of the internal alkyne.

alkyne inserts into the C-H bonds through the carbon atom towards the alkyl part while the aryl substituted carbon center of the internal alkyne is connected to the nitrogen atom (**Figure 6**). This preferential reactivity of the nitrogen atom at the benzylic carbon of an unsymmetrical internal alkynes leading to regioselective annulation is quite similar to that of C-H/O-H C-H/S-H annulation reactions [24, 25].

6. Ru(II)-catalyzed C-H activation and oxidative alkyne annulation reactions for the synthesis of *N*-heterocycles

In the chelation-assisted Ru(II)-catalyzed C-H bond activation the nitrogen-containing directing groups have been consistently used for the reaction with internal alkynes to access *N*-heterocycles through the formation of C-C and C-N bonds respectively [26–34]. In this annulation processes the lone pair of nitrogen atom directs the active ruthenium complex to get inserted into the *ortho*-C-H bond, thereby forming a cyclic ruthenium complex. This cyclic ruthenium complex on subsequent alkyne insertion and finally reductive elimination of the active Ru(II) catalyst left the nitrogen atom becomes part of the final cyclic product.

i. In 2012, Ackermann *et al.* reported a cationic ruthenium(II)-catalyzed efficient redox-neutral annulations of alkynes with readily available oximes for the synthesis of isoquinolines (**Figure 7**) [26]. Herein, C-H/N-O functionalizations occurs by carboxylate-free cationic ruthenium(II) catalyst in the absence of external oxidants through a reversible Ru-C cycloruthenation.

ii. In 2012, Jeganmohan and co-workers reported the synthesis of substituted isoquinolines *via* ruthenium(II)-catalyzed C-H bond activation using ketoximes with internal alkynes (**Figure 8**) [27].

iii. Cheng and co-workers developed a one pot three-component reaction for the synthesis of isoquinolinium salts from benzaldehydes, amines, and alkynes using Ru(II)-catalyst via C-H bond activation and annulation (**Figure 9**) [28]. In this reaction, the active Ru(II) complex first coordinates with the nitrogen atom of the in situ generated imine followed by *ortho*-C-H activation forming a five membered ruthenacycle, this is followed by an alkyne insertion, reductive elimination of the ruthenium to afford the isoquinolinium salts and finally reoxidation to the active Ru(II) by Cu $(BF_4)_2$ allows its further participation in the catalytic cycle.

iv. In 2013, Cheng *et al.* used the in-situ generated Ru(II) catalyst for vinylic C-H bond activation and alkyne annulation to synthesize quinazoline salts

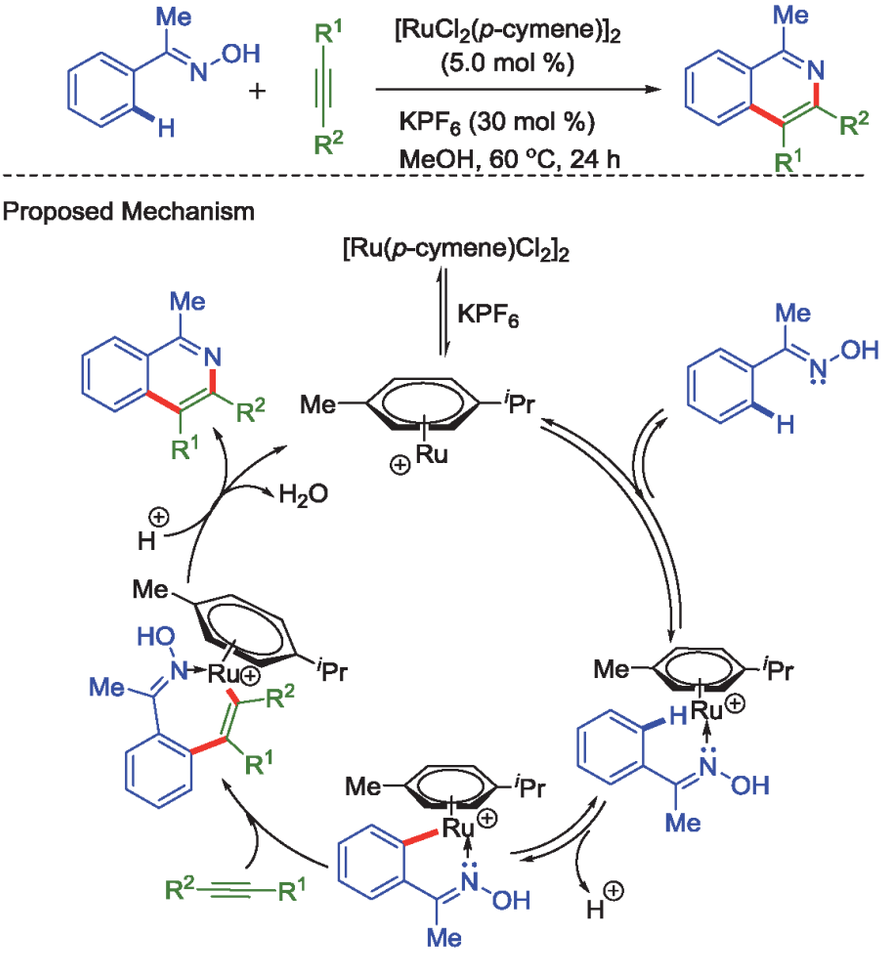

Figure 7.
Carboxylate-free Cataionic ruthenium(II)-catalyzed synthesis of Isoquinolines.

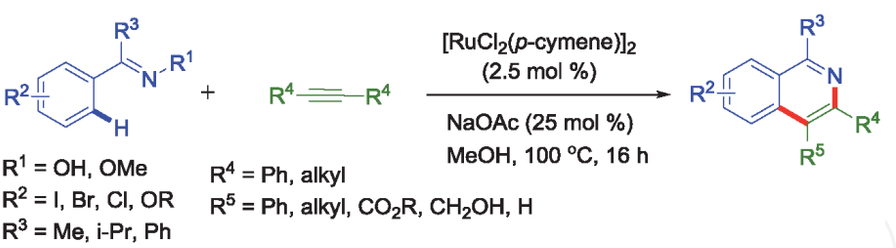

Figure 8.
Ruthenium(II)-catalyzed synthesis of substituted Isoquinolines.

(**Figure 10**) [29]. A possible mechanism involving pyridine assisted vinylic *ortho*-C-H activation of 2-vinylpyridines, followed by an alkyne insertion and reductive elimination is proposed.

v. In 2014, Ackermann *et al.* effectively used carboxylate-assisted cationic Ru (II) complex for the synthesis of exo-methylene-1,2-dihydroisoquinolines via imine-assisted C-H bond activation and oxidative alkyne annulation reaction of ketimines with alkynes (**Figure 11**) [30]. This C-H bond functionalization proceeded with excellent chemo-, site-, and regio-selectivity under an ambient atmosphere of air. The mechanistic studies were indicative of a reversible C-H bond ruthenation step followed by tautomeraization and migratory insertion of the alkyne.

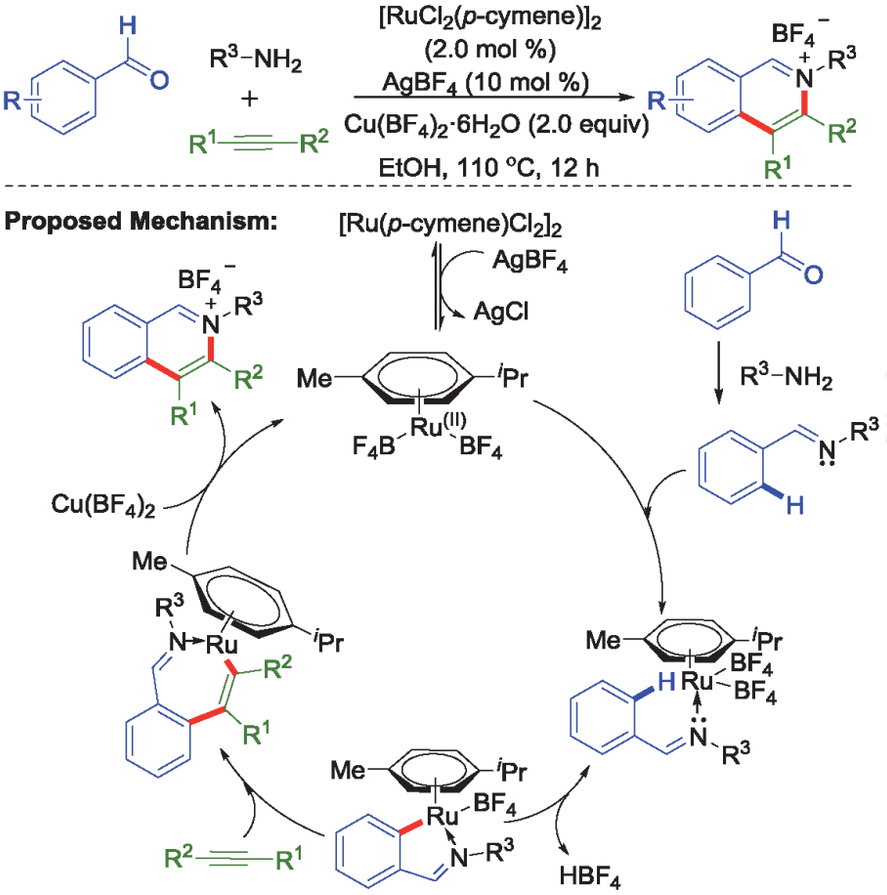

Figure 9.
Ruthenium(II)-catalyzed synthesis of Isoquinolinium salt.

