Review

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 not only because it saves reaction time and reduces waste, but also, more importantly, it allows the reaction to be performed in a highly region specific 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 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, has been described and presented in numerous reviews. This review discusses the recent development of C–H bond functionalization with various ruthenium-based catalysts. The first section of the review presents arylation reactions covering arylation directed by N–Heteroaryl groups, oxidative arylation, dehydrative arylation and arylation involving decarboxylative and sp³-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

1. Introduction

Synthesis of organic compounds with a heterocyclic ring and natural product scaffolds are extremely important as they form an indispensable structural unit of bioactive compounds and pharmacophores [1,2]. Tremendous effort has been made in the designing and development of organic synthesis that 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 neither environmentally friendly nor economically viable. To overcome these problems, an alternative synthetic method with better atom and step economical process is highly desirable. In the recent past, in order to overcome the above shortcomings, organic synthesis has 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 more economical pathway for ready access to various functional organic compounds.

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 produces a stoichiometric amount of
metal salt as the site product, the process is not attractive (Scheme 1a). During the past few decades, organic synthesis through C–H bond functionalization has emerged as one of the most viable methods not only for selective organic synthesis [5] but also for ready access to a 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 provides a greener reaction protocol but also reduces waste. 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 1b). On the other hand, the coupling of arene or alkene with an organometallic reagent requires an oxidant to generate the metal species (Scheme 1c).

In both the direct C–H functionalization methods, a 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 a Pd catalyst, is the most step-and atom economical process, as it does not require any pre-functionalized starting materials (Scheme 1d).

During the last decade, 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 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 the oxidative addition pathway and the deprotonation pathway. C–H bond functionalization via the oxidative pathway is usually performed with low valent ruthenium complexes, such as [RuH₂(CO)(PPh₃)₃] or [Ru₃(CO)₁₂], whereas ruthenium(II) complexes, viz. [RuCl₂(PPh₃)₃] and [RuCl₂(p-cymene)]₂ in association with acetate or carbonate bases, are used for the C–H bond functionalization via the 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.

In recent years, the ruthenium-catalysed C–H bond functionalization has been explored with a variety 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, [RuCl₂(p-cymene)]₂/AgSbF₆ or [RuCl₂(p-cymene)]₂/KPF₆ have been used for C–H bond functionalization, directed by a 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 groups of Jeganmohan [21,22], Ackermann [23] and others [24]. Recently, the benefits of the carboxylic acid ligand in C–H bond functionalization reaction have 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 to offer an attractive pathway for the C–H bond functionalization, allowing the reaction to operate under mild conditions and even in water [30,31].

Recently, ruthenium-catalysed C–H bond functionalization has been studied in various reactions, namely arylation [15], alkenylation [16], and annulation [26]. Subsequently, several new reactions have been discovered, such as 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 [15,16,25,26,38–40]. Furthermore, the mechanistic study of ruthenium-catalysed C–H bond functionalization was recently described by the research group of Lan [41] in the context of arylation, alkenylation and alkenylation, and by Nelson and co-workers on selective ortho-arylation directed by Lewis basic groups [42]. However, new reactions and methodologies of C–H bond functionalization with ruthenium-based catalysts are being discovered. Keeping this in mind, this review describes the recent development on the C–H bond functionalization reactions covering arylation, alkenylation, alkylation and annulation reactions with ruthenium-based catalysts. The review focusses on the developments in this field over the past eight years and includes reports that have appeared up 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 with substrates with an N–Heteroaryl ring as the directing group such as 2-phenylpyridine, 1-phenylpyrazole, quinoline, tetrazole, imidazole, 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 reactions that have employed a variety of ruthenium catalysts. In 2001, Oi et al. described the arylation of 2-phenylpyridine with aryl halide using \([\text{RuCl}_2(\eta^6-C_6H_6)]_2\) in the presence of 4 equiv. of PPh₃ and a base (Scheme 2a) [43]. In subsequent years, they reported the arylation of aromatic 2-alkenylpyridines and aryl bromides with \([\text{RuCl}_2(\eta^6-C_6H_6)]_2\) 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.](image)

In 2008, Ackerman’s research group studied for the first time the beneficial effects of carboxylic acid in the ruthenium-catalysed direct arylation of arene in toluene, a less coordinating and apolar solvent [45]. They 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
[RuCl₂(p-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, direct arylation did not occur with ortho-substituted aryl chloride; instead, the reaction led to a homo-coupling product.

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

Christakakou et al. reported the arylation of 2-phenylpyridine using aryl bromide in the presence of [RuCl₂(p-cymene)]₂, DBU and PPh₃ (Scheme 4) [46]. The arylated product formed depending on the nature of the aryl bromide employed. Thus, employing bromobenzene as an arylating agent gave 26% and 71% yield of mono- and diarylated products, whereas bromo-anisaldehyde gave only the monoarylated product. However, aryl bromides such as p-bromotoulune and p-bromotrifluorotolune gave a mixture of mono- and diarylated products; in contrast, no arylated product was observed for p-nitrobromobenzene.

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

Pozgan and co-workers 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 an 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 mol %), 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 the direct arylation of aldimines or ketimines as well. Furthermore, it was 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 for the synthesis of functionalized aldehydes (Scheme 6, [48]).

Scheme 6. Ruthenium-catalysed synthesis of diphenylated benzaldehyde.

Initially, the ruthenium-catalysed arylation was performed mostly using $[\text{RuCl}_2(\text{arene})]_2$ catalysts. Later, the reaction was explored with several other ruthenium catalysts. Ackermann’s research group reported an arylation of 2-phenylpyridine with aryl halides directly employing $[\text{Ru}(\text{MesCO})_2(p\text{-cymene})]$ using the aprotic solvent toluene [49]. Subsequently, the arylation reaction of 2-phenylpyridine was performed by Dixneuf and co-workers using the ruthenium catalyst $[\text{Ru(OAc)}_2(p\text{-cymene})]$ in NMP [50] followed by $[\text{Ru(}^8\text{BuCO})_2(p\text{-cymene})]$ in water [51]. They have also performed the direct diarylation of 2-phenylpyridine with aryl chloride including hetero arylchloride using $[\text{RuCl}_2(p\text{-cymene})]_2$/KOPiv catalytic system in diethyl carbonate [52]. This catalytic system has produced a diarylated product tolerant to various functional groups such as cyanide and esters.
The arylation reaction of 2-phenylpyridine has been studied with several other ruthenium(II) catalysts such as O’O and N’O chelate ruthenium(II) complexes as well. Singh and Dixneuf described the catalytic activity of water-soluble (O’O) and (N’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 a catalytic amount of KOPiv or KOAc in water.

