

Recent Advances in C-H Bond Functionalization with Ruthenium-Based Catalysts

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Abstract:

The past decades have witnessed rapid development in organic synthesis *via* catalysis particularly the reactions through C-H bond functionalization. Transition metals such as Pd, Rh and Ru constitute a crucial catalyst in these C-H bond functionalization reactions. This process is highly attractive as it provides not only a step economy and reduces wastes but also more importantly allowed the reaction to perform in a highly regiospecific manner. Indeed, several organic compounds could be readily accessed *via* C-H bond functionalization with transition metals. In the recent past, tremendous progress has been made on the C-H bond functionalization *via* ruthenium catalysis including less expensive but more stable ruthenium(II) catalysts. The ruthenium-catalysed C-H bond functionalization *viz.*; arylation, alkenylation, annulation, oxygenation, and halogenation involving C-C, C-O, C-N, and C-X bond forming reactions have been described and presented in numerous reviews. This review discussed the recent development of the C-H bond functionalization with various ruthenium-based catalysts. The first section of the review presented arylation reactions covering arylation directed by *N*-heteroaryl groups, oxidative arylation, dehydrative arylation and arylation involving decarboxylative and sp^3 -C-H bond functionalization. Subsequently, the ruthenium-catalysed alkenylation, alkylation, allylation including oxidative alkenylation and *meta*-selective C-H bond alkylation has been presented. Finally, the oxidative annulation of various arenes with alkynes involving C-H/O-H or C-H/N-H bond cleavage reactions has been discussed.

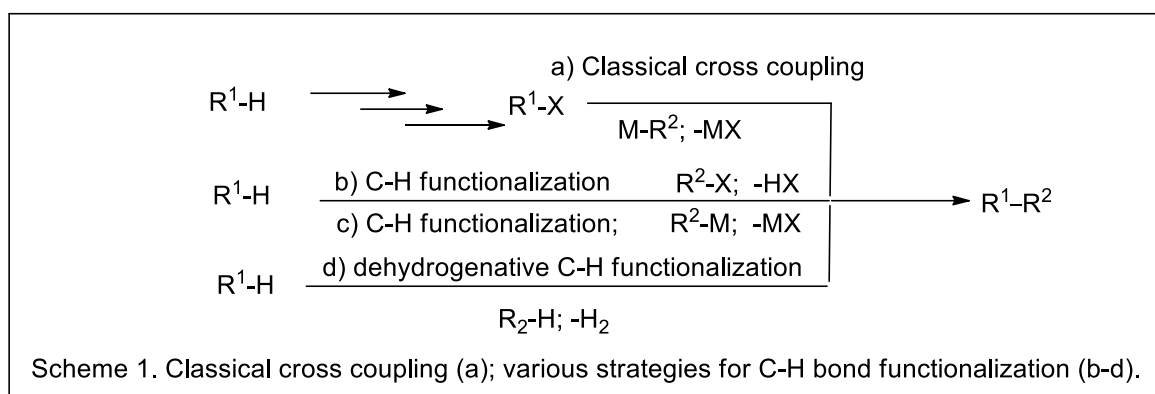
Keywords: C-H bond Functionalization; Annulation reaction; Organic synthesis; Isocoumarins; Oxidant; Carboxylate ligand; Ruthenium catalysts.

Introduction

Synthesis of organic compounds with a heterocyclic ring and natural product scaffolds are extremely important as they form an indispensable structure unit of bioactive compounds and pharmacophores [1, 2]. Tremendous effort has been made in the designing and development of organic synthesis which could provide ready access to these valuable organic compounds. The traditional organic synthesis often requires multistep reactions with the use of several hazardous reagents, and thus, the process is environmentally not friendly and economically not viable. To overcome these problems an alternative synthetic method with better atom and step economy is highly desirable. In recent past, in order to overcome the above shortcoming, organic synthesis has been steadily shifted towards a catalytic pathway. It is noteworthy that in organic molecules, C-H bonds often outnumber the other type of bonds, therefore; a direct functionalization of C-H bonds could drastically shorten the synthetic route of any organic synthesis. Indeed, a direct C-H bond functionalization pathway is expected to provide a greener and economical pathway for a ready access to various functional organic compounds.

The classical C-C cross coupling was first studied with Ni and Pd catalysts [3, 4]. Since this classical cross coupling requires pre-functionalized starting materials and produced a stoichiometric amount of metal salt as side product, the process is not attractive (Scheme 1, a). During the past decades, the organic synthesis through C-H bond functionalization has emerged as one of the most viable methods not only to the selective organic synthesis [5] but also for ready access to the variety of functional molecules including pharmaceutical relevant compounds [6] and natural products [7,8]. The cross-coupling through direct C-H bond functionalization is highly attractive as the process not only provided greener reaction protocol but also reduces wastes. Generally, three types of direct C-H functionalization strategies are known in the transition metal-catalysed C-H bond functionalization [9]. The direct C-H bond functionalization with aryl halides or alkyl halides usually requires an addition of a base to neutralize the generated acid, HX (Scheme 1, b). On the other hand, the coupling of arene or alkene with an organometallic reagent is essentially required an oxidant to generate the metal species (Scheme 1c).

In both the direct C-H functionalization methods, some pre-functionalised starting material is required. On the contrary, the dehydrogenative method involving the coupling of two C-H bonds first discovered by Moritani and Fujiwara with Pd catalyst, is the most step-and atom economical reaction, as it does not require any pre-functionalized starting materials (Scheme 1, d).



During the last decade, the transition metal-catalysed C-H bond functionalization has rapidly developed and its utility in the synthesis of organic compounds is well documented [10]. Initially, transition metals such as Pd [11,12,] and Rh [13, 14,] have contributed enormously in these transition metal-catalysed C-H bond functionalizations. In the recent past, the reactions have been explored with the much cheaper ruthenium complexes particularly with the more stable ruthenium(II) catalysts [15]. In general, the ruthenium-catalysed C-H bond functionalization has been done in two pathways namely; oxidative addition pathway and deprotonation pathway. The C-H bond functionalization *via* the oxidative pathway is usually performed with low valent ruthenium complexes, such as $[RuH_2(CO)(PPh_3)_3]$ or $[Ru_3(CO)_{12}]$ whereas; ruthenium(II) complexes *viz.* $[RuCl_2(PPh_3)_3]$ and $[RuCl_2(p\text{-cymene})]_2$ in association with acetate or carbonate bases are used for the C-H bond functionalization *via* deprotonation pathway [16]. In the deprotonation pathways, transition metals with low valent oxidation states such as Pd(0), Rh(I) or Ru(0) are required to oxidize to the higher oxidation state *viz.* Pd(II), Rh(III) and Ru(II) in the presence of organic or inorganic oxidants to regenerate the active species.

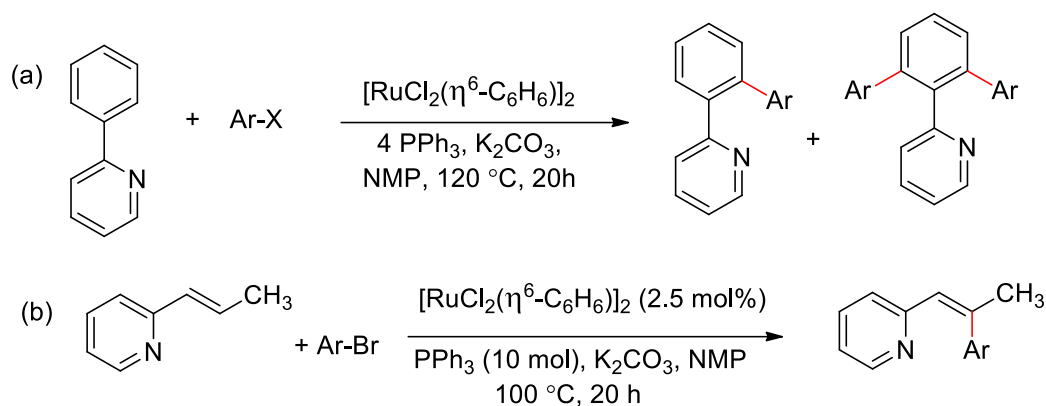
During the past years, the ruthenium-catalysed C-H bond functionalization has been explored with varieties of *N*-heteroaryl directing groups [15] as well as other directing groups such as ketones [17], esters [18], amides [19], carboxylic acids [20] etc. Generally, the cationic ruthenium species, $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ or $[RuCl_2(p\text{-cymene})]_2/KPF_6$ have been used for the C-H bond functionalization directed by weakly coordinated oxygen and π -bond donor group. The C-H bond functionalization of weakly coordinated directing groups has been extensively studied by the research group of Jeganmohan [21, 22], Ackermann [23] and others [24]. Recently, benefit of carboxylic acid ligand in C-H bond functionalization reaction has been explored. Indeed the carboxylic acid assisted reaction revolutionized the C-H bond functionalization by transition metals including ruthenium catalysts [25]. The carboxylate assisted C-H bond functionalization with ruthenium(II)-catalysts has been studied extensively by Ackermann [26, 27], Dixneuf [15, 28] and

later by others [29]. It is noteworthy that ruthenium(II) catalysts partner with carboxylate ligands offer an attractive pathway for the C-H bond functionalization allowing the reaction to operate under mild condition and even in water [30, 31].

Over the past years, the ruthenium-catalysed C-H bond functionalization has been studied for the various reaction namely; arylation [15], alkenylation [16], and annulation [26] reactions. Subsequently, several more new reactions have been discovered such as the direct C-H bond oxygenation [32], amidation [33], amination [34], cyanation [35], halogenations [36], and selenylation [37]. These reactions on ruthenium-catalysed C-H bond functionalization have been presented in numerous research papers and review articles by several groups [15, 16, 25, 26, 38, 39,40]. Further, the mechanistic study of ruthenium-catalysed C-H bond functionalization have been described very recently by the research group of Lan [41] in the context of arylation, alkylation and alkenylation whereas, by Nelson and coworkers on selective ortho arylation directed by Lewis basic groups [42]. However, new reaction and methodology on C-H bond functionalization with ruthenium-based catalysts are being discovered and added steadily. Keeping this in mind, this review described the recent development on the C-H bond functionalization reactions covering arylation, alkenylation, alkylation, and annulation reactions with ruthenium-based catalysts. The review is focussed mainly on the development in this field during the past eight years and included those reports appeared until 2018.

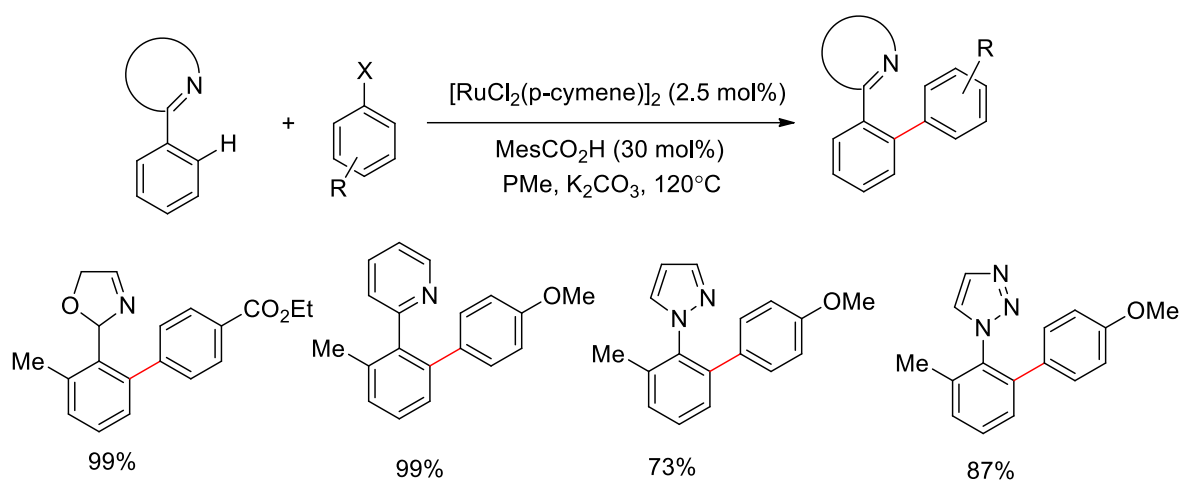
2. Ruthenium-catalysed C-H bond arylation

2.1. *C-H bond Arylation directed by N-heteroarenes*: Ruthenium-catalysed C-H bond arylation has been studied with various substrates, in particular, the substrate with N-heteroaryl ring as directing group such as 2-phenylpyridine, 1-phenylpyrazole, quinoline, tetrazole, imidazole, and pyrimedyl etc. The catalytic C-H bond arylation has been progressing steadily and covers several other substrates apart from the nitrogen heteroaryl directing groups and also the reactions have employed a variety of ruthenium catalysts. In 2001, Oi *et al.* described the arylation of 2-phenylpyridine with aryl halide using $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ in the presence of 4 equiv. of PPh_3 and a base (Scheme 2a) [43]. In subsequent years, they have reported the arylation of aromatic 2-alkenylpyridines and aryl bromides with $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ in the presence of a base (Scheme 2b) [44].



Scheme 2. Arylation of (a) 2-phenylpyridine with aryl halides; (b) alkenyl pyridine with aryl bromides.

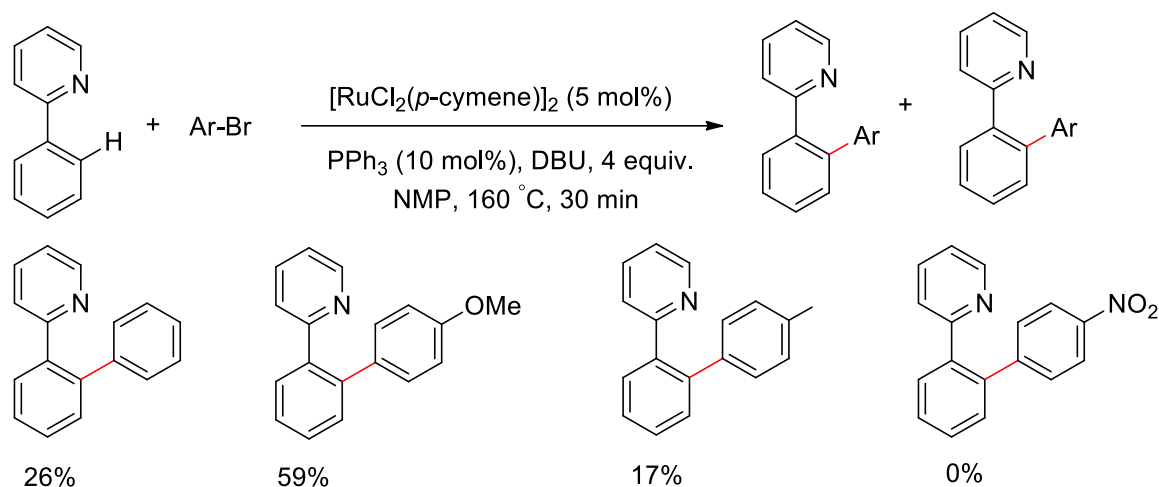
In 2008, Ackerman's research group has initiated for the first time the beneficial effect of carboxylic acid in the ruthenium-catalysed direct arylation of arene in toluene, a less coordinating and apolar solvent [45]. They have performed the arylation of several arenes with nitrogen-containing directing groups including 2-pyridyl, oxazolin-2-yl, *N*-pyrazolyl and *N*-triazolyl with aryl bromide using $[\text{RuCl}_2(p\text{-cymene})]_2$ (2.5 mol%) in the presence of mesitylic acid (30 mol%) to give arylated products (Scheme 3). They have shown that the reaction could be performed using cheaper but less reactive aryl chlorides. The reaction scope has extended to 1,4-disubstituted 1,2,3-triazoles leading to *ortho*-arylated products. However, under this reaction condition, the direct arylation did not occur with *ortho*-substituted aryl chloride instead the reaction leads to a homo-coupling product.



Scheme 3. Ruthenium-catalysed direct arylation of *N*-heteroarenes with aryl halides.

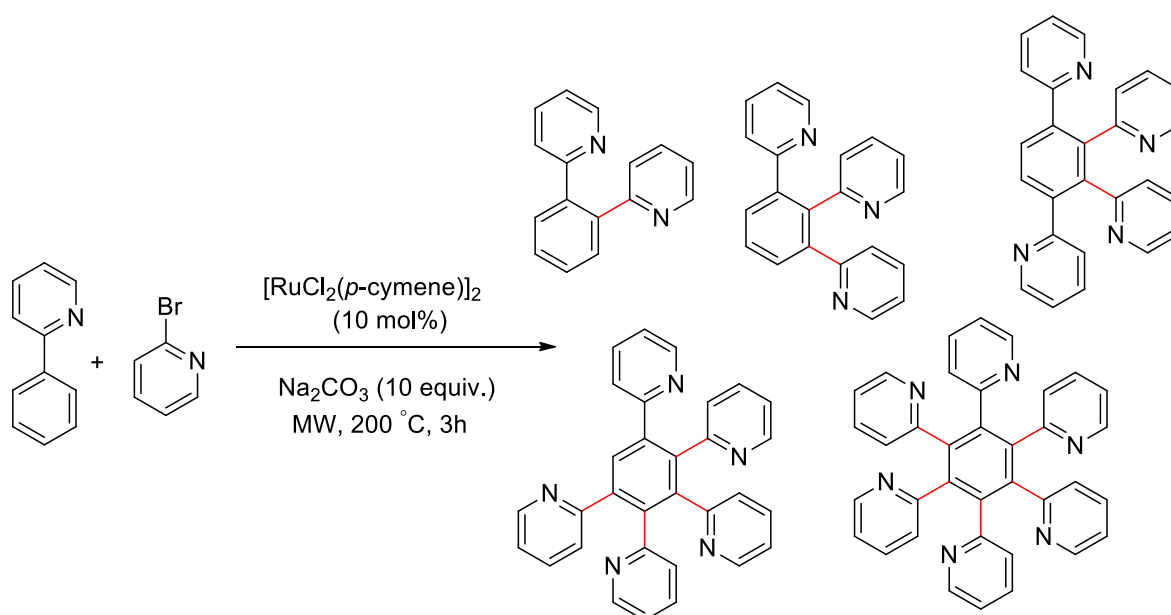
Christakakou *et al.* have reported the arylation of 2-phenylpyridine using aryl bromide in the presence $[\text{RuCl}_2(p\text{-cymene})]_2$, DBU and PPh_3 (Scheme 4) [46]. The arylated product formed depending on the nature of aryl bromide employed. Thus, employing, bromobenzene as arylating agent, gave 26 and 71% yield of mono and diarylated products whereas; bromo-anisaldehyde gave only the monoarylated product. However, aryl bromide such as *p*-bromotoulune and *p*-

bromotrifluorotoluene gave a mixture of mono and diarylated products, in contrast, no arylated product observed for *p*-nitrobromobenzene.



Scheme 4. Ruthenium(II)-catalysed direct arylation of 2-phenylpyridine with aryl bromides.

Pozgan and co-workers have just demonstrated a ruthenium-catalysed multiple C-H bonds arylation of 2-phenylpyridine with 2-bromopyridine promoted by microwave radiation (Scheme 5) [47].

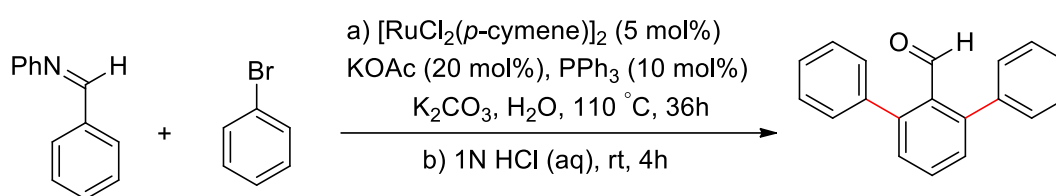


Scheme 5. Ruthenium-catalysed microwave assisted multiple C-H activation of 2-phenylpyridine.

The reaction proceeded using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of additive heated at 200 °C under microwave radiation. The reaction performed in water without additive resulted in a mixture of multiarylated products comprising mono-, di-, tri- tetra- and pentarylated products with the predominant formation of hexa(2-pyridyl)benzene. The reaction was best performed employing

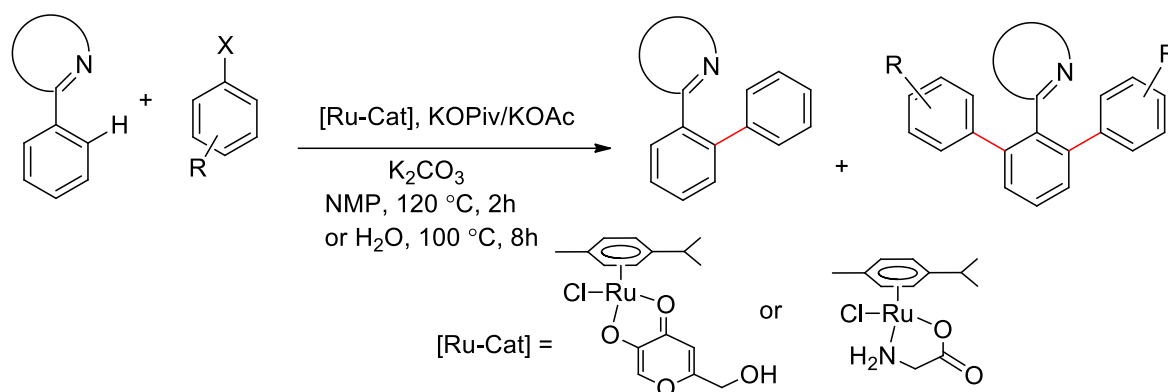
$[\text{RuCl}_2(p\text{-cymene})]_2$ (10 mole%), KOPiv (40 mol%) and PPh_3 (20 mol%) giving hexa(2-pyridyl)benzene in quantitative yields (Scheme 5).

