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Ruthenium-catalyzed C-H bond functionalization in cascade and one-pot transformations

Rafael Gramage-Doria*, Christian Bruneau*

Univ Rennes, CNRS, ISCR-UMR6226, F-35000 Rennes, France.

E-mail: rafael.gramage-doria@univ-rennes1.fr, christian.bruneau@univ-rennes1.fr

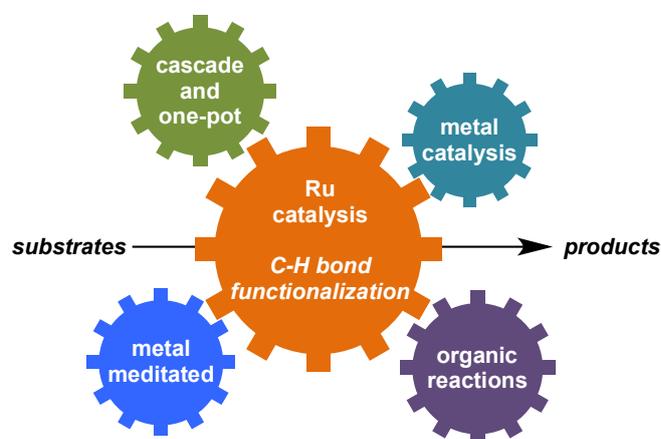
Dedicated to our friend Dr. Maurizio Peruzzini at the occasion of his 65th birthday and for his outstanding contribution to coordination chemistry and catalysis

Abstract. Ruthenium complexes are well known as remarkable pre-catalysts for challenging C-H bond functionalizations. Combining them with other types of chemical reactions in a tandem or one-pot fashion is appealing from a sustainable point of view because it gives access to new strategies to diminish steps devoted to purification and isolation of (sometimes unstable) intermediates. This non-exhaustive review highlights the different approaches enabling these technologies with a particular focus on the understanding for the compatibility of the different reaction sequences. More precisely, ruthenium-catalyzed C-H bond functionalization turned out to be compatible with several organic transformations, metal-mediated reactions and transition metal catalysis.

Keywords:

Ruthenium catalysis; C-H bond functionalization; Cascade reactions; One-pot sequential reactions; green chemistry

Graphical abstract



Highlights

- Ruthenium complexes are compatible with one-pot and tandem transformations involving C-H bond functionalization.
- Ruthenium-catalyzed C-H bond functionalization has been successfully coupled with other C-H bond functionalization reactions.
- Different organic and metal-mediated transformations operate in a concerted manner with ruthenium-catalyzed C-H bond functionalization.
- The merger of ruthenium-catalyzed C-H bond functionalization strategies with several transition metal catalysis is attractive for green chemistry and sustainable approaches.

Introduction

Contemporary homogeneous metal catalysis aims at preparing elaborated organic molecules with the aid of transition metal complexes. This is of utmost importance as regards of the multiple applications found in pharmaceutical, agrochemical and material science industries, essentially by forming unique carbon-carbon and carbon-heteroatom bonds in a controlled manner. In the last half century, cross-coupling reactions with pre-activated scaffolds, essentially catalyzed by palladium complexes, have become ubiquitous for designing efficient retrosynthetic sequences as well as for accessing unprecedented molecular structures [1-4]. Although useful, the fact of using pre-activated building blocks leads to significant amounts of chemical wastes and high production costs associated to the introduction of such functional groups and purifications from undesired side-products [5-8].

In this respect, a clear paradigm shift was conceived from the pioneering contributions of Lewis [9] and Murai, [10] independently, dealing with direct C-H bond functionalization by means of transition metal catalysts. This concept circumvented the requirements for pre-functionalization in the desired building blocks at the expenses of using appropriate directing groups to place the catalytically relevant metal center nearby the targeted C-H bond to be activated. The field of C-H bond functionalization has rapidly evolved in the last two decades showing its full potential by introducing new, useful and cleavable directing groups as well as devising non-directed strategies [11-17]. Nowadays, the most powerful and selective homogeneous catalysts for sp^2 and sp^3 C-H bond functionalization are based on precious metals such as palladium, rhodium, ruthenium and iridium [18-21]. Recently, more sustainable earth-abundant metals including nickel, iron, and cobalt have also revealed interesting catalytic properties [22-26].

From the many metal catalysts, those derived from ruthenium are particularly intriguing, not only owing to the distinct manifolds (nucleophilic Ru(0) and electrophilic Ru(II) as well as radical-involved selectivity), but also because some of them were compatible with reactions different from C-H bond functionalization in a simultaneous or tandem manner. Transformations associated to cascade and tandem approaches compatible with C-H bond functionalization are appealing in view of the green aspects and sustainability they are associated with [27]. Higher synthetic efficiency and higher complexity of designed target molecules can be obtained when the C-H bond activation/functionalization represents one step in a multistep transformation carried out in one pot (**Figure 1**). However, this is far from trivial, as the reaction conditions need to be carefully studied and designed to be compatible with each steps. For instance, harsh reaction conditions may prevent the action of other catalysts and/or reagents in the same reaction vessel. In this review we showcase the most important advances (up to 2020) involving at least one C-H bond functionalization step catalyzed by a ruthenium catalyst and followed or preceded by another catalytic or organic reaction. They correspond to an association of either two catalytic cycles, or one catalytic cycle and one stoichiometric reaction (**Figure 1**). The mechanistic aspects [28] and catalytic cycles, which have been previously presented in articles and reviews on ruthenium-catalyzed C-H bond functionalizations [29-41], are not described in detail, but quoted when necessary for the understanding of the sequence. *Bis*-functionalization reactions represented by *ortho*, *ortho*'-C-C bond formation such as double arylation or double alkenylation for instance, are not considered since the same catalytic cycle operates twice [42]. Examples including the formation/cleavage of multiple bonds *via* annulation [43-44], carbonylation [45-48], decarboxylation [49-51] or other multicomponent reactions [52] operating with a single ruthenium catalytic cycle are also not discussed herein.

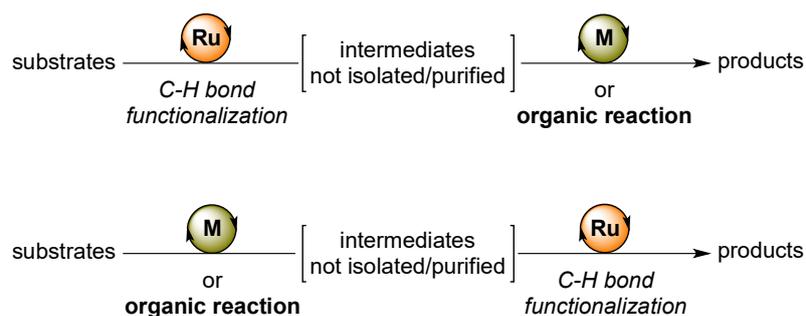
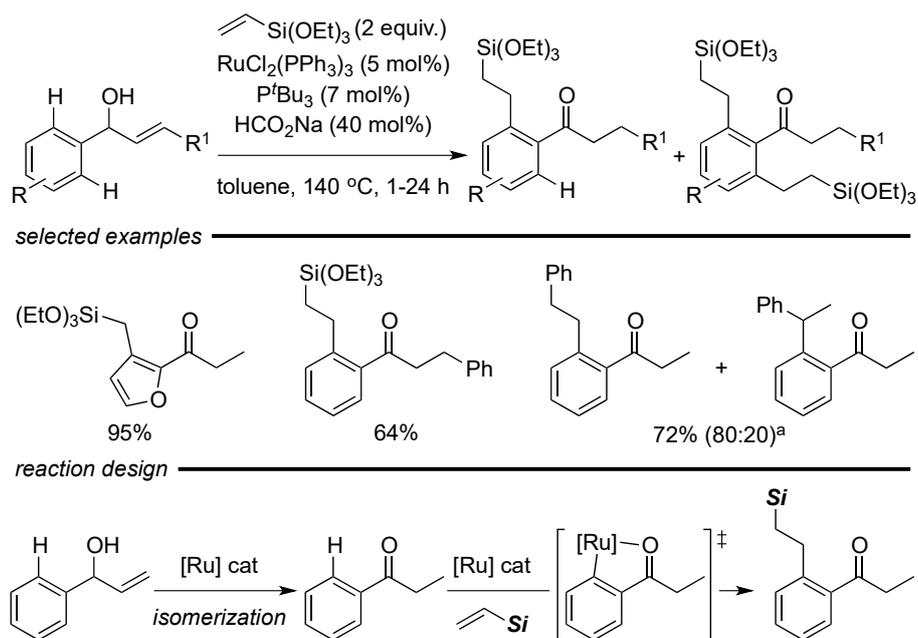


Figure 1. Overview of the chemical approaches covered in this review: combining ruthenium-catalyzed C-H bond functionalization with other transformations *via* one-pot or tandem strategies.

1. Ruthenium complexes catalyzing C-H bond functionalization and other transformations in a tandem manner

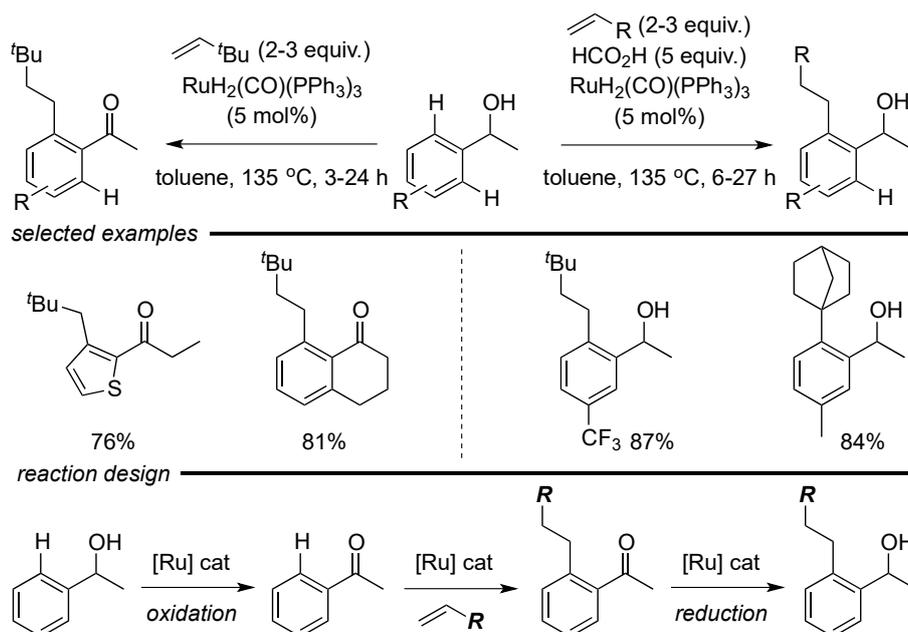
In 2009, Martin-Matute and co-workers reported the first examples of a simultaneous, one-pot transformation involving ruthenium catalysts for C-H bond functionalization and another transformation [53]. They designed a very elegant methodology consisting of a tandem ruthenium-catalyzed isomerization/C-H bond functionalization (**Scheme 1**). The core idea was that the same ruthenium pre-catalyst would catalyze the isomerization of allyl alcohol substrates into ketones as well as the aromatic C-H bond functionalization of the formers. As such, the ketone group formed in the first catalytic event served as *ortho*-directing group to assist the aromatic C-H bond activation. This was applied for the C-H bond alkylation with vinyl silanes. The optimal catalytic system was obtained by mixing $\text{RuCl}_2(\text{PPh}_3)_3$, P^tBu_3 and HCO_2Na , although other well-defined ruthenium(II) complexes (i.e. $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$, $\text{RuH}_2(\text{PPh}_3)_4$ or $[\text{RuCl}_2(p\text{-cymene})]_2$) were efficient in a similar way. Mixtures of mono- and *bis*-alkylated products were obtained, whose selectivity was controlled by fine-tuning the stoichiometry of the vinyl silane. Interestingly, the approach could be applied to substrates bearing the alkene double bond one bond away from the carbinol. This pioneering contribution showed the unprecedented behavior of ruthenium catalysts to perform two concurrent reactions, one of them involving a synthetically appealing C-H bond functionalization. Then, many relevant contributions appeared, thus expanding this knowledge and they are highlighted in the following section.



Scheme 1. Tandem, ruthenium-catalyzed isomerization/C-H bond alkylation. ^aMixtures of linear and branched, mono-functionalized products obtained by replacing vinyl silane for styrene.

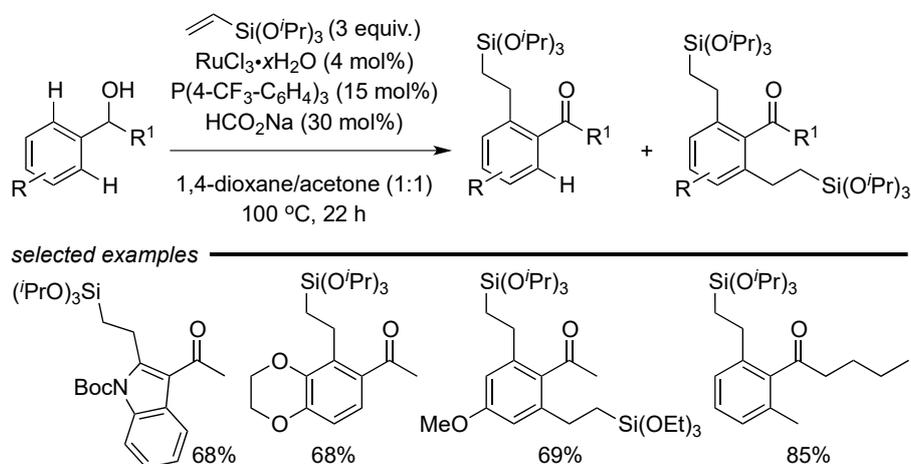
1.1. Hydrogen borrowing and hydrogenation

In the last decades, hydrogen borrowing catalysis (i.e. hydrogen auto-transfer) has appeared as a powerful tool for application in the synthesis of valuable fine chemicals [54-61]. This is largely attributed to the unique reversibility of this process in which a formal dihydrogen from the molecule is abstracted (oxidation without oxidant) and/or restored (hydrogenation) in a specific functional group, typically alcohols or amines. Among the different metal catalysts suitable for hydrogen borrowing, those derived from ruthenium complexes turned out to be very robust and reliable [54-61]. Consequently, their application in tandem processes with ruthenium-catalyzed C-H bond functionalization was indeed an interesting challenge to overcome. In 2010, Williams and co-workers disclosed the first example of a ruthenium-catalyzed hydrogen borrowing operating simultaneously with a C-H bond functionalization [62]. Using solely $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ as the pre-catalyst, benzylic alcohols underwent dehydrogenation (i.e. oxidation) leading to ketones, which were further alkylated at the *ortho*-C-H bond of the aromatic ring with terminal alkenes (**Scheme 2, left**). *Bis*-alkylation was made possible by increasing the amount of the terminal alkenes. Importantly, they managed to take full potential of the hydrogen borrowing catalysis by performing an additional hydrogenation *in situ* using formic acid as the hydrogen source in order to deliver the corresponding *ortho*-alkylated alcohols (**Scheme 2, right**). Consequently, up to three distinct and simultaneous reactions, one of them involving a C-H bond functionalization, were performed in the presence of ruthenium catalysts. Interestingly, this approach shows how simple reagents and catalysts can lead to reaction loops by smart reaction design.



Scheme 2. Tandem, ruthenium-catalyzed oxidation/C-H bond alkylation (left) and ruthenium-catalyzed oxidation/C-H bond alkylation/hydrogenation (right).