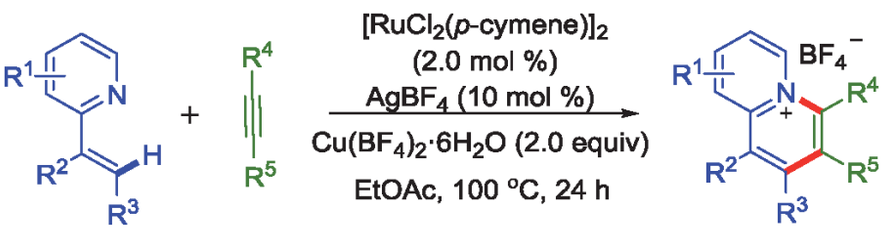

Figure 10.
Ruthenium(II)-catalyzed synthesis of Quinazoline salt.

vi. In 2014, Kundu and co-workers developed an in situ generated iminophosphoranes directed efficient synthesis of isoquinoline-2(1*H*)-ones *via* the Ru(II)-catalyzed ortho C-H bond activation (**Figure 12**) [31]. The reaction involves the coordination of the active Ru(II) catalyst with the *N*-atom of the iminophosphorane intermediate, *ortho* C-H cycloruthenation, insertion of an alkyne into the Ru-C bond, and protonative reductive elimination.

vii. In 2014, Ackermann *et al.* reported a Ru(II)-catalyzed annulation reaction of redox-active challenging ferrocenylalkynes with oximes via C-H/N-O bond functionalization to afford isoquinolines bearing a ferrocene moiety (**Figure 13a**) [32]. They extended the annulations reaction of ferrocenylalkynes with *N*-methoxybenzamides via a ruthenium(II)-catalyzed carboxylate-assisted C-H/N-H bond activation for an efficient

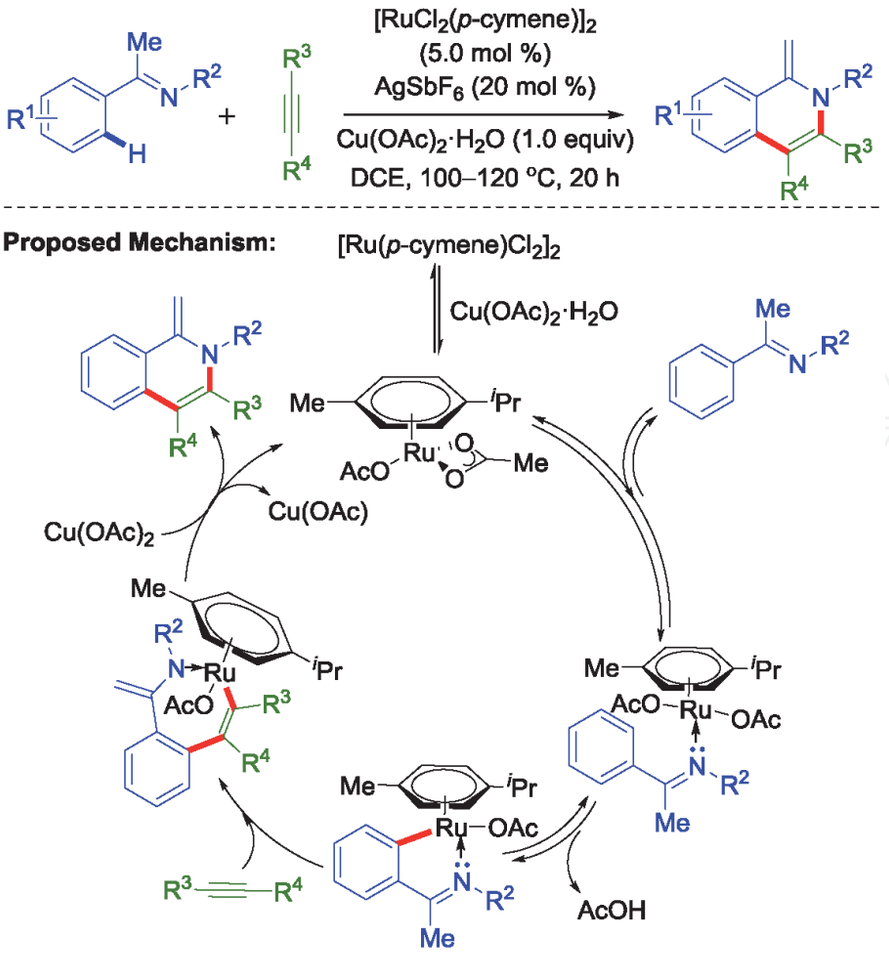

Figure 11.
Ruthenium(II)-catalyzed synthesis of Exo-methylene-1,2-dihydroisoquinolines.

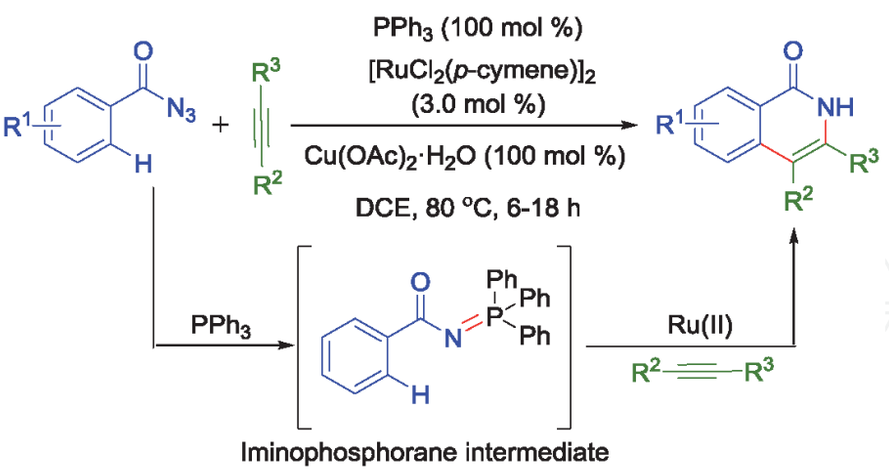

Figure 12.
*Ruthenium(II)-catalyzed synthesis of Isoquinoline-2(1*H*)-ones.*

syntheses of ferrocenated isoquinolones in water as a sustainable reaction medium (**Figure 13b**).

viii. In 2015 wang *et al.* Reported a ruthenium(II)-catalyzed dehydrative [4 + 2] cycloaddition between enamides and alkynes for the construction of a highly substituted pyridines (**Figure 14**) [33]. Herein, instead of the N atom, the carbonyl group of the enamide coordinated to the Ru center to

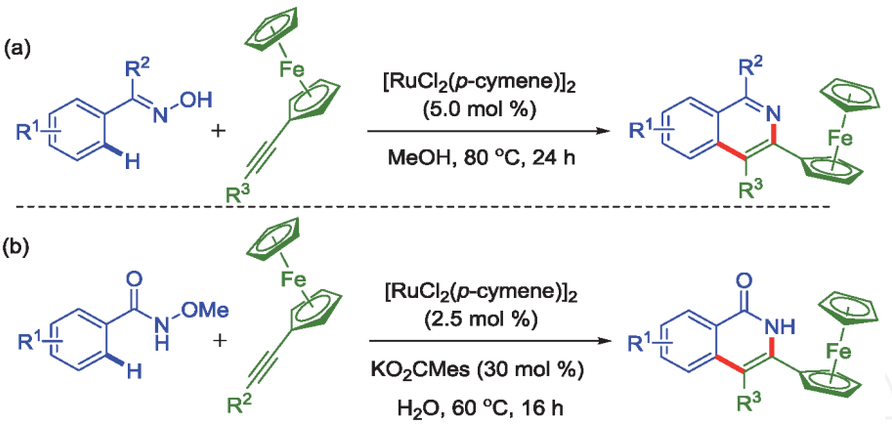

Figure 13.
Ruthenium(II)-catalyzed synthesis Isoquinolines/Isoquinolones.