The arylation of heteroarene containing an oxazoline ring as the directing group was reported by the research group of Dixneuf using $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with PPh_3 in the presence of cheaply available potassium acetate as an additive [48]. This catalytic system was successfully used for direct arylation of aldimines or ketimines as well. Further, they have shown that the diarylated aldimines could be readily hydrolyzed under acidic conditions to give the arylated benzaldehydes thus, the process proved to be an efficient method in the synthesis of functionalized aldehydes (Scheme 6, [48]).



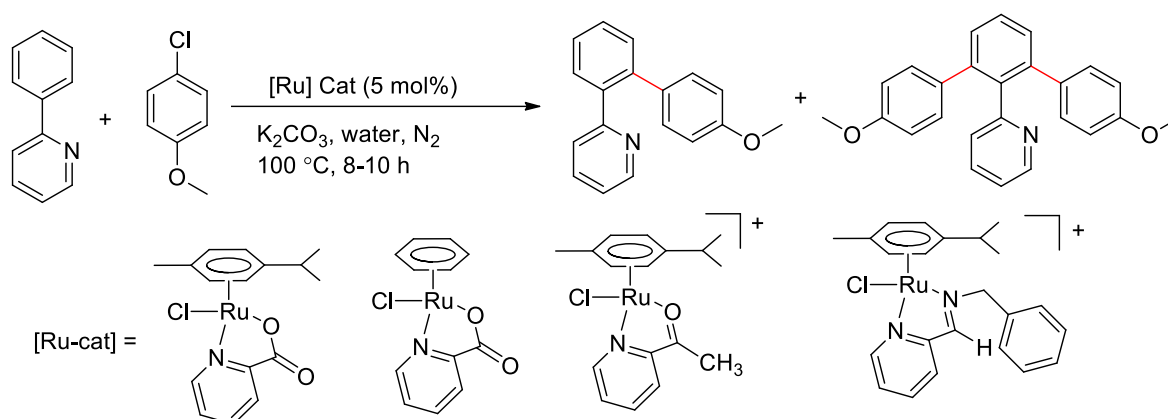
Scheme 6. Ruthenium-catalysed synthesis of diphenylated benzaldehyde.

Initially, the ruthenium-catalysed arylation has been performed mostly using $[\text{RuCl}_2(\text{arene})]_2$ catalysts. Later, the reaction has been explored with several other ruthenium catalysts. Ackermann's research group has reported an arylation of 2-phenylpyridine with aryl halides directly employing $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ using aprotic solvent, toluene [49]. Subsequently, the arylation reaction of 2-phenylpyridine was performed by Dixneuf and co-workers using the ruthenium catalyst $[\text{Ru}(\text{OAc})_2(p\text{-cymene})]$ in NMP [50] followed by $[\text{Ru}(t\text{BuCO}_2)_2(p\text{-cymene})]$ in water [51]. They have also performed the direct diarylation of 2-phenylpyridine with aryl chloride including hetero arylchloride using $[\text{RuCl}_2(p\text{-cymene})]_2/\text{KOPiv}$ catalytic system in diethyl carbonate [52]. This catalytic system has produced a diarylated product and tolerated to various functional groups such as cyanide and esters. Arylation reaction of 2-phenylpyridine has been studied with several other ruthenium(II) catalysts such as $\text{O}^{\wedge}\text{O}$ and $\text{N}^{\wedge}\text{O}$ chelate ruthenium(II) complexes as well. Singh and Dixneuf described the catalytic activity of water-soluble ($\text{O}^{\wedge}\text{O}$) and ($\text{N}^{\wedge}\text{O}$) chelate ruthenium(II) catalysts towards arylation of 2-phenylpyridine with aryl chlorides or aryl bromides (Scheme 7) [53]. These water-soluble ruthenium(II) complexes were efficient for the arylation of 2-phenylpyridine affording predominantly diarylated products in the presence of catalytic amount of KOPiv or KOAc in water.



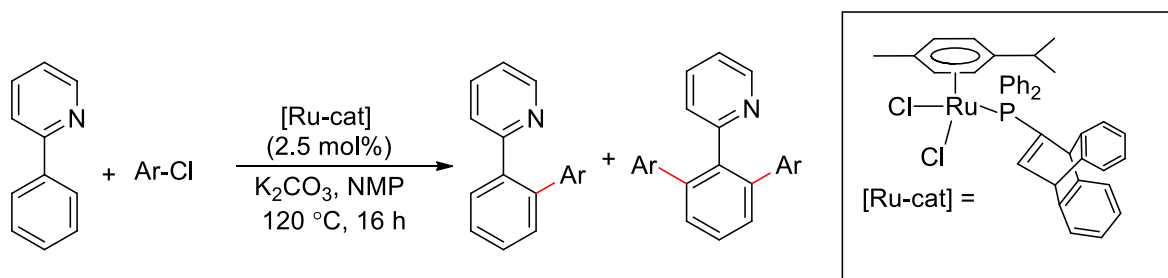
Scheme 7. Arylation of heteroarene with aryl halides by O[^]O or N[^]O chelate ruthenium(II)-catalysts.

Very recently, Binnani *et al.* had employed the ruthenium(II) complexes with N[^]O donor pyridine ligands for the arylation of 2-phenylpyridine with aryl halides [54]. The reaction gave both diarylated and monoarylated product with diarylated as the major product. They have tested even cationic ruthenium(II) complexes with N[^]N donor pyridine ligand as a catalyst in the arylation of 2-phenylpyridine but it was shown to be less effective as compared to the neutral ruthenium(II) complexes with N[^]O donor pyridine ligands.



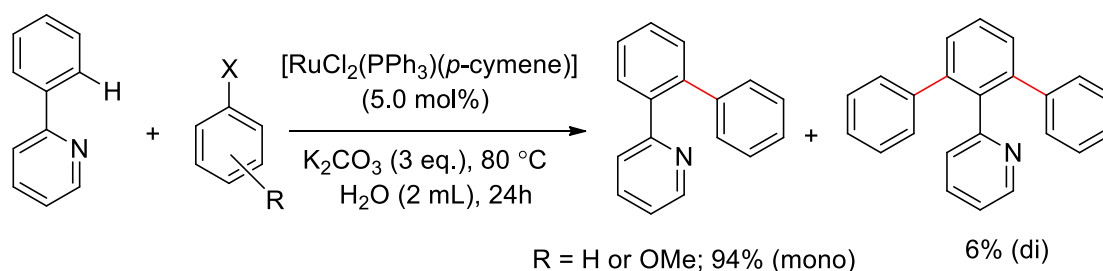
Scheme 8. Arylation of 2-phenylpyridine with N[^]O and N[^]N chelate ruthenium-catalysts.

2.2. *Ruthenium-catalysed selective monoarylation:* Doherty *et al.* achieved theselective monoarylation of 2-phenylpyridine and phenylpyrazoles using ruthenium(II) catalysts, [RuCl₂(*p*-cymene)(PPh₂L)] which gave predominantly monoarylated products with a minor or insignificant amount of diarylated products (Scheme 9) [55]. The reaction gave 76% of monoarylation and 9% diarylation with chlorobenzene as the arylating agent. Other arylating agent such as ethyl-4-chlorobenzene also gave good selectivity affording 64% monoarylation and only 3% diarylation product.



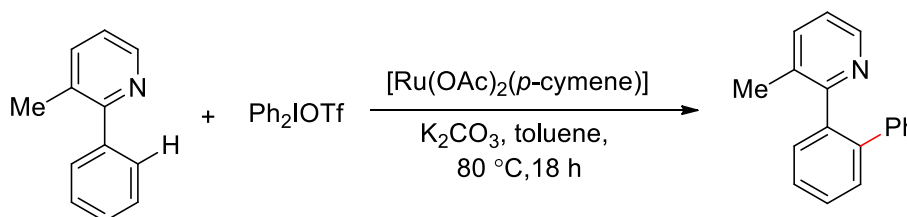
Scheme 9. Selective monoarylation of 2-phenylpyridine with ruthenium(II)-catalyst.

In 2013, Dixneuf and co-workers have reported a highly attractive selective monoarylation of 2-phenylpyridine and phenylpyrazoles using aryl chlorides and heteroaryl halides in water [56] (Scheme 10). They have screened the monoarylation using various ruthenium(II) catalysts and found that ruthenium catalyst with the association of bulky phosphine ligands or phosphine containing ruthenium compound, $[\text{RuCl}_2(\text{PPh}_3)(p\text{-cymene})]$ preferentially formed monoarylated product providing mono/diarylated product ratios up to 96/4.



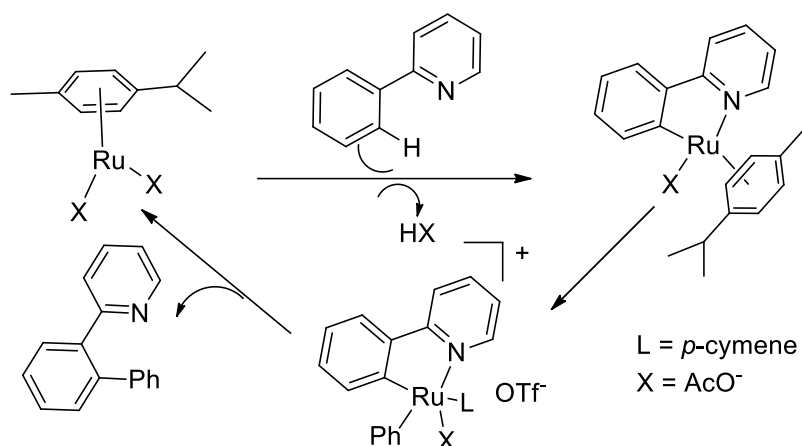
Scheme 10. Ruthenium(II)-catalysed selective monoarylation in water.

In 2014, Luise *et al.* reported a chelated assisted ruthenium(II)-catalysed arylation of 2-phenylpyridine with Ph_2IOTf as arylating agent which gave high yield of the monoarylated product in up to 95% (Scheme 11) [57].

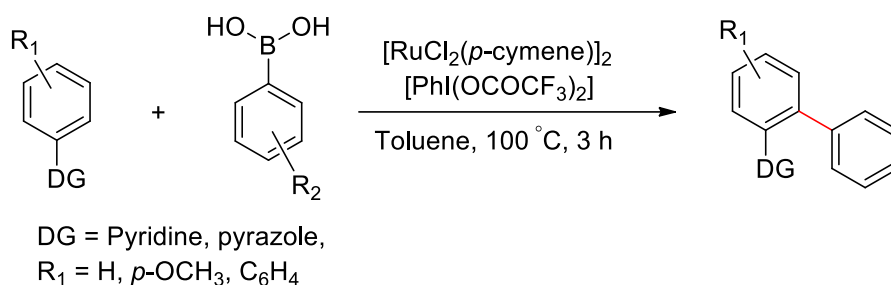


Scheme 11. Selective monoarylation of phenylpyridine with Ph_2IOTf .

They have proposed that the arylation reaction proceeded by a mechanism similar to Pd-catalysed C-H arylation reaction (Scheme 12). The reaction was proceeded efficiently with $[\text{Ru}(\text{OAc})_2(p\text{-cymene})]$ in the presence of K_2CO_3 in toluene at 80°C .

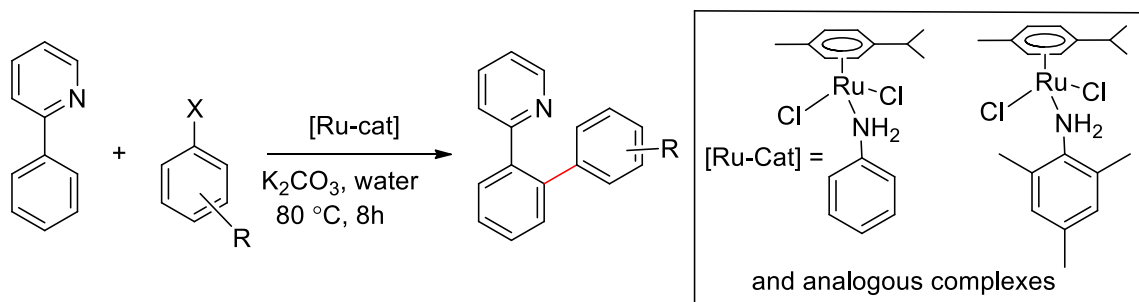
Scheme 12. Proposed mechanisms for the *ortho*-phenylation of C-H bonds [57].

Following this, Reddy *et al.* described a versatile monoarylation of 2-phenylpyridine and phenylpyrazole using aryl boronic acids as arylating agent with $[\text{RuCl}_2(\textit{p}\text{-cymene})]_2$ in the presence of $\text{PhI}(\text{OCOCF}_3)_2$ (Scheme 13) [58].



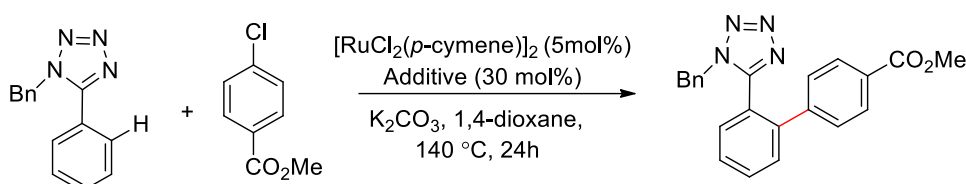
Scheme 13. Ruthenium-catalyzed monoarylation of arenes with phenyl boronic acids.

The selective monoarylation of 2-phenylpyridine has been studied with various ruthenium catalysts by several research groups. Recently, Binnani *et al.* have demonstrated a selective monoarylation of 2-phenylpyridine with aryl halide using the water-soluble ruthenium(II) aniline complexes, $[\text{RuCl}_2(\text{NH}_2\text{-Ar})(\textit{p}\text{-cymene})]$ (Scheme 14) [59]. This C-H bond *ortho* arylation reaction gave predominantly monoarylated products showing electronic and steric properties of the coordinated aniline ligands have a significant effect on the catalytic activity.



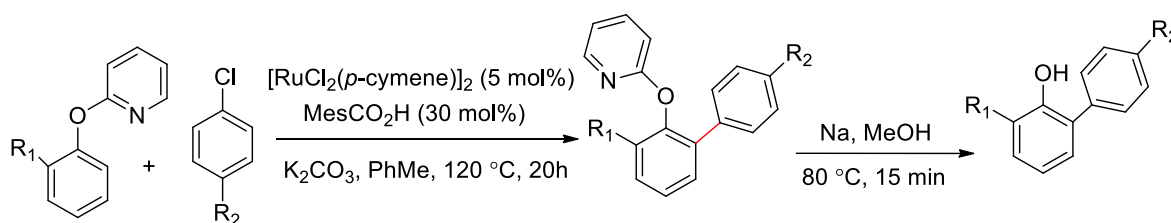
Scheme 14. Selective mono arylation of 2-phenylpyridine with arene-ruthenium(II)-amine catalysts.

In 2011, a highly efficient catalytic system for the arylation of phenyl tetrazole with aryl bromide was reported by Seki using the ruthenium(III) catalyst, $[\text{RuCl}_3 \cdot x\text{H}_2\text{O}]$ [60]. This catalytic process provided a greener and sustainable approach to the access of Angiotensin II Receptor Blockers (ARBs) which is considered to be one of the most efficient antihypertensives [61]. Recently, Ackermann performed this arylation using the less expensive aryl chloride and stable ruthenium(II) catalyst, $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with amino acid ligands in the presence of potassium carbonate in 1,4-dioxane (Scheme 15) [62].



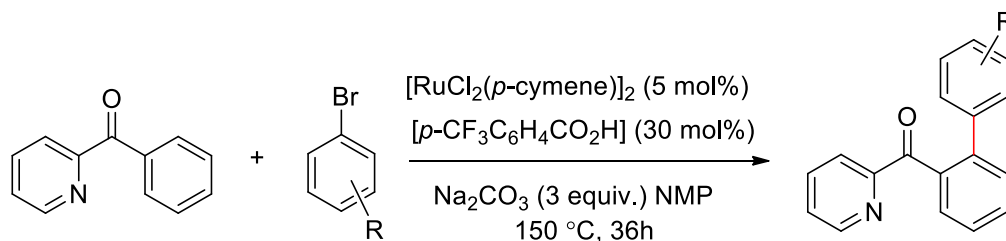
Scheme 15. Arylation of aryltetrazole with aryl chloride via ruthenium-catalyst promoted by amino acid ligands.

Ackermann and co-workers described arylation of 2-phenoxy pyridine with aryl halides providing ready access to arylated phenols [63]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of additive and a base. The presence of a base is essential for this reaction as no reaction has occurred when performed without a base. They have observed that the reaction conducted in *N*-Methyl-2-Pyrrolidone (NMP), a solvent usually used in ruthenium-catalysed direct arylation of arenes gave predominantly diarylated product. However, when the reaction was performed in toluene improvement in the reaction efficacy and mono selectivity was observed. Thus the best condition was obtained when the reaction was performed in toluene at 120 °C using mesitylic acid and K_2CO_3 . They proposed that reaction proceeds through a six-member ruthenacycle cyclometallated species. Further, the arylated 2-phenoxy pyridine gave monoarylated pyridine on treatment the arylated product of 2-phenoxy pyridine with MeOTf followed by sodium in methanol (Scheme 16).



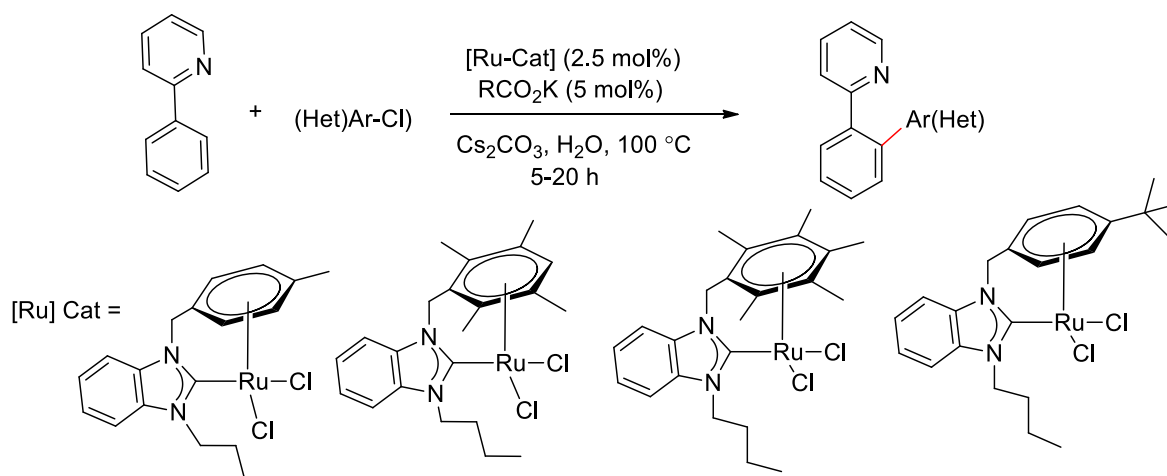
Scheme 16. Arylation of 2-phenoxy pyridines with aryl chlorides and synthesis of arylated phenols.

In 2014, a selective monoarylation of 2-pyridylketones with aryl bromide via six-membered ruthenium cyclometalated species was described by Dixneuf and co-workers employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of a base and additive (Scheme 17) [64]. The reaction was performed in NMP employing K_2CO_3 as base and KOAC as additive leading to 82:18 mono/diarylated products. The selectivity further enhanced by employing Na_2CO_3 as the base in the presence of 30 mol% of $p\text{-CF}_3\text{C}_6\text{H}_4\text{CO}_2\text{H}$ affording 90:10 mono/diarylated products.



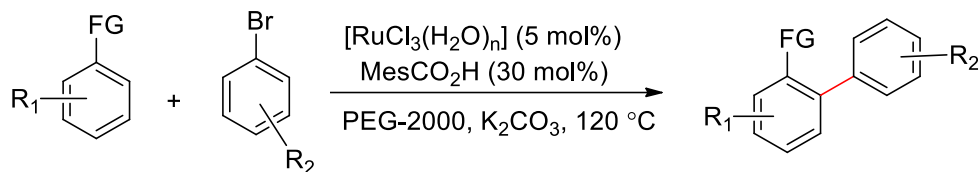
Scheme 17. Ruthenium-catalysed selective arylation of 2-pyridyl aryl ketone with aryl bromide.

The direct C-H arylation of 2-phenylpyridine with aryl chlorides in water has been just reported by Kaloğlu *et al.* employing a ruthenium-NHC complex as catalyst (Scheme 18) [65].



Scheme 18. Selective mono arylation of 2-phenylpyridine with arene-ruthenium(II)-NHC catalysts.

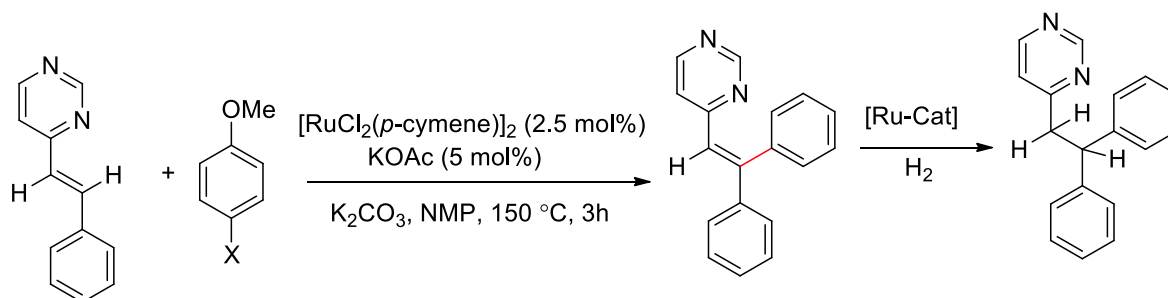
The reaction was performed in the presence of KOAc and a base producing only the monoarylated product. The selective monoarylation of 2-phenylpyridine was also performed with $[\text{RuCl}_3 \cdot x\text{H}_2\text{O}]$ using mesitylic acid as the additive in nontoxic PEG-2000 by Ackermann [9, 66] (Scheme 19), followed by Luo & Yu [67], then by the research group of Gimeno in water [68].