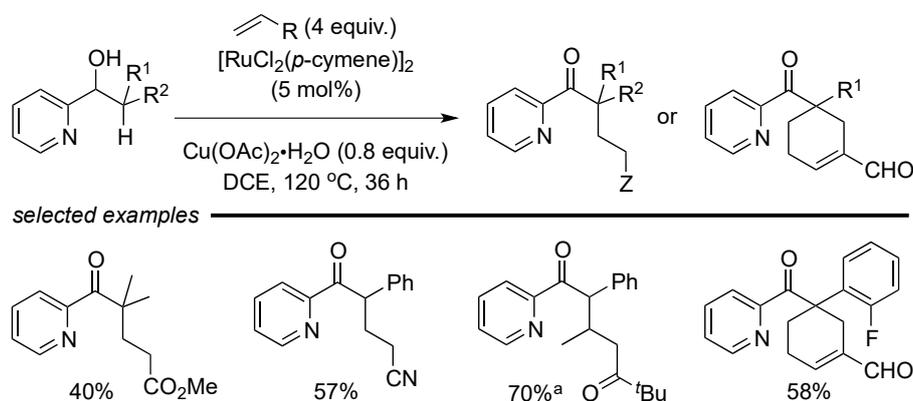
Analogously, Darses and co-workers reported the same approach but using vinyltriisopropylsilane as the coupling partner for the C-H bond functionalization event [63]. In this case, $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$, $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$ and HCO_2Na formed the active catalyst for this tandem reaction using a mixture of 1,4-dioxane and acetone as solvent (**Scheme 3**).



Scheme 3. Tandem, ruthenium-catalyzed oxidation/C-H bond alkylation.

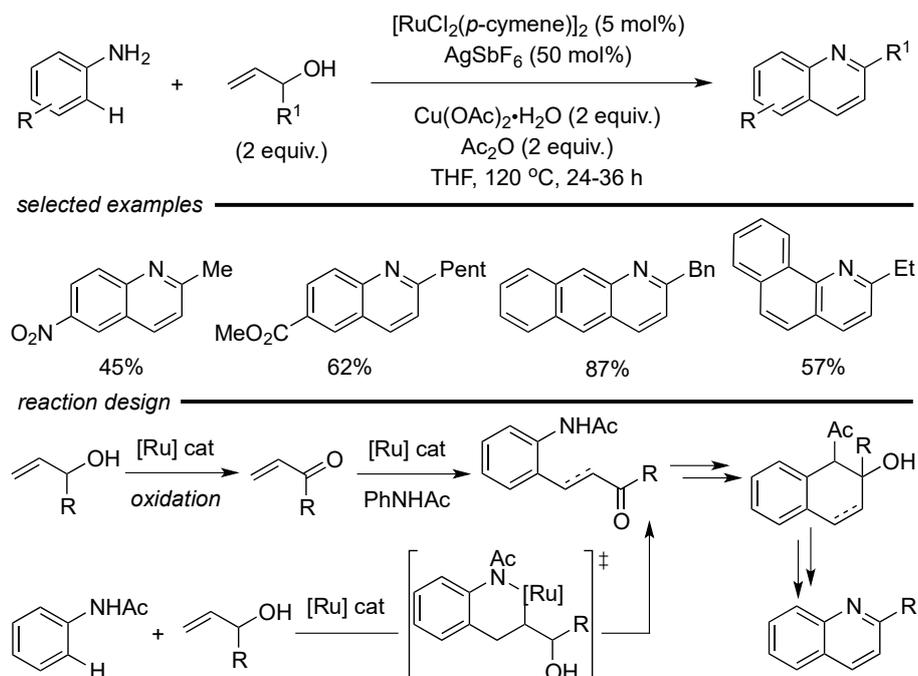
Substrates with nitrogen-containing strong directing groups are also suitable for tandem reactions involving ruthenium-catalyzed oxidations and C-H bond alkylations. Dixneuf and co-workers showed that 2-pyridylethanol derivatives underwent oxidation followed by *in situ* C-H bond alkylation with a variety of electron withdrawing olefins [64]. This methodology employed $[\text{RuCl}_2(p\text{-cymene})]_2$ as the pre-catalyst with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (**Scheme 4**). Besides the presence of a heteroaromatic C-H bond in close proximity to the alcohol group as in the examples described above (**Schemes 1-3**), the C-H bond that was exclusively activated was the α -carbon atom with respect to the carbonyl group. Control experiments supported that the *in situ* formed 2-benzoylpyridyl fragment behaved as the true directing group for the $\text{sp}^3\text{C-H}$ bond alkylation *via* *N*-coordination to ruthenium that is the formation of a five-

membered ruthenacycle. When acrolein was utilized as the coupling partner, the products resulting from a double Michael addition were formed (**Scheme 4**).



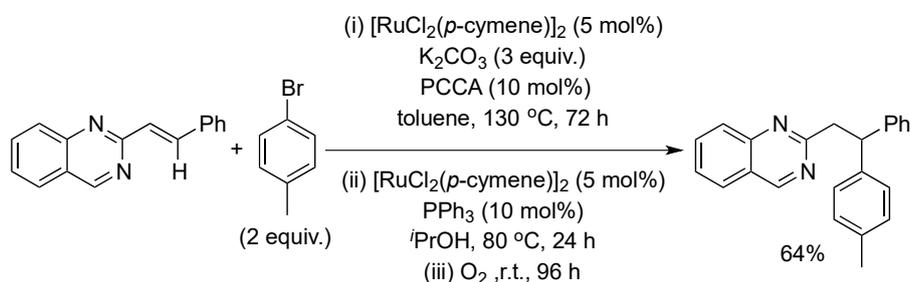
Scheme 4. Tandem, ruthenium-catalyzed oxidation/ sp^3 C-H bond alkylation. ^aThe internal olefin $\text{CH}_3\text{CH}=\text{CHCO}^t\text{Bu}$ was used as the coupling partner.

In 2017, Kapur and co-workers reported the ruthenium-catalyzed synthesis of 2-substituted quinolines by means of a one-pot, tandem oxidation and C-H bond functionalization [65]. The methodology employed readily available aniline and allyl alcohol derivatives. The approach was designed in such a way that the directing group formed in a traceless fashion upon reaction with acetic anhydride, which was released at the end of each catalytic cycle. Although the exact mechanism remained elusive, several mechanistic hypotheses may account for the observed chemoselectivity. On one hand, the oxidation can take place on the allylic alcohol, or, on the other hand, two distinct β -hydride eliminations can occur with or without oxidation of the allyl alcohol at the expense of a subsequent β -hydride elimination or isomerization/condensation sequence. Unexpectedly, the reaction with non-substituted allyl alcohol did not lead to quinolines, but quinolones, a similar finding that was previously observed under rhodium catalysis [66].



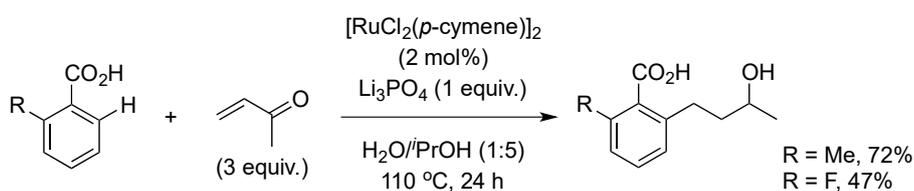
Scheme 5. One-pot, tandem ruthenium-catalyzed oxidation/C-H bond functionalization leading to *ortho*-functionalized quinolines applying a traceless directing group strategy.

In the above-described examples (**Scheme 1-5**), all the reagents were introduced at the beginning of the catalytic transformation. However, a few examples exist in which the hydrogen borrowing/C-H bond functionalization approach has been studied in a single-vessel, stepwise fashion. Pozgan and co-workers reported a single example to access a sp^3C-H bond functionalized molecules in a one-pot, three step reaction sequence involving ruthenium complexes as catalysts (**Scheme 6**) [67]. The substrate of interest, (*E*)-2-styrylquinazoline, was arylated at the alkenylic C-H bond using $[RuCl_2(p\text{-cymene})]_2$ pre-catalyst with no control of the *cis-trans* selectivity. In a stepwise manner and without any purification, a reduction step using $[RuCl_2(p\text{-cymene})]_2$ pre-catalyst in isopropanol as the hydrogen source mainly led to the product resulting from hydrogenation of the alkenyl double bond but also partial saturation of the heteroaromatic ring. An *in situ* switch of the atmosphere by molecular oxygen re-aromatized the heteroaromatic ring resulting in the product from a formal sp^3C-H bond arylation of 2-phenethyl-quinazoline, a type of substrates that are known not to undergo direct sp^3C-H bond arylation with ruthenium catalysts so far.



Scheme 6. Ruthenium-catalyzed C-H bond arylation/reduction/oxidation. PCCA = 1-phenylcyclopentane-1-carboxylic acid

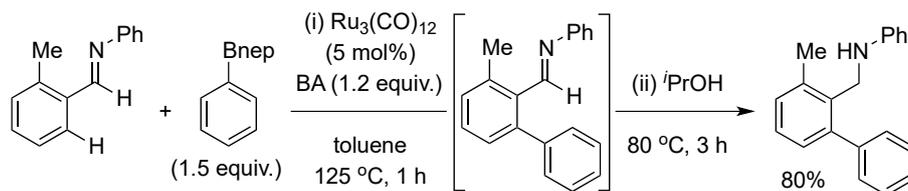
Goossen and co-workers developed a ruthenium-catalyzed C-H bond *ortho*-alkylation of benzoic acids with vinyl ketone derivatives as the coupling partners in aqueous media [68]. They found that switching from water to a mixture of water/isopropanol as solvent led to the reduction of the carbonyl group introduced during the C-H bond alkylation event into a hydroxyl group (**Scheme 7**). Therefore, it was established that hydrogen borrowing was compatible with carboxylate-assisted C-H bond functionalization with the help of $[RuCl_2(p\text{-cymene})]_2$ as the pre-catalyst for both catalytic cycles.



Scheme 7. Tandem ruthenium-catalyzed C-H bond alkylation/hydrogenation with benzoic acid derivatives.

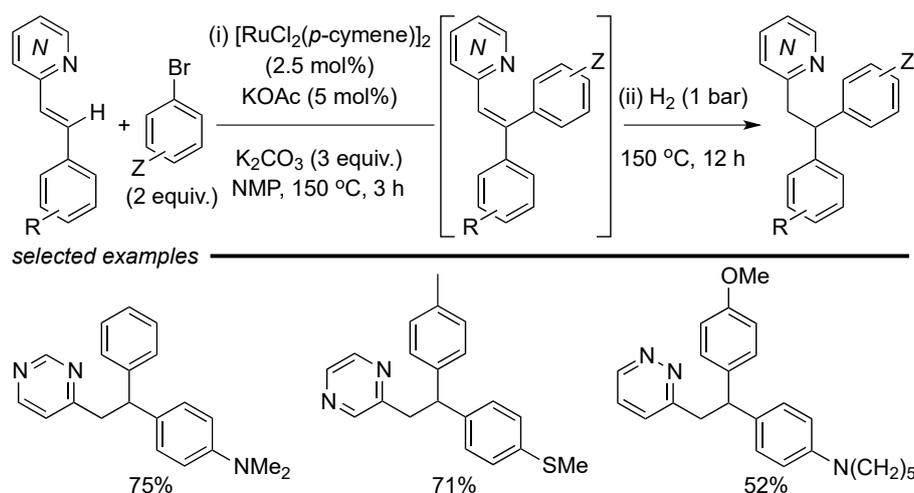
The previous examples feature ruthenium(II) complexes as pre-catalysts for both C-H bond functionalization and hydrogen borrowing. In 2019, Szostak and co-workers reported the first example involving ruthenium(0) species such as $Ru_3(CO)_{12}$ [69]. However, the reaction was not performed in a simultaneous manner but in a one-pot, two step fashion (**Scheme 8**). The key of the success for the first ruthenium(0)-catalyzed process, namely the C-H bond arylation of imine derivatives with organoboranes, was the use of stoichiometric amounts of benzylideneacetone (BA) as a ruthenium-

hydride acceptor. For the second step, switching the solvent to isopropanol triggered the transfer hydrogenation event catalyzed by the previously introduced ruthenium species.



Scheme 8. One-pot, ruthenium-catalyzed C-H bond arylation/hydrogenation with imine derivatives. Bnep = 5,5-dimethyl-1,3,2-dioxaborolane.

Alternatively to hydrogen borrowing, ruthenium-catalyzed hydrogenation using H_2 coupled with ruthenium-catalyzed C-H bond functionalization has been accomplished [70]. Alkenylic C-H bond arylations were carried out using 1,*n*-diazines ($n = 2, 3, \text{ or } 4$) followed by a switch of atmosphere to H_2 that enabled the hydrogenation of the olefin (**Scheme 9**). The initial ruthenium pre-catalyst turned out to be efficient for both catalytic events in a stepwise manner. Importantly, the diazine motif survived the reaction conditions and remained untouched as a consequence of the exquisite chemoselectivity of the ruthenium-catalyzed hydrogenation under 1 bar of H_2 . This one-pot, two-step strategy may serve as a valid approach to overcome the more difficult, direct ruthenium-catalyzed sp^3C-H bond functionalization.

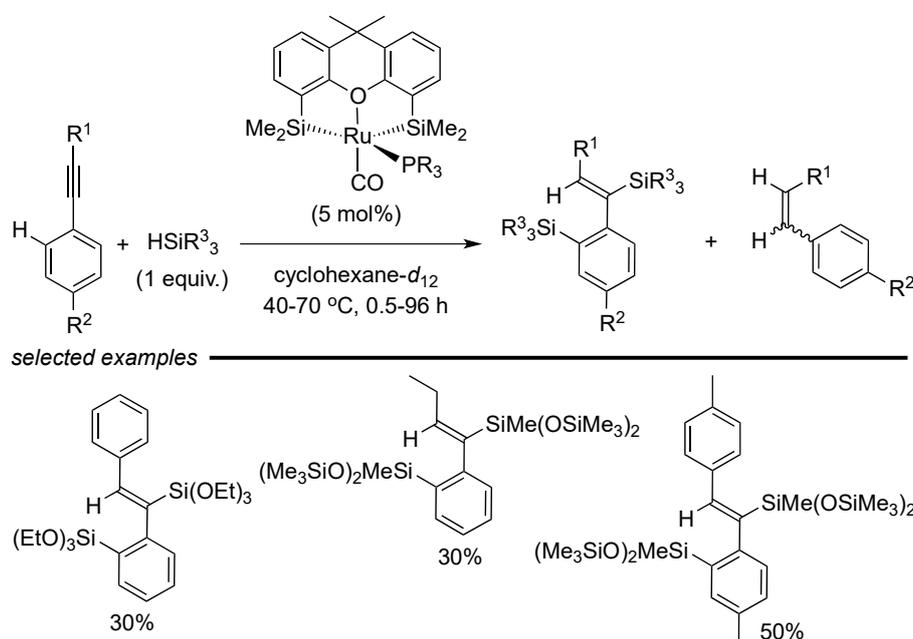


Scheme 9. Tandem, ruthenium-catalyzed C-H bond arylation/hydrogenation with styryldiazine derivatives.