Recently, Binnani et al. employed ruthenium(II) complexes with N’O donor pyridine ligands for the arylation of 2-phenylpyridine with aryl halides (Scheme 8) [54]. The reaction gave both diarylated and monoarylated products, with diarylated as the major products. They have even tested cationic ruthenium(II) complexes with a 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.

2.2. Ruthenium-Catalysed Selective Monoarylation

Doherty et al. achieved the selective 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 arylation agent. Other arylation agents such as ethyl-4-chlorobenzene also gave good selectivity, affording 64% monoarylation and only 3% diarylation product.
In 2013, Dixneuf and co-workers reported a highly attractive selective monoarylation of 2-phenylpyridine and phenylpyrazoles using aryl chlorides and heteroaryl halides in water [56] (Scheme 10). They screened the monoarylation using various ruthenium(II) catalysts and found that a 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 a monoarylated product providing mono/diarylated product ratios up to 96/4.

In 2014, Luise et al. reported a chelated-assisted ruthenium(II)-catalysed arylation of 2-phenylpyridine with \(\text{Ph}_2\text{IOTf}\) as arylating agent that gave a high yield of the monoarylated product of up to 95% (Scheme 11) [57].

They proposed that the arylation reaction proceeded by a mechanism similar to the Pd-catalysed C–H arylation reaction (Scheme 12). The reaction proceeded efficiently with \([\text{Ru(OAc)}_2(p\text{-cymene})]\) in the presence of \(\text{K}_2\text{CO}_3\) in toluene at 80 °C.
Following this, Reddy et al. described a versatile monoarylation of 2-phenylpyridine and phenylpyrazole using aryl boronic acids as arylating agent with [RuCl$_2$(p-cymene)]$_2$ in the presence of PhI(OCOCF$_3$)$_2$ (Scheme 13) [58].

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

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 [RuCl$_3$·xH$_2$O] [60]. This catalytic process provided a greener and more sustainable approach to the access of Angiotensin II Receptor Blockers.
(ARBs), which are considered among 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 aryletrazole with aryl chloride via rutheniumcatalyst promoted by amino acid ligands.](image)

Ackermann and co-workers described the arylation of 2-phenoxypyridine 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 an additive and a base. The presence of a base is essential for this reaction as no reaction occurred when performed without a base. They observed that the reaction conducted in $N$-Methyl-2-Pyrrolidone (NMP), a solvent usually used in ruthenium-catalysed direct arylation of arenes, gave a 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 the reaction proceeds through a six-member ruthenacycle cyclometallated species. Furthermore, the arylated 2-phenoxypyridine gave a monoarylated pyridine on treatment of the arylated product of 2-phenoxypyridine with MeOTf followed by sodium in methanol (Scheme 16).

![Scheme 16. Arylation of 2-phenoxy pyridines with aryl chlorides and synthesis of arylated phenols.](image)

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 a base and KOAC as an additive, leading to 82:18 mono/diarylated products. The selectivity was further enhanced by employing $Na_2CO_3$ as the base in the presence of 30 mol% of $p\text{-CF}_3C_6H_4CO_2H$, affording 90:10 mono/diarylated products.

![Scheme 17. Ruthenium-catalysed selective arylation of 2-pyridyl aryl ketone with aryl bromide.](image)
The direct C–H arylation of 2-phenylpyridine with aryl chlorides in water has been reported by Kaloğlu et al. employing a ruthenium-NHC complex as catalyst (Scheme 18) [65].

\[
\text{[Ru-Cat]} (2.5 \text{ mol%}) \quad \text{RCO}_2\text{K} (5 \text{ mol%}) \quad \text{Cs}_2\text{CO}_3, \text{H}_2\text{O}, 100 ^\circ \text{C} \quad 5-20 \text{ h}
\]

**Scheme 18.** Selective mono arylation of 2-phenylpyridine with arene-rutenium(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 [RuCl₃·xH₂O] using mesitylic acid as the additive in nontoxic PEG-2000 by Ackermann [9,66] (Scheme 19), followed by Luo and 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 the alkenylic C–H bond containing diazine as a directing group has been reported by Dori et al. using aryl halide as an arylating agent with [RuCl₂(p-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 that remained from the reaction of the first step, resulting in \(\text{sp}^3\)C–H bond functionalization product. Thus, this catalytic process provided an alternative approach to the more difficult \(\text{sp}^3\)C-H bond functionalization.

**Scheme 20.** Ruthenium-catalysed C-H arylation of alkenylic diazines.
Recently, Poli and co-workers demonstrated a C-3 arylation of furfural imines with [Ru$_3$(CO)$_{12}$] in the presence of benzylidene acetone 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 fufural 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 [RuCl$_2$($p$-cymene)$_2$] first in DMA [71], subsequently in water employing [Ru(MesCO)$_2$($p$-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.]

Recently, Roger et al. described the arylation of phenylpyrazole using a phenol derivative of aryl triflate as the arylating agent with [RuCl$_2$($p$-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, predominantly diarylated product was formed. 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 the arylation of indole and pyrrole containing a pyrimidyl group with aryl bromide, employing [RuCl$_2$($p$-cymene)$_2$] in the presence of (1-Ad)CO$_2$H and a base [74]. In later years, Sollert et al. performed this arylation using the same catalyst but in the presence of an oxidant [75]. This oxidative arylation method gave slightly higher yields and a shorter reaction time (Scheme 24).
The ruthenium-catalysed ortho-arylation of N-alkyl benzamide with phenylboronic acid was described by Jagenmohan’s group using [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} in the presence of AgSbF\textsubscript{6} and the oxidant, Ag\textsubscript{2}O (Scheme 25) [76]. They found that the presence of Ag\textsubscript{2}O is essential for the arylation to occur as the absence of it resulted in no coupling reaction, even when using a stoichiometric amount of AgSbF\textsubscript{6}. Furthermore, they have shown that the ortho-arylated N-alkyl benzamide on treatment with trifluoroacetic acid and HCl could lead to fluorenones.