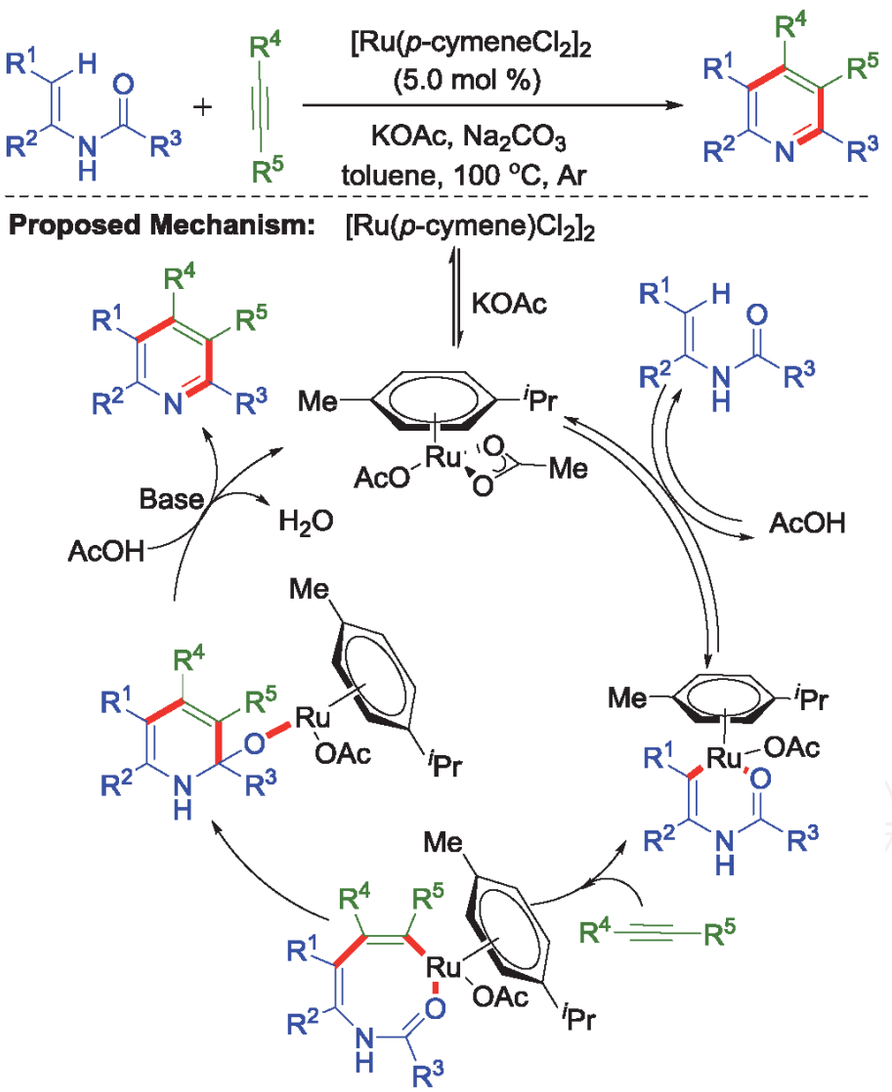

Figure 14.
Ruthenium(II)-catalyzed substituted pyridine synthesis.

direct the C-H activation to generates a six-membered ruthenacycle intermediate. Then the alkyne is inserted into the Ru-C bond giving rise to an eight-membered ruthenacycle intermediate and finally afforded the pyridine analogue through a dehydration path with excellent regioselectivities.

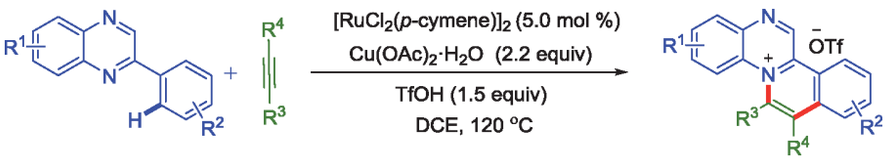

Figure 15.
Ruthenium(II)-catalyzed synthesis of Quinoxalinium salts.

ix. In 2019 our group reported a Ru(II)-catalyzed synthesis of highly luminescent quinoxalinium salt *via* quinoxaline *N*-directed oxidative annulation of 2-arylquinoxalines with an internal alkyne in the presence of a $Cu(OAc)_2 \cdot H_2O$ via the formation of C-C and C-N bonds (**Figure 15**) [34].

7. Synthesis of *N*-heterocycles *via* Ru(II)-catalyzed C-H/N-H dual activation and alkyne annulation reactions

Simultaneously activation of C-H and N-H bonds occurs when the nitrogen atom of the directing group possesses an acidic hydrogen atom. The active Ru(II) catalyst first forms a cyclic Ru complex via a concerted deprotonative metalation generally through acetate/carboxylate assisted N-H/C-H activation. A subsequent alkyne insertion and reductive elimination of the ruthenium affords various *N*-hetreocyclic molecules particularly pyrroles, 2-pyridones, indoles, isoquinolines/isoquinolones derivatives, and various others π-conjugated polycyclic *N*-heteroaromatic molecules in a step-economical fashion *via* C-C and C-N bond formation [35–58].

7.1 Synthesis of *pyrroles via* C-H/N-H alkyne annulation

i. In 2013, Ackermann group reported a versatile synthesis of pyrrole through a ruthenium(II)-catalyzed C-H/N-H bond functionalization and oxidative annulation reaction of electron-rich enamines with various alkynes utilizing air as the ideal oxidant (**Figure 16**) [35].

ii. Baiquan Wang and co-workers reported an efficient and regioselective Ru (II)-catalyzed *N*-acetyl-substituted pyrroles synthesis *via* the cleavage of C (sp^2)-H/N-H bonds and oxidative annulation reaction of enamides with alkynes (**Figure 17**) [36]. The reaction afforded *N*-acylated pyrroles by addition of $AgSbF_6$ as an additive in MeOH solvent.

iii. In 2013, Liu *et al.* developed an efficient cationic Ru(II)-catalyzed oxidative annulation of enamides with alkynes for the synthesis of N-acetylpyrrole derivatives in dimethoxyethane solvent (**Figure 18**) [37]. Further, the reaction can be carried out in an aqueous medium providing 95% yield when diphenylacetylene was used. The yield decreased significantly in aqueous medium when substituted diphenylacetylenes were employed as the coupling partner.

7.2 Synthesis of 2-pyridones *via* C-H/N-H alkyne annulation

In 2011, Ackermann and co-workers used a ruthenium catalyst to execute the C-H/N-H activation and oxidative alkyne annulation reaction to synthesize substituted 2-pyridones via C-C and C-N bond formation (**Figure 19**) [38]. They

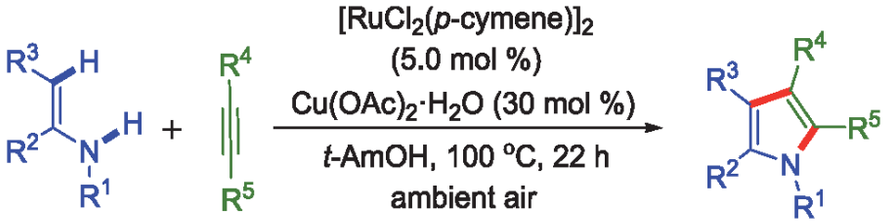

Figure 16.
Ruthenium(II)-catalyzed pyrrole synthesis via *C-H/N-H alkyne annulation.*

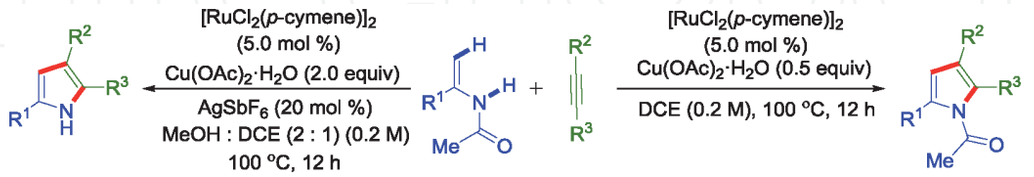

Figure 17.
Ruthenium-catalyzed pyrrole synthesis.