Scheme 19. Ruthenium-catalysed direct arylation of arenes with aryl bromides in PEG-2000.

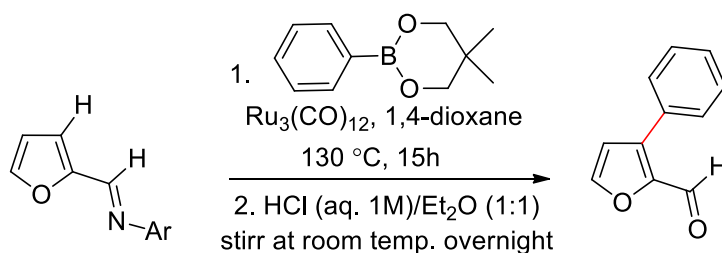
2.3. Arylation of arenes with imine and diazine as directing groups

The arylation of alkenylic C-H bond containing diazine as a directing group has been just reported by Dori *et al.* using aryl halide as an arylating agent with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of a base (Scheme 20) [69]. The reaction gave isomeric products in some of the cases which were further hydrogenated using the ruthenium catalyst remained from the reaction of the first step resulting in sp^3 C-H bond functionalization product. Thus, this catalytic process provided an alternative approached to the more difficult sp^3 -CH bond functionalization.



Scheme 20. Ruthenium-catalysed C-H arylation of alkenylic diazines.

Very recently, Poli and co-workers have demonstrated a C-3 arylation of furfural imines with $\text{Ru}_3(\text{CO})_{12}$ in the presence of benzylideneacetone as a sacrificial hydride acceptor [70]. This arylation was performed using aryl boronates as an arylating agent in 1,4-dioxane leading to C-H arylated furfural imines which on subsequent acid hydrolysis gave C-3 arylated furfural (Scheme 21).

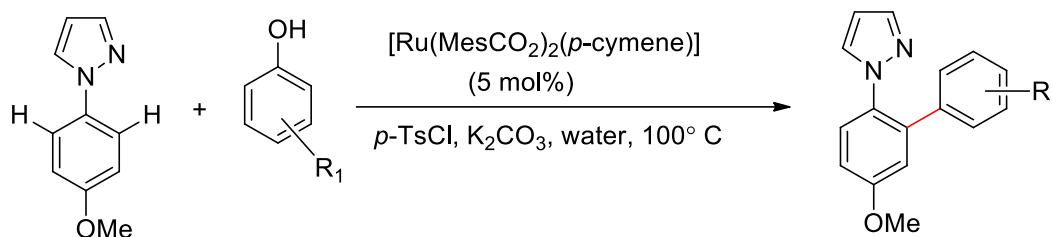


Scheme 21. Ruthenium-catalysed C-3 arylation of furfural imines with aryl boronate.

2.4. Arylation involving dehydrative, oxidative and weakly coordinated directing groups:

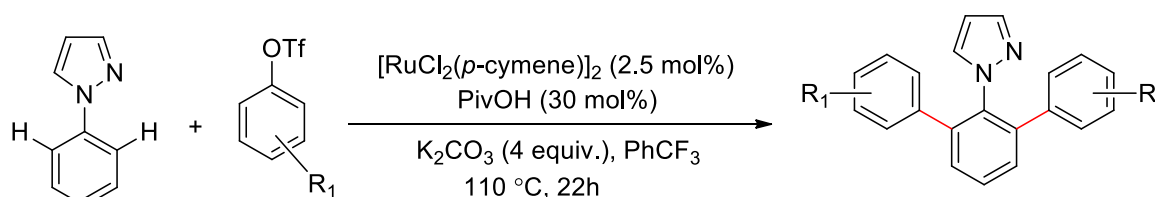
In 2008, Ackermann's research group demonstrated a highly attractive ruthenium-catalysed dehydrative arylation of phenylpyrazole with phenol using $[\text{RuCl}_2(p\text{-cymene})]_2$ first in DMA [71], subsequently in water employing $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]_2$ as the catalyst [72]. This reaction

protocol gave a direct C-H/O-H arylation with phenol in the presence of TsCl and a base (Scheme 22).



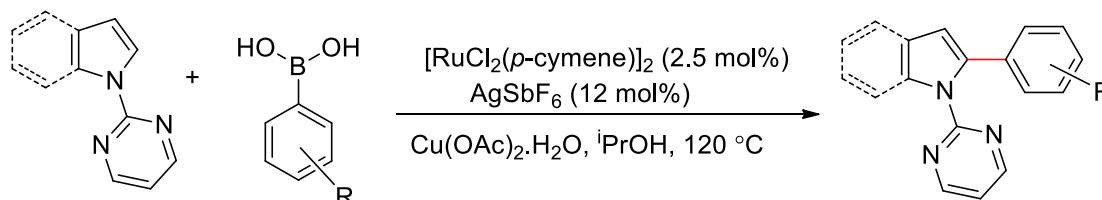
Scheme 22. Ruthenium-catalysed dehydrative arylation of pyrazole with phenols.

Very recently, Roger *et al.* have described the arylation of phenylpyrazole using a phenol derivative of aryl triflate as the arylating agent with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of a base [73]. The reaction produced a mixture of monoarylated and diarylated products. However, when the reaction was conducted in the presence of additive the diarylated product was formed predominantly. The reaction was best performed with PivOH as an additive in trifluorotoluene affording only diarylated azole in 99% (Scheme 23).



Scheme 23. Ruthenium-catalysed diarylation of phenyl-1H-pyrazole from functional aryl triflates.

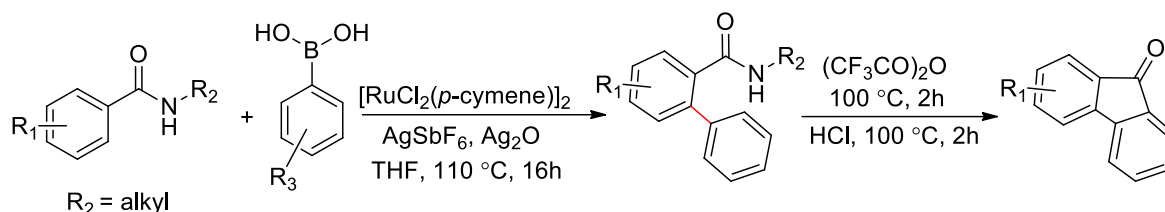
In 2011, Ackermann's research group reported arylation of indole and pyrrole containing a pyrimidyl group with aryl bromide employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $(1\text{-Ad})\text{CO}_2\text{H}$ and a base [74]. In later years, Sollert *et al.*, have performed this arylation using the same catalyst but in the presence of an oxidant [75]. This oxidative arylation method gave slightly higher yields and shorter reaction time (Scheme 24).



Scheme 24. Ruthenium-catalysed oxidative arylation of pyrrole or indole derivatives.

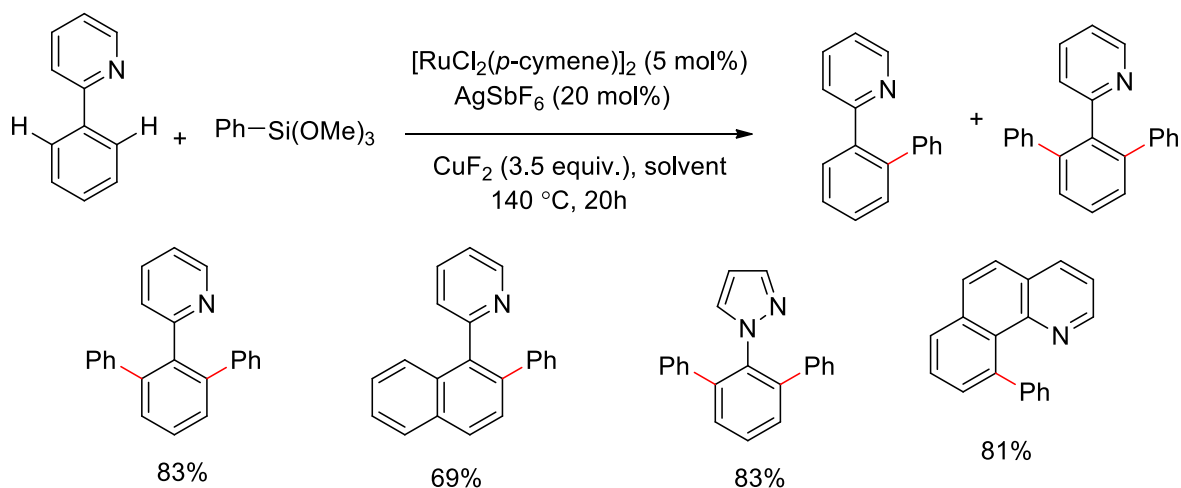
The ruthenium-catalysed *ortho*- arylation of *N*-alkyl benzamide with phenylboronic acid was described by Jagenmohan's group using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of AgSbF_6 and the

oxidant, Ag₂O (Scheme 25) [76]. They have found that the presence of Ag₂O is essential for the arylation to occur as the absence of it resulted in no coupling reaction even by using a stoichiometric amount of AgSbF₆. Further, they have shown that the *ortho*-arylated *N*-alkyl benzamide on treatment with trifluoroacetic acid and HCl could lead to fluorenones.



Scheme 25. Oxidative arylation of alkylbenzamide with aryl boronic acid and synthesis of fluorenones.

Recently, Szostak and co-workers described the first ruthenium-catalysed arylation of heteroarene containing pyridyl ring as the directing group with an organosilane as the arylating agent using [RuCl₂(*p*-cymene)]₂ in the presence of AgSbF₆ and an oxidant, CuF₂ [77]. The oxidant, CuF₂ served a dual role both for the arylsilane activator as well to re-oxidise Ru(0) to active Ru(II) species. The reaction produced exclusively diarylated product (94%) as compared to the monoarylated product (6%) when employed 2-phenylpyridine in DCE but a modest yield of mono-selectivity was observed with other solvents such as toluene, THF, ⁱPrOH, and DMF. Surprisingly, when the reaction was performed using Ag₂O as oxidant resulted in a high monoselectivity with 95:5 monoarylated/diarylated products but the overall yield was reduced to 40% (Scheme 26, Table 1).

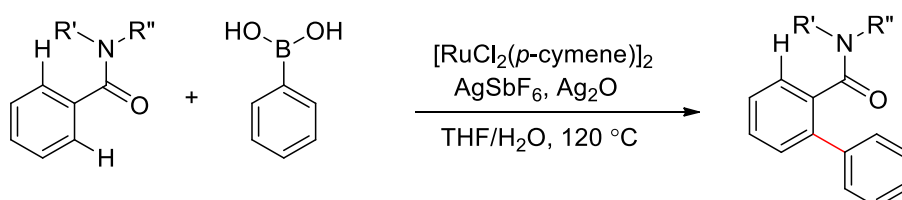


Scheme 26. Ruthenium-catalysed oxidative arylation of N-heterocycle with aryl silane.

Table 1. Solvent and oxidant effects on mono-diarylated product formation in the arylation of 2-phenylpyridine with aryl silanes.

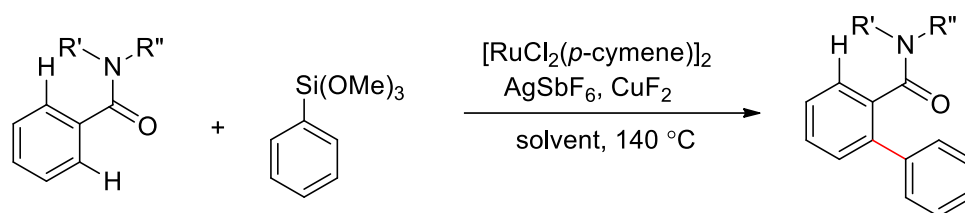
Additive	oxidant	Solvent	Mono/Di	Yield
CuF ₂	–	DEC	6:94	>95
CuF ₂	–	Toluene	69:31	>95
CuF ₂	–	THF	75:25	>95
CuF ₂	–	NMP	–	<2
CuF ₂	AgF	DCE	–	<2
CuF ₂	Ag ₂ O	DCE	95:5	40

In 2016, the research group of Szostak demonstrated the *ortho*-selective direct arylation of cyclic and *N,N*-dialkylbenzamides containing a weakly coordinated group using aryl boronic acid as arylating agent [78]. They have performed the reaction with [RuCl₂(*p*-cymene)]₂ in the presence of AgSbF₆ and Ag₂O to give the *ortho*-arylated products. The reaction has a wide substrate scope with high selectivity of monoarylation, over 95% thus, providing the valuable tertiary amide biaryl compounds (Scheme 27).



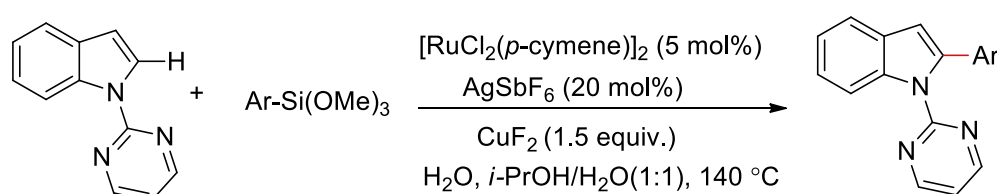
Scheme 27. Ruthenium-catalysed oxidative arylation of *N,N*-dialkylbenzamides with phenylboronic acid.

Subsequently, they have conducted this direct arylation reaction employing arylsilanes as the arylating agent instead of aryl boronic acid [79]. This reaction showed a high chemo-selectivity and effective when [RuCl₂(*p*-cymene)]₂ was employed in association with AgSbF₆ in the presence of CuF₂ (Scheme 28). The reaction was best performed in THF or DCE affording only the monoarylated products.



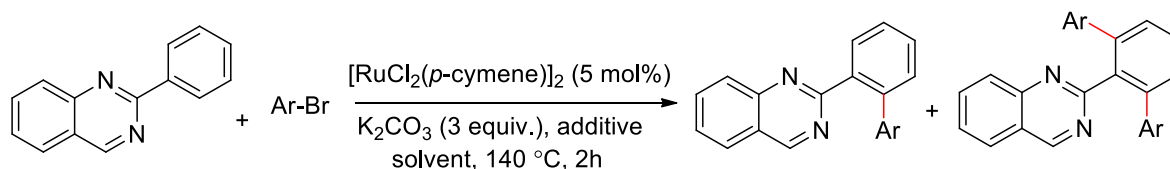
Scheme 28. Ruthenium-catalysed oxidative arylation of N,N'-dialkylbenzamides with phenylsilane.

Further, in continuation on the oxidative arylation using aryl silanes as the arylating agent, Szostak and co-workers have just reported the ruthenium-catalyzed arylation of pyrimidyl indole in water [80]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of an oxidant leading to the selective arylation at the C-2 position (Scheme 29).



Scheme 29. Ruthenium-catalysed direct C-2 arylation of indoles with arylsilanes in water.

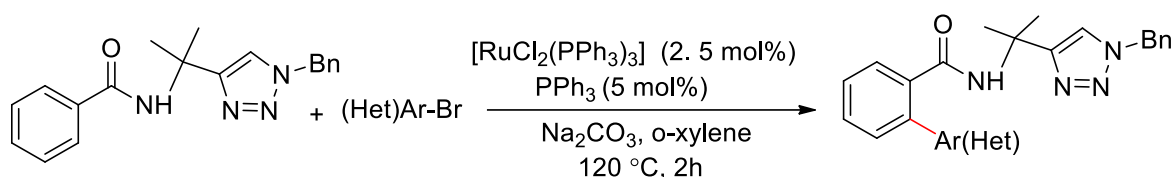
It is noteworthy that a few reports on the direct *ortho*-C-H arylation of arenes bearing pyrimidine ring as the directing group was reported by Nakamura [81], Gu [82] and Cheng [83], and later by Pozgan [84]. Very recently, Pozgan and co-workers demonstrated a ruthenium-catalysed direct arylation of arenes with aryl bromides directed by quinazoline [85]. The arylation was proceeded with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of a base and an additive affording *ortho*-diarylated arene as the major product along with minor monoarylated arene. The reaction was most effectively performed when 1-phenylcyclopentane-1-carboxylic acid (PCCA) was used as an additive in 1, 4-dioxane affording only diarylated product in 98% yield (Scheme 30).



Scheme 30. Ruthenium(II)-catalysed C-H arylation of arene with aryl bromide directed by quinazoline.

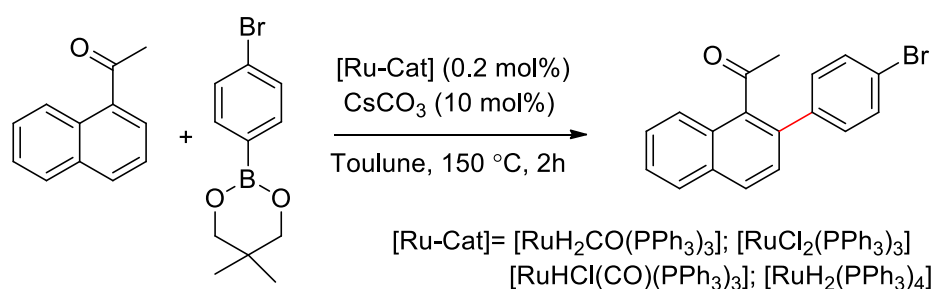
In 2014, Zhao *et al.* have demonstrated the arylation of tertiary amide *viz.* furan-3-carboxamide with $[\text{Ru}(\text{H}_2)(\text{CO})(\text{PPh}_3)_3]$ to give 2-aryl-3-furanamides [86]. This direct arylation of carboxamide has employed mostly the directing groups containing heteroatoms such as pyridine, pyrazole and oxazoline. In the same year, Ackermann and co-workers demonstrated a triazole assisted C-H bond

arylation of an amide with aryl bromide using $[\text{RuCl}_2(\text{PPh}_3)_3]$ in the presence of Na_2CO_3 (Scheme 31) [87]. The reaction was favorably proceeded with secondary amide having acidic $-\text{NH}$ free group, while the tertiary amide with no free $-\text{NH}$ group failed to give the desired product. They have found that other amide derivative such as pyridyl substituted amide or the substrate derived from 8-aminoquinoline gave an inferior result which indicated a superior directing-group power of the triazole auxiliary for this reaction. The screening of the reaction showed that an electron donating substituent on the 1, 2, 3-triazole proved to be most suitable for this amide C-H arylation.



Scheme 31. Triazole assisted ruthenium-catalysed C-H arylation of aryl amide.

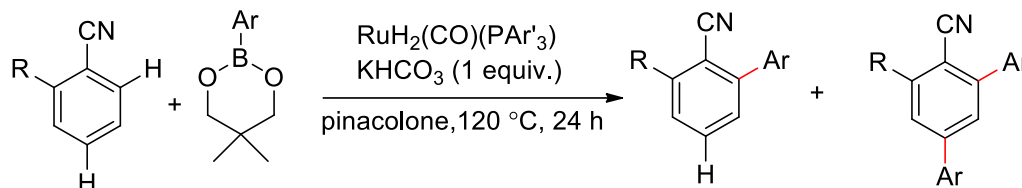
The ruthenium-catalysed $\text{sp}^2\text{-C-H}$ bond arylation of arenes directed by ketones has been studied by several research groups. In 2015, Yamamoto and Yamakawa described the arylation of acylarene with halogenated aryl boronic acids using various ruthenium(II) catalysts *viz.*, $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$, $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$, $[\text{RuCl}_2(\text{PPh}_3)_3]$ and $[\text{RuH}_2(\text{PPh}_3)_4]$ in the presence of Cs_2CO_3 [88]. They have found that the ruthenium complexes, $[\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]$ and $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$ were effective for the arylation in the presence of a base (10 mol%). When the reaction was performed in the absence of base resulted in extremely low yields. Moreover, the reaction was favoured using a halogenated aryl boronic acid (Scheme 32).



Scheme 32. Ruthenium-catalysed arylation of acylarenes with halogenated arylboronates.

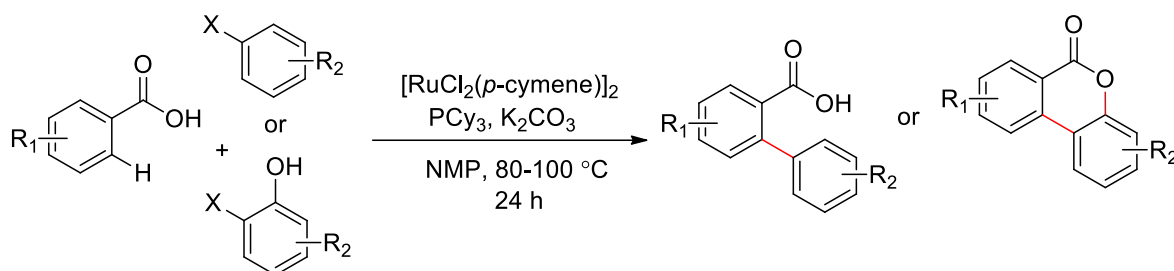
Recently, Kakiuchi's research group has successfully utilized a cyano ($-\text{CN}$) group as the directing group in the ruthenium-catalyzed C-H bond arylation reaction [89]. They have performed the arylation of aromatic nitrile with aryl boronic esters using $[\text{RuH}_2(\text{CO})(\text{PAR}_3)_3]$ in the presence of

KHCO_3 resulting in the *ortho*-arylated product along with a minor *para*-diarylated product (Scheme 33).



Scheme 33. Ruthenium-catalysed arylation of aromatic nitriles with arylboronates.

In 2016, Huang *et al.* demonstrated the arylation of a carboxylic acid with aryl and heteroaryl halides leading to *ortho* arylated products [90]. The reaction was conducted employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of K_2CO_3 and PCy_3 ligand in NMP at 80 °C. This protocol was successfully used for the *ortho*-arylation of aromatic or heteroaromatic carboxylic acids with diverse aryl and heteroaryl halides. Interestingly, the reaction gave annulation product when iodophenol was used in the reaction instead of aryl halide (Scheme 34).