Recently, Szostak and co-workers described the first ruthenium-catalysed arylation of heteroarene containing a pyridyl ring as the directing group with an organosilane as the arylating agent using [RuCl\textsubscript{2}(p-cymene)]\textsubscript{2} in the presence of AgSbF\textsubscript{6} and an oxidant, CuF\textsubscript{2} [77]. The oxidant CuF\textsubscript{2} served a dual role—in both the arylsilane activation and oxidisation of Ru(0) to an active Ru(II) species. The reaction produced exclusively diarylated product (94%) as compared to monoarylated product (6%) when employing 2-phenylpyridine in DCE, but a modest yield of mono-selectivity was observed with other solvents such as toluene, THF, \textsuperscript{1}PrOH, and DMF. Surprisingly, when the reaction was performed using Ag\textsubscript{2}O as an oxidant, it resulted in high monoselectivity with 95:5 monoarylated/diarylated products, but the overall yield was reduced to 40% (Scheme 26, Table 1).
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 |
|----------|---------|---------|---------|-------|
| CuF₂     | –       | DEC     | 6:94    | >95   |
| CuF₂     | –       | Toluene | 69:31   | >95   |
| CuF₂     | –       | THF     | 75:25   | >95   |
| CuF₂     | –       | NMP     | –       | <2    |
| CuF₂     | AgF     | DCE     | –       | <2    |
| CuF₂     | Ag₂O    | 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 performed the reaction with [RuCl₂(p-cymene)]₂ in the presence of AgSbF₆ and Ag₂O to give ortho-arylated products. The reaction has a wide substrate scope with a 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.

Furthermore, in a continuation of the oxidative arylation using aryl silanes as the arylating agent, Szostak and co-workers have reported the ruthenium-catalysed arylation of pyrimidyl indole in water [80]. The reaction was performed with a [RuCl₂(p-cymene)]₂/AgSbF₆ catalytic system in the presence of an oxidant, leading to selective arylation at the C-2 position (Scheme 29).

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

The direct ortho-C–H arylation of arenes bearing a pyrimidine ring as the directing group has been reported by Nakamura [81], Gu [82] and Cheng [83], and later by Pozgan [84]. Recently,
Pozgan and co-workers demonstrated the ruthenium-catalysed direct arylation of arenes with aryl bromides directed by quinozolene [85]. The arylation 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 quinozoline.

In 2014, Zhao et al. demonstrated the arylation of tertiary amide, viz. furan-3-carboxamide with \([\text{Ru(H}_2\text{)(CO)(PPh}_3)_3]\), to give 2-aryl-3-furanamides [86]. This direct arylation of carboxamide mostly employed directing groups containing hetero atoms 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 \([\text{RuCl}_2(P\text{Ph}_3)_3]\) in the presence of Na\textsubscript{2}CO\textsubscript{3} (Scheme 31) [87]. The reaction was favourably proceeded with secondary amide having an acidic –NH free group, while the tertiary amide with no free –NH group failed to give the desired product. They found that other amide derivatives such as pyridyl substituted amide or the substrate derived from 8-aminoquinoline gave inferior results, 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 was most suitable for this amide C–H arylation.

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

The ruthenium-catalysed sp\textsuperscript{2}-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., \([\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]\), \([\text{RuHCl(}CO)(\text{PPh}_3)_3]\), \([\text{RuCl}_2(\text{PPh}_3)_3]\) and \([\text{RuH}_2(\text{PPh}_3)_4]\), in the presence of Cs\textsubscript{2}CO\textsubscript{3} [88]. They found that the ruthenium complexes \([\text{RuH}_2(\text{CO})(\text{PPh}_3)_3]\) and \([\text{RuHCl(}CO)(\text{PPh}_3)_3]\) were effective for the arylation in the presence of a base (10 mol%). When the reaction was performed in the absence of a base it resulted in extremely low yields. Moreover, the reaction was best performed when using a halogenated aryl boronic acid (Scheme 32).

Scheme 32. Ruthenium-catalysed arylation of acylarenes with halogenated arylboronates.
Recently, Kakiuchi’s research group successfully utilized a cyano (–CN) group as the directing group in the ruthenium-catalysed C–H bond arylation reaction [89]. They performed the arylation of aromatic nitrile with aryl boronic esters using [RuH₂(CO)(PAr₃)] in the presence of KHCO₃, resulting in *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 [RuCl₂(p-cymene)]₂ in the presence of K₂CO₃ and PCy₃ 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 an 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 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 first performed the reaction with [Ru(OPiv)₂(p-cymene)] in the presence of a base, but no desired product was formed. They observed a quantitative dissociation of *p*-cymene ligand at the end of the reaction. Therefore, in order to prevent the dissociation of the arene ligand, they performed the reaction with an analogous ruthenium complex [Ru(OPiv)₂(C₆Me₆)] containing a less labile arene ligand, C₆Me₆. However, in this case only 32% of arylated product was observed despite only 14% of C₆Me₆ ligand being found to be dissociated during the reaction. From this finding, they hypothesized that, under the reaction conditions, the dissociation of arene ligand might be necessary for the reaction to occur. Furthermore, they proposed that a ruthenium complex without arene ligand could also promote a 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 a significant improvement in the reaction when an arene-free cationic ruthenium complex, [Ru⁵(BuC₅N)₆](BF₄)₂, was employed, obtaining a good yield of the desired arylated product (Scheme 35).
Subsequently, they demonstrated ruthenium-catalysed arylation of aromatic acids with aryl iodides using the same cationic ruthenium catalyst, \([\text{Ru}\text{((BuCN)}_6\text{)(BF}_4\text{)}_2]\) [93]. The reaction was performed in the presence of \(\text{K}_2\text{CO}_3\) and an additive such as KOPiv or KOC(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 demonstrated the direct arylation of cyclic amines, especially pyrrolidines involving an sp\(^3\) C–H bond functionalization, using ruthenium(0) catalyst, [Ru\(_3\)(CO)\(_{12}\)] and aryl boronic acid as arylating reagents [94]. In subsequent years, Peschiulli et al. performed a similar arylation of a saturated cyclic amine with aryl boronic esters in the presence of [Ru\(_3\)(CO)\(_{12}\)] [95]. Following this early discovery, Mihovilovic and co-workers have shown that a ruthenium(II) catalyst could efficiently activate the sp\(^3\) C–H bond of benzylic amine [96]. They 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 a catalytic amount of KOPiv and a base. In later year, this arylation reaction was performed by Ackermann and co-workers, employing \([\text{Ru(MesCO}_2)_2(p\text{-cymene})]_2\) without an additional 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 decarboxylation. In 2007, a new ruthenium(0)-catalysed reaction involving a decarboxylative arylation of cyclic-2-aminooester 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. reported a highly efficient ruthenium(II)-catalysed arylation involving decarboxylative C–C bond functionalization (Scheme 38) [99]. They 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 the absence of either of them resulted in extremely poor yield or no reaction.