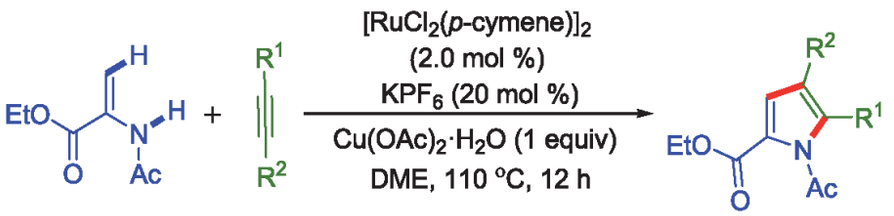

Figure 18.
Cationic Ru(II)-catalyzed synthesis of N*-acetylpyrroles.*

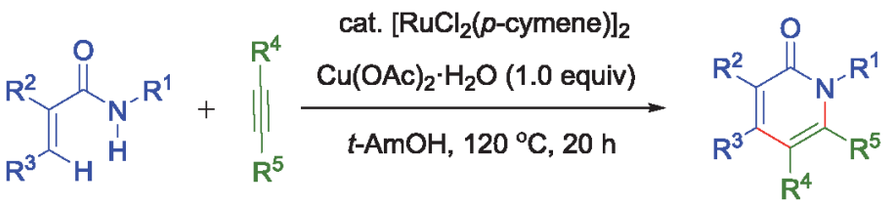

Figure 19.
Ruthenium(II)-catalyzed synthesis of 2*-Pyridones.*

used various electron-rich and electron-deficient *N*-substituted acrylamides as well as diaryl- and dialkyl-substituted internal alkynes which shows a broad and improved range of substrate scope.

7.3 Synthesis of indoles *via* C-H/N-H alkyne annulation

i. In 2012, Ackermann and co-workers demonstrated an cationic Ru(II) catalyzed (generated *in situ*) oxidative C–H/N–H bond functionalizations of anilines using a removable directing group to synthesize various bioactive substituted indole derivatives (**Figure 20**) [39]. Herein, the oxidative alkyne annulation occurs through the construction of C-C and C-N bonds using water as the solvent. Mechanistic studies indicate that the reaction proceeds through the reversible formation of a six-membered ruthenacycles as the key intermediates.

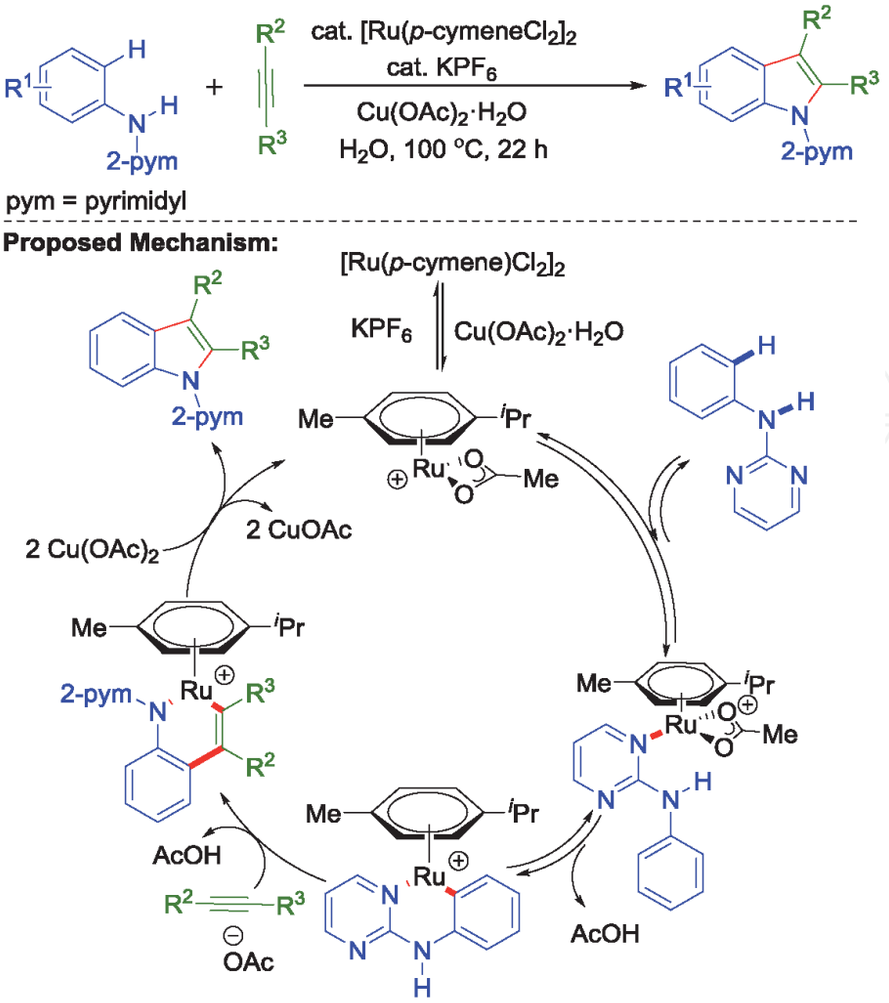

Figure 20.
Cationic ruthenium(II)-catalyzed synthesis of indoles.

ii. In 2014, Huang *et al.* for the first time developed a Ru(II)-catalyzed redox-neutral C-H activation reaction via N-N bond cleavage for the regioselective synthesis of *N*-substituted indoles (**Figure 21**) [40]. The N-N bond of pyrazolidin-3-one acts as the directing group that enables C-H activation and annulation reactions with a broad scope of alkynes. The reaction proceeds via Ru(II)-catalyzed N-H/C-H bond activation, alkyne insertion, internal oxidation of Ru(II) to Ru(IV) and reductive elimination pathways.

iii. In 2018 Xu *et al*. established a ruthenium(II)-catalyzed electrochemical dehydrogenative C-H/N-H bond activation and annulation reaction for the efficient synthesis of indoles using N-2-pyrimidyl-substituted anilines and internal alkynes (**Figure 22**) [41]. Here, the electrolysis reaction proceeds in a simple undivided cell in an aqueous solution and instead of any external oxidant the electric current is used to regenerate the active ruthenium catalyst.

7.4 Synthesis of Isoquinolines/Isoquinolones *via* C-H/N-H alkyne annulation

i. In 2011, Ackermann *et al.* reported an unparalleled ruthenium(II)-catalyzed annulations of alkynes using *N*-benzyl-substituted benzamides as the substrates and internal alkynes as the annulating partner. Here,