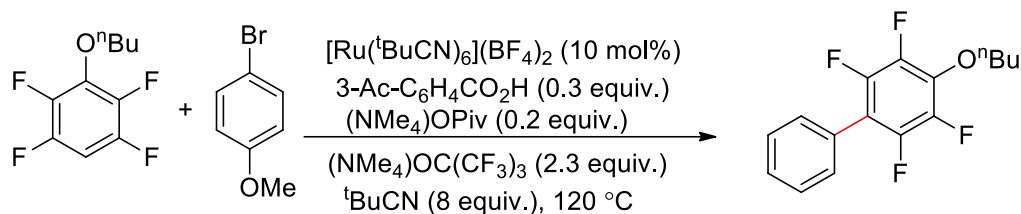
Scheme 34. Ruthenium-catalysed arylation of with aryl or heteroaryl halides.

2.5.

Arylation of C-H bond without a directing group:

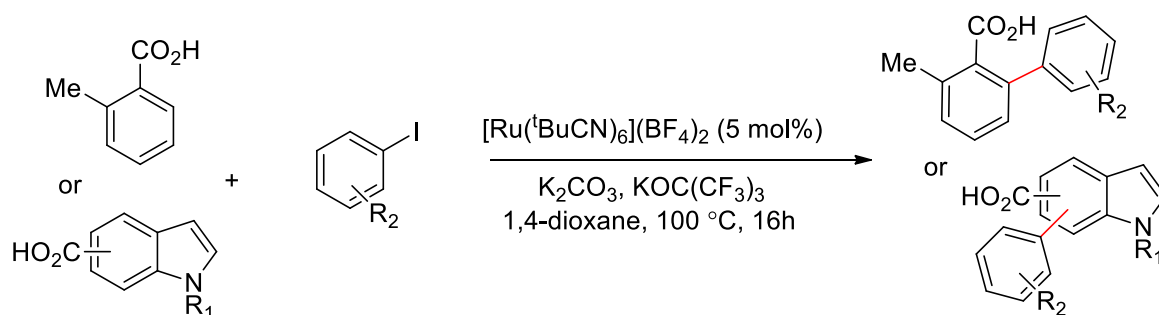
In 2016, Larrosa and co-workers have described the C-H bond arylation of fluoroarenes with aryl halides using various ruthenium(II) complexes as the catalyst in the presence of a base [91]. They have performed the reaction, first with $[\text{Ru}(\text{OPiv})_2(p\text{-cymene})]$ in the presence of a base but no desired product was formed. They have observed a quantitative dissociation of *p*-cymene ligand at the end of the reaction. Therefore, in order to prevent dissociation of arene ligand, they have performed the reaction employing an analogous ruthenium complex, $[\text{Ru}(\text{OPiv})_2(\text{C}_6\text{Me}_6)]$ containing a less labile arene ligand, C_6Me_6 . However, in this case only 32% of arylated product was observed despite only 14% of C_6Me_6 ligand was found to be dissociated during the reaction. From this finding, they hypothesized that under the reaction condition, dissociation of arene ligand might be necessary for the reaction to occur. Further, they have proposed that a ruthenium complex without arene ligand could also promote cross-coupling reaction. Previously, it was reported that the presence of *p*-cymene ligand was necessary for the cross-coupling of cycloruthenated phenylpyridine complexes

[92]. Interestingly, they found that a significant improvement in the reaction when employed with an arene free cationic ruthenium complex, $[\text{Ru}(\text{tBuCN})_6](\text{BF}_4)_2$, obtaining a good yield of the desired arylated product (Scheme 35).



scheme 35. Ruthenium-catalysed C-H arylation of fluoroaromatics with aryl halides.

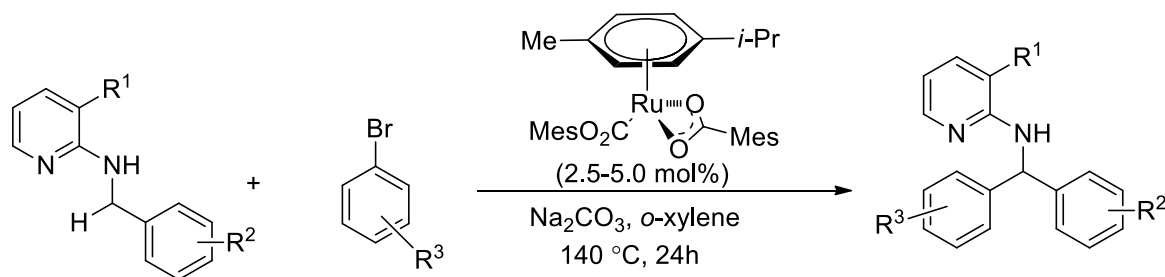
Subsequently, they demonstrated ruthenium-catalysed arylation of aromatic acids with aryl iodides using the same cationic ruthenium catalyst, $[\text{Ru}(\text{tBuCN})_6](\text{BF}_4)_2$ [93]. The reaction was performed in the presence of K_2CO_3 and an additive such as KOPiv or $\text{KOC}(\text{CF}_3)_3$ in 1,4-dioxane affording *ortho*-arylation of carboxylic acids without decarboxylation (Scheme 36).



Scheme 36. Ruthenium-catalysed arylation of carboxylic acids with aryl iodides.

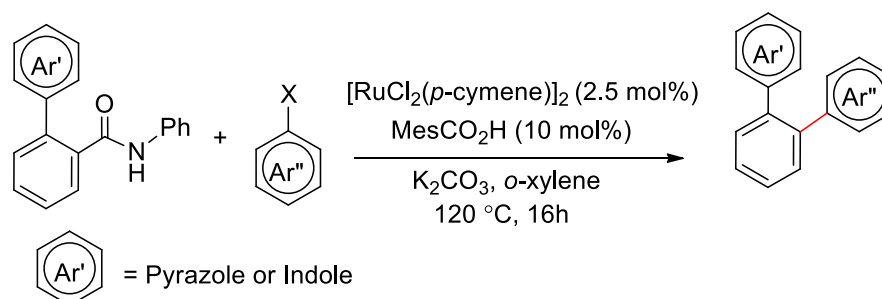
2.6. Arylation involving decarboxylative and sp^3 C-H Bond functionalization

In 2006, Sames's research group has demonstrated the pioneer work on the direct arylation of cyclic amines especially pyrrolidines involving an sp^3 C-H bond functionalization using ruthenium(0) catalyst, $[\text{Ru}_3(\text{CO})_{12}]$ and aryl boronic acid as arylating reagents [94]. In subsequent years, Peschiulli *et al.* have performed a similar arylation of a saturated cyclic amine with aryl boronic esters in the presence of $\text{Ru}_3(\text{CO})_{12}$ [95]. Following this early discovery, Mihovilovic and co-workers have shown that ruthenium(II) catalyst could efficiently activate sp^3 C-H bond of benzylic amine [96]. They have performed sp^3 C-H bond arylation of benzylic amine using an aryl halide with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of catalytic amount of KOPiv and a base. In later year, this arylation reaction was performed by Ackermann and co-workers employing the $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ without additional use of carboxylic acid but in the presence of a base (Scheme 37) [97].



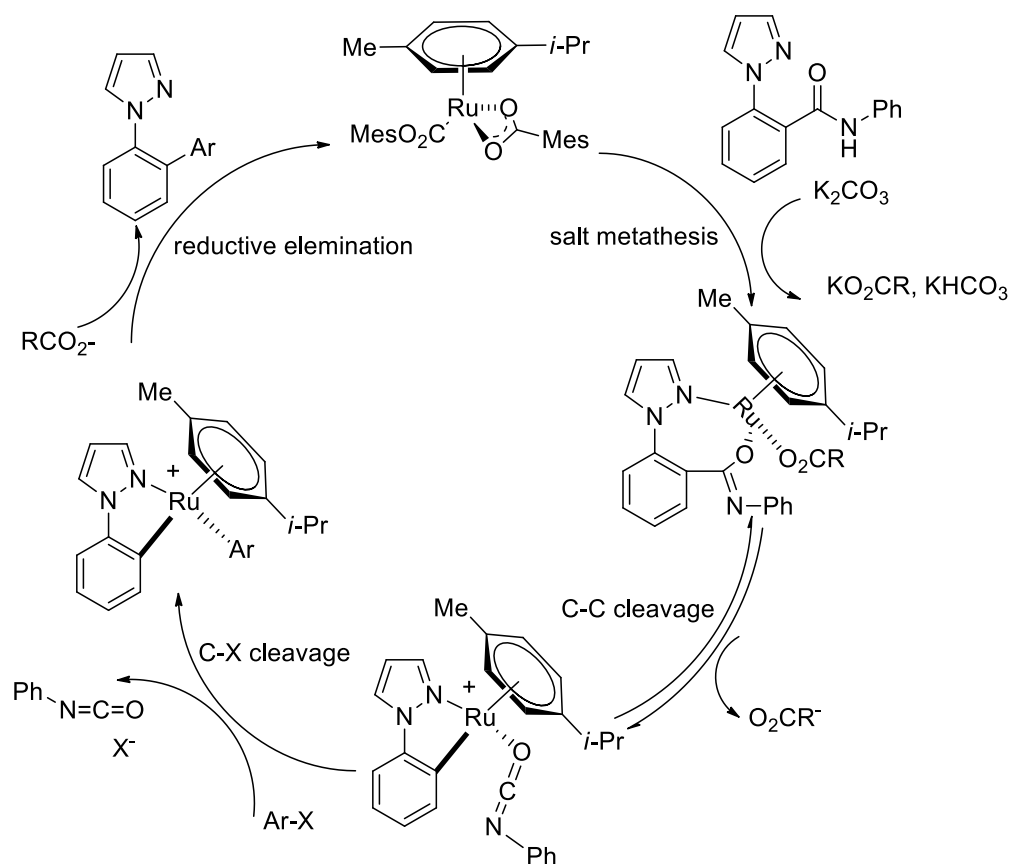
Scheme 37. Ruthenium(II)-catalysed sp^3 C-H bond arylation of benzylic amines with aryl halides.

Arylation of a carboxylic acid with transition metals such as Pd or Ru often involved a decarboxylation. In 2007, a new ruthenium(0)-catalysed reaction involving a decarboxylative arylation of cyclic-2-aminoester was described by Sames and co-workers [98]. The arylation was performed using $Ru_3(CO)_{12}$ with boronates in xylene at 180 °C resulting in decarboxylative arylation at the sp^3 carbon centre. Recently, Moselage *et al.* have reported a highly efficient ruthenium(II)-catalysed arylation involving decarboxylative C-C bond functionalization (Scheme 38) [99]. They have performed the reaction in the presence of a carboxylic acid and a base. The presence of both the carboxylic acid and a base is essential as in the absence of either of them resulted in extremely poor yield or no reaction.



Scheme 38. Ruthenium(II)-catalysed decarboxylative arylation of pyrazole and indole with aryl halides.

This reaction was proceeded effectively using $[RuCl_2(p\text{-cymene})]_2$ in association with mesitylic acid or directly employing $[Ru(MesCO_2)_2(p\text{-cymene})]$ without additional use of mesitylic acid with compatible results and thus, clearly suggested that the reaction proceeded through carboxylate assisted route (Scheme 39). Among the carboxylic acids tested, mesitylic acid gave the best beneficial effect. However, the reaction performed with $RuCl_3(H_2O)_3$ or $Ru_3(CO)_{12}$ did not give satisfactory result even in the presence of mesitylic acid under the similar reaction condition indicating Ru(III) and Ru(0) species were not suitable for this arylation [99].



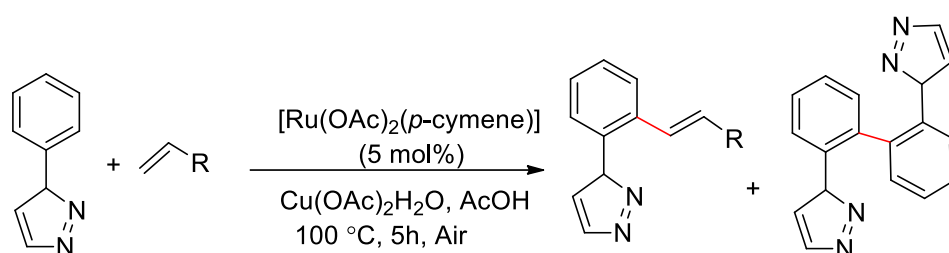
Scheme 39. Proposed mechanism for the ruthenium-catalysed decarbonylative arylation of pyrazole [99].

3. Ruthenium-catalysed C-H bond alkenylation

The direct alkenylation of sp^2 or sp^3 C-H bond is a powerful method in C-C cross-coupling reactions. Many aromatic and heteroaromatic C-H bonds could be readily alkenylated through transition metal catalysts leading to various alkenylated products. The Heck coupling is the most pronounced method in the alkenylation process. However, it requires a pre-functionalization of starting materials which limit the scope of the reaction. The oxidative alkenylation of C-H bond was discovered for the first time by Fujiwara-Moritani also known as Fujiwara-Moritani reaction or oxidative Heck reaction which was reported as early as in 1967 much before the Heck reaction. The reaction involved the coupling of arenes with an alkene in the presence of palladium catalyst and oxidant to give an alkenylated product. Initially, palladium and rhodium catalysts contributed enormously in this oxidative alkenylation, however, with the pioneering work of Milstein *et al.* [100] in 2001 followed by Yi and Lee [101], the ruthenium-catalysed oxidative alkenylation reaction has been progressed rapidly [15]. The oxidative alkenylation of C-H bond has been performed profitably using stable ruthenium(II)-catalysts from 2011 onwards successively by the groups of Satoh and Miura [102], Ackermann [103], Bruneau and Dixneuf [104], Jeganmohan [32] and several others [105, 106].

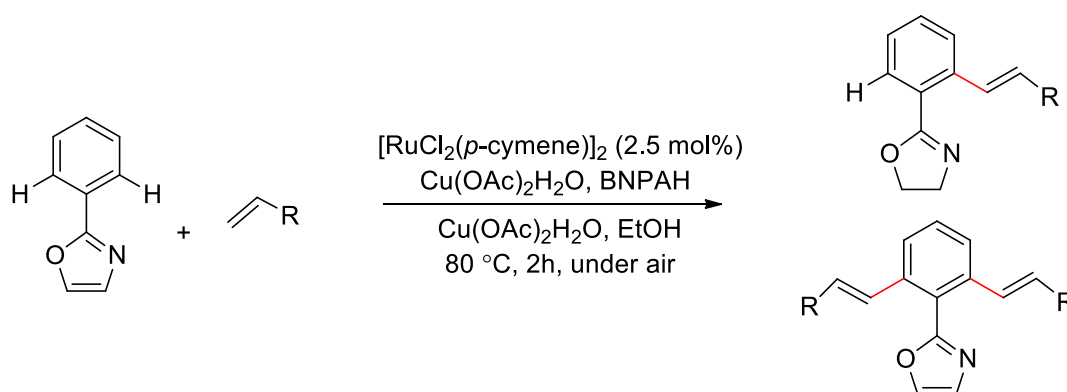
3.1. Alkenylation involving sp^2 C-H bond directed by Nitrogen containing hetroaryl ring:

The ruthenium(II)-catalysed alkenylation of sp^2 C-H bond directed by the nitrogen-heteroaryl group has been studied enormously by several groups from 2011 onwards. Dixneuf and co-workers have described the alkenylation of 1-phenyl-1-pyrazole with acrylates using $[\text{Ru}(\text{OAc})_2(p\text{-cymene})]$ in the presence of an oxidant in acetic acid at 100 °C [104]. The reaction gave predominantly monoalkenylated product along with minor homocoupling product with alkyl acrylates but a mixture of monoalkenylated and homocoupling product were observed in 56:44 ratios with styrene (Scheme 40). However, homocoupling product was formed exclusively when employed the less reactive alkene, such as *N,N*-dimethyl acrylamide [104].



Scheme 40. Ruthenium(II)-catalysed alkenylation of *N*-aryl pyrazoles.

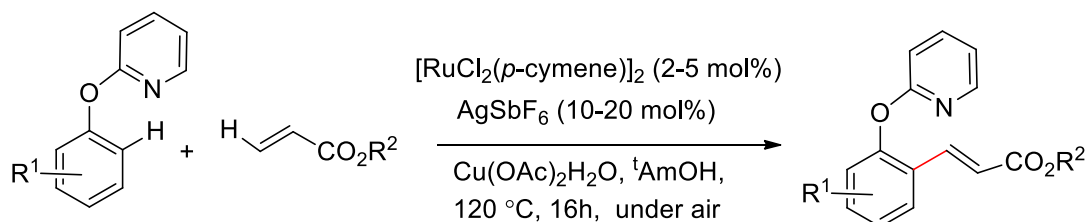
Later, his research group described the alkenylation of 2-phenyloxazoline with an alkene to give *ortho*-monoalkenylated and dialkenylated products [107]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an additive and an oxidant in ethanol at 80 °C. They have screened several additives of which binaphthyl phosphoric acid (BNPAH) was found to be the most effective leading to 85/14 mono/dialkenylated products with methyl acrylate whereas; the monoalkenylated product was formed exclusively with styrene (Scheme 41).



Scheme 41. Ruthenium-catalysed alkenylation of phenyloxazolines with alkenes.

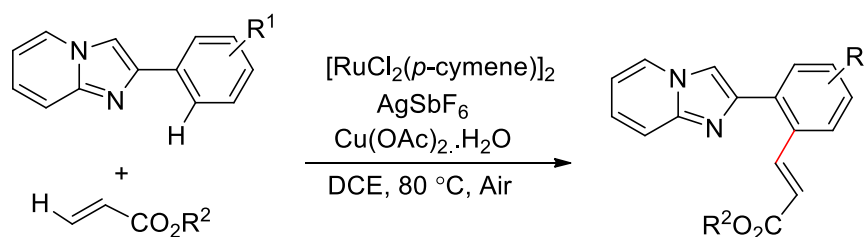
Alkenyl esters and ethers were also successfully used in the alkenylation of 2-phenylpyridine derivative in the presence of ruthenium(0) catalyst, $[\text{Ru}(\text{COD})(\text{COT})]$ in *xylene* at 150 °C affording exclusively a monoalkenylated product [108]. In 2013, Ackermann and Ma have demonstrated a

ruthenium-catalysed oxidative C-H bond alkenylation of 2-phenoxy pyridine possessing a removal directing group [109]. They have performed the reaction using $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with AgSbF_6 in the presence of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ at $120\text{ }^\circ\text{C}$ for 16h. The reaction involved the C-H bond functionalization *via* the formation of six-membered ruthenacycle as the key intermediate affording a monoalkenylated product (Scheme 42).



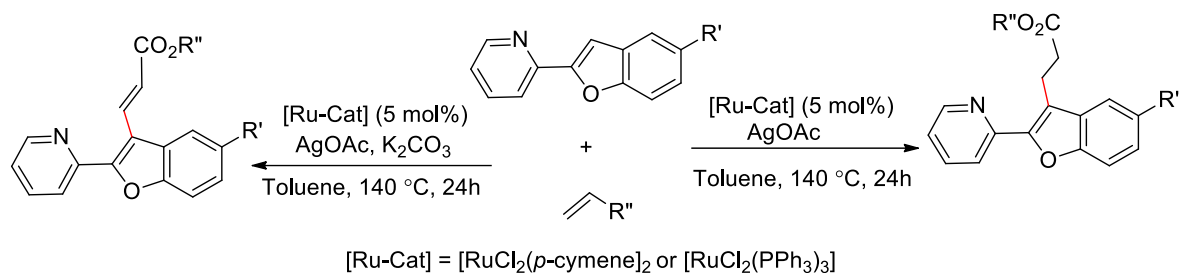
Scheme 42. Alkenylation of 2-phenoxy pyridines with acrylates.

The ruthenium-catalysed alkenylation has been studied with several other nitrogen heteroaryl directing groups. For instance, alkenylation of 2-phenylimidazo[1,2-a]pyridine leading to a monoalkenylated product was described by Sawant *et al.* employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with AgSbF_6 in the presence of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ in DCE (Scheme 43) [110]. The reaction proceeds regioselectively through *ortho*-C-H bond activation *via* the formation of a five-membered ruthenacycle intermediate.



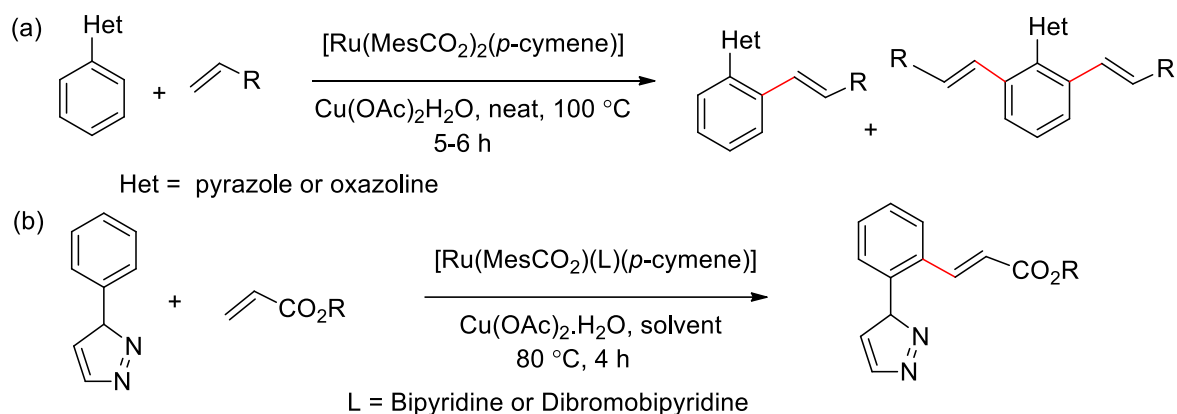
Scheme 43. Ruthenium-catalysed alkenylation of 2-phenylimidazo[1,2-a] pyridine.