1.2. Hydrosilylation and beyond

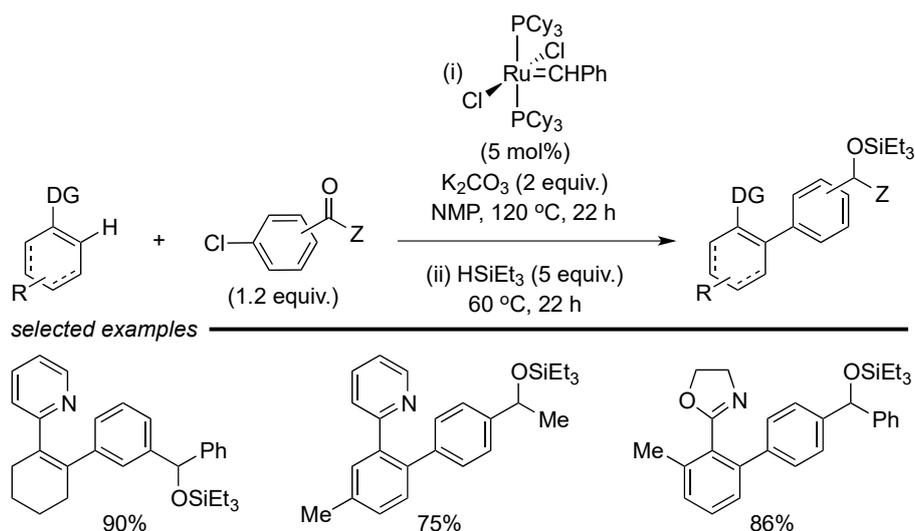
Since the end of the 20th century, an important number of transition metal-derived complexes were shown to be highly active and selective for hydrosilylation reactions, that is, the addition of hydrosilanes to unsaturated substrates [71-74]. In particular, ruthenium complexes have been extensively used as catalysts, especially considering their availability and tolerance to sensitive functional groups [71-74]. Some examples involving ruthenium-catalyzed C-H bond functionalizations and hydrosilylations have been achieved. Tobita and co-workers developed the sole example of this tandem approach in a simultaneous manner [75]. They managed to couple an *ortho*- sp^2C-H bond silylation with a *trans*-selective hydrosilylation of a carbon-carbon triple bond (**Scheme 10**). The reaction was catalyzed by a ruthenium(II) complex comprising a $\kappa^3(Si,O,Si)$ -xantsil ligand

and mechanistic studies suggested that the hydrosilylation of the carbon-carbon triple bond occurred first. A maximum yield up to 50% was obtained because the arylalkyne derivatives also served as hydrogen acceptors, which explained the formation of (*E*)-/(*Z*) arylalkenes as by-products in similar yields.



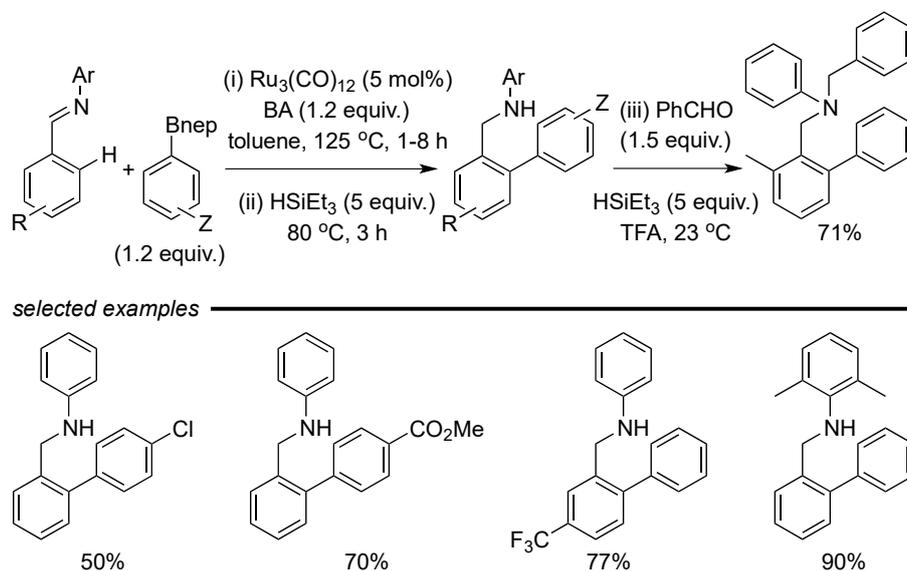
Scheme 10. Tandem ruthenium-catalyzed hydrosilylation/C-H bond silylation. R = N(CH₂)₄.

Considering ruthenium-catalyzed C-H bond functionalization/hydrosilylation in a stepwise fashion, Ackermann and co-workers reported the one-pot, ruthenium-catalyzed arylation/hydrosilylation of a variety of alkene-substituted heterocycles [76]. A ruthenium(IV) alkylidene pre-catalyst enabled the C-H bond arylation using less expensive, yet more difficult to activate, aryl chlorides containing carbonyl groups as well as the hydrosilylation of the formers (**Scheme 11**). The strategy was compatible with aryl and alkyl substituents so far and different directing groups (DGs) were studied such as pyridine, pyrazole and oxazole. In some cases, a further *in situ* treatment with TBAF (tetrabutylammonium fluoride) cleaved the “OSiEt₃” group leading to the corresponding alcohol derivatives. This contribution highlighted the fact that the reagents introduced in the C-H bond functionalization (first step) did not poison the performance of the hydrosilylation in the second step. It is relevant to note that a similar strategy under ruthenium(II) catalysis was shown later by Dixneuf and co-workers using imines as directing groups, aryl bromides as coupling partners and H₂SiPh₂ as the silylating reagent [77]. However, a purification work-up was required between the two steps.



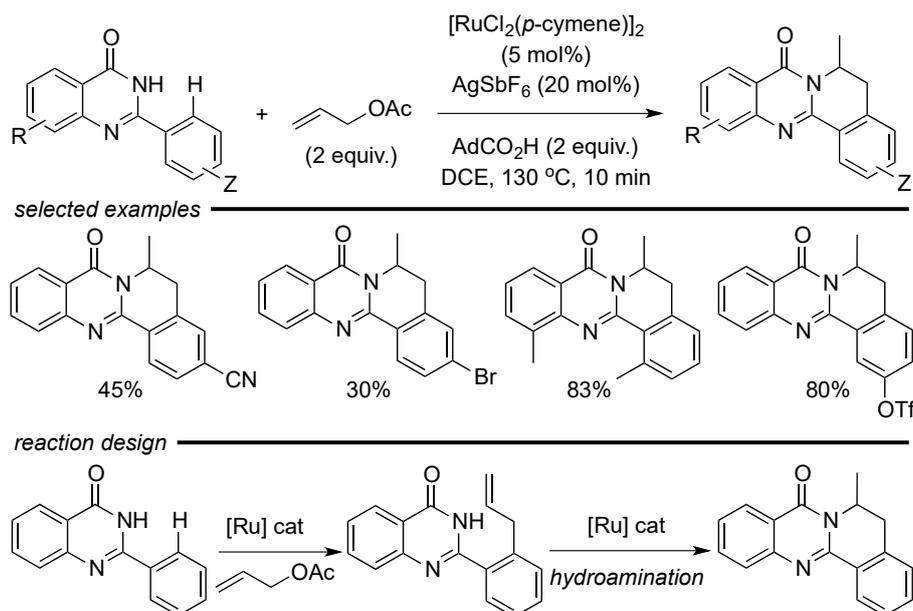
Scheme 11. One-pot, ruthenium(IV)-catalyzed C-H bond arylation/hydrosilylation.

A one-pot, ruthenium(0)-catalyzed C-H bond arylation/hydrosilylation version was disclosed by Szostak and co-workers [69]. They used simple imines as directing groups with arylboranes as coupling partners for the C-H bond functionalization followed by *in situ* addition of HSiEt_3 (**Scheme 12**). As such, ruthenium(0) species appeared to be active and compatible for both transformations. Importantly, the reaction was tolerant to many functional groups including bromides, which is not very common for ruthenium-catalyzed C-H bond arylations. Interestingly, this methodology was coupled with a reductive amination process to access sterically hindered amines in a one-pot, three-step strategy (**Scheme 12**).



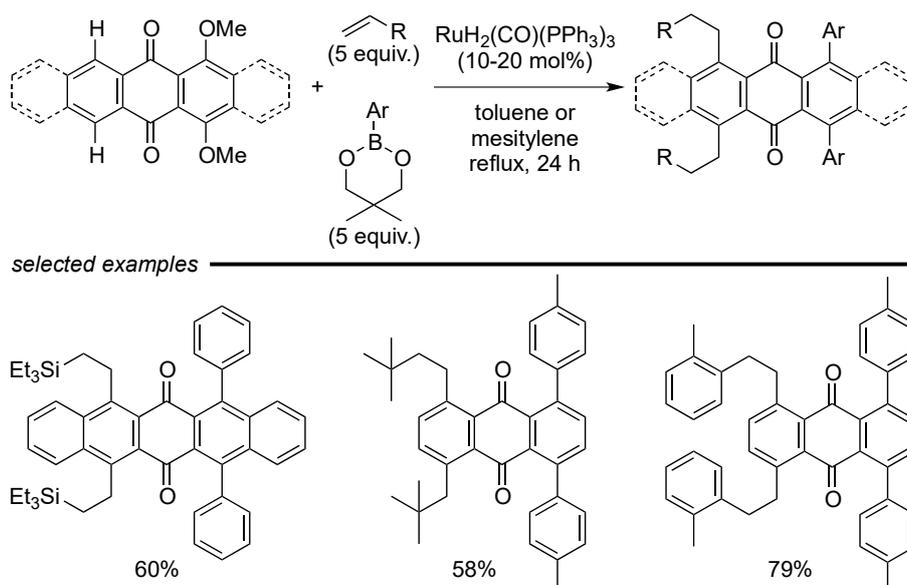
Scheme 12. One-pot, ruthenium(II)-catalyzed C-H bond arylation/hydrosilylation and one-pot, ruthenium(II)-catalyzed C-H bond arylation/hydrosilylation/reductive amination.

In the same vein, Jana and co-workers reported a tandem C-H bond functionalization/hydroamination under ruthenium(II) catalysis [78]. 2-Arylquinazolinone derivatives underwent *ortho*- $\text{sp}^2\text{C-H}$ bond allylation with allyl acetate as coupling partner and subsequent intramolecular hydroamination (**Scheme 13**). Besides the excellent chemoselectivity and functional group tolerance, the reactions were exceedingly fast and they were typically completed after only 10 minutes.



Scheme 13. One-pot ruthenium(II)-catalyzed C-H bond allylation/hydroamination.

Kakiuchi and co-workers reported pioneering examples of ruthenium-catalyzed C-O bond arylations [79] and later they performed simultaneous C-H and C-O bond functionalizations under ruthenium(II) catalysis [80]. This proof-of-concept methodology was applied to dimethoxy-substituted acenequinones as substrates. Both ketone groups behaved as directing groups for the double C-H bond alkylation using terminal olefins as well as for the double C-O bond arylation using arylboronate derivatives (**Scheme 14**). The resulting functionalized acenequinones are not trivial considering that up to four challenging new chemical bonds were selectively formed. From the point of view of the applications, the resulting acenequinone derivatives were readily reduced with LiAlH_4 leading to functionalized acenes that are promising building blocks for material sciences, i.e. as p-type organic field-effect transistors (OFETs).

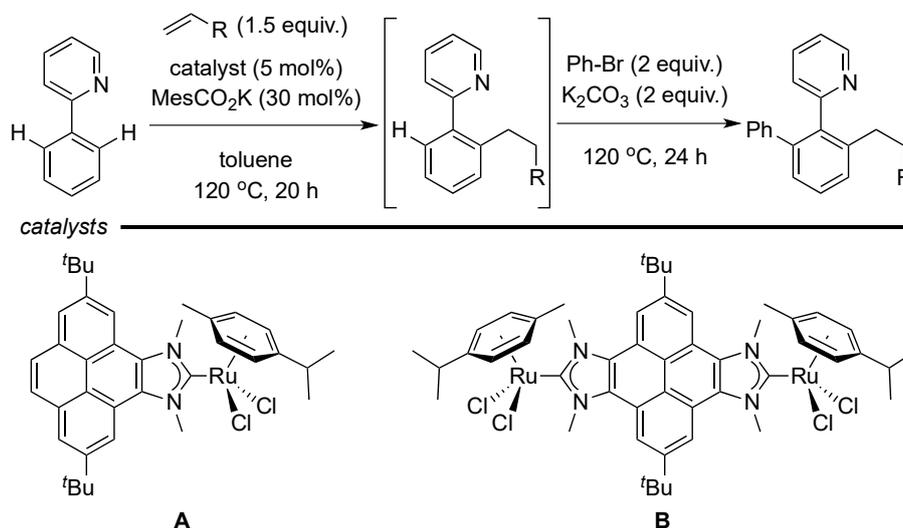


Scheme 14. One-pot ruthenium(II)-catalyzed double C-H bond alkylation/double C-O bond arylation.

2. Different ruthenium-catalyzed C-H bond functionalizations in one-pot or tandem manner

2.1. Ruthenium-catalyzed C-H bond alkylation followed by another ruthenium-catalyzed C-H bond functionalization

Mono- and symmetrical Janus type *bis-N*-heterocyclic carbenes were coordinated to the $\text{RuCl}_2(p\text{-cymene})$ moiety to give the corresponding mono- and dinuclear ruthenium complexes **A** and **B** (Scheme 15). These complexes have been evaluated in two *ortho*-directed C-H bond functionalization reactions, namely the alkylation and arylation of 2-phenylpyridine with alkenes and aryl halides, respectively. The alkylation of 2-phenylpyridine with 1-hexene, 1-octene and 1-decene led to the selective mono-*ortho*-alkylation in more than 94% yield, when the reaction was performed in the presence of 5 mol% (based on the amount of metal) of complex **A** or **B** and 30 mol% of potassium mesitylenecarboxylate (KO_2CMes) in toluene at 120 °C for 20 h. On the other hand, exclusive *bis*-arylation of 2-phenylpyridine was observed in more than 95% yield, when an aryl chloride or bromide was reacted with 2-phenylpyridine in the presence of 5 mol% of **A** or **B** in NMP under classical arylation conditions with KOAc (10 mol%) and K_2CO_3 (2.5 equiv.) as additives at 120 °C for less than 5 h. These selective reactions were perfectly suited to achieve a tandem alkylation/arylation of 2-phenylpyridine with the same catalytic system. Indeed, even though toluene was not the best solvent for the arylation reaction, the reaction of 2-phenylpyridine with a terminal alkene in toluene at 120 °C for 20 h, in the presence of KO_2CMes and 5 mol % of catalyst, followed by addition of phenyl bromide and K_2CO_3 and further heating at 120 °C for an extended period of time led to the expected unsymmetrically *ortho,ortho'*-disubstituted 2-phenylpyridine derivatives in about 70% overall yield (Table 1). It can be noted that this tandem transformation has also been achieved with $[\text{RuCl}_2(p\text{-cymene})]_2$ as catalyst under similar conditions leading to comparable results [81].



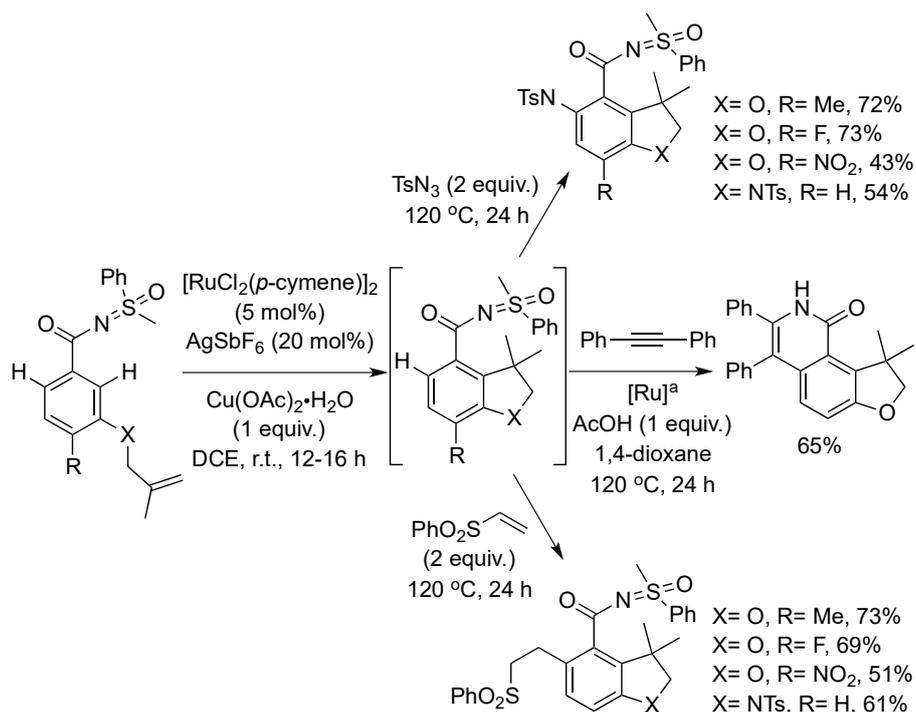
Scheme 15. Tandem ruthenium-catalyzed C-H bond *ortho*-alkylation/*ortho'*-arylation from 2-phenylpyridine.