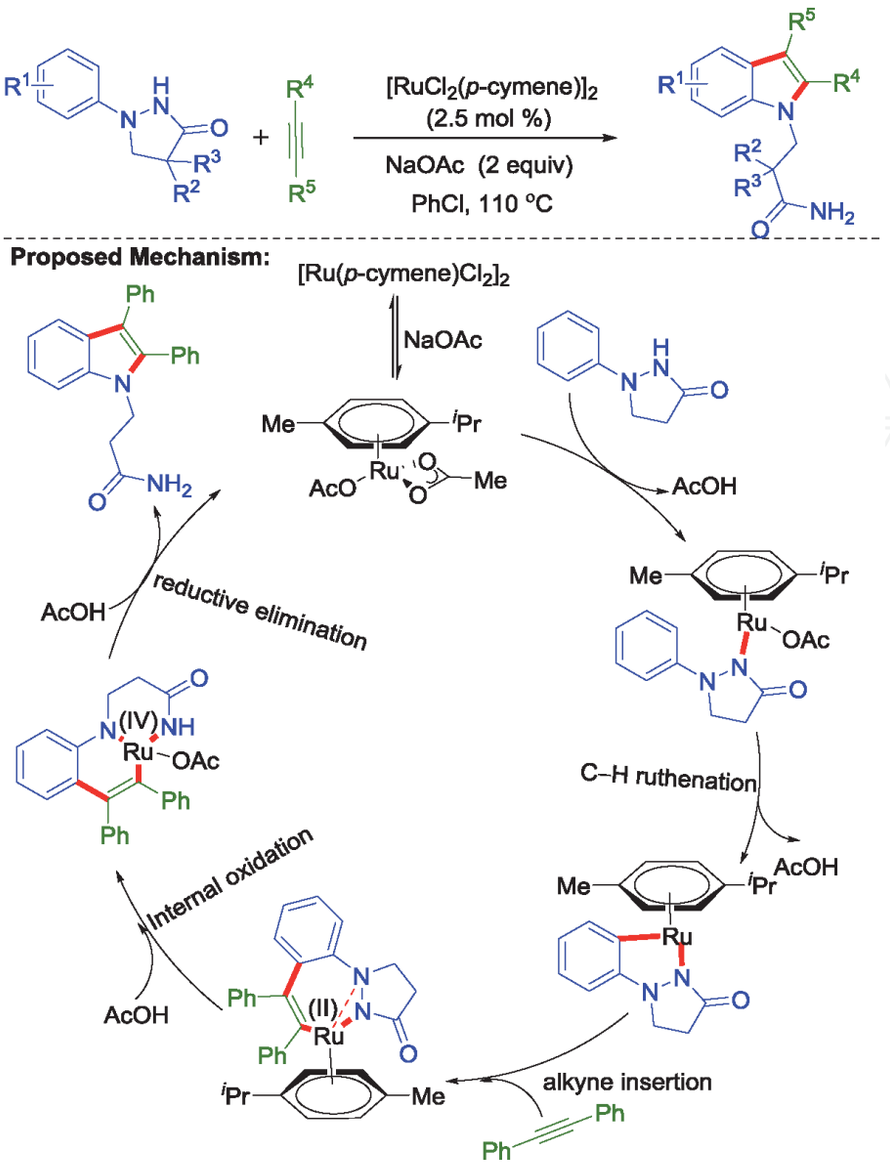

Figure 21.
Ruthenium(II)-catalyzed synthesis of indoles via *N-N cleavage.*

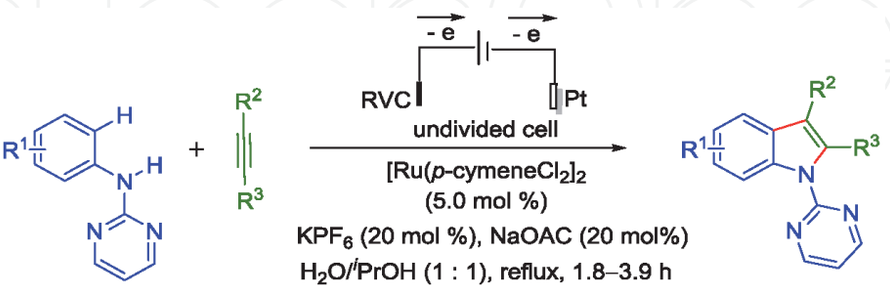

Figure 22.
Ruthenium(II)-catalyzed electrochemical synthesis of indoles.

chemo- and site-selective functionalization of both C-H and N-H bonds occurs during the synthesis of isoquinolone derivatives (**Figure 23**) [42]. Mechanistic studies in deuterated ^{t}AmOH suggests an irreversible C-H bond ruthenation. Further, the kinetic isotope effect (KIE) study provided strong evidence for a rate-limiting C-H bond ruthenation through carboxylate assistance.

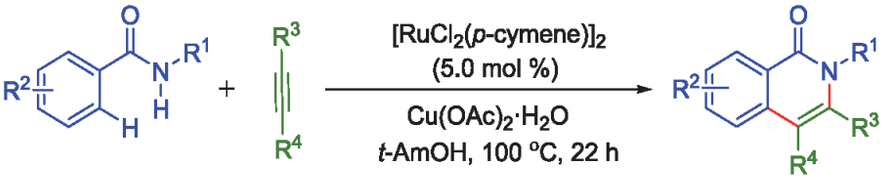

Figure 23.
Ruthenium(II)-catalyzed synthesis of Isoquinolones.

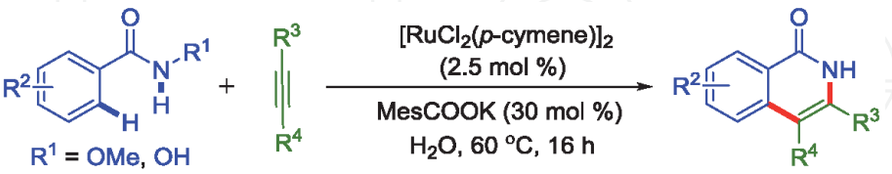

Figure 24.
Ruthenium(II)-catalyzed external oxidant free synthesis of Isoquinolones.

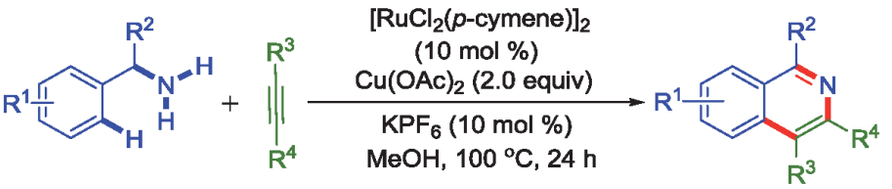

Figure 25.
Ruthenium catalyzed synthesis of Isoquinoline derivatives.

ii. Ackermann group established an external oxidant-free annulation reaction for the synthesis of isoquinolones which proceeds via N-H/C-H activation. The reaction is accomplished through a carboxylate assisted ruthenium(II) catalyst with ample substrate scope in an aqueous medium. In this annulation reaction, the N-O bond of N-methoxybenzamides served as the internal oxidant and free hydroxamic acids were also found to be good substrates for this alkyne annulation due to chemoselectivity of the ruthenium(II) carboxylate catalyst (**Figure 24**) [43].

iii. In 2013, Urriolabeitia and co-workers have developed an unprotected primary amine (benzylamines) directed Ru(II)-catalyzed oxidative coupling with internal alkynes for the synthesis of isoquinolines (**Figure 25**) [44].

iv. In 2014, another external oxidant-free alkyne annulation reaction was reported by Ackermann *via* an *in situ* generated ruthenium(II) biscarboxylate catalyst. This dehydrative alkyne annulations proceeds via a C − H/N − H activation followed by N-OH cleavage of NH-free hydroxamic acids in water producing water as the sole by product (**Figure 26**) [45]. The ruthenium(II) catalyst derived from the electron-deficient carboxylic acid *m*-$(F_3C)C_6H_4CO_2H$ displayed highly regio- and site-selective C − H functionalizations with a broad substrate scope. Further, detailed mechanistic studies suggest a kinetically relevant C − H metalation by carboxylate assistance along with subsequent migratory alkyne insertion, reductive elimination, and intramolecular oxidative addition.

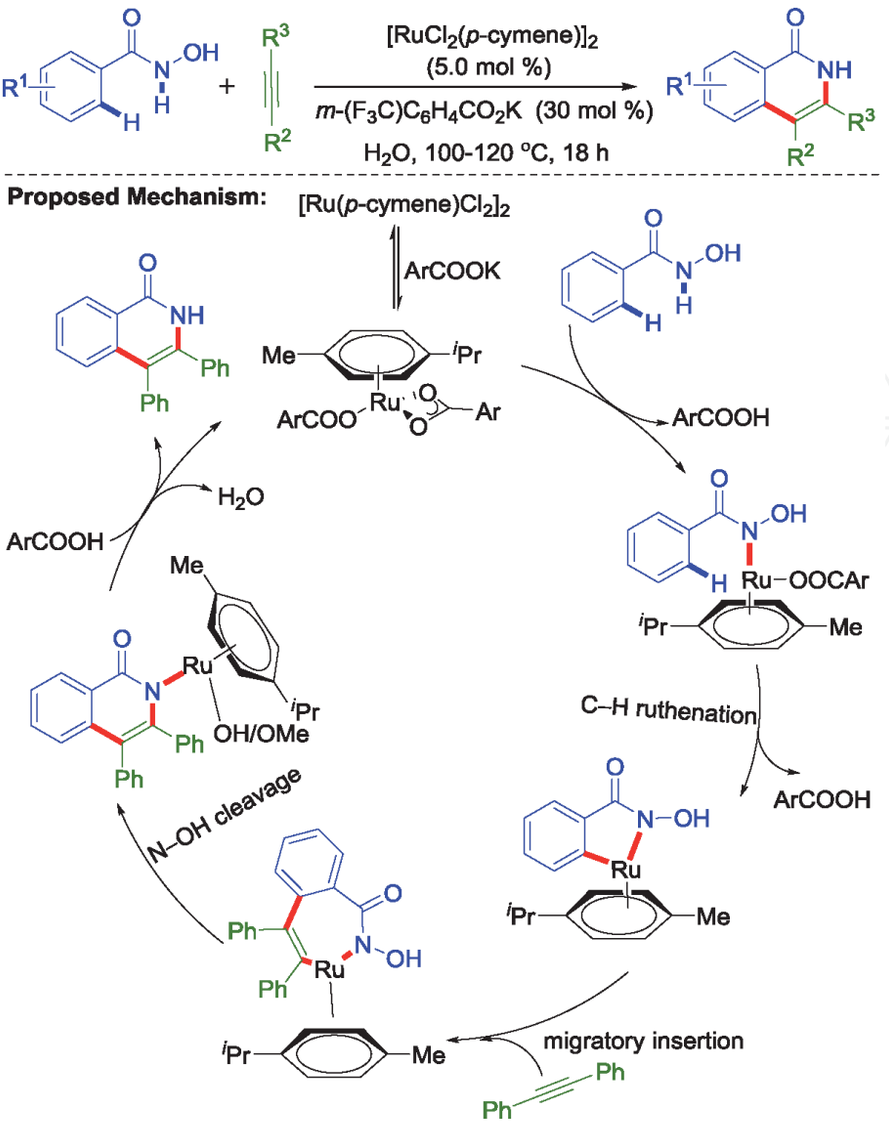

Figure 26.
Ruthenium(II)-catalyzed external oxidant free synthesis of Isoquinolones.