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

This reaction proceeded effectively using [RuCl₂(p-cymene)]₂ in association with mesitylic acid or employing [Ru(MesCO₂)₂(p-cymene)] directly without the additional use of mesitylic acid with compatible results; this clearly suggests that the reaction proceeded through a carboxylate-assisted route (Scheme 39). Among the carboxylic acids tested, mesitylic acid gave the most beneficial effects. However, the reaction performed with RuCl₃(H₂O)₃ or Ru₃(CO)₁₂ did not give satisfactory results even in the presence of mesitylic acid under similar reaction conditions, indicating that 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 the sp² or sp³C–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. Heck coupling is the most effective method in the alkenylation process. However, it requires a pre-functionalization of starting materials, which limits the scope of the reaction. The oxidative alkenylation of the C–H bond is also known as the Fujiwara-Moritani reaction or oxidative Heck reaction, and was reported as early as 1967, long 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 to 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 progressed rapidly [15]. The oxidative alkenylation of the C–H bond has been performed successfully using stable ruthenium(II)-catalysts from 2011 onwards 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 sp²C–H Bond Directed by Nitrogen-Containing Heteroaryl Ring

The ruthenium(II)-catalysed alkenylation of sp²C–H bond directed by the nitrogen N–Heteroaryl group has been studied by several groups from 2011 onwards. Dixneuf and co-workers described the alkenylation of 1-phenyl-1-pyrazole with acrylates using [Ru(OAc)₂(p-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 was observed in 56:44 ratios with styrene (Scheme 40). However, homocoupling product was formed exclusively when a less reactive alkene, such as N,N-dimethyl acrylamide, was employed [104].

![Scheme 40. Ruthenium(II)-catalysed alkenylation of N-aryl pyrazoles.](image)

Later, Dixneuf’s research group described the alkenylation of 2-phenyloxazoline with an alkene to give ortho-monoalkenylation and dialkenylated products [107]. The reaction was performed with [RuCl₂(p-cymene)]₂ in the presence of an additive and an oxidant in ethanol at 80 °C. They 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 mono-alkenylation product formed exclusively with styrene (Scheme 41).

![Scheme 41. Ruthenium-catalysed alkenylation of phenyloxazolines with alkenes.](image)
Alkenyl esters and ethers were also successfully used in the alkenylation of 2-phenylpyridine derivative in the presence of ruthenium(0) catalyst [Ru(COD)(COT)] in xylene at 150 °C, affording exclusively monoalkenylated product [108]. In 2013, Ackermann and Ma demonstrated the ruthenium-catalysed oxidative C–H bond alkenylation of 2-phenoxypyridine possessing a removable directing group [109]. They performed the reaction using [RuCl$_2$(p-cymene)$_2$] in association with AgSbF$_6$ in the presence of Cu(OAc)$_2$·H$_2$O at 120 °C for 16h. The reaction involved C–H bond functionalization via the formation of a six-membered ruthenacycle as the key intermediate, affording a monoalkenylated product (Scheme 42).

![Scheme 42](image)

**Scheme 42.** Alkenylation of 2-phenoxypyridines with acrylates.

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 [RuCl$_2$(p-cymene)$_2$] in association with AgSbF$_6$ in the presence of Cu(OAc)$_2$·H$_2$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](image)

**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 analogues, many of which are the structural units of pharmaphores and natural products. They performed the reaction employing [RuCl$_2$(p-cymene)$_2$] or [RuCl$_2$(PPh$_3$)$_3$] in the presence of AgOAc as the additive with or without a base. The reaction produced only C-3 alkylated product when [RuCl$_2$(p-cymene)$_2$] was used without a base, which is comparable to the yield of C-3 alkenylated product in the presence of K$_2$CO$_3$ (Scheme 44).

![Scheme 44](image)

**Scheme 44.** Ruthenium-catalysed switchable C-3 alkylation and alkenylation of 2-pyridinebenzofurans.
In 2017, Shome et al. demonstrated that 2-phenylpyrazole or 2-phenyloxazoline could be alkenylated with alkene employing \([\text{Ru(MesCO}_2\text{)}_2(p\text{-cymene})]\) in the presence of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) at 100 °C under solvent-free condition (Scheme 45a) [111]. Recently, they also demonstrated the alkenylation of 1-phenylpyrazole with acrylate using a ruthenium(II) bipyridine complex, \([\text{Ru(MesCO}_2\text{)}(\text{L})(p\text{-cymene})]^+\), in the presence of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in ethanol at 80 °C, predominantly producing a monoalkenylated product (Scheme 45b) [112].

Recently, the alkenylation of benzimidazoles with acrylates affording various annulated products was performed by Selvaraju et al. using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \(\text{AgSbF}_6\) and \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in \(\text{o-xylene}\) (Scheme 46) [113].

They evaluated the efficacy of other oxidants such as \(\text{CuBr}_2\), \(\text{AgOAc}\) and \(\text{AgCO}_3\) as well, but they were found to be less effective. Furthermore, they proposed that the alkenylated product is formed by the protonation of a seven-membered ruthenacycle intermediate [113] (Scheme 47).
Gholamhosseyni and Kianmehr reported a ruthenium-catalysed alkenylation-annulation approach that leads to indazole derivatives [114]. The coupling of \( N \)-aryl pyridazinediones and \( N \)-aryl phthalazinediones with acrylates proceeded using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \( \text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) and additive in water (Scheme 48). The reaction was most effective when \( \text{AgSbF}_6\) was used as the additive, giving up to 95% of the desired product. The desired product can be obtained in a competitive yield with \( \text{KPF}_6\). However, when conducted without an additive, the reaction resulted in lower efficacy, affording only a modest yield of the desired products.

### 3.2. Alkenylation with Carboxylic Acids and Sulfonic Acids

In 2011, Miura, Satoh and co-workers reported a carboxylic acid directed alkenylation of heteroaromatic \( \text{sp}^2\text{C-H} \) bonds with acrylate [102]. The reaction was performed with \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \( \text{LiOAc}\) and \( \text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in DMF, leading to ortho-monoalkenyalted 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 reported the dehydrogenative alkenylation of aromatic carboxylic acids with $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of Cu(OAc)$_2$·H$_2$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 occurred in the absence of an oxidant.