Table 1. Tandem alkylation/arylation of 2-phenylpyridine.

Catalyst	Time (h)	GC Yield (%)		
		R= <i>n</i> -butyl	R= <i>n</i> -hexyl	R= <i>n</i> -octyl
A	24	37	32	38
A	48	49	42	
B	24	45	44	52
B	72	70	73	61
[RuCl ₂ (<i>p</i> -cymene)] ₂	24	45	51	52

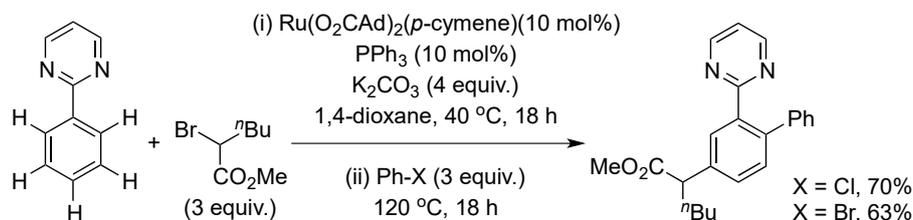
The intramolecular alkylation of an aryl moiety directed by the methylphenylsulfoximine group has been carried out in the presence of 5 mol% of [RuCl₂(*p*-cymene)]₂ as pre-catalyst, AgSbF₆ (20 mol%) and Cu(OAc)₂ (1 equiv.) at room temperature in DCE (DCE = 1,2-dichloroethane). From benzoic acid derivatives bearing an *O*- or *N*-tethered allylic group, the reaction performed under mild conditions led to dihydrobenzofuran and indoline derivatives, thus blocking one *ortho*-position of the starting aryl substrate (**Scheme 16**). The second *ortho*-position could be functionalized *via* C-H bond functionalization with the same catalytic system in a one-pot procedure. Indeed, in the presence of a sulfonylazide introduced at the outset of the reaction, the intramolecular C-C bond formation occurred at room temperature and further heating at 120 °C led to *ortho*-directed amination in a straightforward tandem catalytic sequence. Similarly, a second intermolecular C-H bond alkylation was performed when the phenylvinylsulfone was initially added to the reaction mixture and the same temperature sequence applied. In these conditions, dihydrofurans and indolines formally resulting from two regioselective alkylation reactions involving C-H bond activation were obtained in 51-73% yield (**Scheme 16**).

A slightly different catalytic system operating in the presence of 1 equivalent of acetic acetic but in the absence of copper(II) acetate was used to introduce isoquinolone motifs into heteroarene structures upon annulation resulting from reaction of a dihydrobenzofuran with an internal alkyne. This sequential alkylation/annulation reaction, also based on a C-H bond activation process and requiring isolation of the intermediate dihydrobenzofuran and application of a new catalytic system, was successful to produce various fused dihydrofuran-isoquinolone compounds from symmetrical and unsymmetrical internal alkynes and dihydrofurans in 64-77% yields (**Scheme 16**) [82].



Scheme 16. Tandem ruthenium-catalyzed C-H bond alkylation/amination, double C-H bond alkylation and sequential C-H bond alkylation/annulation with alkynes. ^aThe same catalytic system as in the previous step was used.

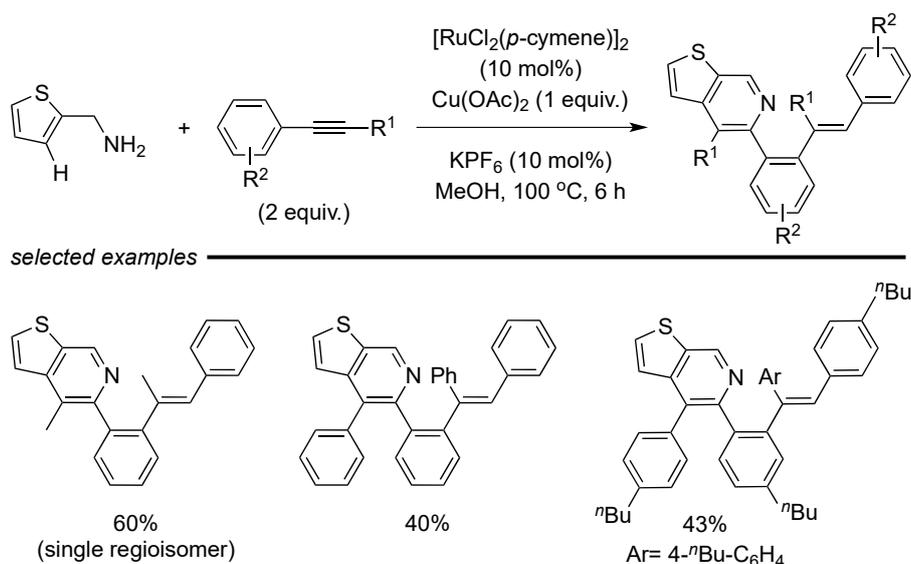
Another tandem alkylation/arylation transformation with a different regioselectivity was demonstrated by Ackermann. The ruthenium-catalyzed *meta*-C-H bond alkylation of a phenyl group substituted by an heterocyclic directing group such as an oxazoline, a pyrimidine, a pyrazole, or a 2-pyridine was successfully performed with α -bromo-substituted esters, amides, and ketones as electrophiles in the presence of 10 mol% of $\text{Ru}(\text{carboxylate})_2(p\text{-cymene})$ pre-catalyst (carboxylate= mesitylenecarboxylate or adamantylcarboxylate) associated with 10 mol% of PPh_3 and K_2CO_3 as a base. The reaction took place in 1,4-dioxane at low temperature ($40\text{-}60\text{ }^\circ\text{C}$) for 20 h according to a radical process leaving two *ortho*-positions free for further ruthenium-catalyzed C-H bond arylation. Addition of an aryl halide and subsequent heating at $120\text{ }^\circ\text{C}$ without extra-addition of catalyst made the arylation possible. It is worth noting that when the aryl halide was introduced at the outset of the reaction, the same sequence was achieved. In both cases, only monoarylation in *para*-position of the alkyl group took place probably guided by steric factors (**Scheme 17**). This overall one-pot transformation constitutes an efficient regioselective tandem transformation with large substrate scope [83].



Scheme 17. Tandem ruthenium-catalyzed *meta*-alkylation/*ortho*-arylation.

2.2. Ruthenium-catalyzed C-H bond annulation followed by other ruthenium-catalyzed C-H bond functionalizations

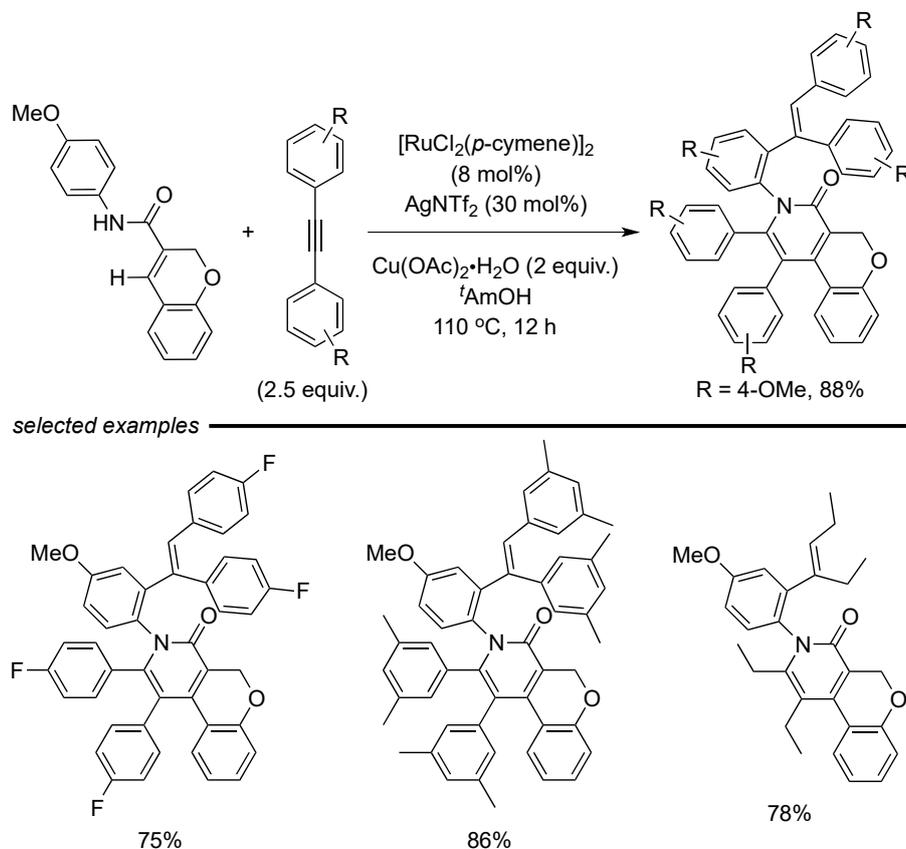
The directed C-H activation process leading to deshydrogenative coupling of internal alkynes with annulation involving the heteroatom of the directing group has recently emerged as an efficient route for the synthesis of heterocycles. With their primary amine functionality used as directing group, benzylamines and thiophene-2-methylamine have been used as privileged substrates to prepare isoquinolines and thieno[2,3-*c*]pyridines upon reaction with aliphatic internal alkynes in the presence of $[\text{RuCl}_2(p\text{-cymene})]_2$ as pre-catalyst [84]. With 1,2-diarylalkynes, the corresponding product contains a 2-arylpyridine moiety that is prone to give another *ortho*-directed C-H bond activation/functionalization with the same catalytic system. In the presence of an excess of alkyne, a second alkyne insertion took place to give the corresponding alkenylated product (**Scheme 18**) [84,85]. This one-pot transformation is made possible by an auto-tandem catalytic process involving two *ortho*-directed C-H bond functionalizations and the incorporation of two molecules of alkynes with different mechanisms leading to annulation and alkenylation products. The same authors have shown that a similar double alkyne insertion took place from aryl-containing alkynes and thiophene-2-carboxamide in the presence of a catalytic system based on $[\text{RuCl}_2(p\text{-cymene})]_2$ (10 mol%), KPF_6 (10 mol%), $\text{Cu}(\text{OAc})_2$ (1 equiv.), NaOAc (2 equiv.) operating in toluene at 120 °C during 24 h. From 1-methyl-2-phenylethyne and 1,2-diphenylethyne, the corresponding alkenylated thieno[2,3-*c*]pyridin-7(6H)-ones were isolated in 28 and 19% yield, respectively [86].



Scheme 18. Regioselective synthesis of alkenylated thieno[2,3-*c*]pyridines *via* auto-tandem C-H bond annulation/alkenylation under ruthenium catalysis.

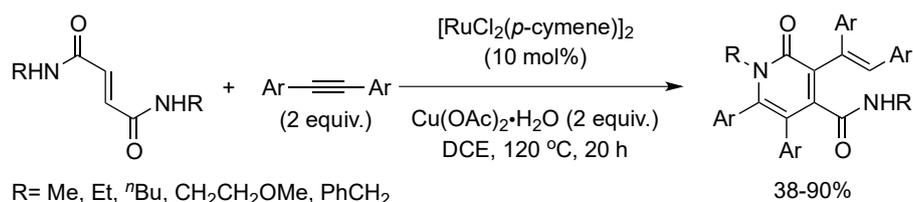
Secondary amides have been extensively used as directing groups for various $\text{sp}^2\text{C-H}$ bond functionalization. It has been shown that in the presence of one equivalent of internal alkyne, chromene-3-*N*-arylcarboxamide led to fused chromene-pyridone upon annulation resulting from activation of the chromene C(4)-H bond directed by the coordination of the nitrogen atom to the ruthenium center. When an excess of alkyne was used, a second C-H bond functionalization took place directed this time by the carbonyl group of the pyridone moiety and led to C-H bond alkenylation of the aryl group connected to the nitrogen atom of the pyridone. This tandem reaction required the presence of copper(II) acetate as oxidant and source of carboxylate anions, and AgNTf_2 , and it was more efficient in *tert*-amyl alcohol at 110 °C in the presence of 8 mol% of catalyst. Under these

conditions, both diaryl and dialkylethyne reacted very well and gave the doubly functionalized products in more than 75% yield (**Scheme 19**) [87].

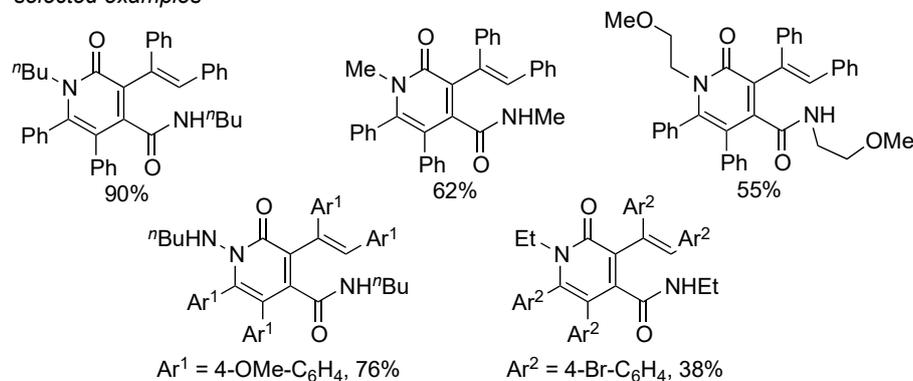


Scheme 19. Tandem annulation/C-H bond alkenylation with alkynes under ruthenium catalysis.

Another strategy involving successive annulation/C-H bond alkenylation by means of ruthenium catalysis has been reported using amides as directing groups for the functionalization of the $\text{sp}^2\text{C-H}$ bond of symmetrical fumaramides with internal alkynes as shown in **Scheme 20**. The catalytic system was based on the association of $[\text{RuCl}_2(p\text{-cymene})]_2$ and $\text{Cu}(\text{OAc})_2$ without any base. With this system, alkenylated pyridones resulting from annulation directed by one amide group followed by *ortho*-C-H bond alkenylation of the initially formed heterocycle directed by the other exocyclic secondary amide group, were formed as the major products [88]. In this reaction sequence, the intermediate pyridone resulting from the primary annulation was not observed but some trace amounts of *bis*-annulation were sometimes detected. The scope was demonstrated with symmetrical 1,2-diarylethyne and various secondary *N*-alkyl fumaramides. A modification of the catalytic system by introduction of a base allowed to favour the double annulation reaction.

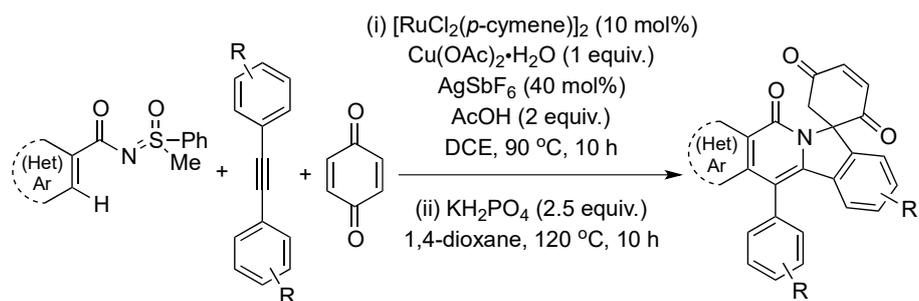


selected examples

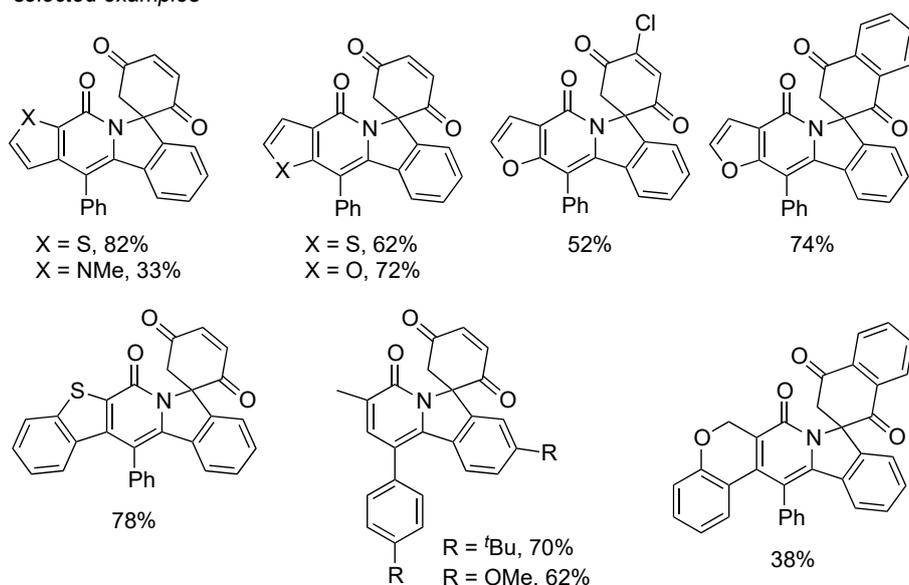


Scheme 20. Ruthenium-catalyzed formation of pyridones *via* an annulation/C-H bond alkenylation tandem process.