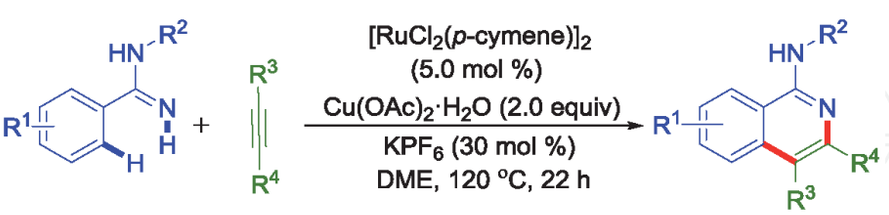

Figure 27.
Ru(II)-CatalyZed synthesis of 1-Aminoisoquinolines derivatives.

v. In the same year, Ackermann group developed an efficient C-H functionalizations and oxidative annulation reaction on aryl and heteroaryl amidines with internal alkynes to access 1-aminoisoquinolines (**Figure 27**) [46]. Herein, the in situ generated cationic Ru(II) complexes derived from KPF_6 or AgOAc displayed a reversible C-H bond activation and C-H/N-H alkyne annulation with high site-, regio- and, chemoselectivity.

vi. In the year 2014, Swamy and co-workers use 8-aminoquinoline moiety as an auxiliary bidentate directing group for ruthenium(II)-catalyzed oxidative annulation of *N*-quinolin-8-yl-benzamides with alkynes to

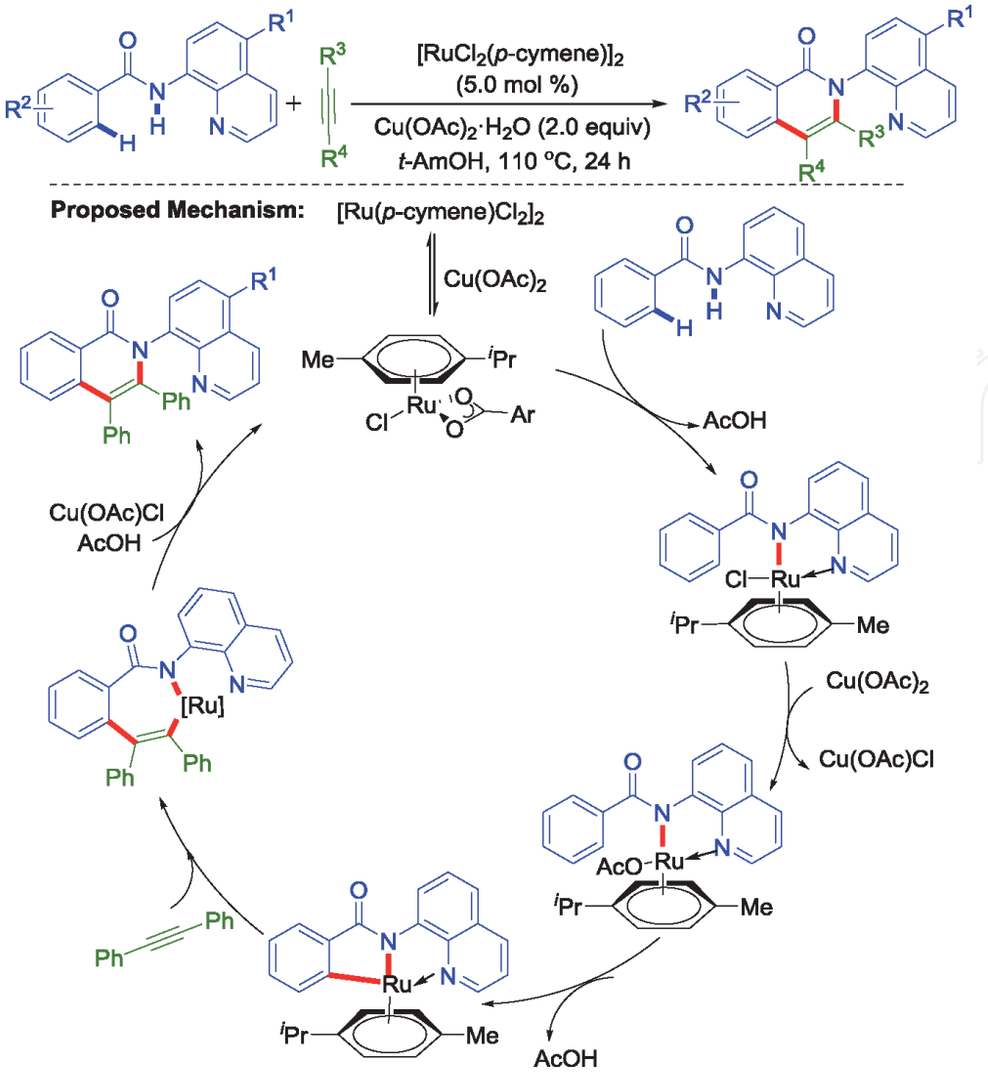

Figure 28.
Ruthenium(II)-catalyzed synthesis of Isoquinolone derivatives.

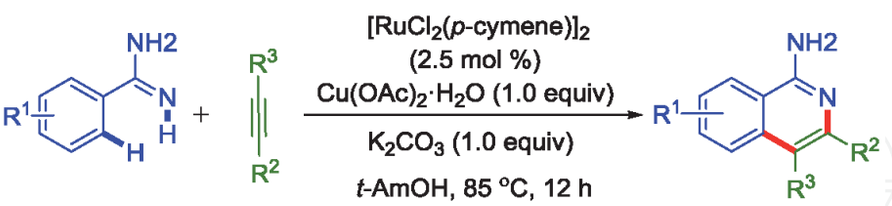

Figure 29.
Ru(II)-catalyzed synthesis of Isoquinoline derivatives.

achieve isoquinolones with high regioselectivity, broad substrate scope and broad functional group tolerance (**Figure 28**) [47]. The reaction occurs in the presence of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an oxidant with the involvement of a monoacetate complex [RuCl(OAc)(*p*-cymene)] instead of the bis-acetate complex $[Ru(OAc)_2(p\text{-cymene})]$. The mechanistic studies reveals involvement of a ruthenium N-quinolin-8-yl- benzamide complex (i.e. N,N-bidentate chelate complex).

vii. In 2017, Gogoi *et al.* reported a Ru(II)-catalyzed C-H/N-H activation and oxidative annulation of benzamidines and internal alkynes for the facile synthesis of 1-aminoisoquinolines with excellent regioselectivity (**Figure 29**) [48].

viii. In 2017, Urriolabeitia *et al.* described a carboxylate assisted Ru(II)-catalyzed synthesis of isoquinoline-1-carboxylate derivatives through C-H/N-H oxidative annulation reaction between *N*-unprotected methyl esters of phenylglycine and internal alkynes (**Figure 30**) [49]. The *N*-fluoro-2,4,6-trimethylpyridinium triflate works as the terminal oxidant and the process shows a remarkable tolerance to the presence of diverse electron-releasing and electron-donating functional groups at the phenyl ring of the amino acid.

7.5 Synthesis of π-conjugated polycyclic *N*-Heteroaromatic molecules *via* C-H/N-H oxidative alkyne annulation

i. In 2012, Ackermann *et al.* reported a ruthenium(II)-catalyzed aerobic oxidative coupling of alkynes with 2-arylindoles in the presence of a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ and air as the oxidants for the facile synthesis of fused polycyclic indolo[2,1-*a*]isoquinolines (**Figure 31a**) [50]. Further, they extended the scope of this C-H/N-H oxidative annulations reaction between 2-arylpyrroles and alkynes which afforded good yields of pyrrolo[2,1-*a*]isoquinolines (**Figure 31b**) [50].

ii. In the same year, Ackermann group developed a cationic ruthenium(II)-catalyzed effective oxidative annulations of aryl- and alkyl-substituted alkynes with 5-aryl-1H-pyrazoles with excellent chemo- and regioselectivities. This C-H/N-H bond functionalization strategy provided conjugated pyrazolo[5,1-*a*]isoquinolines derivatives with ample substrate scope. Detailed mechanistic investigation agreed for a reversible C-H bond ruthenation with the cationic ruthenium(II) catalyst (**Figure 32**) [51].

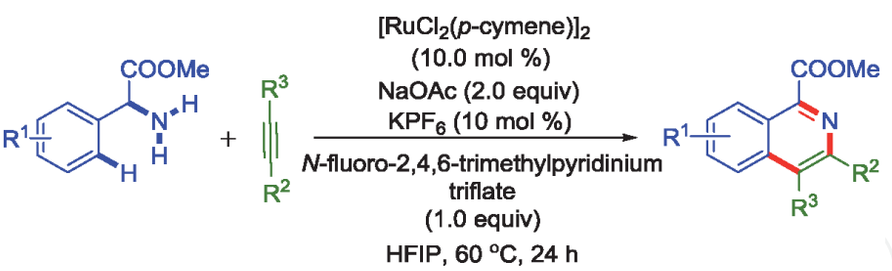

Figure 30.
Ru(II)-catalyzed synthesis of Isoquinoline derivatives.