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

Recently, Ackermann and co-workers have also demonstrated ruthenium-catalysed meta-selective C–H alkenylation of aromatic carboxylic acid involving decarboxylation [116]. This reaction proceeds efficient with 10 mol% of $[\text{Ru(MesCO}_2)_2(p\text{-cymene})]$ 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 Na$_2$S$_2$O$_7$, tBuC(O)Me and MnO$_2$ could be employed, the best result was obtained when V$_2$O$_5$ was used as the additive in toluene.

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

Recently, Jin et al. 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$_2$CO$_3$ in aqueous media under oxygen, leading to tetrahydropyridoindoles at up to 78% yield (Scheme 52).

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

Dana et al. reported an orthoC–H bond monoalkenylation of an aromatic carboxylic acid with styrene without a decarboxylation [118]. The reaction proceedsefficiently with $[\text{RuCl}_2(p\text{-cymene})]_2$
in the presence of CuO and KHPO₄ in methanol at 85 °C to give the desired product at 92% yield. The product can be obtained as an ester derivative by further treatment of the acid derivative with methyl iodide (3 eq.), K₂CO₃ (2 equiv.) in acetonitrile at room temperature (Scheme 53).

They observed that an alteration of the base KHPO₄ leads to inferior results, whereas replacing CuO by Cu(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).

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 [RuCl₂(p-cymene)]₂ in the presence of an additive in DMA at 120 °C. They found that the reaction can proceed even without an additive; however, the presence of AgSbF₆ as an additive boosts the reaction efficacy considerably. Alkenylation of sulfonic acid or sulfonyl chloride with an alkene afforded mono-alkenylation, whereas oxidative alkenylation of sulphonamides led to C–H/N–H alkene annulation, affording a high yield of annulated products (Scheme 55).

3.3. Alkenylation Involving Weakly Coordinated Directing Group and Dehydrogenative Coupling

Weakly coordinated groups such as ketones, esters, amides and anilides have been successfully used as directing groups in ruthenium-catalysed C–H bond functionalization. The ruthenium-catalysed
C–H alkenylation of aromatic ketones with olefins was initiated as early as 1993 with the pioneering work of Murai and co-workers [120], followed by several other groups [121–123]. However, in all these attempts, only alkylated products were observed. In 2012, Padala and Jeganmohan described the C–H bond alkenylation of an aromatic ketone with alkene using a \([\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6\) catalytic system in the presence of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in DCE (Scheme 56) [124]. The reaction proceeds 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 the alkenylation of a ferrocenyl ketone using \([\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6\) in the presence of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) [125]. The reaction leads to the ortho-alkenylation of ferrocene C–H bond when ferrocenyl methyl ketone 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 proceeds efficiently under air at room temperature in DCE, leading to the ortho-alkenylated product at high yield (up to 97%), demonstrating the strong influence of the ferrocenyl group on the arene C–H functionalization.

In 2012, Jeganmohan’s research group described an alkenylation of the aromatic sp\(^2\)C–H bond directed by an aldehyde [126]. The ortho-alkenylation was achieved using a \([\text{RuCl}_2(p\text{-cymene})]/\text{AgSbF}_6\) 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 \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in open air and the reaction proceeded in a highly stereoselective manner. Furthermore, they have shown that the alkenylated product could be converted into 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 a \([\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6\) catalytic system in the presence of \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) in DCE under open air. The reaction was tolerated by 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, Jeganmohan and co-workers demonstrated the alkenylation of aromatic nitriles with activated alkenes using $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{AgSbF}_6$ and $\text{AgOAc}$ in acetic acid providing ortho-alkenylated products [127]. Initially, they reacted nitriles with activated alkenes in the presence of $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ but failed to produce alkenylated product; instead, the reaction only afforded an amide due to the hydration of nitrile, indicating that copper salts were not suitable for this reaction. They evaluated the alkenylation of nitrile using several Lewis acids such as $\text{Mn(OAc)}_2$, $\text{AgOAc}$, $\text{Ag(CF}_3\text{COO)}$ and $\text{Ag}_2\text{CO}_3$, of which $\text{AgOAc}$ produced the best results (Scheme 59).

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

Furthermore, Jeganmohan’s research group have shown that the alkenylation of 2-cyanothiophene gave a monoalkenylated product, whereas 3-cyanothiophene provided a dialkenylated product (Scheme 60).

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

In 2012, Miura and co-workers demonstrated the alkenylation of $N,N$-dimethyl benzamide with acrylate using a $[\text{RuCl}_2(p\text{-cymene})]_2/\text{AgSbF}_6$ catalytic system in the presence of $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ in $^1\text{AmOH}$ affording ortho-alkenylated products [19]. The dehydrogenative alkenylation of benzamide and anilide was described by the research group of Ackermann using a $[\text{RuCl}_2(p\text{-cymene})]_2$ catalyst. This reaction was performed in water in the presence of an additive and an oxidant [128]. It was found that the most efficient catalysis could be achieved with a cationic ruthenium(II) species. Thus, employing $\text{KPF}_6$ as an additive achieved the best catalytic activity, giving 87% yield, whereas $\text{AgSbF}_6$ gave a modest yield of 54%. The presence of an additive is essential for this reaction as the absence of it resulted in extremely poor yield, giving only 2% under the same reaction conditions (Scheme 61).
In 2013, Li et al. demonstrated a ruthenium-catalysed C-2 alkenylation of pyrrole and indole derivative directed by an amide group [129]. The reaction proceeded regio- and stereoselectively with [RuCl₂(p-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 [RuCl₂(p-cymene)]₂ in the presence of additive and oxidant in 1,4-dioxane at 100 °C (Scheme 62) [130].

Recently, Ackermann and co-workers demonstrated a ruthenium-catalysed dehydrogenative alkenylation of aromatic tosylamide, aromatic acid and 2-phenoxypyridine with alkene using molecular oxygen as the sole oxidant [131]. The reaction proceeded efficiently with [RuCl₂(p-cymene)]₂ or [Ru(MesCO)₂(p-cymene)] in the presence of CsOAc or KOAc as additive under an oxygen atmosphere. The reaction of 2-phenoxypyridine and alkene led to ortho-alkenylated products; however, under similar reaction conditions tosylamide and aromatic carboxylic acid gave annulated products (Scheme 63a,b).