Recently, Ramana and co-workers showed the C-H bond alkenylation of 2-pyridyl benzofurans leading to C-3 alkylated and alkenylated products [106]. This approach is attractive as it could provide ready access to various biological relevant benzofuran analogs many of which are the structural units of pharmacophores and natural products. They have performed the reaction employing $[\text{RuCl}_2(p\text{-cymene})]_2$ or $[\text{RuCl}_2(\text{PPh}_3)_3]$ in the presence of AgOAc as the additive with or without a base. The reaction produced only the C-3 alkylated product when $[\text{RuCl}_2(p\text{-cymene})]_2$ was used without a base which is switchable to C-3 alkenylated product in the presence of K_2CO_3 (Scheme 44).



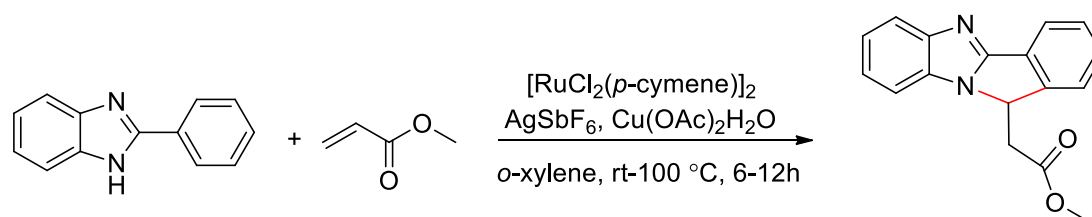
Scheme 44. Ruthenium-catalysed switchable C-3 alkylation and alkenylation of 2-pyridinebenzofurans.

In 2017, Shome *et al.* have demonstrated that, 2-phenylpyrazole or 2-phenyloxazoline could be alkenylated with alkene employing [Ru(MesCO₂)₂(*p*-cymene)] in the presence of Cu(OAc)₂·H₂O at 100 °C under solvent-free condition (Scheme 45a) [111]. Very recently, they have also demonstrated the alkenylation of 1-phenylpyrazole with acrylate using a ruthenium(II) bipyridine complex, [Ru(MesCO₂)(L)(*p*-cymene)]⁺ in the presence of Cu(OAc)₂·H₂O in ethanol at 80 °C producing predominantly a monoalkenylated product (Scheme 45b) [112].



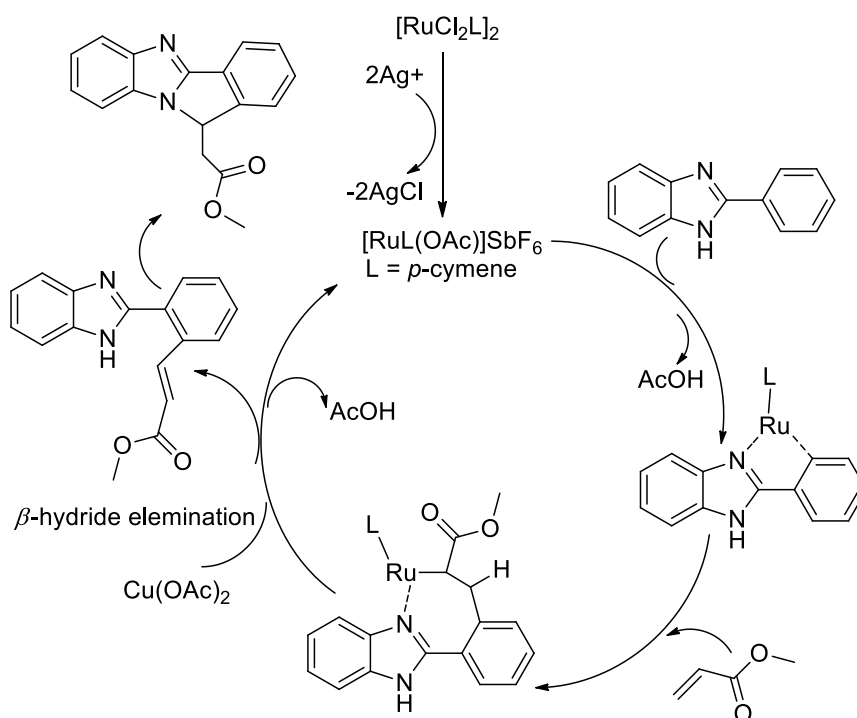
Scheme 45. Alkenylation of Pyrazole/oxazoline with alkenes under neat condition (a); Alkenylation of Pyrazoles with acrylates (b).

Recently, alkenylation of benzimidazoles with acrylates affording various annulated products was performed by Selvaraju *et al.* using [RuCl₂(*p*-cymene)]₂ in the presence AgSbF₆ and Cu(OAc)₂·H₂O in *o*-xylene (Scheme 46) [113].



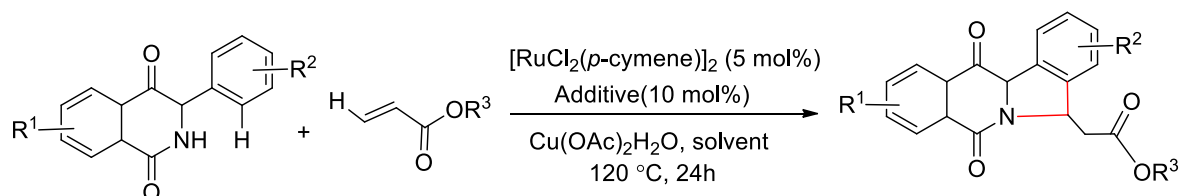
Scheme 46. Alkenylation/annulation of benzimidazoles with acrylates to benzoimidazoisoindoles.

They have evaluated the efficacy of other oxidants such as CuBr_2 , AgOAc and AgCO_3 as well but they were found to be less effective. Further, they have proposed that the alkenylated product is formed by the protonation of a seven-membered ruthenacycle intermediate [113] (Scheme 47).



Scheme 47. Proposed mechanism for the formation of benzoimidazoisoindoles [113].

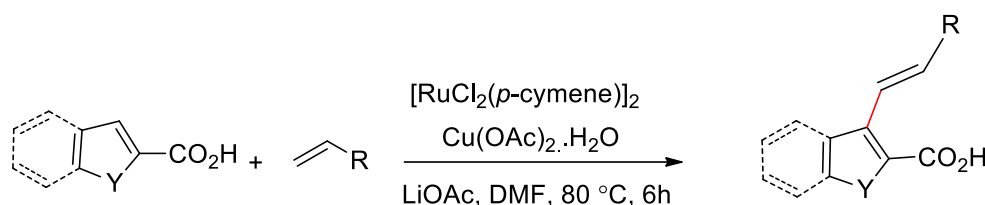
Gholamhosseyni and Kianmehr have just reported the ruthenium-catalysed alkenylation-annulation approach that lead to indazole derivatives [114]. The coupling of *N*-aryl pyridazinediones and *N*-aryl phthalazinediones with acrylates were proceeded using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and additive in water (Scheme 48). The reaction was best performed when AgSbF_6 was used as additive giving up to 95% of the desired product. The desired product can be obtained in a competitive yield with KPF_6 . However, the reaction when conducted without an additive resulted in lower efficacy affording only a modest yield of the desired products.



Scheme 48. Ruthenium-catalysed synthesis of indazole derivatives via alkenylation-annulation approach.

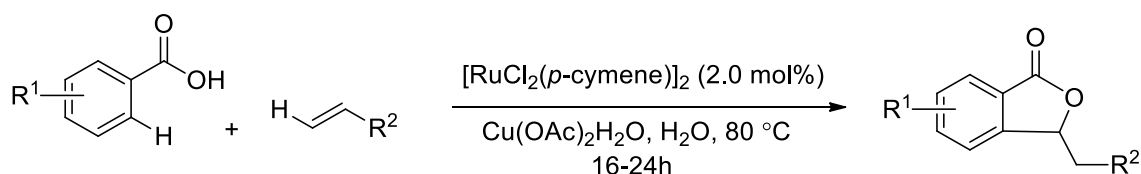
3.2. Alkenylation with carboxylic acids and sulfonic acids:

In 2011, Miura, Satoh, and co-workers have reported a carboxylic acid directed alkenylation of heteroaromatic sp^2 -C-H bonds with acrylate [102]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of LiOAc and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in DMF leading to *ortho*-monoalkenylated arenes without decarboxylation (Scheme 49).



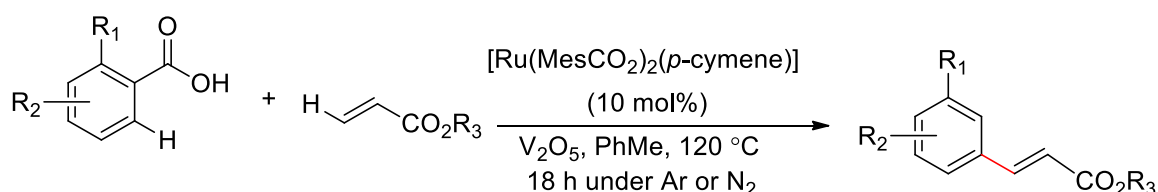
Scheme 49. Ruthenium-catalysed alkenylation of heteroaromatic carboxylic acids with alkenes.

In the same year, the research group of Ackermann has reported the dehydrogenative alkenylation of aromatic carboxylic acids with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in water [115] resulting in annulated lactones (Scheme 50). The optimization of the reaction showed that the reaction proceeded most efficiently without an additive, however, the presence of oxidant is essential as no reaction has occurred in the absence of oxidant.



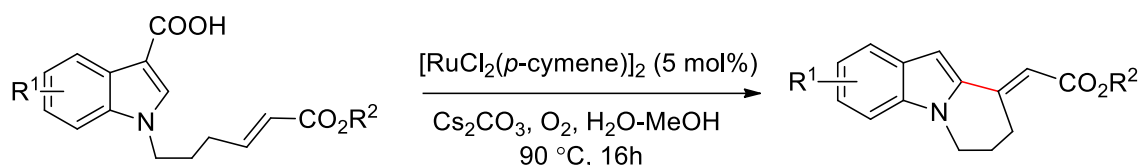
Scheme 50. Ruthenium-catalysed alkenylation of carboxylic acids leading to annulated lactones.

Recently, Ackermann and co-workers have also demonstrated a ruthenium-catalysed *meta*-selective C-H alkenylation of aromatic carboxylic acid involving decarboxylation [116]. This reaction undergoes efficiently with 10 mol% of $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ in the presence of an additive affording *meta*-alkenylated product involving a decarboxylation under a nitrogen atmosphere (Scheme 51). Although several other additives such as $\text{Na}_2\text{S}_2\text{O}_7$, $t\text{BuC}(\text{O})\text{Me}$, MnO_2 could be employed, the best result was obtained when used V_2O_5 as the additive in toluene.



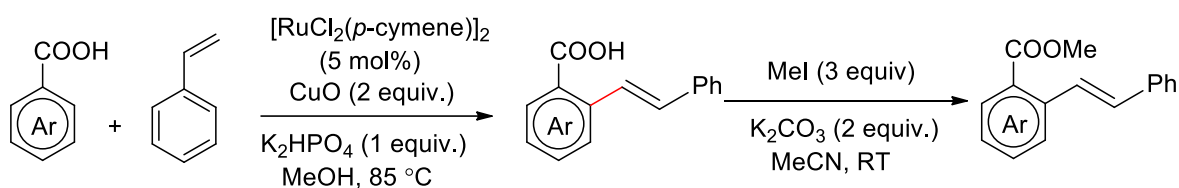
Scheme 51. Ruthenium-catalysed decarboxylative *meta*-alkenylation of aromatic carboxylic acids.

Very recently, Jin *et al.* have reported an intramolecular C-H bond alkenylation involving a decarboxylation of carboxylic acid with the 5 mol% of $[\text{RuCl}_2(p\text{-cymene})]_2$ [117]. The reaction was performed in the presence of Cs_2CO_3 in aqueous media under oxygen leading to tetrahydropyridoindoles in up to 78% yield (Scheme 52).



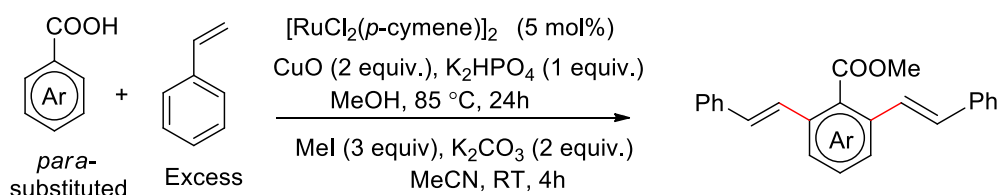
Scheme 52. Ruthenium-catalysed decarboxylative intramolecular alkenylation of indole derivatives.

Dana *et al.* have just reported an *ortho* C-H bond monoalkenylation of an aromatic carboxylic acid with styrene without a decarboxylation [118]. The reaction undergoes efficiently with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of CuO and KHPO_4 in methanol at 85 °C to give the desired product in 92% yield. The product can be obtained as ester derivative by further treatment acid derivative with methyl iodide (3 eq.), K_2CO_3 (2 equiv.) in acetonitrile at room temperature (Scheme 53).



Scheme 53. Ruthenium catalysed mono alkenylation of aromatic acids without decarboxylation.

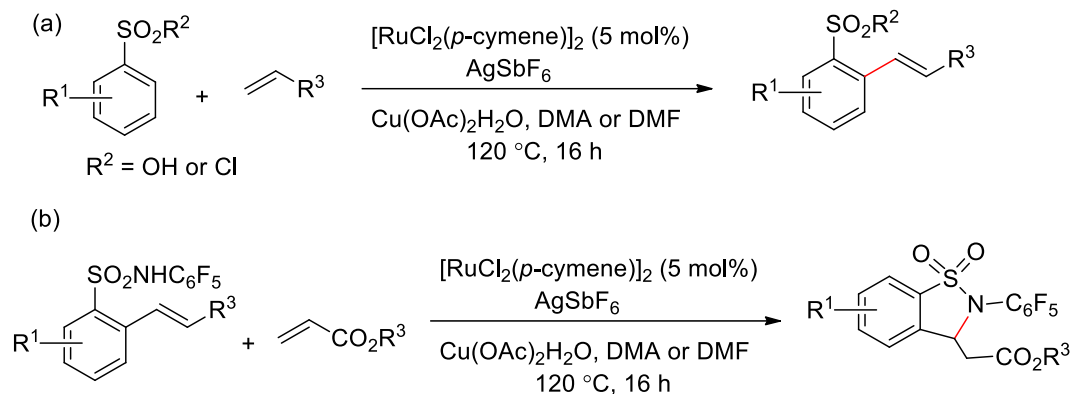
They have observed that an alteration of the base KHPO_4 , by other lead to inferior result whereas replacing CuO by $\text{Cu}(\text{OAc})_2$ drastically reduced the yield to 31%. The reaction gave dialkenylated product when *para*-substituted benzoic acids were treated with an excess of styrene (Scheme 54).



Scheme 54. Ruthenium catalysed dialkenylation of *para*-substituted aromatic acids without decarboxylation.

In 2014, Ackermann and co-workers successfully performed a ruthenium-catalysed alkenylation of aromatic sulfonic acids, sulfonyl chlorides and sulfonamides [119]. This C-H bond alkenylation was achieved using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an additive in DMA at 120 °C. They have found that the reaction can undergo even without an additive, however, the presence of AgSbF_6 as additive boost the reaction efficacy considerably. Alkenylation of sulfonic acid or sulfonyl chloride

with an alkene afforded mono-alkenylation whereas, oxidative alkenylation of sulphonamides lead to C-H/N-H alkene annulation affording a high yield of annulated products (Scheme 55).

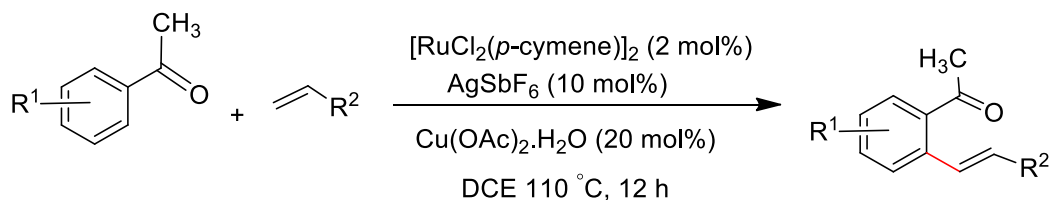


Scheme 55. Ruthenium-catalysed (a) ortho alkenylation of sulfonic acids or sulfonyl chlorides; (b) Oxidative alkenylation of sulfonylamides.

3.3.

Alkenylation involving weakly coordinated directing group and dehydrogenative coupling

The weakly coordinated group such as ketones, esters, amides, and anilides have been successfully used as a directing group in the ruthenium-catalysed C-H bond functionalization. The ruthenium-catalysed C-H alkenylation of aromatic ketones with olefins was initiated as early as in 1993 with the pioneering work of Murai and co-workers [120], followed by several other groups [121, 122, 123]. However, in all these attempts, only the alkylated products were observed. In 2012, Padala and Jeganmohan described the C-H bond alkenylation of an aromatic ketone with alkene using $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ in DCE (Scheme 56) [124]. The reaction undergoes in a highly regio- and stereoselective manner resulting in the *ortho*-alkenylated product with acetophenone but a mixture of mono- and dialkenylated products were observed for benzophenone.

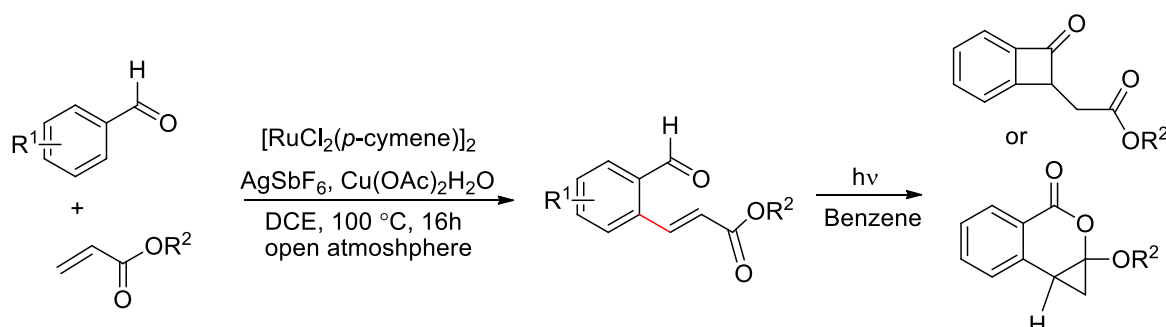


Scheme 56. Ruthenium(II)-catalysed alkenylation of aromatic ketones.

Subsequently, Singh and Dixneuf demonstrated alkenylation of a ferrocenyl ketone using $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ in the presence of $\text{Cu}(\text{OAc})_2\cdot\text{H}_2\text{O}$ [125]. The reaction leads to the *ortho*-alkenylation of ferrocene C-H bond when ferrocenyl methyl ketone was reacted with acrylate

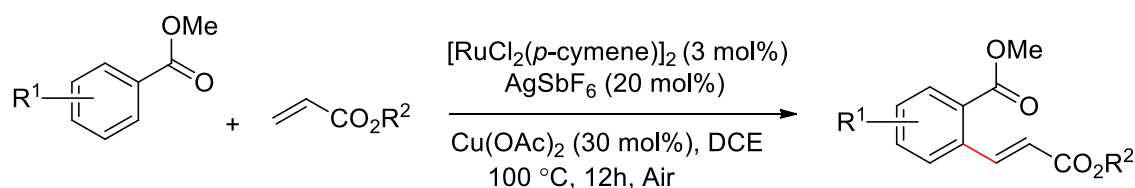
obtaining a modest yield of the alkenylated product. However, when the reaction was performed with ferrocenyl phenyl ketone, *ortho* alkenylation occurred at the phenyl ring. The reaction undergoes efficiently under air at room temperature in DCE leading to the *ortho*-alkenylated product in high yield (up to 97%) demonstrating the strong influence of ferrocenyl group on the arene C-H functionalization.

In 2012, Jeganmohan's research group described an alkenylation of aromatic sp^2 C-H bond directed by an aldehyde [126]. The *ortho*-alkenylation was achieved using $[\text{RuCl}_2(p\text{-cymene})]/\text{AgSbF}_6$ catalytic system which is usually employed for the C-H bond activation directed by a weakly coordinated group such as ester and ketone. The alkenylation was performed in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in open air and the reaction was proceeded in a highly stereoselective manner. Further, they have shown that the alkenylated product could be converted into a four-membered or five-membered cyclic ketones or a polycyclic isochromanone *via* a photochemical rearrangement (Scheme 57).



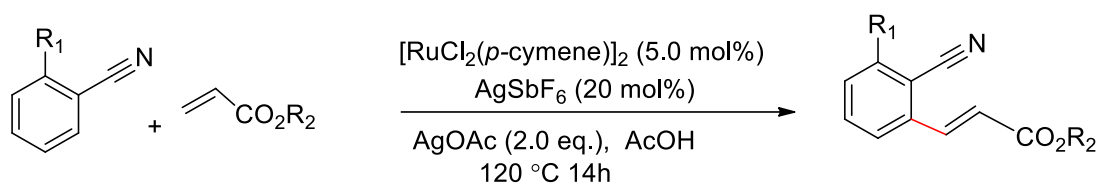
Scheme 57. Alkenylation of aromatic aldehydes and photochemical rearrangement to cyclic ketones or polycyclic isochromanone.

In the same year, Jeganmohan's research group described the ruthenium(II) catalysed alkenylation of aromatic esters to give *ortho*-alkenylated products [18]. The alkenylation was performed with $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in DCE under open air. The reaction was tolerated to various aromatic and heteroaromatic esters such as thiophene-3-carboxylate and indole-3-carboxylate giving an excellent yield of the alkenylated products (Scheme 58).