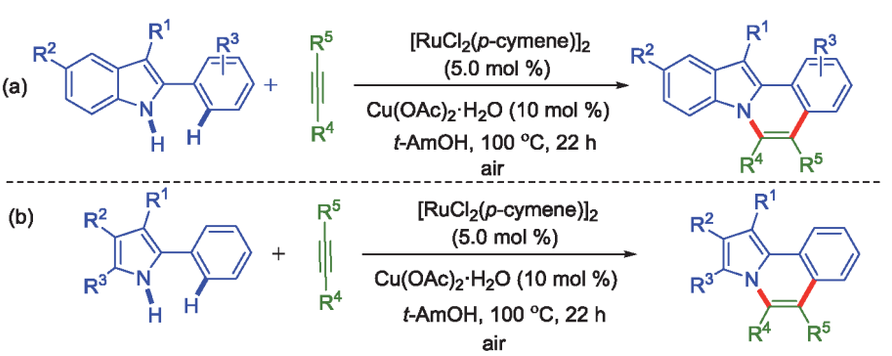

Figure 31.
Ruthenium(II)-catalyzed synthesis of Indolo[2,1-a]isoquinolines and Pyrrolo[2,1-a]isoquinolines.

DOI: http://dx.doi.org/10.5772/intechopen.95987

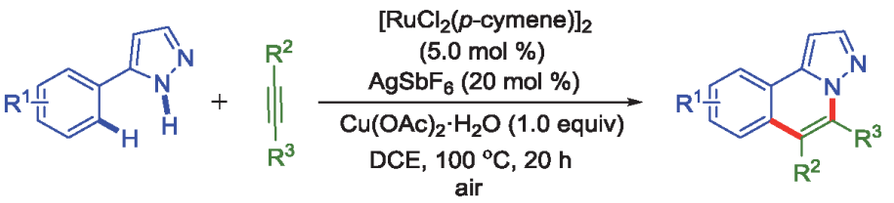

Figure 32.
Cationic ruthenium(II)-catalyzed synthesis of Pyrazolo[5,1-a]isoquinolines.

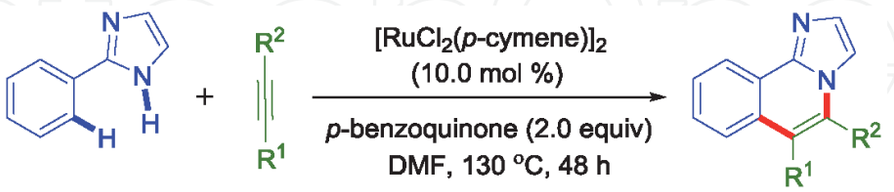

Figure 33.
Ruthenium(II)-catalyzed synthesis of Imidazo[2,1-a]isoquinolines.

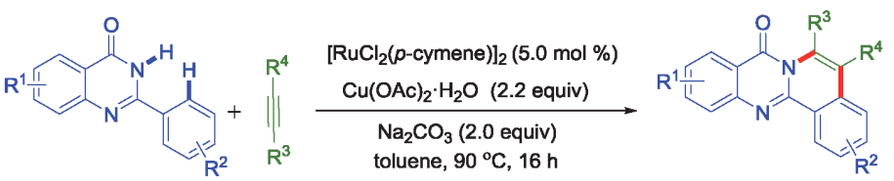

Figure 34.
Ruthenium(II)-catalyzed synthesis of tetracyclic Heteroarenes.

iii. In 2014, Wang and co-workers reported an efficient access to various imidazo[2,1-*a*]isoquinolines via a ruthenium(II)-catalyzed oxidative alkyne annulation reaction of 2-phenylimidazole in the presence of para-benzoquinone as the oxidant (**Figure 33**) [52]. In this cascade C-H/N-H bond functionalization reaction a wide range of electron deficient alkynes are converted into the fused isoquinolines with high chemo- and regioselectivity.

iv. In the same year, Peng group published C-H/N-H bond activation of quinazolones with internal alkynes for the facile construction of fused tetracyclic heteroarenes in the presence of $[RuCl_2(p\text{-cymene})]_2$ and Cu $(OAc)_2{\cdot}H_2O$ under mild reaction conditions (**Figure 34**) [53].

v. In 2015 a one-pot synthesis of fused polycyclic nitrogen-heteroarenes was reported via the Ru(II)-catalyzed oxidative dehydrogenation followed by C-H/N-H activation and annulation reaction of heteroaryl dihydroquinazolinones and internal alkynes. This one-pot method does not require any copper salt as the external oxidant, rather the oxidation occurs by the molecular oxygen (**Figure 35**) [54].

vi. In 2017, Swamy and co-workers achieved an amide group-directed, Ru(II)-catalyzed highly regioselective C-H/N-H activation and oxidative annulation reaction between 2*H*-chromene-3-carboxamides with internal alkynes for the synthesis of benzopyran-fused 2-pyridones (**Figure 36**) [55]. In addition, a double C-H activation reaction was also developed in the same one-pot using an excess of the alkyne. Herein, the first C-H

functionalization involves Ru-N covalent bond while the second C-H functionalization most likely involves Ru-O coordinate bond.

vii. In 2018 Gogoi et al. reported an unprecedented Ru(II)-catalyzed N-H/C-H activation and annulation reaction of of *N*-arylpyrazol-5-ones and diaryl/arylalkyl-substituted alkynes in the presence of bidented ligand 1,3-bis(diphenylphosphino)propane for the synthesis of quinazolines

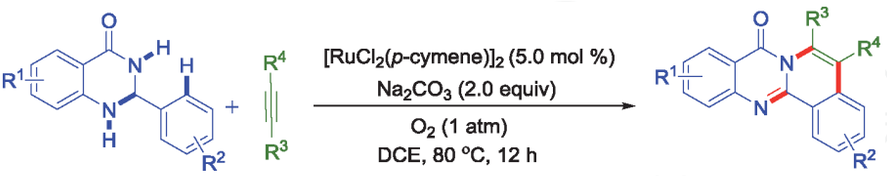

Figure 35.
Ruthenium(II)-catalyzed external oxidant FreeSynthesis of tetracyclic Heteroarenes.

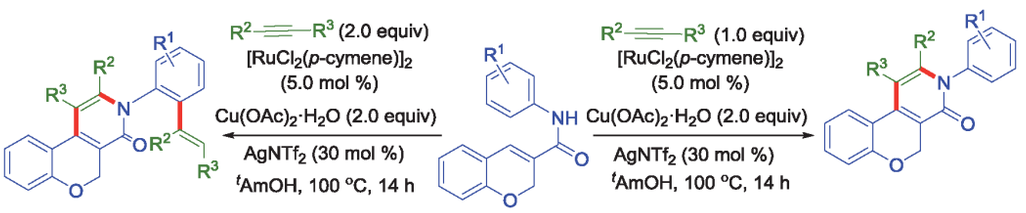

Figure 36.
Ruthenium catalyzed synthesis of Benzopyran-fused 2-pyridones.