Alkenylarenes could also be obtained efficiently via catalytic hydroarylation of alkynes. In 2008, Zhang and co-workers demonstrated for the first time the alkenylation of heteroarenes with alkene using molecular oxygen as the sole oxidant [132]. This alkenylation of heteroarenes was performed using simple RuCl₃ as the catalyst in the presence of potassium carbonate as a base. Subsequently, Wu’s group described the catalytic alkenylation of 2-phenylpyridine with terminal
alkynes using ruthenium or zinc compounds containing 12 metalocrown-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 performed the alkenylation of 2-phenyltriazole derivatives with alkynes using [RuCl₂(p-cymene)]₂/AgSbF₆ in the presence of an additive, leading to dialkenylated products (Scheme 64).

Scheme 64. Ruthenium-catalysed 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 alkenylated products, on further treatment with 17% HCl:THF (1:1), could lead to the ortho-alkenylated anilines. Recently, Ackermann’s research group demonstrated the hydroarylation of carboxylic acids with diphenylacetylene to give alkenylated products (Scheme 65) [116]. This hydroarylation was performed with [Ru(MesCO₂)₂(p-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 ortho alkylation with the un-reactive alkyl halides. In 1986, Lewis and Smith reported pioneering work on the 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 a ruthenium(II)-catalyst [135]. The reaction proceeded with [RuCl₂(p-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 MesCO₂K and AdCO₂K were used as additives. However, when the reaction was conducted using an additive such as PPh₃, AgOTf or AgOAc, it resulted in little or no beneficial effect. On the other hand, no reaction occurred without an additive or when employing KPF₆ or NaPF₆ as the additive.

Scheme 66. Ruthenium-catalysed alkylation of 2-phenylpyridine with alkene via hydroarylation.
Subsequently, Ackermann’s research group described an sp$^3$C–H bond alkylation of aryl pyrrolidines with alkenes via hydroarylation using [RuCl$_2$(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 sp$^3$ C–H alkylation via hydroarylation (A) and removal of directing group leading to free pyrrolidines (B).

In 2010, Cadierno et al. described the 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 screened the reaction using various ruthenium catalysts such as [RuCl$_2$(η$^6$-C$_6$Me$_6$)]$_2$, [RuCl$_2$(PPh$_3$)$_3$], [RuCl$_2$(p-cymene)]$_2$, [RuCl$_3$·xH$_2$O], etc., of which [RuCl$_2$(p-cymene)]$_2$ and [RuCl$_2$(η$^6$-C$_{10}$H$_{16}$)]$_2$ gave the best results (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 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 proceeded efficiently with [RuCl$_2$(p-cymene)]$_2$ in the presence of AdCO$_2$H and K$_2$CO$_3$ 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(MesCO$_2$)$_2$(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 2-phenylpyridine derivative with alkyl bromides.

Recently, Li et al. reported a meta-selective C–H bond alkylation of phenol derivative using secondary or tertiary alkyl bromide with [RuCl$_2$(p-cymene)]$_2$ in the presence of AdCO$_2$H and
Interestingly, the directing group could be removed by treatment of 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 in the synthesis of etoxazole, a marketed pesticide.

Furthermore, Li’s research group have demonstrated a ruthenium-catalysed ortho- and meta-selective C–H bond alkylation of azoarenes using alkyl bromides [143]. The reaction was performed with $[\text{RuCl}_2(\text{p-cymene})]_2$ in the presence of carboxylic acid and a base in dioxane. The presence of carboxylic acid ligand is essential for this reaction. The most efficient ligand was found to be $t\text{BuCO}_2\text{H}$, which gave 75% of the alkylated product, whereas employing MesCO$_2$H 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).

Recently, Ackermann and co-workers demonstrated a highly efficient ruthenium-catalysed C–H bond alkylation reaction to give a diverse meta-alkylated product [144]. The reaction proceeded profitably with $[\text{RuCl}_2(\text{p-cymene})]_2$ (5 mol%) in the presence of carboxylic acid and K$_2$CO$_3$ in tert-butylbenzene at 120 $^\circ$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 direct reaction with alkyl bromides.
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 \(\text{K}_2\text{CO}_3\) 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 a carboxylate ligand. However, the reaction being performed at a higher temperature, say 140 °C, led to the formation of a minor amount of meta-alkylated product.

![Scheme 73](image)

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

In the same year, Frost and co-workers also demonstrated the ruthenium-catalysed remote C-6 alkylation of \(N\)-pyrimidinyl indole with ethyl α-bromoisobutyrate [146]. The reaction 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 the reaction was performed with 2 eq. of \(\text{AcOH}\) and \(\text{KOAc}\) in THF. The reaction conducted in other solvents such as DME or 1, 4-dioxane gave dialkylated and monoalkylated products in quantitative yields. However, the alkylation proceeded selectively, giving 91% monoalkylated and only 5% dialkylated product when the reaction was performed in acetic acid.

![Scheme 74](image)

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

Allylic alcohol could also participate as an alkylating agent in the ruthenium-catalysed alkylation reaction. Thus, the ruthenium-catalysed alkylation of an aromatic carboxylic acid with allylic alcohol has been reported by Kumar et al. using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \(\text{Cu(OAc)}_2\) and \(\text{KOAc}\) in dichloroethane to give the desired alkylated product [147]. However, the reaction conducted using \(\text{AgSbF}_6\) as an additive in place of \(\text{KOAc}\) in THF did not produce alkylated product; instead, an alkenylated product was formed (Scheme 75).

![Scheme 75](image)

Scheme 75. Ruthenium-catalysed C-H bond 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 was performed under an oxygen atmosphere at 120 °C, affording the functionalized quinolines (Scheme 76) [148].

\[
\text{R}^1 \text{H} \quad + \quad \text{R}^2 \text{CHO} \quad \xrightarrow{[\text{RuCl}_2(p\text{-cymene})]_2 \text{ (1 mol%)}} \quad 4\text{-nitrobenzoic acid (50 mol%)} \quad \xrightarrow{p\text{-xylene, O}_2 \text{ balloon}} \quad \text{R}^1 \text{H} \quad + \quad \text{R}^2 \quad 120 \degree \text{C, 16-28h}
\]

**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. reported ortho-allylation of 2-phenylpyridine with allyl acetate using \([\text{RuCl}_2(\text{cod})]_n\) in association with \(\text{PPh}_3\) in the presence of \(\text{K}_2\text{CO}_3\) [149]. Later, Zhang and co-workers performed the ortho-allylation of 2-phenylpyridine with terminal alkynes using \(\text{RuCl}_3\) as the catalyst in the presence of benzoic acid and \(\text{K}_2\text{CO}_3\) [132]. Following this early discovery, Goriya and Ramana described the allylation of 2-phenylpyridine with allyl bromide using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \(\text{K}_2\text{CO}_3\) and \(\text{AdCO}_2\text{H}\) in toluene (Scheme 77) [150]. However, this reaction did not give ortho-allylation product but instead afforded a C-2 allylation product on the pyridine ring of the 2-phenylpyridine.