A rapid access to spiro-isoquinolones based on a sequence of two ruthenium-catalyzed reactions has been described. It involves first an annulation resulting from C-H bond activation and mono-insertion of internal alkyne with a heterocycle featuring a methyl phenyl sulfoximine directing group followed by a base-promoted annulation with quinone [89]. In the presence of 10 mol% of $[\text{RuCl}_2(p\text{-cymene})]_2$, 40 mol% of AgSbF_6 , 100 mol% of $\text{Cu}(\text{OAc})_2$ and 2 equivalents of acetic acid, the condensation of the two initial substrates, namely the heterocycle and the internal alkyne gave an intermediate pyridone derivative resulting from directed monoarylation with annulation. Then, the quinone and KH_2PO_4 were added to trigger a new catalytic cycle in the presence of the same ruthenium catalyst affording a spiro product resulting from a base-promoted cyclization. A variety of internal alkynes substituted by aromatic groups were efficient for this sequential transformation, and thiophenes, furans and pyrroles substituted in position 2 or 3 by the directing group as well as acyclic olefins and chromenes appeared to be suitable substrates (**Scheme 21**) [89].

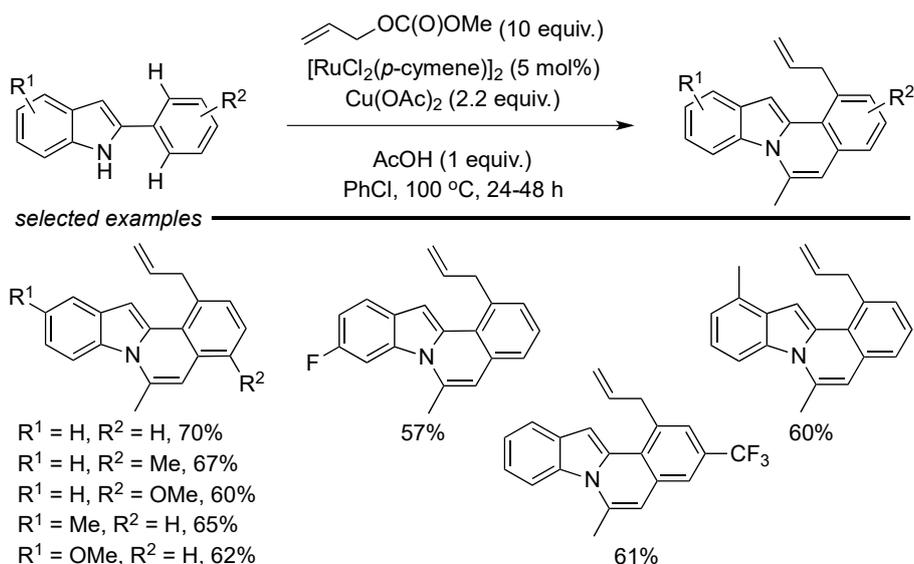


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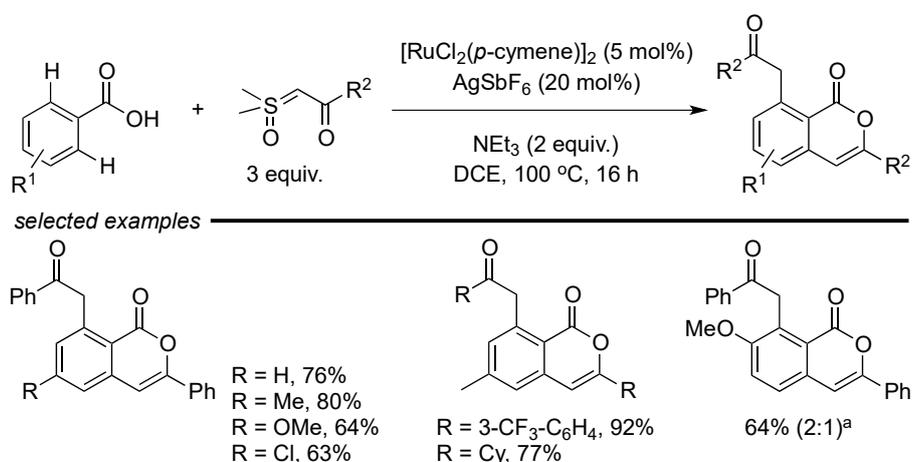
Scheme 21. Ruthenium-catalyzed sequential one-pot annulation/cyclizing alkylation.

The previous examples of tandem reactions involved an annulation with an internal alkyne as coupling partner. Alternatively, it is also possible to generate a cyclic structure starting from a carbon-carbon double bond and a heterocycle with the heteroatom atom as directing group. Thus, 2-phenylindoles reacted with an excess allyl methyl carbonate to give 1-allyl-6-methyl indolo[2,1-*a*]isoquinolines under ruthenium(II) catalysis conditions. It has been demonstrated that the reaction proceeded first *via* double *ortho*-C-H bond allylation of the phenyl substituent followed by subsequent intramolecular oxidative cyclization of one of the allylic group. In this case the annulation represents the last step of the cascade reaction. The scope of this tandem transformation included a large variety of indole substrates with both electron-donating and -withdrawing groups on the indole and the phenyl moieties, and the main limitations were caused by steric hindrance considerations. Considering the allylic substrate, unsubstituted allyl carbonates were the best substrates (**Scheme 22**) [90].



Scheme 22. Ruthenium-catalyzed tandem *bis*-C-H bond-allylation/cyclization.

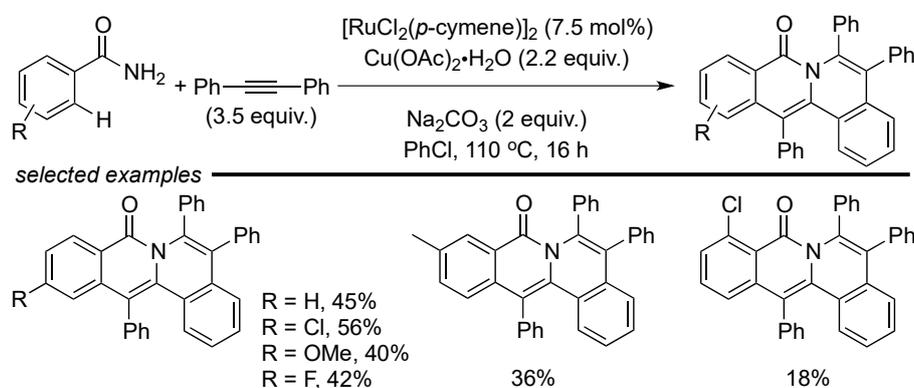
In a subsequent study, it has been shown that the weakly coordinating carboxylic group from *ortho*-substituted benzoic acids acted as a soft directing group in the presence of a ruthenium(II) catalyst allowing the selective functionalization by sulfoxonium ylide to give 3,4-benzo-2-pyrones *via* concomitant C-H/O-H activations and annulation resulting from Lewis acid-mediated cyclization of an *ortho*-2-aryl-2-oxoethyl benzoic acid intermediate. However, in the presence of 3 equivalents of sulfoxonium ylide, a second C-C bond formation took place at the other *ortho*-position of *para*- or *meta*-substituted benzoic acids. The tandem C-H bond functionalization resulting in the formation of two C-C and one C-O bond was catalyzed by 5 mol% of $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of 20 mol% of AgSbF_6 and 2 equivalents of triethylamine in 1,2-dichloroethane at 100 °C for 16 h. A variety of benzoic acids with functional groups such as halide, methoxy, dimethylamino, methylthio and carboxylic ester were tolerated. Concerning the other partner, aryl-substituted sulfoxonium ylides bearing electron-donating or -withdrawing groups as well as alkyl sulfoxonium ylides were viable substrates (**Scheme 23**) [91]. Mechanistic studies revealed that the presence of carboxylates generated *in situ* from the substrate under basic conditions was crucial for the ruthenium-catalyzed C-H bond alkylation step, and that electron-rich benzoic acids reacted preferentially.



Scheme 23. Ruthenium-catalyzed tandem annulation/alkylation for the one-pot preparation of 3,4-benzo-2-pyrones. ^aRegioisomeric ratio, only the major isomer is depicted.

2.3. Multiple annulations involving successive C-H bond activation

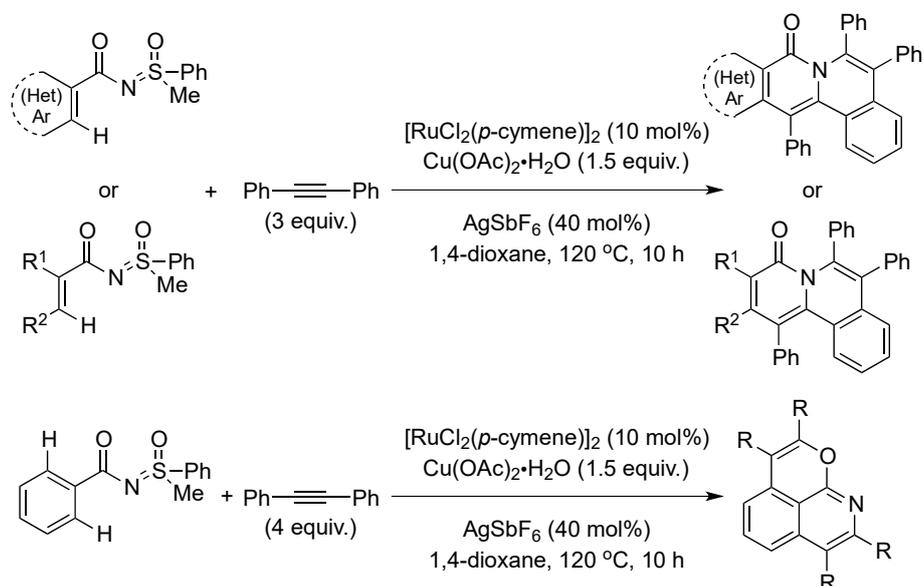
Multiple annulations involving alkynes and aromatic substrates equipped with appropriate directing groups have also been reported. Primary benzamides incorporated two molecules of diphenylacetylene to give tricyclic products. *Para*- and *meta*-substituted benzamides were substrates of choice leading to the expected polycyclic isoquinolones in 36-56% yield, whereas the steric hindrance in *ortho*-substituted ones had a detrimental effect (**Scheme 24**) [92]. The second C-H bond activation took place on the phenyl group introduced in the first oxidative annulation, this domino catalysis required the utilization of internal alkynes bearing at least one phenyl substituent. The same transformation of benzamides with internal alkynes has recently been achieved with a ruthenium-based catalytic system where the redox steps were achieved electrochemically [93]. $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%) was also used as catalyst precursor associated with 1 equivalent of sodium pivalate and ${}^t\text{Bu}_4\text{NClO}_4$ as conducting salt but copper salt was replaced by an undivided cell with a Pt cathode and a reticulated vitreous carbon (RVC) anode with a constant current of 10 mA. In these processes, two successive N-H bond activation took place making the double annulation possible.



Scheme 24. Ruthenium-catalyzed double annulation with alkynes assisted by primary amides.

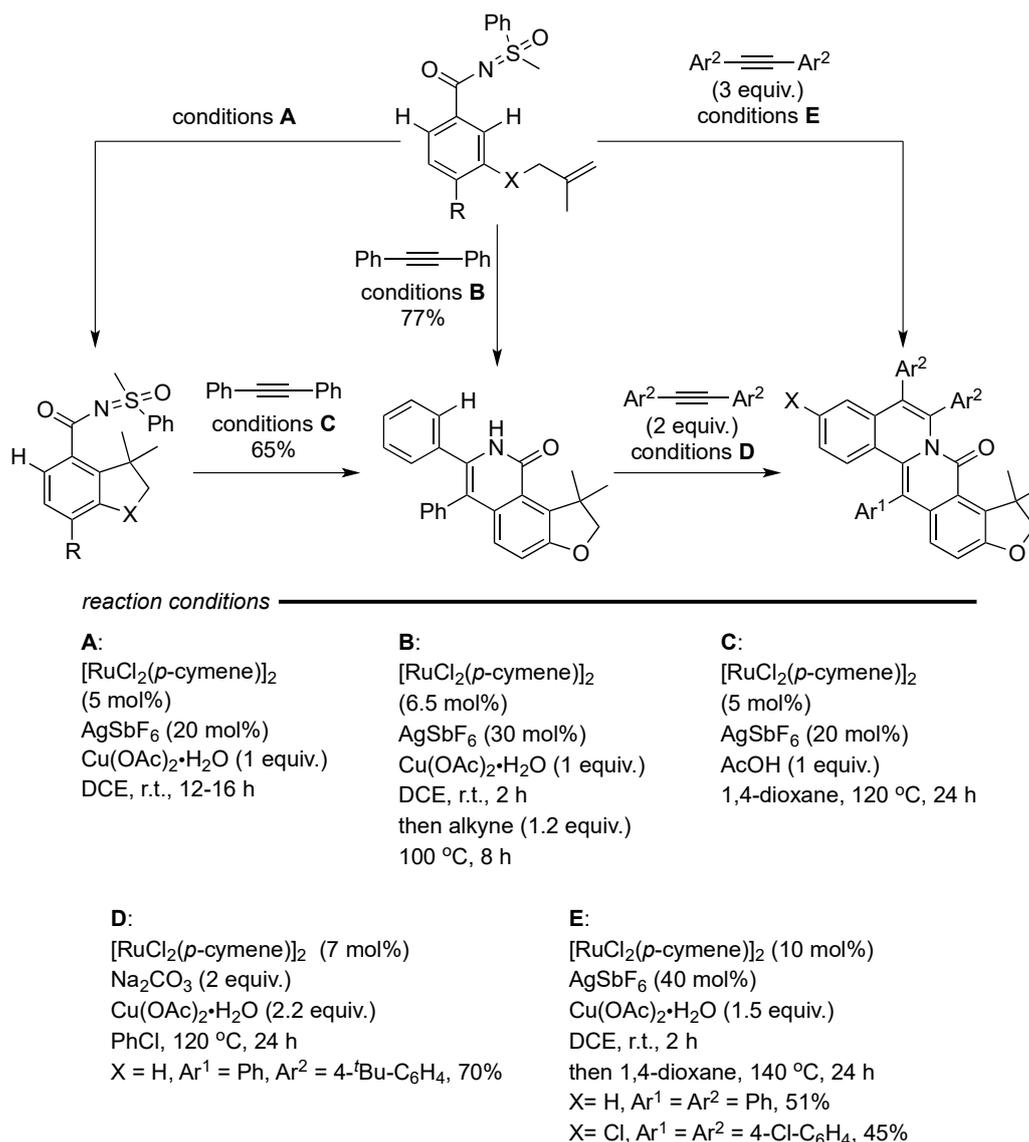
A complementary approach to obtain multiple annulations with alkyne is the utilization of a transformable directing group, which is released in the first step to generate a secondary amide, which then acts as directing group for the second annulation. This strategy has been extensively investigated by the group of Sahoo with ruthenium catalysts, who used methylphenylsulfoximine as directing group of various aryl, heteroaryl and olefinic cores for annulation with internal alkynes [94,95]. The first annulation generated a pyridone motif with elimination of methylphenylsulfoxide, which allowed further annulation with another alkyne molecule. These domino reactions corresponding to the selective formation of two C-C and two C-N bonds were catalyzed by $[\text{RuCl}_2(p\text{-cymene})]_2$ in combination with AgSbF_6 as chloride abstractor and $\text{Cu}(\text{OAc})_2$ as oxidant and source of acetate in 1,4-dioxane at 120 °C, and afforded the corresponding conjugated polycyclic amides in very good yields with a large functional group and substitution position tolerance for both substrates (**Scheme 25**, top). Mechanistic investigations have shown that the mono-annulation could be achieved when the reaction was carried out without copper(II) acetate but in the presence of acetic acid. Then, addition of copper(II) acetate made the second annulation possible, allowing the sequential addition of another type of aromatic or aliphatic alkyne. These transformations with formation of two C-N bonds were possible from initial annulation with a diarylacetylene derivative only. On the other hand, when dialkylacetylene substrates were used, another double annulation took place with formation of one C-N and one C-O bond (**Scheme 25**, bottom) [96]. Following the same strategy as previously described, it was easy to prepare less symmetrical products in a two-step protocol involving first

mono-annulation with a dialkylacetylene in the presence of acetic acid followed by a second C-H bond activation of the isoquinolone and annulation with diverse alkynes in the presence of copper(II) acetate under ruthenium catalysis [96].