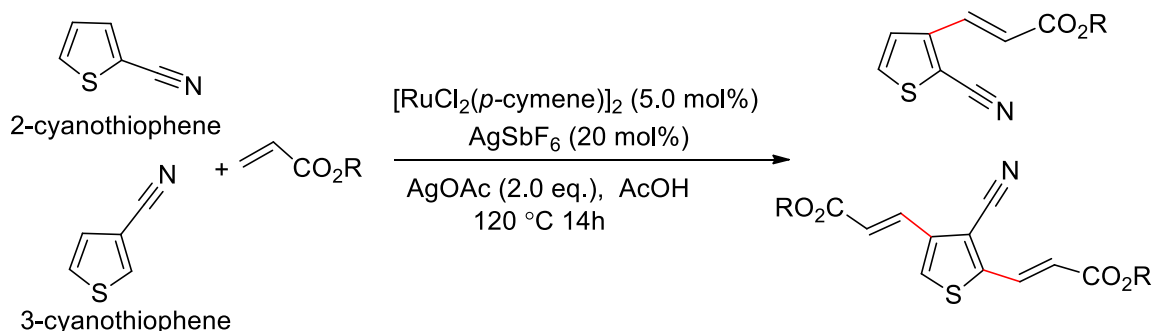
Scheme 58. Ruthenium-catalysed oxidative alkenylation of aromatic esters.

In the following years, they have demonstrated the alkenylation of aromatic nitriles with activated alkenes using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of AgSbF_6 and AgOAc in acetic acid providing *ortho*-alkenylated products [127]. Initially, they have reacted nitriles with activated alkenes in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ but failed to give alkenylated product instead the reaction afforded only an amide due to hydration of nitrile indicating copper salts were not suitable for this reaction. They have evaluated the alkenylation of nitrile using several Lewis acids such as $\text{Mn}(\text{OAc})_2$, AgOAc , $\text{Ag}(\text{CF}_3\text{COO})$ and Ag_2CO_3 of which AgOAc produced the best result (Scheme 59).



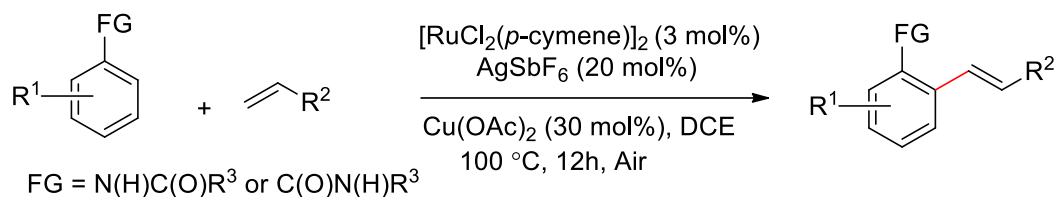
Scheme 59. Ruthenium-catalysed alkenylation of aromatic nitriles with activated alkenes.

Further, they have shown that the alkenylation of 2-cyanothiophene gave a monoalkenylated product whereas, 3-cyanothiophene provided dialkenylated product (Scheme 60).



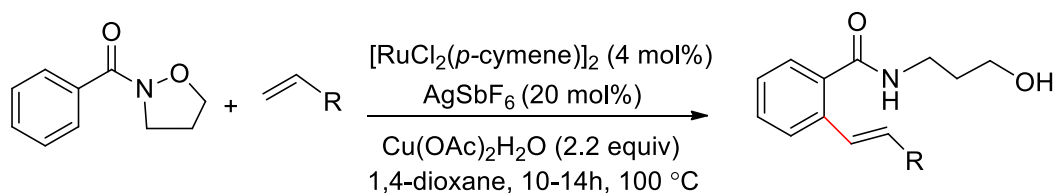
Scheme 60. Alkenylated products of 2-cyanothiophene and 3-cyanothiophene with acrylates.

In 2012, Miura and co-workers have demonstrated the alkenylation of *N,N*-dimethyl benzamide with acrylate using $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in $t\text{-AmOH}$ affording *ortho*-alkenylated products [19]. Whereas, the dehydrogenative alkenylation of benzamide and anilide was described by the research group of Ackermann using $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst. This reaction was performed in water in the presence of additive and an oxidant [128]. They have found that the most efficient catalysis could be achieved with a cationic ruthenium(II) species. Thus, employing KPF_6 as additive achieved the most efficient catalytic activity giving 87% yield, whereas, AgSbF_6 gave a modest yield of 54%. The presence of additive is essential for this reaction as the absence of it resulted in extremely poor yield giving only 2% under the same reaction condition (Scheme 61).



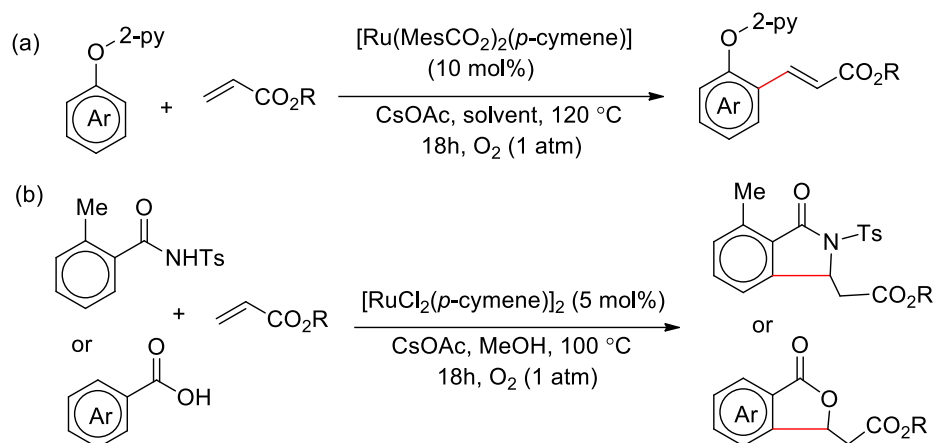
Scheme 61. Ruthenium-catalysed oxidative alkenylation of benzamides and anilides.

In 2013, Li *et al.* has demonstrated a ruthenium-catalysed C-2 alkenylation of pyrrole and indole derivative directed by an amide group [129]. The reaction proceeded with regio- and stereoselectively with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an oxidant. In later years, Das and Kapoor demonstrated the *ortho*-alkenylation of amides including acyclic and cyclic Weinreb amides with alkenes using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of additive and oxidant in 1,4-dioxane at 100 °C (Scheme 62) [130].



Scheme 62. Ruthenium-catalysed alkenylation of Weinreb's amides.

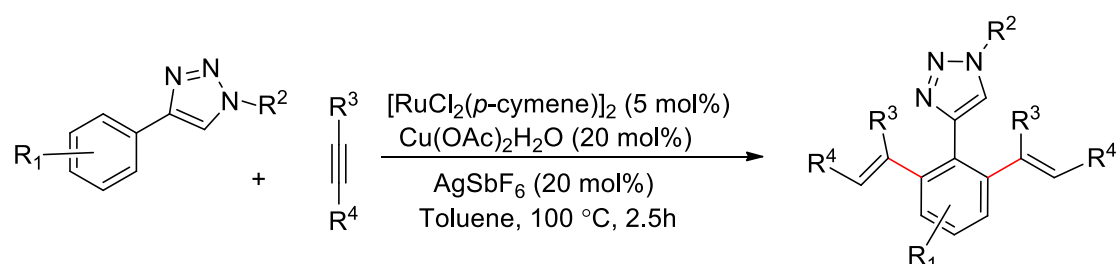
Recently, Ackermann and co-workers have demonstrated a ruthenium-catalysed dehydrogenative alkenylation of aromatic tosylamide, aromatic acid and 2-phenoxy pyridine with alkene using molecular oxygen as the sole oxidant [131]. The reaction proceeded efficiently with $[\text{RuCl}_2(p\text{-cymene})]_2$ or $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ in the presence of CsOAc or KOAc as additive under an oxygen atmosphere. The reaction of 2-phenoxy pyridine and alkene lead to the *ortho*-alkenylated products, however under the similar reaction condition tosylamide and aromatic carboxylic acid gave the annulated product (Scheme 63a & b).



Scheme 63. Ruthenium catalyzed alkenylation of removable phenol derivatives (a); alkenylation of amide or acid with acrylates (b).

3.4. Alkenylation through hydroarylation with alkynes

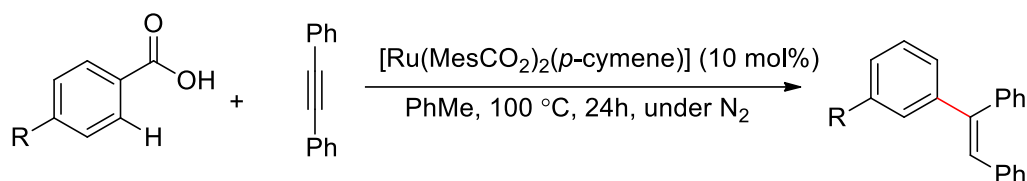
Alkenylarenes could also be obtained efficiently *via* catalytic hydroarylation of alkynes. In 2008, Zhang and co-workers have demonstrated for the first time the alkenylation of arylpyridimidine and aryl pyridine with terminal alkyne using a ruthenium catalyst [132]. This alkenylation of heteroarenes was performed using simple RuCl₃ as the catalyst in the presence of potassium carbonate as base. Subsequently, Wu's group has described the catalytic alkenylation of 2-phenylpyridine with terminal alkynes using ruthenium or zinc compounds containing 12 metallocrown-6 as catalysts in the presence of a base in NMP at 150 °C. In later years, Li *et al.* have extended the catalytic alkenylation *via* hydroarylation of alkynes to other arene compounds [133]. They have performed alkenylation of 2-phenyltriazole derivatives with alkynes using [RuCl₂(*p*-cymene)]₂/AgSbF₆ in the presence of additive leading to dialkenylated products (Scheme 64).



Scheme 64. Ruthenium-catalyzed hydroarylation of phenyltriazoles with alkynes.

The alkenylation *via* hydroarylation of alkynes was studied with several other arenes as well. Jeganmohan and Manikandan have described the alkenylation of anilide *via* hydroarylation using [RuCl₂(*p*-cymene)]₂ in the presence of AgSbF₆ and pivalic acid at 100 °C [134]. They have shown that the alkenylated products on further treatment with 17% HCl:THF (1:1) could lead to the *ortho*-alkenylated anilines. Recently, Ackermann's research group has demonstrated hydroarylation of carboxylic acids with diphenylacetylene to give alkenylated products (Scheme 65) [116]. This

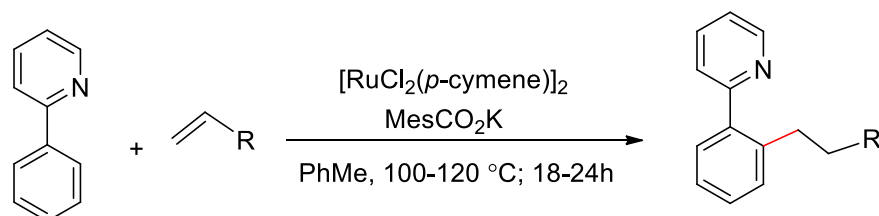
hydroarylation was performed with $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ under nitrogen and the reaction involved a decarboxylation of carboxylic acid.



Scheme 65. Ruthenium-catalysed hydroarylation of aromatic acids with decarboxylation.

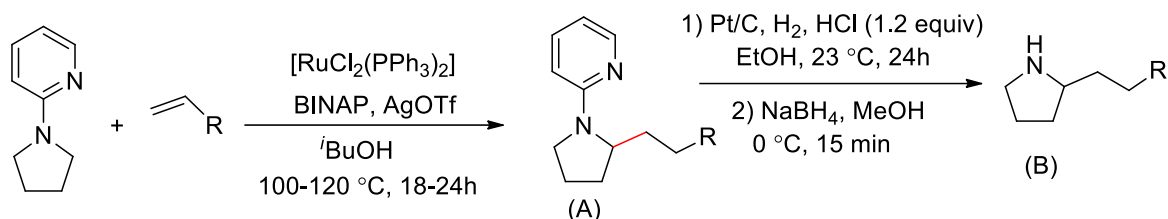
4. Ruthenium-catalysed C-H bond alkylation and allylation

The transition metal-catalysed C-H bond alkylation was usually achieved in two ways namely, the hydroarylation of alkene and the alkylation with the un-reactive alkyl halides. In 1986, Lewis and Smith reported the pioneering work on regioselective *ortho*-alkylation *via* hydroarylation of an alkene. In later years, Ackermann and co-workers described the alkylation of 2-phenylpyridine with acrylates *via* hydroarylation using ruthenium(II)-catalyst [135]. The reaction proceeded with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an additive in toluene or 1,4-dioxane at 80-120 °C (Scheme 66). The reaction achieved the highest efficacy when MesCO_2K and AdCO_2K were used as additives. However, when the reaction conducted using the additive such as PPh_3 , AgOTf , and AgOAc resulted in little or no beneficial effect. On the other hand, no reaction has occurred without an additive or employing KPF_6 or NaPF_6 as the additives.



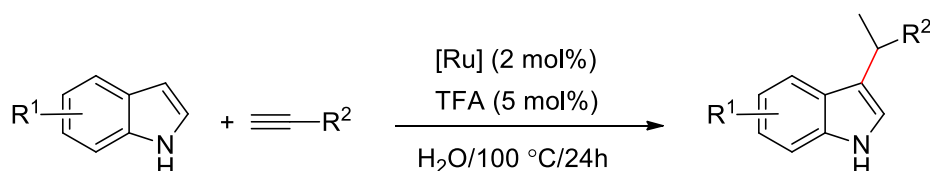
Scheme 66. Ruthenium-catalysed alkylation of 2-phenylpyridine with alkene via hydroarylation.

Subsequently, Ackermann's research group has described an sp^3 C-H bond alkylation of aryl pyrrolidines with alkenes *via* hydroarylation using $[\text{RuCl}_2(\text{PPh}_3)_3]$ in the presence of BINAP and AgOTf [136]. They have shown that the pyridyl group could be removed to generate an N-H free amine by treatment of the product with Pt/C followed by acid hydrolysis and fluxing with hydrogen gas (Scheme 67).



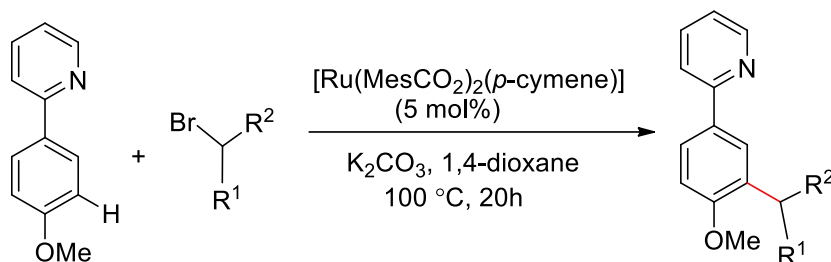
Scheme 67. Ruthenium-catalysed sp³ C-H alkylation via hydroacylation (A) and removal of directing group leading to free pyridines (B).

In 2010, Cadierno *et al.* described a C-3 alkylation of indole with a terminal alkyne in the presence of ruthenium catalysts [137]. The reaction has been performed with 2 mol% of ruthenium catalyst in the presence of TFA in water at 100 °C for 24h. They have screened the reaction using various ruthenium-catalysts such as [RuCl₂(η⁶-C₆Me₆)₂], [RuCl₂(PPh₃)₃], [RuCl₂(*p*-cymene)]₂ and [RuCl₃.xH₂O] etc., of which [RuCl₂(*p*-cymene)]₂ and [RuCl₂(η⁶-C₁₀H₁₆)₂] gave the best result (Scheme 68).



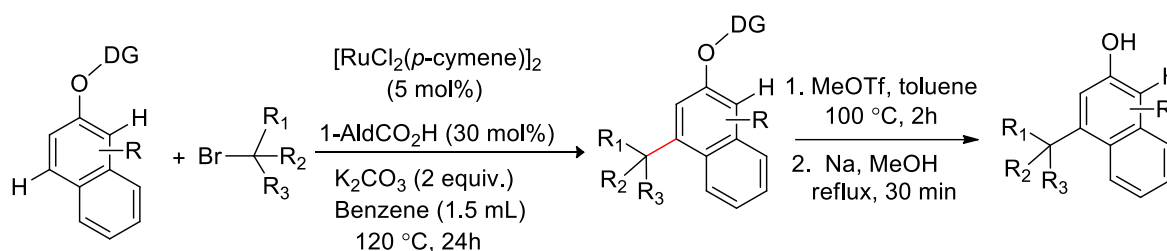
Scheme 68. Ruthenium-catalysed C-3 alkylation of indoles with alkynes.

The direct alkylation of arenes with alkyl halides is another pathway usually employed to obtain alkylated products. The direct alkylation with alkyl halides was initially studied with palladium catalysts but the reaction scope was limited only to heteroarenes [138, 139]. In 2009, Ackermann's research group demonstrated the direct alkylation of aryl pyridines with alkyl halides using inexpensive ruthenium catalysts [140]. The reaction was proceeded efficiently with [RuCl₂(*p*-cymene)]₂ in the presence of AdCO₂H and K₂CO₃ in NMP at 120 °C. The reaction has a wide substrate scope and could also be performed using pyrazoles and ketimines. In the following years, his research group demonstrated a *meta*-selective C-H bond alkylation of aromatic C-H bond of ketimine with secondary alkyl halide using [Ru(MesCO₂)₂(*p*-cymene)] in the presence of a base in 1,4-dioxane at 100 °C (Scheme 69) [141].



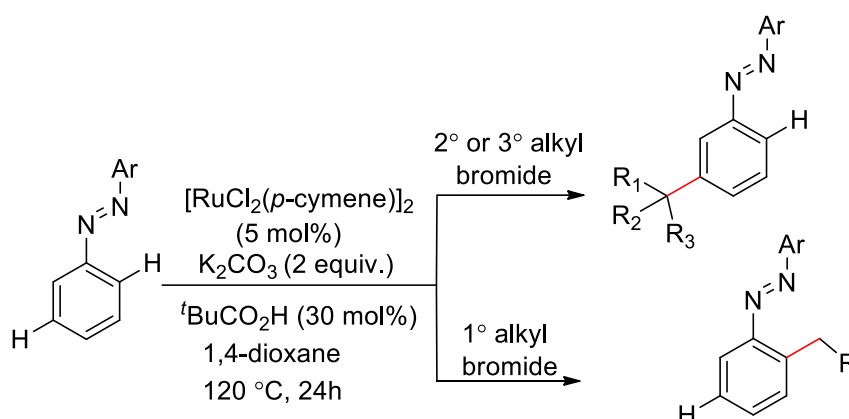
Scheme 69. Ruthenium-catalysed meta-selective alkylation of phenylpyridine with alkyl bromides.

Recently, Li *et al.* has reported a *meta*-selective C-H bond alkylation of phenol derivative using secondary or tertiary alkyl bromide with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of AdCO_2H and K_2CO_3 in benzene [142]. Interestingly, the directing group could be removed by treatment the product with MeOTf followed by dry methanolic solution of sodium to give *meta*-alkylated phenol derivative (Scheme 70). Notably, this reaction has found application to the synthesis of etoxazole, a marketed pesticide.



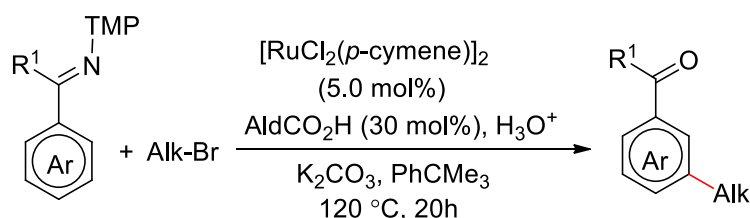
Scheme 70. Ruthenium-catalysed meta-selective C-H alkylation of phenol derivatives.

Further, they have demonstrated a ruthenium-catalysed *ortho*- and *meta*-selective C-H bond alkylation of azoarenes using alkyl bromides [143]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of carboxylic acid and a base in dioxane. The presence of carboxylic acid ligand is essential for this reaction without which the reaction turned to be unreactive. The most efficient ligand was found to be $t\text{BuCO}_2\text{H}$ which gave 75% of the alkylated product whereas; employing MesCO_2H gave a moderate yield, 35%. Interestingly, the *meta*-selective alkylated product was obtained with secondary and tertiary alkyl bromides whereas; primary alkyl bromide gave an *ortho*-alkylated product (Scheme 71).



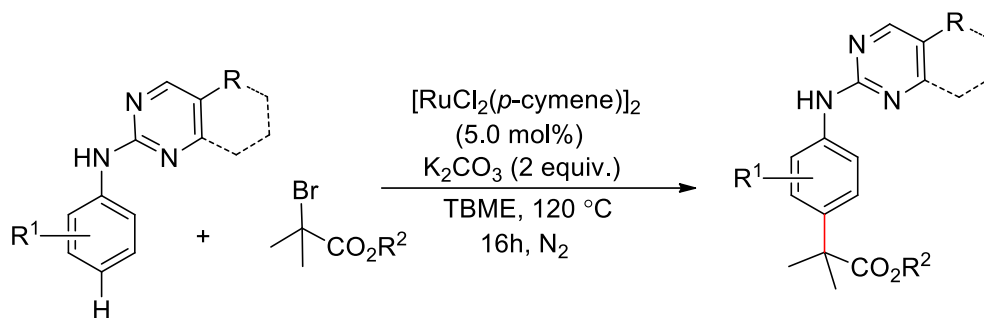
Scheme 71. Ruthenium-catalysed ortho- and meta-selective alkylation of azoarenes.