\[
\text{C} \quad + \quad \text{X} \quad \xrightarrow{\text{[RuCl}_2(p\text{-cymene})]_2 \text{, K}_2\text{CO}_3, \text{AdCO}_2\text{H}} \quad \xrightarrow{\text{solvent, 120 \degree \text{C}}} \quad \text{15-20h}
\]

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

In 2015, Jeganmohan’s research group succeeded in the ortho-allylation of 2-ketoxime with allyl acetate using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \(\text{AgSbF}_6\) in DCE at room temperature (Scheme 78) [151]. They found that the use of a silver salt such as \(\text{AgSbF}_6\), \(\text{AgBF}_4\) or \(\text{AgOTf}\) as an additive is essential for the reaction to occur.

\[
\text{C} \quad + \quad \text{OAc} \quad \xrightarrow{\text{[RuCl}_2(p\text{-cymene})]_2 \text{ (5 mol%)} \text{, AgSbF}_6} \quad \xrightarrow{\text{DCE, 120 \degree \text{C, RT, 12 h}}} \quad \text{C}
\]

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

Regio- and stereoselective allylation of indole derivatives with allylic alcohols was reported by Wu and Ji using \([\text{RuCl}_2(p\text{-cymene})]_2\) in the presence of \(\text{NaOAc}\) in DCE to give a C-2 allylated product (Scheme 79) [152]. This allylation reaction was performed under mild conditions and was free from oxidant.
5. Ruthenium-Catalysed Annulation Reaction of Arenes with Alkynes

Annulation is one of the most convenient methods for the synthesis of various heterocyclic compounds. Several transition metal catalyst derivatives of Cu [153], Pd [154,155], Ru [23,156], Rh [157] and Ir [158] promote 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], isocoumarins [163], etc. have been reported by several groups.

In 2012, Ackermann’s research group demonstrated annulations of phenylpyrazole and alkyne with a [RuCl₂(p-cymene)]₂/AgSbF₆ catalytic system in the presence of Cu(OAc)₂·H₂O under air [164]. The reaction did not require a prefunctionalized pyrazole such as the 3-(2-bromophenyl)pyrazole derivative that has been used in similar annulation reactions with copper catalysts [165]. Subsequently, Ackermann’s research group reported oxidative annulation involving C–H/N–H bond functionalization of aniline derivatives containing a removable directing group with [RuCl₂(p-cymene)]₂ in the presence of KPF₆ and Cu(OAc)₂·H₂O in water at 100 °C, affording diverse indole derivatives [166]. Furthermore, 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 [RuCl₂(p-cymene)]₂ in the presence of Cu(OAc)₂·H₂O in ⁴AmOH at 100 °C (Scheme 80).

In 2012, Jeganmohan’s research group demonstrated the ruthenium-catalysed regioselective annulation of aromatic carboxylic acids and alkynes, leading to isocoumarins [168]. The reaction was conducted employing a [RuCl₂(p-cymene)]₂/AgSbF₆ catalytic system with Cu(OAc)₂·H₂O as oxidant and involved a C–H/O–H bond cleavage process (Scheme 81).
In the same year, Ackermann and co-workers demonstrated the annulation of aromatic acids and alkynes with $[\text{RuCl}_2(p\text{-cymene})_2]$ in the presence of KPF$_6$ and Cu(OAc)$_2$·H$_2$O [169]. The reaction was best performed in $^1$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).

They proposed a plausible catalytic cycle that 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 a 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 $O_2$ as oxidant \[170\].

The reaction was evaluated using other ruthenium catalysts as well, such as $[\text{RuCl}_2(p\text{-cymene})]_2$ and $[\text{RuCl}_2(\text{benzene})]_2$, which produced the annulated products in 78% and 76% yields, respectively, with diphenylacetylene. However, under similar conditions, the reaction performed in other alcohols was not productive; only traces of isocoumarins were formed.

Recently, Singh and Dixneuf 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 $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of $\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}$ but without an additive in DMF. The reaction could also be performed profitably in water with competitive yields. The reaction of 1-methylpyrrole-2-carboxylic acid showed a high regiospecificity when performed with an unsymmetrical alkyne, 1-phenyl-1-propyne, giving only one regioisomer in 90% yield. High regioselectivity was observed in water as well for the annulation of 1-methylpyrrole-2-carboxylic and 1-phenyl-1-propyne. However, the annulation of 1-methylindole-3-carboxylic acid and 1-phenyl-1propyne afforded two isomers in 61% and 13% isolated yields.
Subsequently, Singh et al. have reported the annulation of $N$–heteroaromatic acid derivatives with alkynes using a ruthenium(II) $N\hat{O}$ chelate complex, $[\text{RuCl} \left( \text{PySO}_3 \right) \left( \text{p-cymene} \right)]$ (Scheme 86) [172]. They found that the efficiency of $[\text{RuCl} \left( \text{PySO}_3 \right) \left( \text{p-cymene} \right)]$ is comparable to that of $[\text{RuCl}_2 \left( \text{p-cymene} \right)]_2$ for the reaction conducted in DMF, but the reaction performed with $[\text{RuCl} \left( \text{PySO}_3 \right) \left( \text{p-cymene} \right)]$ was not as productive as $[\text{RuCl}_2 \left( \text{p-cymene} \right)]_2$ when performed in water.