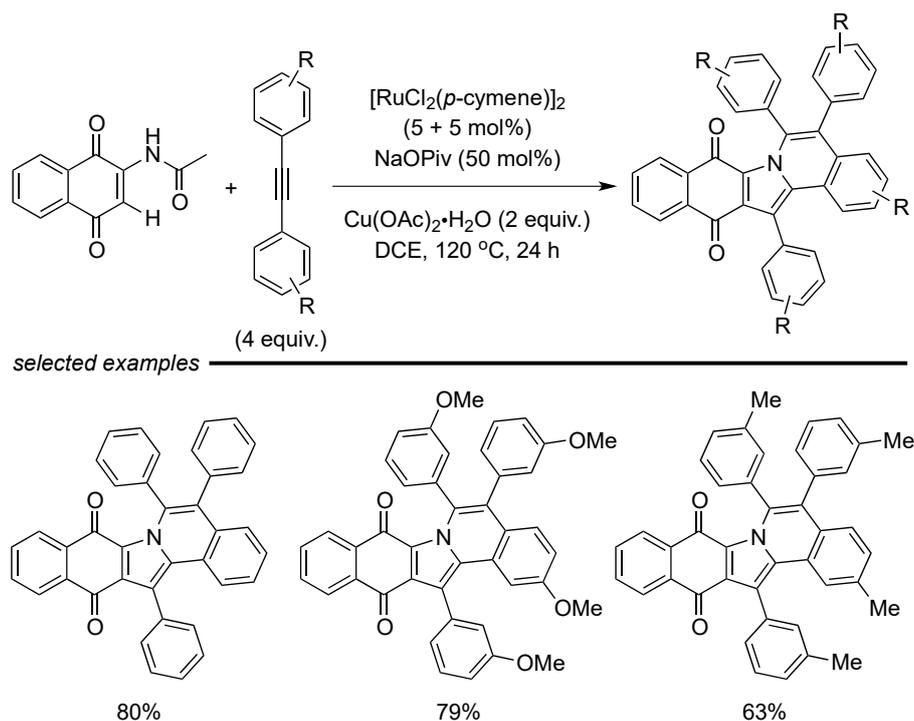
Scheme 25. Ruthenium-catalyzed double annulation domino reactions involving different C-H bond functionalizations.

It was shown in Section 2.1 (**Scheme 2**) that a sequence involving ruthenium-catalyzed C-H bond alkylation followed by annulation with an internal alkyne could be achieved *via* dihydrobenzofuran intermediates from *N*-arylsulfoximine derivatives equipped with a heteroallyl group. The procedure has been improved by performing a one-pot, two-step reaction without isolation of the dihydrobenzofuran intermediate. The first cyclizing alkylation was performed at room temperature and the oxidative annulation with the alkyne was carried out at 120 °C. A third annulation with a second molecule of alkyne to form polycondensed isoquinolones was achieved either in sequential or tandem manner. The important point of the procedure was to first form the dihydrobenzofuran at room temperature and then increase the temperature to make the following annulations possible (**Scheme 26**) [97]. The key points in these transformations were the nature of the directing group, the control of the amount of alkyne and the catalytic system based on $[\text{RuCl}_2(p\text{-cymene})]_2$ in appropriate catalyst loading, in combination with AgSbF_6 as chloride abstractor and Cu(OAc)_2 as oxidant and source of acetates with 1,2-dichloroethane and 1,4-dioxane as solvents of choice.



Scheme 26. Ruthenium-catalyzed multiple annulation reactions involving allylic olefins and alkynes.

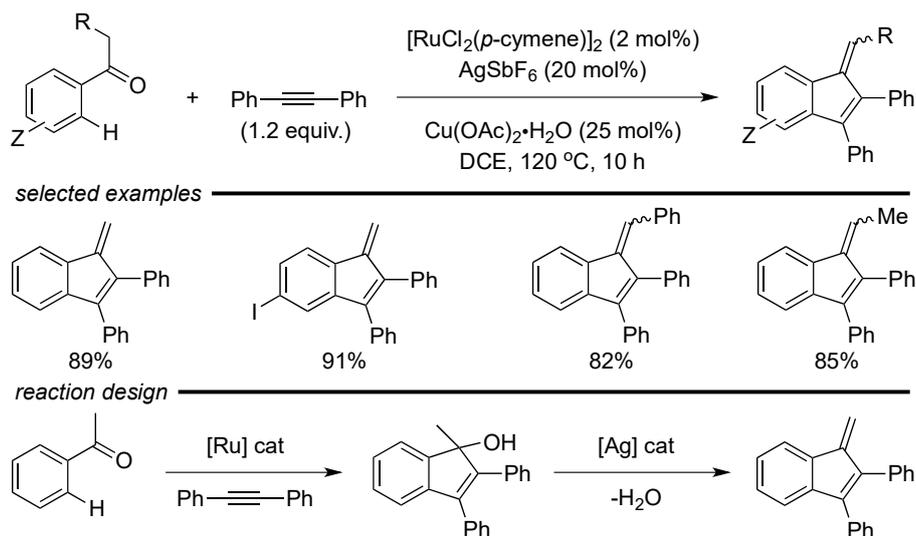
Quinones with extended π -aromatic systems have been prepared by unsymmetrical ruthenium(II)-catalyzed double alkyne annulation starting from 2-acetamido-1,4-naphthoquinone. In the first annulation process, a transient acetylpyrrole was formed. One of the key steps of the tandem sequence is the non-classical removal of the acetyl group, which opens the possibility for a subsequent sequence of C–H/N–H activation leading to the annulation with a second molecule of alkyne. The reaction worked well with electron-rich alkynes bearing methoxy-substituted phenyl groups (**Scheme 27**) but was less efficient with electron-deficient alkynes [98]. The catalyst was generated from [RuCl₂(*p*-cymene)]₂ and sodium pivalate with Cu(OAc)₂ as oxidant, and an experimental protocol with a second addition of the catalyst at half-time was very beneficial to improve the yields of the reaction.



Scheme 27. Ruthenium-catalyzed double annulation reaction between naphthoquinone and symmetrical alkynes.

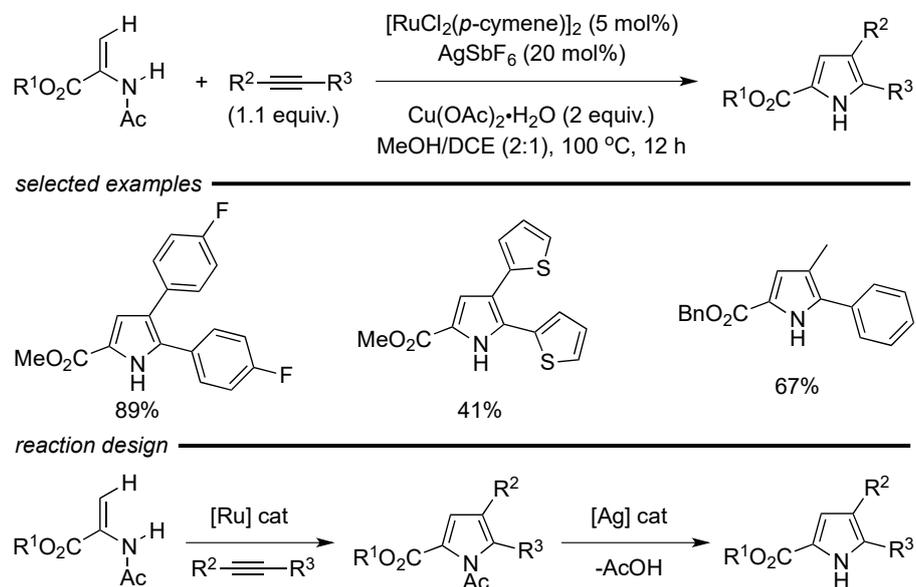
3. Combining ruthenium-catalyzed C-H bond functionalization with other transition metal catalysis.

Merging in a one-pot fashion the ability of ruthenium catalysts for C-H bond functionalization with other metal-catalyzed transformations is highly desirable in view to access molecular diversity in a rapid manner. Unfortunately, the reaction conditions for one step are in general not always compatible with the other one, which makes this approach still challenging. Silver salts, which are typically used as halide scavengers in order to form cationic catalytically active ruthenium species *in situ*, have been serendipitously found to catalyze chemical reactions that were compatible with ruthenium-catalyzed C-H bond functionalization. In this context, Jegamohan and co-workers reported in 2012 a one-pot methodology involving a ruthenium-catalyzed C-H bond functionalization and a silver-catalyzed dehydration [99]. Aromatic ketones reacted with alkynes under ruthenium(II) catalysis conditions leading to indenol derivatives that further underwent dehydration when the loading of AgSbF_6 was raised to 20 mol% affording highly substituted benzofulvene derivatives (**Scheme 28**). In the presence of 8 mol% of AgSbF_6 the reaction stopped before the dehydration process. This finding indirectly shows the two-fold role of silver cations in this tandem multi-catalysis: (1) as halide scavenger for $[\text{RuCl}_2(p\text{-cymene})]_2$ and (2) as catalyst for the dehydration of indenol derivatives into benzofulvene.



Scheme 28. Tandem ruthenium-catalyzed C-H bond cyclization/silver-catalyzed dehydration

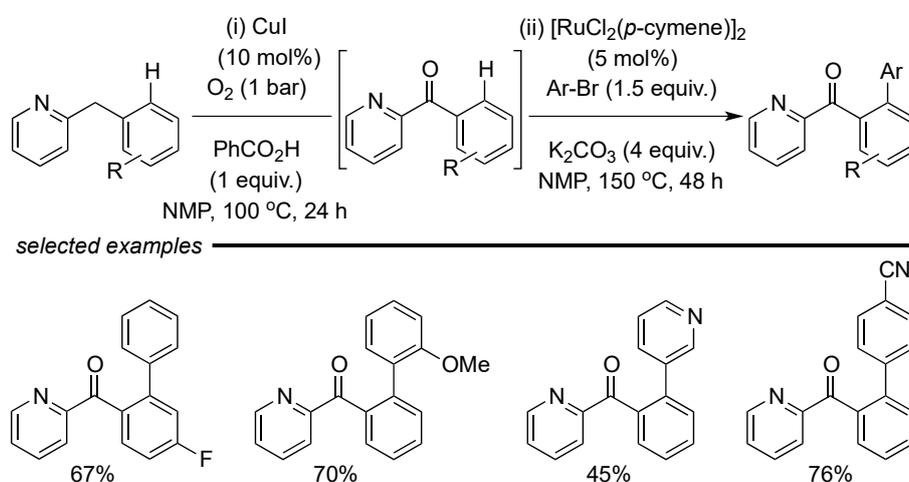
In a similar way, Wang and co-workers reported a tandem ruthenium(II)-catalyzed annulation followed *in situ* by a silver-catalyzed deacetylation [100]. This methodology was applied for the reaction of *N*-acetyl enamides with alkynes to provide 2,3,5-trisubstituted pyrroles in a one-pot fashion (**Scheme 29**). Analogously to the previous example from Jegannathan (**Scheme 28**), control experiments revealed that silver(I) species behaved as the pre-catalyst for the second step and methanol as co-solvent was essential for the efficiency of the catalysis. The reaction exhibited an excellent functional group tolerance including heterocycles. Unsymmetrical alkynes led to pyrroles with the bulkiest substituent in C2 position.



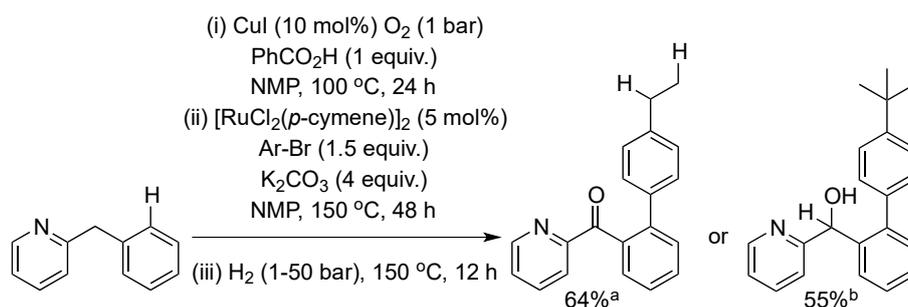
Scheme 29. Tandem ruthenium-catalyzed C-H bond annulation/silver-catalyzed deacetylation

Whereas in the previous cases, the mixed ruthenium/silver catalysis took place in a simultaneous manner, examples with other metal catalysts different from silver have been demonstrated but in a single-vessel stepwise manner. In 2016, our group showed that copper(I) catalysis was compatible with ruthenium(II)-catalyzed C-H bond functionalization [101]. The reagents employed for the benzylic oxidation of 2-benzylpyridine derivatives were compatible with aromatic C-H bond arylation.

After the first step was finished, in the same reaction vessel the reagents for the second step were introduced giving access to arylated 2-benzoylpyridine derivatives (**Scheme 30**). The first step was catalyzed by CuI leading to the formation of 2-benzoylpyridine derivatives, in which the 2-pyridyl-ketone fragment behaved as the directing group for the ruthenium-catalyzed C-H bond functionalization. Importantly, in this case, not only the reagents from the first step did not poison the second step, but they were necessary for the efficiency of the second step. For instance, benzoic acid from the first step served as a source of carboxylate ligands for the next ruthenium(II)-catalyzed C-H bond arylation [102]. In contrast to the hydrogen borrowing approach (see **Schemes 1-3** in Section 1), this methodology enabled the one-pot directing group formation/C-H bond functionalization using a metal different from ruthenium for the first step. Further developments towards oxidation/C-H bond functionalization/hydrogenation were carried out, in which the ruthenium species from the second step were engaged in a hydrogenation step for reducing the ketone from the directing group into an alcohol or for hydrogenating the alkene moiety introduced in the second step into an alkane (**Scheme 31**).