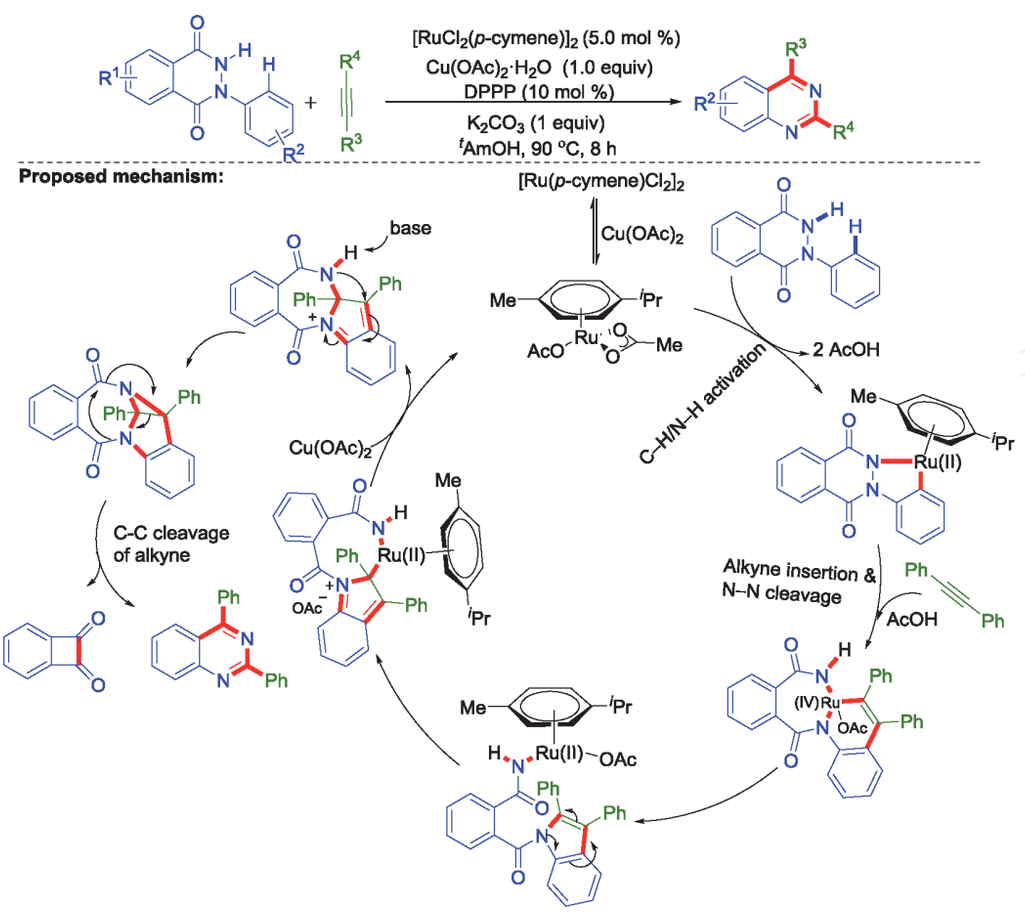

Figure 37.
Ruthenium(II)-catalyzed synthesis of Quinozaline.

DOI: http://dx.doi.org/10.5772/intechopen.95987

(**Figure 37**) [56]. This annulation reaction proceeds mainly via oxidation of Ru(II) to Ru(IV) by cleavage of the N-N bond and cleavage of the triple bond of the alkyne.

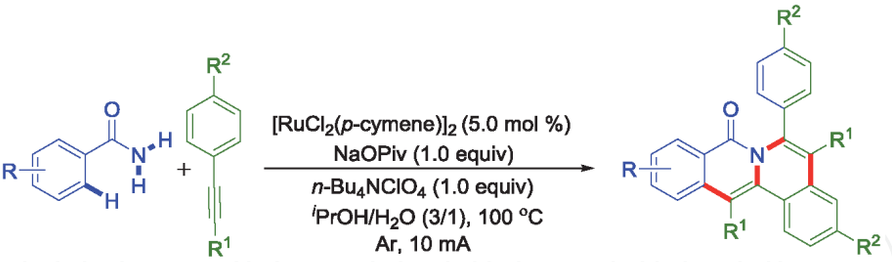

Figure 38.
Ruthenium(II)-catalyzed synthesis of polycyclic Isoquinolinones.

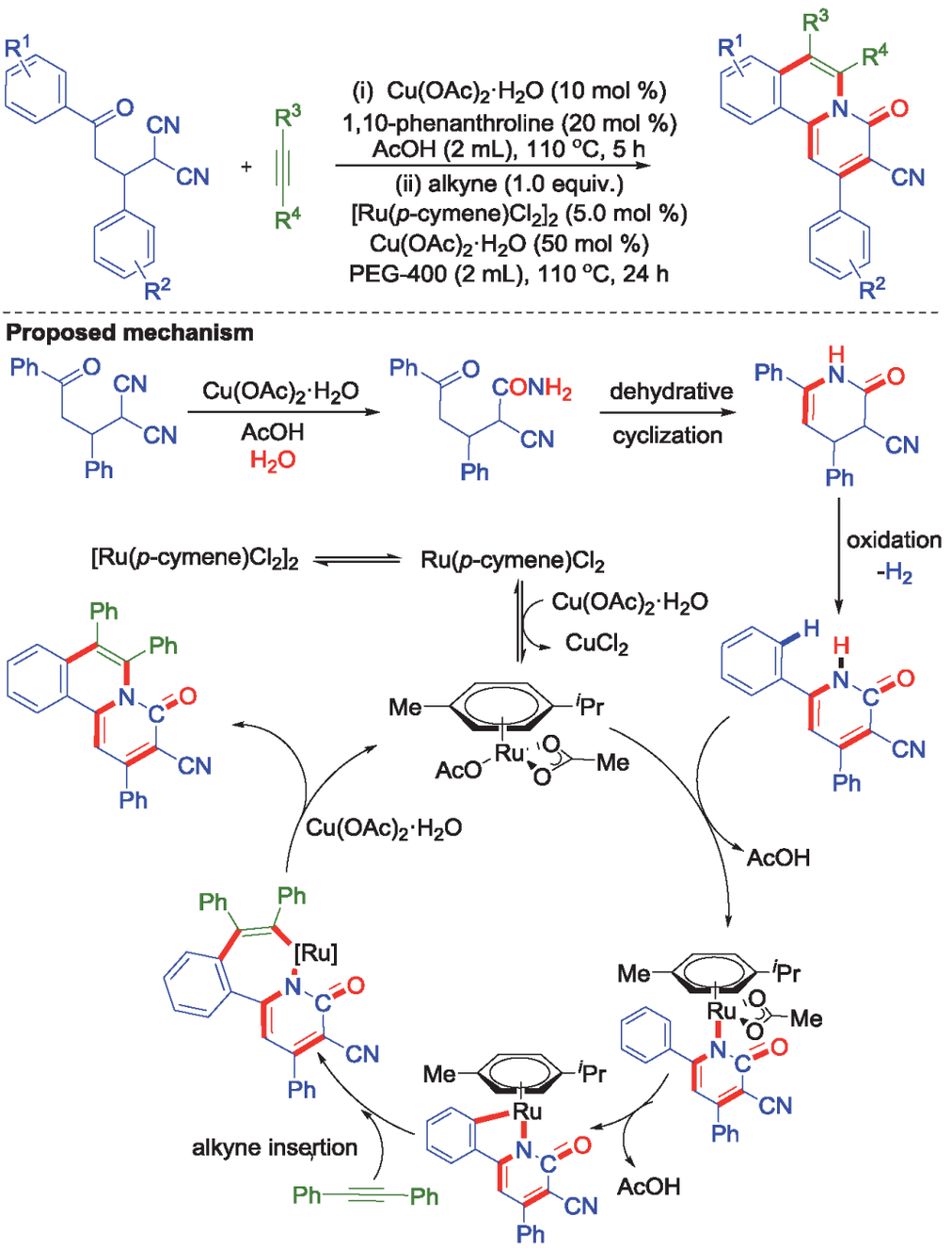

Figure 39.
Ruthenium(II)-catalyzed synthesis of conjugated fused Isoquinolines.

viii. In 2019, Tang and co-workers reported a Ru-catalyzed electrochemically enabled dehydrogenative annulation reaction of amides and alkynes for the synthesis of antitumor polycyclic isoquinolinones through a double C − H bond activation route (**Figure 38**) [57].

ix. In 2019 Patel *et al.* developed a one-pot sequential synthesis of highly conjugated fused isoquinolines via Cu(II)-catalyzed intramolecular cyclization followed by Ru(II)-catalyzed C-H/N-H oxidative alkyne annulation reactions (**Figure 39**) [58]. This one pot synthesis consisting of selective hydrolysis of a cyano group to an amide, dehydrative cyclization of the amide to a cyclic amide, aromatization of the cyclic amide (2-oxo-1,2,3,4-tetrahydropyridine moiety) to a 2-oxo-1,2-dihydropyridine and finally, the C-H/N-H annulation with an internal alkyne.

8. Conclusion

In summary, the ruthenium(II)-catalyzed activation of C-H bonds for the construction of C-C bond in organic synthetic methodologies have caused a revolution. The development of methodologies introducing multiple C-H/N-H activation is an emerging area of research and the oxidative alkyne annulation reactions allowing for the formation of C-C and C-N bonds in a single step. These approaches have already been competently used in the synthesis of several essential *N*-heterocycles from readily available reactants. The presence of nitrogen directing groups appears to be highly useful as starting materials for the direct access of various N-heterocycles in the field of ruthenium (II)-catalyzed C-H activation and oxidative alkyne annulations. Further, these reactions were also extended to other hetero-atoms such as oxygen and sulfur directed groups for the straight forward synthesis of diverse oxygen and sulfur containing heterocyclic molecules. Therefor this methodology can definitely play a very useful part as an application in the field of natural products, biologically important molecules and heterocycles with potential application in the field of material science. Further developments in this area may open up broad opportunities for straightforward, efficient, and atom economical synthesis of various complex *N*-heterocyclic compounds from simple starting materials.

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