The ruthenium-catalysed regioselective cyclization of ketones and alkynes leading to indenols and benzofulvenes was described by Chinnagolla and Jegannathan using $[\text{RuCl}_2 \left( \text{p-cymene} \right)]_2$ in association with $\text{AgSbF}_6$ in the presence of $\text{Cu} \left( \text{OAc} \right)_2 \cdot \text{H}_2\text{O}$ in DCE [173]. In the following year, they achieved ruthenium-catalysed cyclization of aromatic nitriles and alkynes employing $[\text{RuCl}_2 \left( \text{p-cymene} \right)]_2$ in the presence of $\text{KPF}_6$ and $\text{Cu} \left( \text{OAc} \right)_2 \cdot \text{H}_2\text{O}$ in acetic acid under air (Scheme 87) [174].
Jeganmohan co-workers found that the active catalyst was a cationic ruthenium(II) species and the reaction involved deprotonation from aromatic C–H bond, resulting in the formation of a five-membered ruthenacycle as an intermediate. In 2012, the ruthenium(II)-catalysed oxidative coupling of alkyne and naphthol assisted by hydroxyl groups was described by Ackermann and co-workers using \([\text{RuCl}_2(\text{p-cymene})]_2\) in the presence of Cu(OAc)_2·H_2O \[175\]. The presence of Cu(OAc)_2·H_2O was essential for the reaction, as replacing it with CuBr_2 or leaving it out 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. 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.](image)

In 2012, Zhao’s research group demonstrated the annulation of \(N\)-sulfonyl imines and alkynes leading to indenamines \[176\]. The reaction was performed using \([\text{RuCl}_2(\text{p-cymene})]_2\) in association with sulphonamides and AgSbF_6 and 4 equiv. of AcOH in dioxane. The coupling product, indenamines, were obtained at a modest to good yield in the range of 46–88%. In the following year, Zhao’s research group described a ruthenium-catalysed carbocyclization of aromatic ketimines and alkynes (Scheme 89) \[177\]. The reaction proceeded efficiently with \([\text{Ru}(\text{cod})(\eta^3-C_4H_7)_2]\) in the presence of a NHC ligand (IPr) in toluene at room temperature. Zhao and co-workers also evaluated this reaction with a doubly cyclometalated complex, \([\text{Ru}(\text{cod})(\text{C,N-ketimine})]_2\), which was produced from the reaction of \([\text{Ru}(\text{cod})(\eta^3-C_4H_7)_2]\) 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 an NHC ligand affording the annulated product in 45% yield. The reaction was found to be less effective when a saturated NHC ligand (SIPr) was employed. The best reaction condition was achieved when employing \([\text{Ru}(\text{cod})(\eta^3-C_4H_7)_2]\) 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.](image)
Oxidative coupling of aryl benzimidazole with alkynes has been described employing $[\text{RuCl}_2(\sigma\text{-cymene})]_2$ as a catalyst in the presence of Cu(OAc)$_2$·H$_2$O in toluene [178]. The reaction could also be conducted using other oxidants such as NaOAc or Ag$_2$CO$_3$ with a lower efficacy (Scheme 90).

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

Urriolabéitia 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 proceeds with $[\text{RuCl}_2(\sigma\text{-cymene})]_2$ (10 mol%) in the presence of KPF$_6$ and Cu(OAc)$_2$ in alcohol. The reaction requires 24 h for optimum results 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 indole-substituted purines and purine nucleosides, was described by Kumara Swamy and co-workers (Scheme 92) [180]. The annulation was performed employing $[\text{RuCl}_2(\sigma\text{-cymene})]_2$ (5 mol%) in the presence of an additive in methanol. Among the additives tested, CsOAc was found to be the most effective, followed by Cu(OAc)$_2$·H$_2$O and NaOAc. However, the reaction conducted in DCE gave the desired products only in traces, whereas the reaction performed in water or tBuOH was 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 a removable directing group (Scheme 93) [181]. The ruthenium catalyst employed was the most widely explored, $[\text{RuCl}_2(\sigma\text{-cymene})]_2$, in association with AgSbF$_6$ in the presence of Cu(OAc)$_2$ in toluene. The coupling involves various types of alkynes, including aryl-aryl, aryl-alkyl and alkyl-alkyl. However, a 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 a removable benzothiazole group.

The ruthenium(II)-catalysed decarbonylative annulation of 3-hydroxy-2-phenylchromones with alkynes has been reported by Gogoi and co-workers (Scheme 94) [182]. The reaction was performed with [RuCl$_2$(p-cymene)$_2$] in the presence of PPh$_3$ and CsOAc in $^1$AmOH, leading to spirobenzofuranones in up to 86% yield. They proposed that the annulation occurred before the 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 to provide spiro-indenebenzofuranones in good yields.

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

In 2015, a ruthenium-catalysed annulation reaction dictated by a weaker directing group was demonstrated by Patel and co-workers using [RuCl$_2$(p-cymene)$_2$] in the presence of an oxidant (Scheme 95) [183]. They performed the annulation of 2-arylquinolinone and 2-arylbenzoxazinone, which contained two different directing arenes with alkynes using [RuCl$_2$(p-cymene)$_2$] in the presence of an oxidant. They 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 dictated the annulation reaction path. Furthermore, the reaction performed in DCE using Cu(OAc)$_2$ as oxidant produced 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.
Recently, Xu and co-workers 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 proceeded efficiently under reflux condition with \([\text{RuCl}_2(\text{p-cymene})_2]\) in the presence of KPF₆ 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 it was conducted in water:\(^1\)AmOH (1:1), affording 92% of the desired indole derivatives.

![Scheme 96. Ruthenium-catalysed electrochemical dehydrogenative annulation of aniline derivatives and alkynes.](image)

Haak and co-workers reported a cascade annulation reaction of indole with propargyl alcohols using a bifunctional (cyclopentadienone) 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 to provide ready access to various annulated products from simple indolestopropargyl alcohols.

![Scheme 97. Ruthenium-catalysed annulation of indole with propargyl alcohol.](image)

### 6. Conclusions

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 time-saving manner. The ruthenium catalysts participating 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 RuCl₃ species. The C–H bond functionalization reactions with ruthenium complexes such as N’O and O’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 \([\text{RuCl}_2(\text{p-cymene})_2]\) precursor complex, has contributed enormously, and indeed several new reactions and methodologies are being discovered with this ruthenium(II) species. Furthermore, the ruthenium(II) catalysts partnering with carboxylate ligand allowed C–H bond functionalization in a 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; sometimes reactions are even conducted in water. This review presents previous reports on recent developments in C–H bond functionalization reactions, covering arylation, alkenylation, alkylation, allylation and annulation.
reactions. The arylation of nitrogen N–heteroarenes with aryl halides, aryl boronates and aryl silanes as the arylating agents has been discussed. Furthermore, oxidative arylation, decarboxylative arylation and selective monoarylation of 2-phenylpyridine have been presented. Sections 3–5 discussed C–H bond functionalization such as alkenylation, alkylation, allylation and annulation of various arenes. In brief, this review has highlighted the various reactions mentioned above with selected reaction mechanisms that appeared over the past eight years. It is hoped that this review might be helpful in further enhancing the research area, which is already a hot topic in the field of catalysis. Furthermore, I believed that the review will be useful to young researchers working on the metal-catalysed C–H bond functionalization in providing up-to-date information in this field.

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