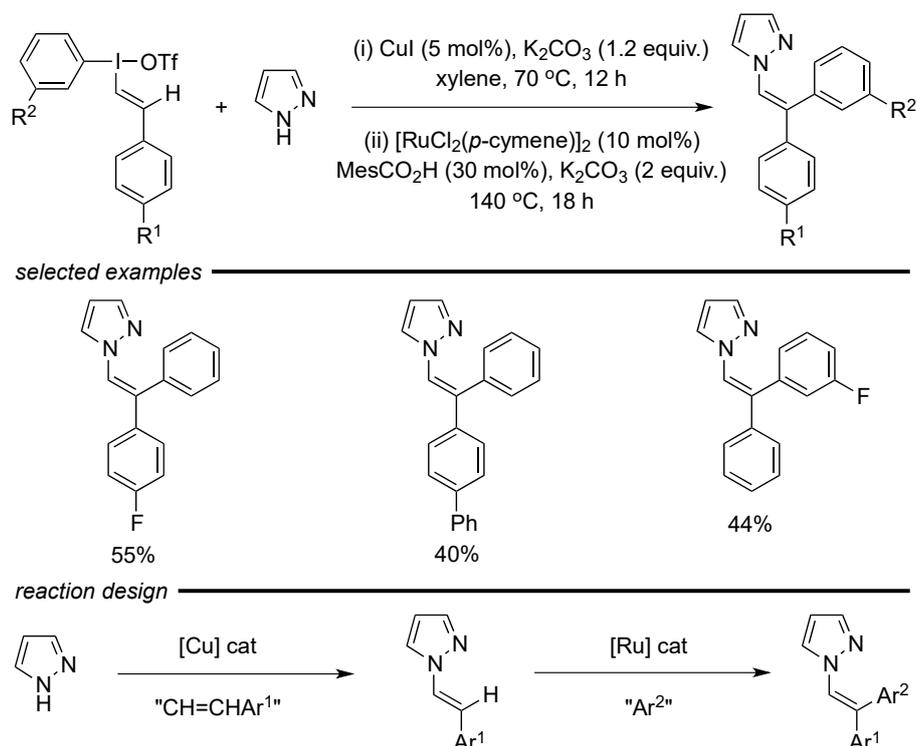
Scheme 30. One-pot copper-catalyzed oxidation (directing group formation)/ruthenium-catalyzed C-H bond arylation.



Scheme 31. One-pot copper-catalyzed oxidation (directing group formation)/ruthenium-catalyzed C-H bond arylation/ruthenium-catalyzed hydrogenation. ^aFrom 4-bromostyrene in (ii) and 1 bar of H₂ in (iii). ^bFrom 1-bromo-4-*tert*-butylbenzene in (ii) and 50 bar of H₂ in (iii).

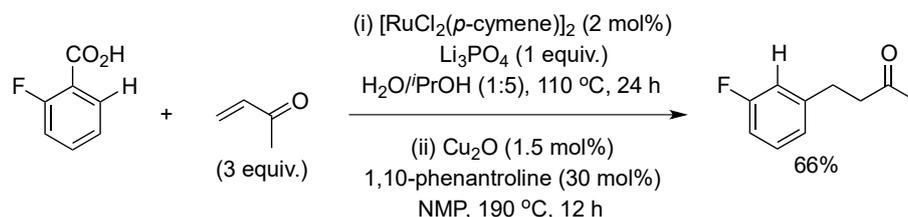
A similar strategy was reported later by Greaney and co-workers combining copper catalysis for installing the directing group (diazole) and ruthenium catalysis for the C-H bond arylation [103]. CuI was a suitable catalyst to form *N*-styryl diazoles whereas [RuCl₂(*p*-cymene)]₂ served as pre-catalyst for the alkenylic C-H bond arylation of the previously introduced styrene fragment (**Scheme 32**). Interestingly, a single coupling partner was introduced for both steps, namely aryl-styryl iodonium

salts. This atom-efficient approach took full advantage of both carbon-containing moieties linked to the iodonium salt coupling partner that were incorporated into the final product.



Scheme 32. One-pot copper-catalyzed *N*-styrylation (directing group formation)/ruthenium-catalyzed C-H bond arylation. MesCO_2H = 2-mesitylenecarboxylic acid.

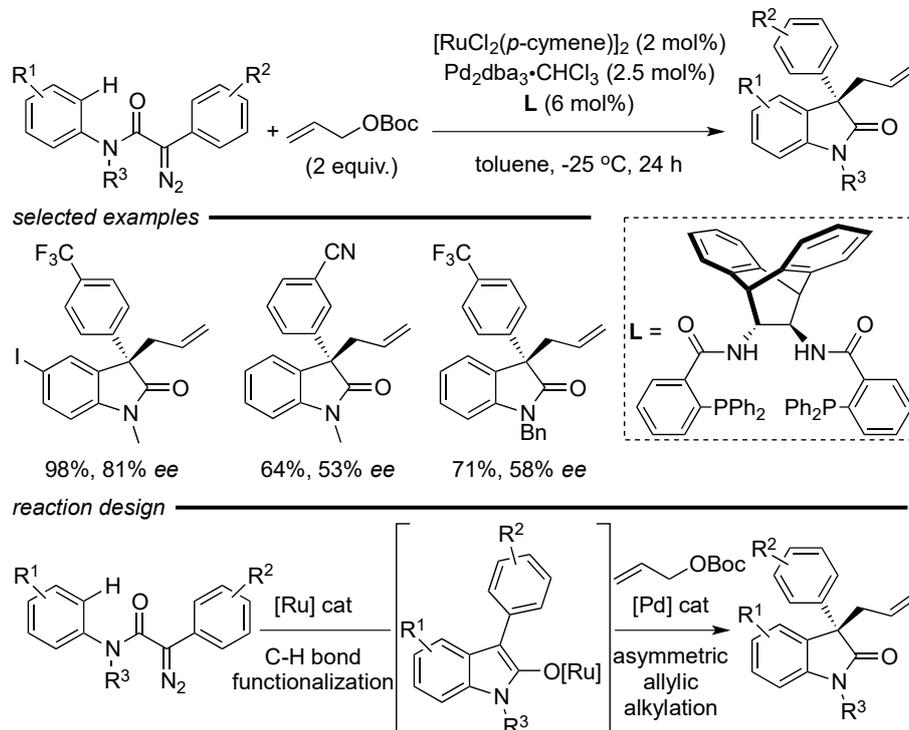
A one-pot ruthenium(II)-catalyzed C-H bond functionalization/copper-catalyzed decarboxylation was reported by Goossen and co-workers in 2018 [68]. This strategy relies on a carboxylate-directed C-H bond alkylation with α,β -unsaturated olefins coupled with a decarboxylation of the substrate by means of copper(I) catalysis (**Scheme 33**). Although only one example was presented, this strategy is appealing for transforming the directing group *in situ* without the undesired requirements for purification/isolation of intermediates.



Scheme 33. One-pot ruthenium(II)-catalyzed C-H bond alkylation/copper-catalyzed decarboxylation.

Lautens group reported what is likely the first example of a ruthenium-catalyzed C-H bond functionalization simultaneously operating with a palladium-catalyzed transformation [104]. This dual catalysis enabled the access to 3-allyl-3-aryl oxindoles starting from aryl α -diazoamide derivatives and allyl *tert*-butyl carbonate as coupling partner (**Scheme 34**). The first catalytic event involved an intramolecular ruthenium-catalyzed C-H bond functionalization using $[\text{RuCl}_2(p\text{-cymene})]_2$ as pre-catalyst followed by an intermolecular palladium-catalyzed allylic alkylation as the second step. Importantly, this last catalytic event was highly enantioselective (up to 85% *ee*) when employing

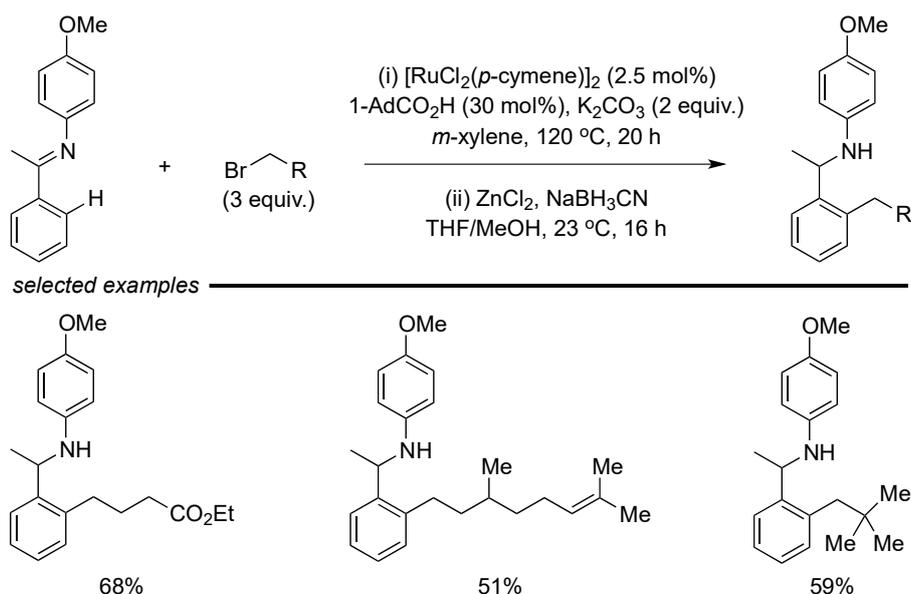
Trost's ligand (**Scheme 34**) and Pd₂dba₃•CHCl₃ as the palladium precursor. The exceedingly mild reaction conditions developed (-25 °C) as well as the choice of the catalytic systems used for each metal were responsible for preventing undesired non-productive reaction pathways.



Scheme 34. One-pot ruthenium(II)-catalyzed C-H bond functionalization/palladium-catalyzed asymmetric allylic alkylation.

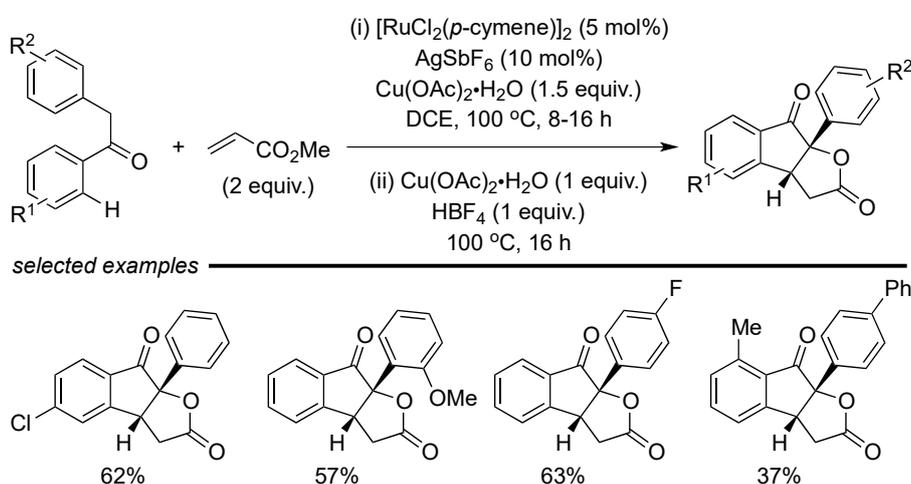
4. Combining ruthenium-catalyzed C-H bond functionalization with transition metal-mediated transformations

Ackermann and co-workers reported a large number of ruthenium-catalyzed C-H bond alkylations of secondary ketimines with alkyl bromides *in situ* followed by zinc-mediated reductions to amines [105,106]. The aromatic C-H bond *ortho*-alkylation took place using carboxylate-ligated ruthenium catalysts and the zinc-mediated reduction occurred in the presence of NaBH₃CN as reducing agent (**Scheme 35**). These examples constitute the first contributions dealing with ruthenium-catalyzed C-H bond functionalizations and *in situ* metal-mediated transformations. Interestingly, the imine moiety behaved as a transformable directing group at the end of the one-pot process. LiAlH₄ as reducing agent for amide directing groups has been used after a ruthenium-catalyzed C-H bond arylation to access benzylic amines, however in a stepwise fashion [107].



Scheme 35. One-pot ruthenium(II)-catalyzed C-H bond alkylation/zinc-mediated reduction. 1-AdCO₂H = 1-Adamantanecarboxylic acid.

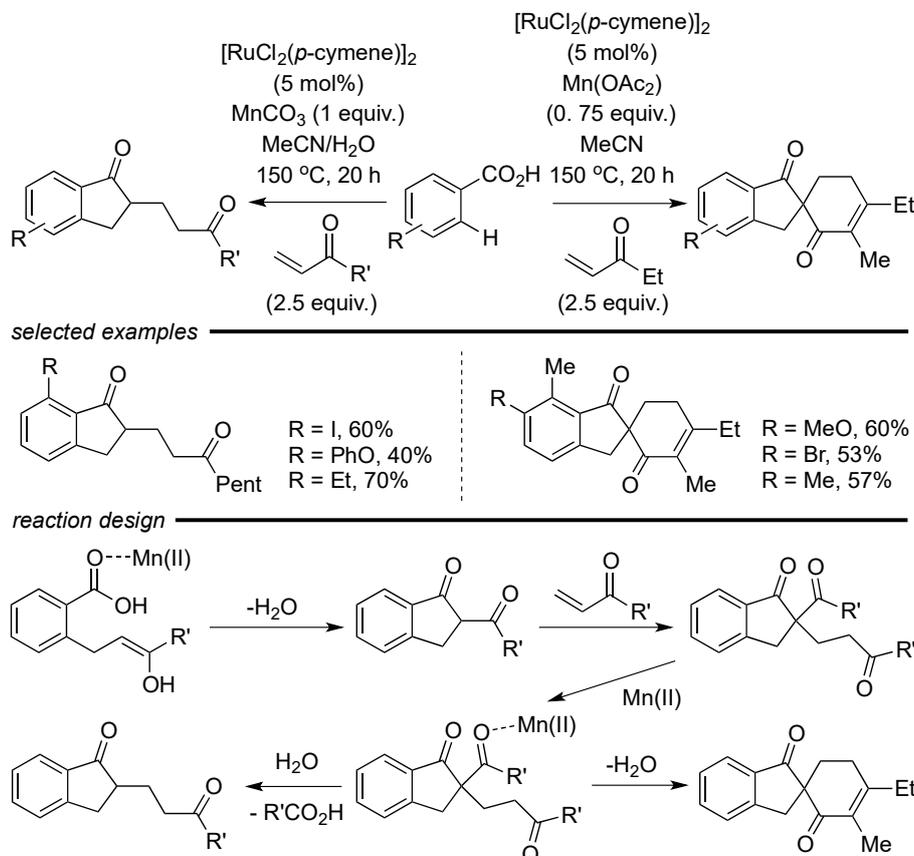
In 2014, Greaney and co-workers found an unexpected yet interesting methodology involving ruthenium-catalyzed C-H bond functionalizations and an *in situ* copper-mediated oxidative oxylation (**Scheme 36**) [108]. In a stepwise fashion, phenyl benzyl ketones reacted with methyl acrylate under ruthenium(II) catalysis followed by copper-mediated intramolecular lactonization in the presence of a Brønsted acid (HBF₄). Excellent diastereoselectivities for the final indenofuranone products were observed, which was likely a consequence of steric factors.



Scheme 36. Tandem ruthenium(II)-catalyzed C-H bond annulation/copper-mediated lactonization.

Examples combining ruthenium-catalyzed C-H bond functionalizations and manganese-mediated cyclizations were reported by Shi and co-workers [109]. Similar to the previous example, benzoic acids were employed as substrates for carboxylate-directed C-H bond alkylations with α,β -unsaturated olefins. However, the presence of manganese(II) salts enabled the intermediate products to undergo a different type of intramolecular cyclization depending on the anion from the manganese(II) salt as well as the structure of the α,β -unsaturated olefin used in the first step (**Scheme 37**). When ethyl vinyl ketone was employed in the presence of Mn(OAc)₂, spiroindanone derivatives were formed as major

products. Alternatively, using MnCO_3 led to 2-substituted 1-indanones. The two possible mechanisms to access different chemoselectivity are highlighted in **Scheme 37**.