Recently, Ackermann and co-workers have demonstrated a highly efficient ruthenium-catalysed C-H bond alkylation reaction to give a diverse *meta*-alkylated product [144]. The reaction has proceeded profitably with $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%) in the presence of carboxylic acid and K_2CO_3 in *tert*-butylbenzene at 120 °C (Scheme 72). This reaction has a broad substrate scope and thus could provide ready access to *meta*-alkylated arenes including ketones, alcohols, amines, and acids by the direct reaction with alkyl bromides.



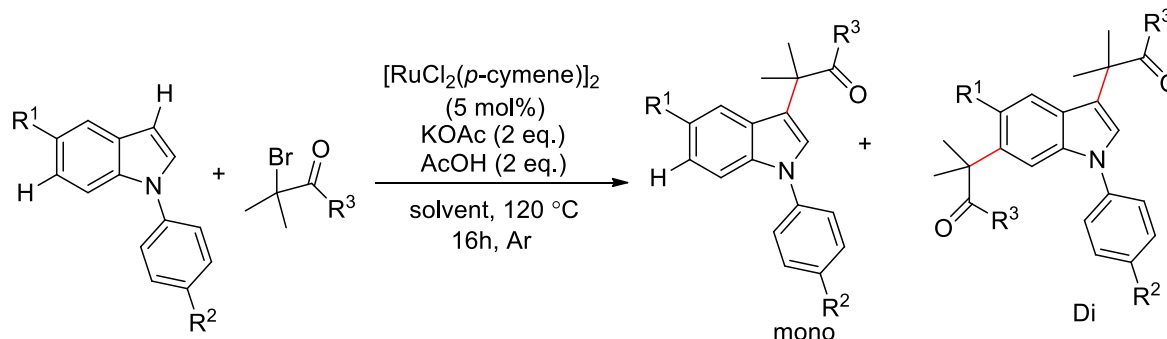
Scheme 72. Ruthenium-catalysed direct *meta*-alkylation of arene with alkyl bromide.

In 2017, Frost and co-workers described a ruthenium-catalysed *para*-selective alkylation of aniline with methyl- α -bromoisobutyrate [145]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of K_2CO_3 and a carboxylate ligand in *tert*-butyl methyl ether (TBME) at 120 °C (Scheme 73). Interestingly, no reaction occurred when the reaction was conducted without carboxylate ligand. However, the reaction performed at a higher temperature, say 140 °C lead to the formation of a minor amount of *meta*-alkylated product.



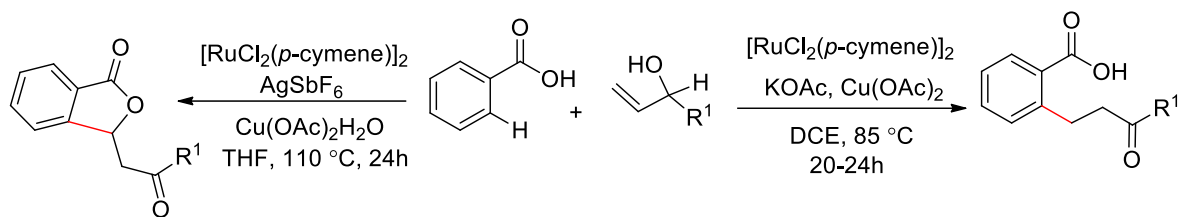
Scheme 73. Ruthenium-catalysed para-selective C-H alkylation of aniline derivatives.

In the same year, they have demonstrated a ruthenium-catalysed remote C-6 alkylation of *N*-pyrimidinyl indole with ethyl α -bromoisobutyrate [146]. The reaction was proceeded with $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%) in the presence of a base and an additive at 120 °C under air (Scheme 74). The dialkylated product involving a remote C-6 alkylation was obtained in 57% yield along with 39% of the C-3 monoalkylated product when performed the reaction with 2 eq. of AcOH and KOAc in THF. The reaction conducted in other solvents such as DME or 1, 4-dioxane giving dialkylated and monoalkylated products in quantitative yields. However, the alkylation was proceeds selectively giving 91% monoalkylated and only 5% dialkylated product when the reaction was performed in acetic acid.



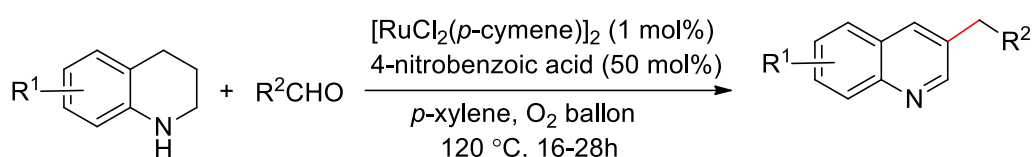
Scheme 74. Ruthenium-catalysed C-6 remote alkylation of indole derivative.

Allylic alcohol could also participate as alkylating agent in the ruthenium-catalysed alkylation reaction. Thus, a ruthenium-catalysed alkylation of an aromatic carboxylic acid with allylic alcohol has been just reported by Kumar *et al.* using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu}(\text{OAc})_2$ and KOAc in dichloroethane to give the desired alkylated product [147]. However, the reaction conducted using AgSbF_6 as an additive in place of KOAc in THF did not produce alkylated product instead an alkenylated product was formed (Scheme 75).



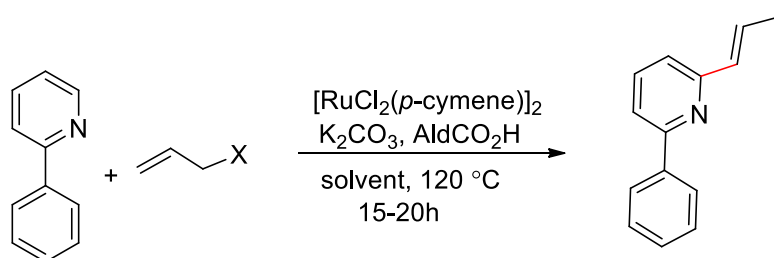
Scheme 75. Ruthenium-catalysed C-H functionalization with allylic alcohols.

The dehydrogenative benzylation of 1,2,3,4-tetrahydroquinolines with aryl aldehydes was carried out catalytically by Zhang and co-workers employing $[\text{RuCl}_2(p\text{-cymene})]_2$. This reaction requires nitrobenzoic acid as an additive and performed under an oxygen atmosphere at 120 °C affording the functionalized quinolines (Scheme 76) [148].



Scheme 76. Ruthenium-catalysed benzylation of 1,2,3,4-tetrahydroquinolines with aryl aldehydes.

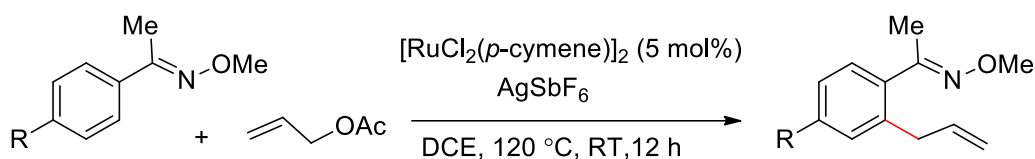
Several ruthenium compounds have been used in the catalytic allylation using allyl halide or allyl acetate. In 2006, Oi *et al.* have reported an *ortho*-allylation of 2-phenylpyridine with allyl acetate using $[\text{RuCl}_2(\text{cod})]_n$ in association with PPh_3 in the presence of K_2CO_3 [149]. Later, Zhang and co-workers have performed the *ortho*-allylation of 2-phenylpyridine with terminal alkynes using RuCl_3 as the catalyst in the presence of benzoic acid and K_2CO_3 [150]. Following this early discovery, Goriya and Ramana described allylation of 2-phenylpyridine with allyl bromide using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of K_2CO_3 and AdCO_2H in toluene (Scheme 77) [151]. However, this reaction did not give to *ortho*-allylation product instead afforded a C-2 allylation product on the pyridine ring of the 2-phenylpyridine.



Scheme 77. Ruthenium-catalysed allylation of 2-phenylpyridine with allyl halide.

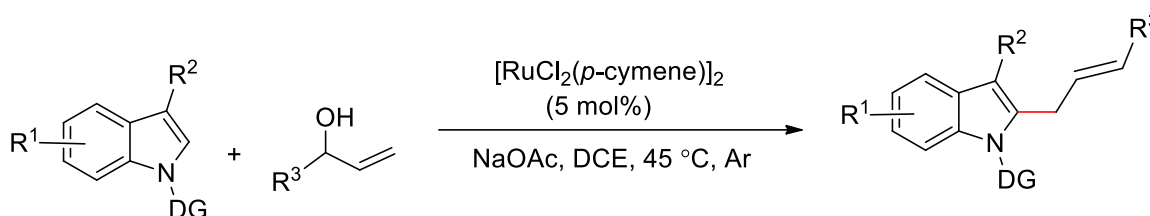
In 2015, Jeganmohan's research group has succeeded in the *ortho*-allylation of 2-ketoxime with allyl acetate using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of AgSbF_6 in DCE at room temperature (Scheme 78) [152]. They have found that the use of silver salts such as AgSbF_6 , AgBF_4 or AgOTf as

an additive is essential for the reaction to occur as replacing these additives with KPF_6 resulted in the reaction un-reactive.



Scheme 78. Ruthenium-catalysed allylation of ketoximes with allyl acetate.

A regio- and stereoselective allylation of indole derivatives with allylic alcohols was just reported by Wu and Ji using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of NaOAc in DCE to give a C-2 allylated product (Scheme 79) [153]. This allylation reaction was performed under a mild condition and free from oxidant.



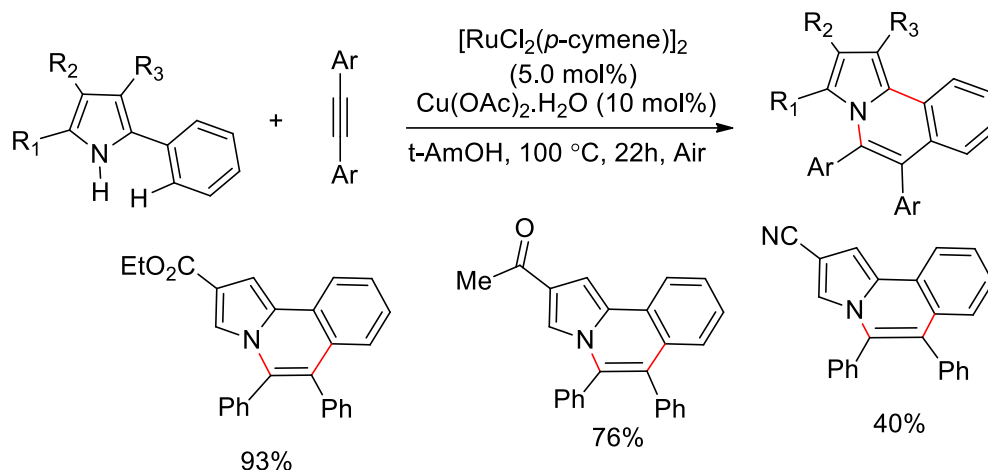
Scheme 79. Ruthenium-catalysed stereoselective C-2 allylation of indoles with allyl alcohols.

5. Ruthenium-catalysed annulation reaction of arenes with alkynes

Annulation reaction is one of the most convenient methods for the synthesis of various heterocyclic compounds. Several transition metal catalyst derivatives of Cu [154], Pd [152], Ru [26, 156], Rh [157] and Ir [158] promoted these annulation reactions providing ready access to various heterocycles. Recently, ruthenium-catalysed C-H/O-H, C-H/N-H bond cleavage reactions leading to pyrroles [159, 160], indoles [161], isoquinolines [162] and isocoumarins [163] etc. have been reported by several groups.

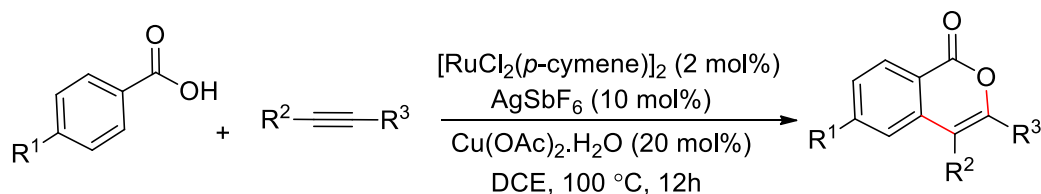
In 2012, Ackermann's research group has demonstrated annulations of phenylpyrazole and alkyne with $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ under air [164]. The reaction did not require a prefunctionalized pyrazole such as 3-(2-bromophenyl)pyrazole derivative that has been used in the similar annulation reaction with copper catalyst [165]. Subsequently, his research group has reported the oxidative annulation involving C-H/N-H bond functionalization of aniline derivatives containing a removable directing group with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of KPF_6 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in water at 100 °C affording diverse indole derivatives [166]. Further, Ackermann and co-workers have described the ruthenium-catalysed annulation of 2-arylsubstituted pyrroles with alkynes leading to pyrrolo[2,1-a]isoquinolines, a

structural unit of biologically active marine lamellarin alkaloids [167]. The reaction involved a C-H/N-H bond cleavage process and proceeded efficiently with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in $t\text{-AmOH}$ at $100\text{ }^\circ\text{C}$ (Scheme 80).



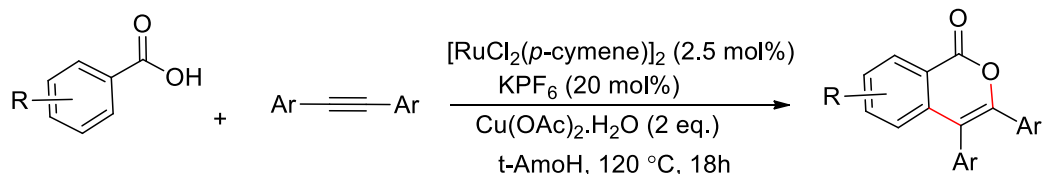
Scheme 80. Ruthenium-catalysed aerobic annulation of 2-substituted pyrroles with alkynes.

In 2012, Jeganmohan's research group has demonstrated the ruthenium-catalysed regioselective annulation of aromatic carboxylic acids and alkynes leading to isocoumarins [168]. The reaction was conducted employing $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as oxidant and involved a C-H/O-H bond cleavage process (Scheme 81).



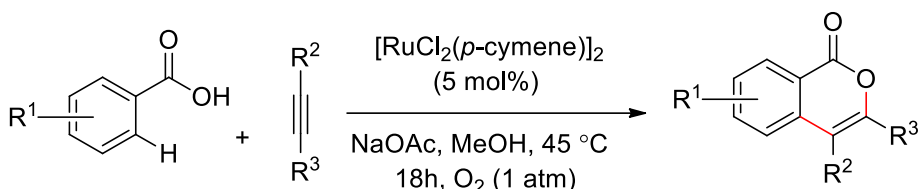
Scheme 81. Ruthenium-catalysed regioselective annulation of aromatic acids with alkynes.

In the same year, Ackermann and co-workers have demonstrated the annulation of aromatic acids and alkynes with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of KPF_6 and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ [169]. The reaction was best performed in $t\text{-AmOH}$ giving 87% of the desired isocoumarin for diphenylacetylene. However, the reaction was not productive when performed in water giving only 52% of the desired isocoumarin (Scheme 82).



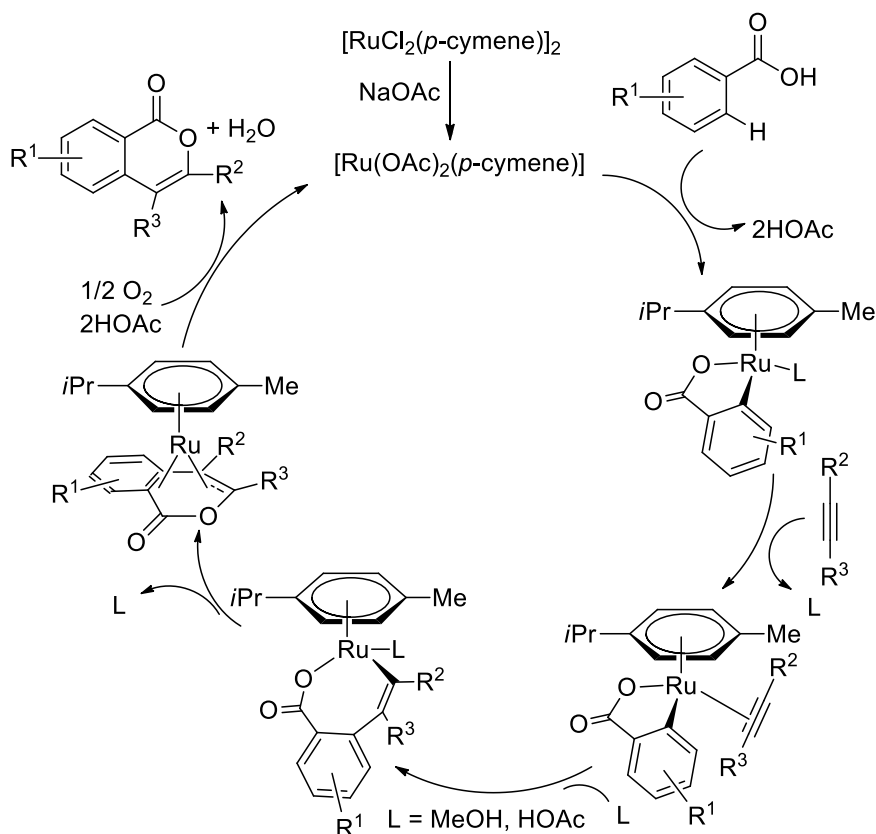
Scheme 82. Ruthenium-catalysed annulation via C-H/O-H bond cleavage of aromatic acids with alkynes.

Subsequently, his group has demonstrated the annulation of aromatic acids and alkynes using molecular oxygen as the sole oxidant instead of $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ which is usually employed in oxidative annulation reactions [170]. They have performed the annulation with $[\text{Ru}(\text{MesCO}_2)_2(p\text{-cymene})]$ in the presence of NaOAc under 1 atmospheric pressure of oxygen or air in methanol leading to isocoumarin in high yields (Scheme 83).



Scheme 83. Ruthenium-catalysed annulation of aromatic acids and alkynes with O_2 as sole oxidant.

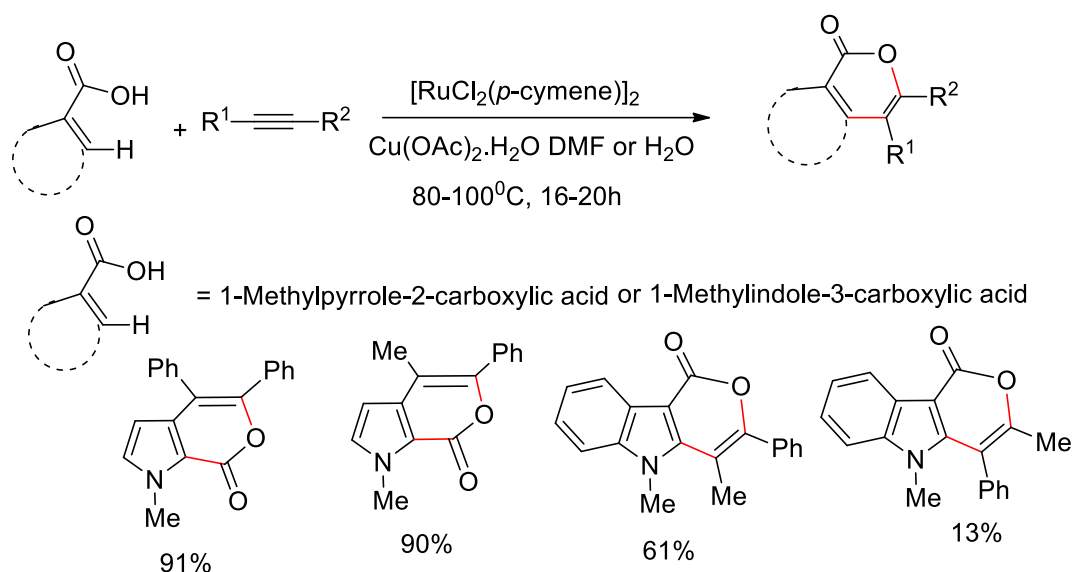
They have proposed a plausible catalytic cycle which involves an initial formation of ruthenium(II) bis-acetate complex (Scheme 84). Thereby, a five-member ruthenacycle is generated along with two equivalent of acetic acid. The next step is the coordination and insertion of alkyne to furnish a seven-membered Ru(II) cycle that rapidly undergoes reductive elimination to yield ruthenium(0) species which is then reoxidized to the active ruthenium(II) species by molecular oxygen.



Scheme 84. Plausible mechanism for annulation of aromatic acids and alkynes with O₂ as oxidant [170].

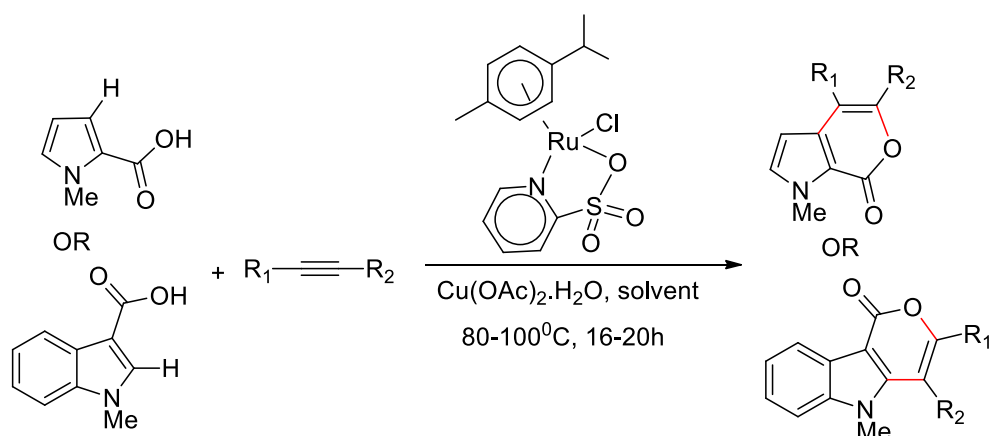
The reaction was evaluated using other ruthenium catalysts as well such as [RuCl₂(*p*-cymene)]₂ and [RuCl₂(benzene)]₂, produced the annulated products in 78 and 76% yields, respectively, with diphenylacetylene. However, under a similar condition, the reaction performed in other alcohols was not productive only traces of isocoumarins were formed.

Recently, Singh and Dixneuf have described the ruthenium-catalysed annulation of pyrrole and indole carboxylic acid derivatives with alkynes leading to pyrrole and indole-fused isocoumarins (Scheme 85) [171]. The reaction was performed using [RuCl₂(*p*-cymene)]₂ in the presence of Cu(OAc)₂·H₂O but without an additive in DMF. The reaction could also be performed profitably in water with competitive yields. The reaction showed a high regioselectivity when performed 1-methylpyrrole-2-carboxylic acid with an unsymmetrical alkyne, 1-phenyl-1-propyne giving only one regioisomer in 90% yield. The high regioselectivity was observed in water as well for the annulation of 1-methylpyrrole-2-carboxylic acid and 1-phenyl-1-propyne. However, the annulation of 1-methylindole-3-carboxylic acid and 1-phenyl-1-propyne afforded two isomers in 61% and 13% isolated yields.



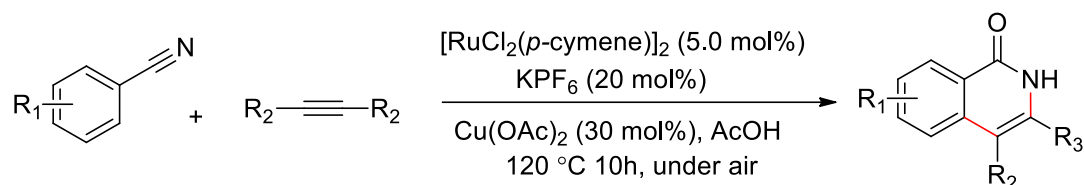
Scheme 85. Ruthenium-catalysed regioselective annulation of *N*-heteroaromatic acids with alkynes.

Subsequently, Singh *et al.* have just reported this annulation of *N*-heteroaromatic acid derivatives with alkynes using ruthenium(II) N[^]O chelate complex, $[\text{RuCl}(\text{PySO}_3)(p\text{-cymene})]$ (Scheme 86) [172]. They have found that the efficiency of $[\text{RuCl}(\text{PySO}_3)(p\text{-cymene})]$ is comparable to that of $[\text{RuCl}_2(p\text{-cymene})]_2$ for the reaction conducted in DMF but the reaction performed with $[\text{RuCl}(\text{PySO}_3)(p\text{-cymene})]$ was not as productive as $[\text{RuCl}_2(p\text{-cymene})]_2$ when performed in water.



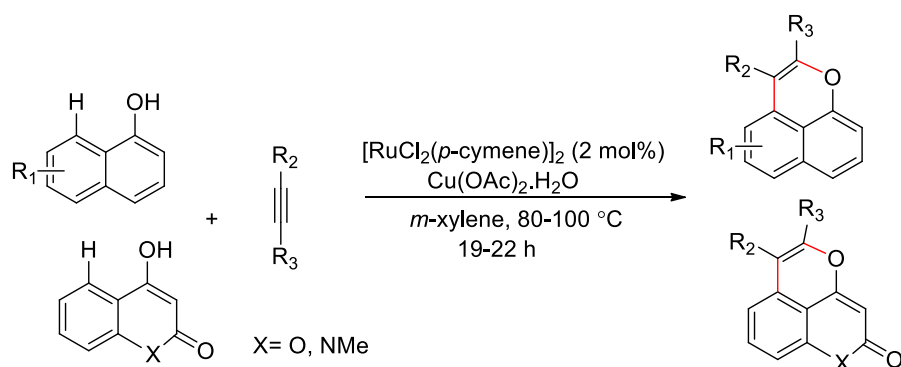
Scheme 86. Annulation of *N*-heteroaromatic acids and alkynes with N[^]O chelate ruthenium(II) catalyst.

The ruthenium-catalysed regioselective cyclization of ketones and alkynes leading to indenols and benzofulvenes was described by Chinnagolla and Jeganmohan using $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with AgSbF_6 in the presence of $\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ in DCE [173]. In the following year, they have achieved a ruthenium-catalysed cyclization of aromatic nitriles and alkynes employing $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of KPF_6 and $\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ in acetic acid under air (Scheme 87) [174].



Scheme 87. Ruthenium-catalysed aerobic annulation of aromatic nitriles with alkynes.

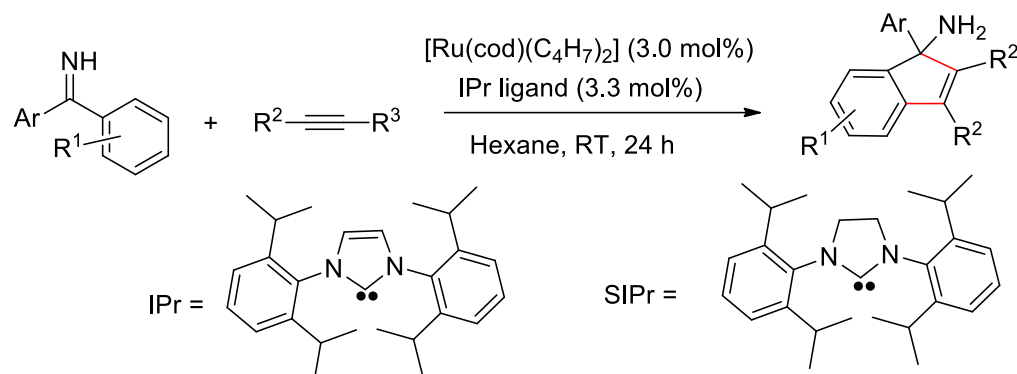
They have found that the active catalyst was cationic ruthenium(II) species and the reaction involved deprotonation from aromatic C-H bond resulting in the formation of a five membered-ruthenacycle as intermediate. In 2012, the ruthenium(II)-catalysed oxidative coupling of alkyne and naphthol assisted by hydroxyl group has been described by Ackermann and co-workers using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ [175]. The presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ was essential for the reaction as replacing it with CuBr_2 or without it resulted in no reaction. However, CuBr_2 in association with NaOAc could be employed for this reaction which leads to a moderate yield of the desired product. This catalytic system was also effective for the annulation of 4-hydroxycoumarin and alkynes. They have found that this annulation reaction was best performed in *m*-xylene at 80 °C affording annulated product pyrans in high yields (Scheme 88).



Scheme 88. Ruthenium-catalysed hydroxy assisted annulation of naphthols or 4-hydroxycoumarins with alkynes.

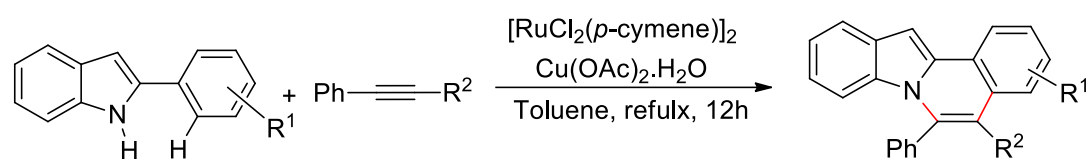
In 2012, Zhao's research group has demonstrated the annulation of *N*-sulfonyl imines and alkynes leading to indenamines [176]. The reaction was performed using $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with sulphonamides and AgSbF_6 and 4 equiv. of AcOH in dioxane. The coupling product, indenamines were obtained in modest to good yield in the range of 46-88%. In the following year, his research group described a ruthenium-catalysed carbocyclization of aromatic ketimines and alkynes (Scheme 89) [177]. The reaction proceeded efficiently with $[\text{Ru}(\text{cod})(\eta^3\text{-C}_4\text{H}_7)_2]$ in the presence of a NHC ligand (IPr) in toluene at room temperature. They have also evaluated this reaction with doubly cyclometalated complex, $[\text{Ru}(\text{cod})(\text{C},\text{N}\text{-ketimine})_2]$ which was produced from the reaction of $[\text{Ru}(\text{cod})(\eta^3\text{-C}_4\text{H}_7)_2]$ with diphenylacetylene. However, this doubly cyclometalated complex alone could not catalyse the coupling of ketimene and alkyne. On the contrary, coupling

was promoted in the presence of NHC ligand affording the annulated product in 45% yield. The reaction was found to be less effective when employed saturated NHC ligand (SIPr). The best reaction condition was achieved employing $[\text{Ru}(\text{cod})(\eta^3\text{-C}_4\text{H}_7)_2]$ in association with unsaturated NHC ligand (IPr) in hexane at room temperature.



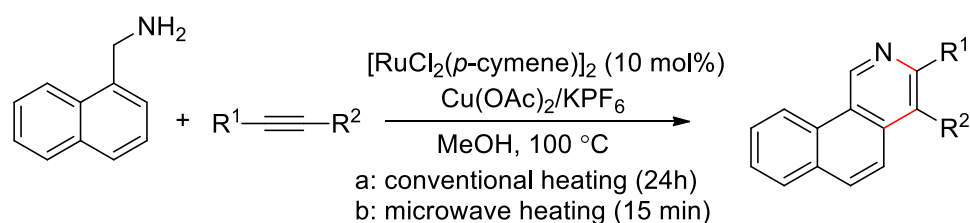
Scheme 89. Ruthenium(II)-catalysed cyclization of ketimines with alkynes promoted by NHC ligands.

Oxidative coupling of aryl benzimidazole with alkynes has been described employing $[\text{RuCl}_2(p\text{-cymene})]_2$ as a catalyst in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in toluene [178]. The reaction could also be conducted using other oxidants such as NaOAc or Ag_2CO_3 with a lower efficacy (Scheme 90).



Scheme 90. Ruthenium(II)-catalysed oxidative annulation of arylbenzimidazoles with alkynes.

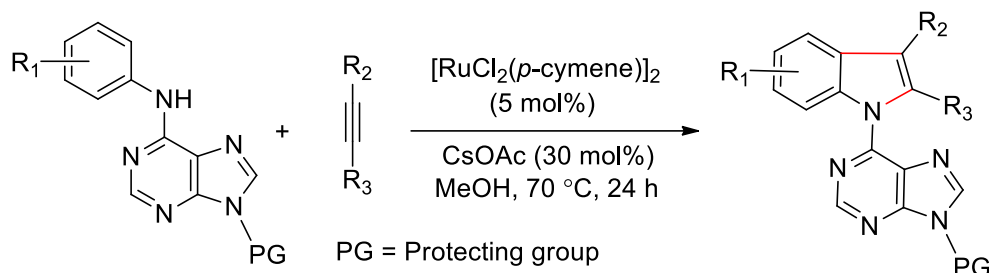
Urriolabeitia and co-workers have described an oxidative coupling of primary amines with alkynes through ruthenium catalysis to give isoquinoline derivatives (Scheme 91) [179]. The coupling undergoes with $[\text{RuCl}_2(p\text{-cymene})]_2$ (10 mol%) in the presence of KPF_6 and $\text{Cu}(\text{OAc})_2$ in alcohol. The reaction requires 24h time for an optimum result in conventional heating but can also be run for only 15 min in a microwave.



Scheme 91. Ruthenium catalysed oxidative annulation of primary amines and alkynes.

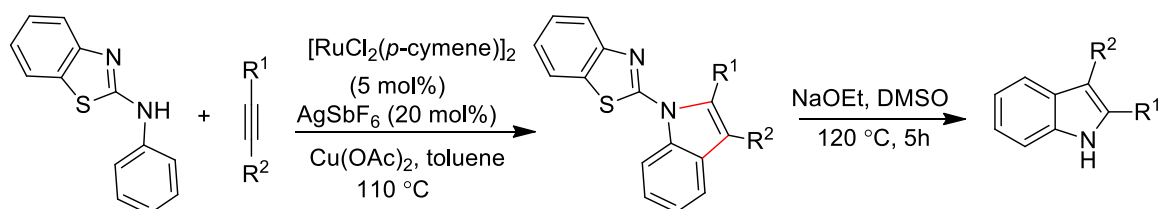
In 2015, the ruthenium(II)-catalysed oxidative annulation of 6-aminopurines with alkynes leading to the indole substituted purines and purine nucleosides has been described by Kumara

Swamy and co-workers (Scheme 92) [180]. The annulation was performed employing $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%) in the presence of an additive in methanol. Among the additive tested CsOAc was found to be the most effective followed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and NaOAc. However, the reaction conducted in DCE gave the desired products only in traces, whereas, the reaction performed in water or $t\text{BuOH}$ were found to be unreactive.



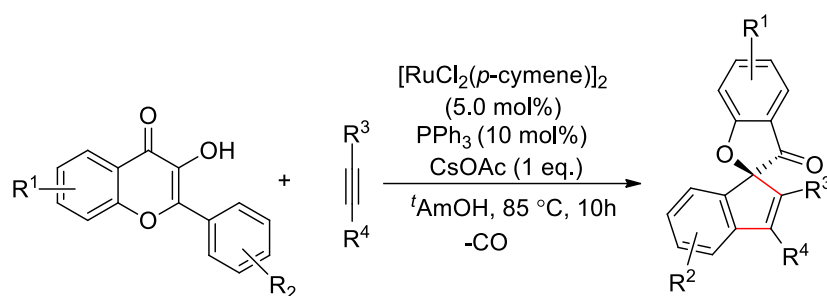
Scheme 92. Ruthenium(II)-catalysed annulation of 6-aminopurines with alkynes.

Recently, Sharma *et al.* described the coupling of alkynes with amine-containing benzothiazole as removal directing group (Scheme 93) [181]. The ruthenium catalyst employed was the most widely explored, $[\text{RuCl}_2(p\text{-cymene})]_2$ in association with AgSbF_6 in the presence of $\text{Cu}(\text{OAc})_2$ in toluene. The coupling has tolerated to various type of alkynes including aryl-aryl; aryl-alkyl and alkyl-alkyl. However, reaction performed with unsymmetrical alkynes afforded a mixture of regioisomers whereas, dicarboxylated alkynes furnished monodecarboxylated products.



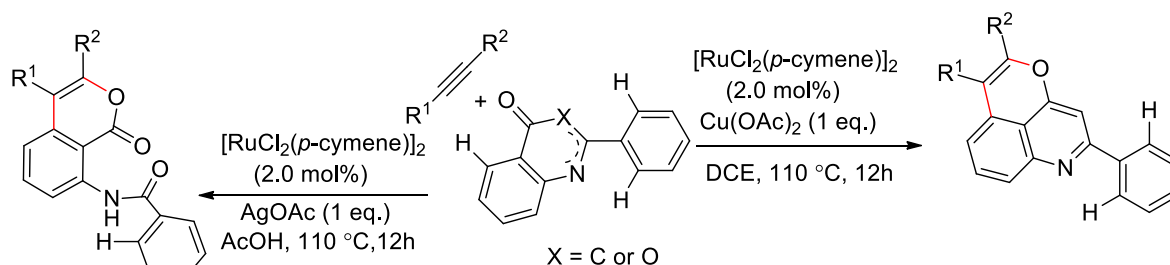
Scheme 93. Ruthenium-catalysed annulation of alkyne and amine containing removable benzothiazole group.

The ruthenium(II)-catalysed decarbonylative annulation of 3-hydroxy-2-phenylchromones with alkynes has been just reported by Gogoi and co-workers (Scheme 94) [182]. The reaction was performed with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of PPh_3 and CsOAc in $t\text{AmOH}$ leading to spirobenzofuranones in up to 86% yield. They have proposed that the annulation occurred before extrusion of CO, unlike other transition metal-catalysed decarbonylative annulation reactions. This annulation has proceeded *via* C-H/C-C activation, alkyne insertion, and decarbonylation reaction to provide the spiroindenebenzofuranones in good yields.



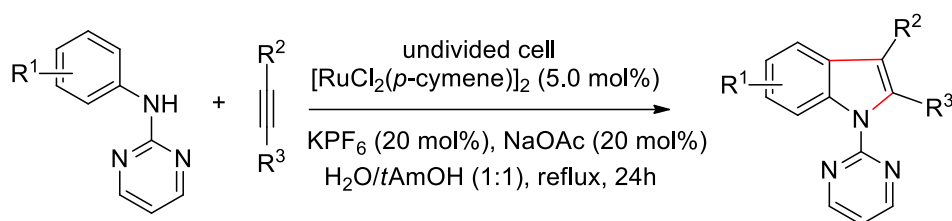
Scheme 94. Ruthenium-catalysed decarbonylative annulation of 3-hydroxy-2-phenylchromones with alkynes.

In 2015, a ruthenium-catalysed annulation reaction that dictated by a weaker directing group was demonstrated by Patel and co-workers using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an oxidant (Scheme 95) [183]. They have performed the annulation of 2-arylquinolinone and 2-arylbenzoxazinone which contained two different directing arenes with alkynes using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of an oxidant. They have observed that the regioselective annulations of 2-arylquinolinone and 2-arylbenzoxazinone containing two different directing arenes with alkynes occurred *via* the assistance of weaker carbonyl oxygen over the stronger nitrogen directing site thus, the weaker directing groups dictate the annulation reaction path. Further, the reaction performed in DCE using $\text{Cu}(\text{OAc})_2$ as oxidant produced the 2-arylquinoline in 68% yield and 2-arylbenzoxazinone in 11%. However, when the reaction was conducted in acetic acid employing AgOAc as an oxidant, 2-arylbenzoxazinone was formed in high yield (78%).



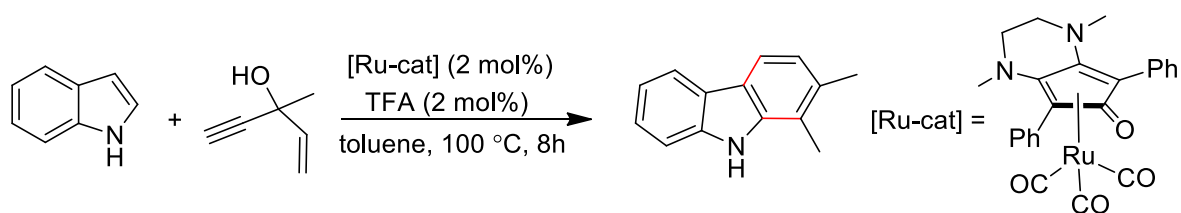
Scheme 95. Ruthenium(II) catalysed regioselective C-H/O-H annulations of directing arenes and alkynes via assistance of weak coordination.

Very recently, Xu and co-workers have demonstrated the ruthenium-catalysed dehydrogenative annulation of aniline derivative and alkyne via electrochemical induced hydrogen generation leading to indole derivatives [184]. The reaction was conducted under constant current electrolysis consisting of an undivided cell equipped with a reticulated vitreous carbon (RVC) anode and a Pt plate cathode. The reaction was proceeded efficiently under reflux condition with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of KPF_6 and NaOAc in water or solvent containing a mixture of water : alcohol (1:1) or water : acetonitrile (1:1) (Scheme 96). However, the best result was obtained when conducted in water: $^t\text{AmOH}$ (1:1) affording 92% of the desired indole derivatives.



Scheme 96. Ruthenium-catalysed electrochemical dehydrogenative annulation of aniline derivatives and alkynes.

Haak and co-workers have just reported a cascade annulations reaction of indole with propargyl alcohols using a bifunctional (cyclopentadiene) ruthenium(0) complex in the presence of trifluoroacetic acid providing a natural product like scaffolds [185] (Scheme 97). This catalytic process can be conveniently performed with microwave irradiation instead of conventional heating. The reaction proceeded with high selectivity avenue to provide ready access to various annulated products from simple indole and propargyl alcohols.



Scheme 97. Ruthenium-catalysed annulation of indole with propargyl alcohol.

Conclusion: The catalytic C-H bond functionalization with ruthenium-based catalysts has emerged a powerful method in organic synthesis for ready access to various functional molecules in a greener and step economy manner. The ruthenium catalysts participated in this C-H bond functionalization reactions are mainly ruthenium(0) and ruthenium(II) species although a few reactions were also known with the simple RuCl_3 species. The C-H bond functionalization reactions with ruthenium complexes such as $\text{N}^{\wedge}\text{O}$ and $\text{O}^{\wedge}\text{O}$ chelate ruthenium(II) complexes as well as ruthenium(II) amine and cationic ruthenium complexes are presented in this review. In the C-H bond functionalization *via* ruthenium catalysis, the stable ruthenium(II) catalysts in particular the $[\text{RuCl}_2(p\text{-cymene})]_2$ precursor complex has contributed enormously and indeed several new reactions and methodologies are being discovered steadily with this ruthenium(II) species. Further, the ruthenium(II) catalysts partner with carboxylate ligand allowed the C-H bond functionalization in highly attractive manner providing profitable organic transformations. Several C-H bond functionalization reactions namely, arylation, alkenylation, alkylation and annulation have been studied employing ruthenium(II) catalysts partnering with carboxylate ligands in an efficient manner with a better atom economy and

sometimes reactions are conducted even in water. This review presents with complement the previous reports the recent development on the C-H bond functionalization reactions covering arylation, alkenylation, alkylation, allylation and annulation reactions. The arylation of nitrogen-heteroarenes with aryl halides, aryl boronates and aryl silanes as the arylating agents has been discussed. Further, oxidative arylation, decarboxylative arylation and selective monoarylation of 2-phenylpyridine has been presented. The sections 3-5 have discussed C-H bond functionalization such as alkenylation, alkylation, allylation and annulation of various arenes. In brief this review highlighted the various reactions mentioned above with selected reaction mechanisms that appeared during the past eight years. It is hoped that this review might be helpful in further enhancing the research area which is already a burning topic in the field of catalysis. Further, I believed that the review will be useful to the young researchers working on the metal catalysed C-H bond functionalization in providing up to date information in this field.

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Author contributions: KSS analyzed the data and wrote the paper.

Conflicts of Interest: Author declares no conflict of interest.

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