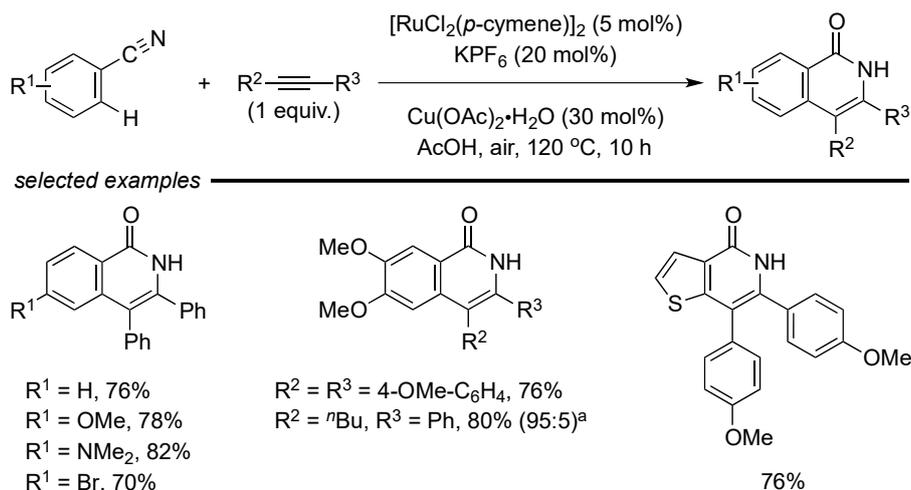
Scheme 37. Tandem ruthenium(II)-catalyzed C-H bond alkylation/manganese-mediated cyclization highlighting the mechanism for the manganese-mediated transformation.

5. Merging ruthenium-catalyzed C-H bond functionalization and organic transformations

This section surveys two types of sequences of one-pot transformations consisting either (1) an organic transformation prior to C-H bond activation, which creates a suitable directing group, or (2) a C-H bond activation/functionalization followed by an organic transformation, which affords functional products *via* directing group modification or intermediate modification.

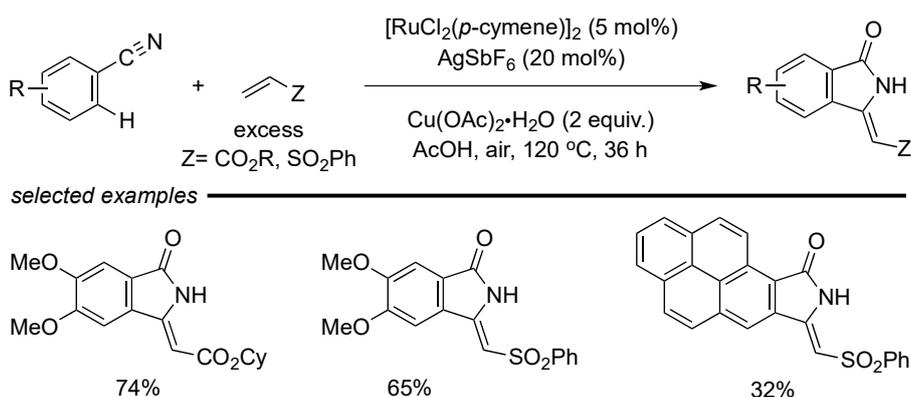
5.1. Directing group formation followed by C-H bond functionalization

The cyano group has been used as directing group but also as masked primary amide for directed C-H bond functionalization. Thus, in acetic acid in the presence of catalytic amounts of copper(II) acetate acting as Lewis acid catalyst, aromatic nitriles were hydrolyzed at 120 °C into primary amides. Then, the ruthenium-catalyzed oxidative annulation with one equivalent of internal alkyne proceeded smoothly under classical conditions to give isoquinolones. Yields above 65% were obtained with a variety of aromatic and heteroaromatic nitriles featuring diverse types of substituents at *para* position or disubstituted at *para* and *meta* positions in this case with high regioselectivity (**Scheme 38**) [110]. Similarly, high regioselectivity in favor of the 3-arylisquinolones (*versus* 4-arylisquinolones) were obtained starting from 1-alkyl-2-arylethynes.



Scheme 38. Hydrolysis of benzonitrile derivatives followed by ruthenium-catalyzed C-H bond functionalization with internal alkynes. ^aRegioisomeric ratio, only the major isomer is depicted.

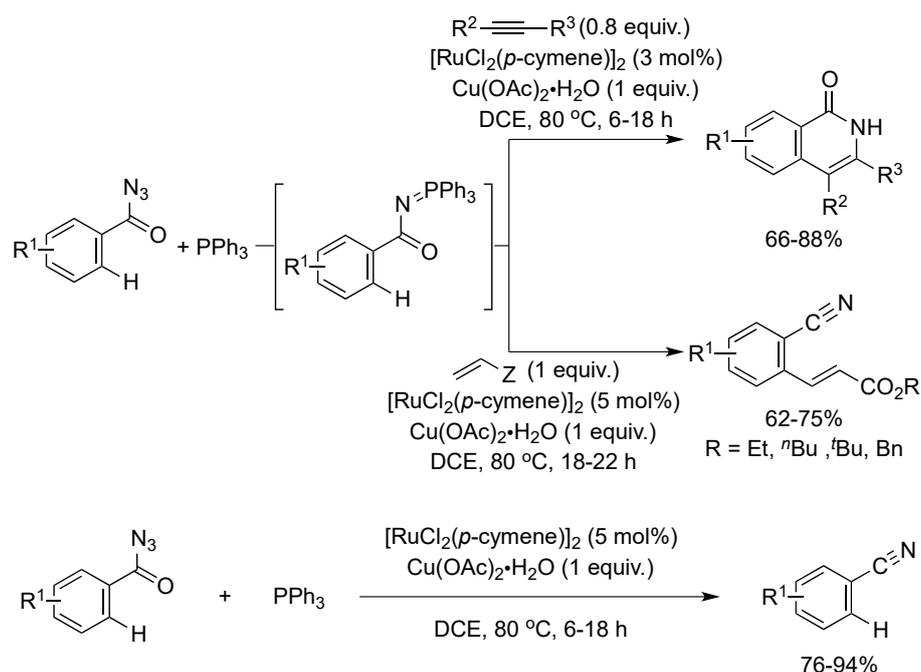
The same strategy has been applied for the *ortho*-functionalization of aromatic nitriles with electron-deficient olefins. Under acetic acid conditions, in the presence of [RuCl₂(*p*-cymene)]₂, AgSbF₆ and Cu(OAc)₂·H₂O, 3-methyleneisoindolidones were obtained with high *Z*-selectivity. This stereoselectivity was attributed to a strong intramolecular hydrogen bonding interaction of the N-H group of the *in situ* generated amide with the carbonyl of the ester or sulfone taking place during the catalytic cycle. It can be noted that the reaction required more drastic conditions than with alkynes: AgSbF₆ instead of KPF₆ and long reaction times (**Scheme 39**) [111]. The aromatic nitriles used with alkynes (**Scheme 38**) were suitable substrates for this cyclizing C-H bond alkenylation transformation. In these two cases, the nitrile was first transformed into an amide, which was then incorporated into the final product as a lactam functionality.



Scheme 39. Hydrolysis of benzonitrile derivatives followed by ruthenium-catalyzed C-H bond functionalization with terminal, electron-deficient olefins.

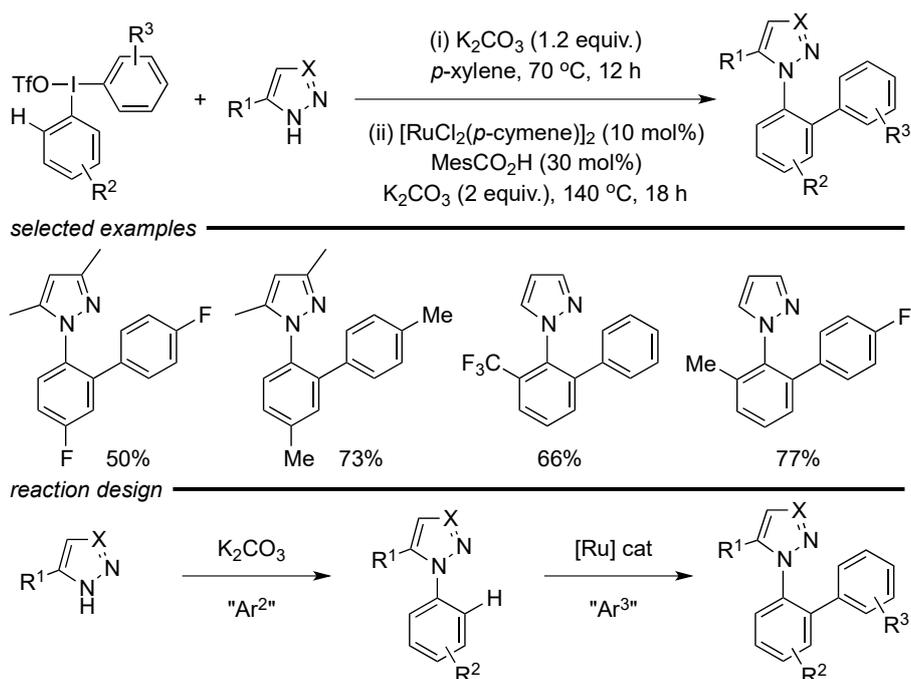
The preparation of isoquinolones (see **Scheme 38**) has recently been investigated using the principle of *in situ* generation of iminophosphoranes as directing group. They were produced upon reaction of triphenylphosphine with aroylazides and were revealed as efficient directing groups for directed *ortho*-C-H bond functionalization. The one-pot condensation with internal alkynes was efficiently achieved in DCE at 80 °C with a catalytic system consisting in 3 mol% of [RuCl₂(*p*-cymene)]₂ and 1 equivalent of Cu(OAc)₂·H₂O. (**Scheme 40**, top) [112]. The annulation reaction appeared to be more selective than

starting directly from benzamides due to inhibition of double annulation process, and a variety of isoquinolones were obtained in 66-88% yields from diversely substituted aroylazides and alkynes. The reaction was also efficient from indole and pyrrole azide substrates. Tentative extension of this strategy based on the utilization of electron-deficient olefins such as acrylates indeed led to *ortho-E*-alkenylated aromatic products but with concomitant transformation of the iminophosphorane into a nitrile group with elimination of triphenylphosphine oxide (**Scheme 40**, middle) [113]. It was shown that in the absence of olefin, this transformation of directing group was catalyzed by a catalytic amount of $[\text{RuCl}_2(p\text{-cymene})]_2$ in the presence of copper(II) acetate at 80 °C in DCE (**Scheme 40**, bottom).



Scheme 40. *In situ* generation of iminophosphorane directing group and its fate in ruthenium-catalyzed C-H bond functionalizations.

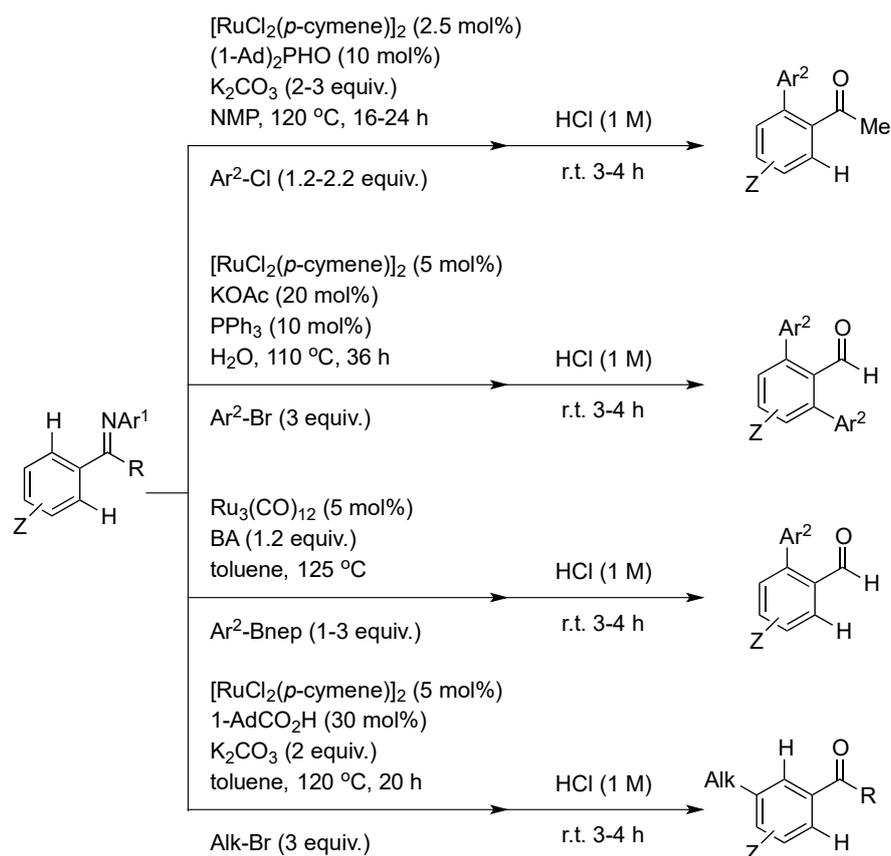
The reaction of diaryliodonium salts with pyrazoles in the presence of a base at 70 °C leads to *N*-arylation of the heterocycle and liberation of an iodoarene. Consequently, a subsequent ruthenium-catalyzed *ortho*-C-H bond arylation directed by the vicinal *N*-pyrazole atom has been disclosed. The best protocol was a one-pot sequential process where the *N*-arylation of pyrazole by diaryliodonium triflate was mediated by K_2CO_3 at 70 °C for 12 h and followed by addition of the ruthenium catalytic system ($[\text{RuCl}_2(p\text{-cymene})]_2$, MesCO_2H and K_2CO_3) for *C*-arylation at 140 °C during 18 h (**Scheme 41**) [103]. The *para*-substituted phenyl substrates gave the best yields (above 70%), and the reaction could be extended to unsymmetrical iodonium salts leading to high selectivity controlled by electronic effect on the two phenyl rings. In some cases, the first step was more efficient in the presence of catalytic amounts of copper in a similar way as it has been described above (**Scheme 32**).



Scheme 41. Base-mediated directing group formation followed by ruthenium-catalyzed aromatic C-H bond arylation with iodonium salts.

5.2. Hydrolysis

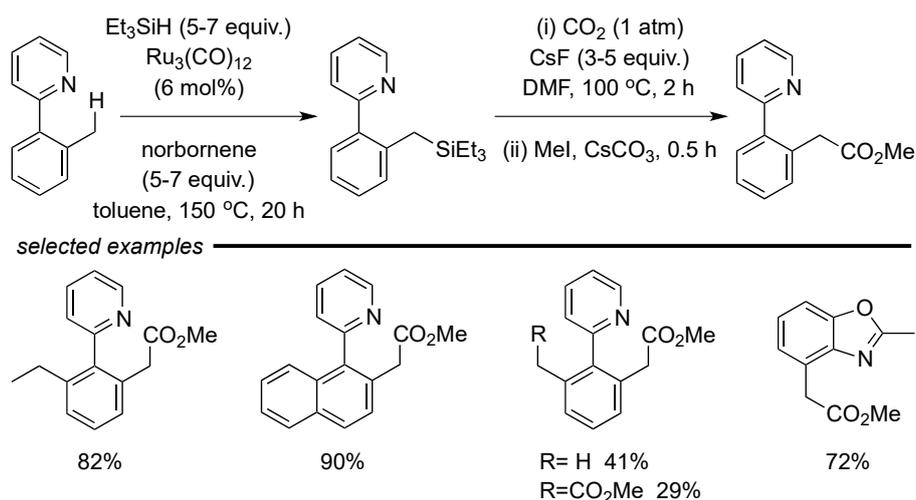
Aldimines and ketimines have been extensively used as efficient directing groups for C-H bond functionalization. They can be used as masked aldehydes and ketones when the catalytic system or the reaction partner does not tolerate these otherwise sensitive carbonyl functionalities. Interestingly, after performing the directed functionalization, a simple treatment under acidic conditions restores the aldehyde or ketone functionality (**Scheme 42**). This is exemplified in the *ortho*-directed mono-C-H bond arylation of ketimines with aryl chlorides catalyzed by $[\text{RuCl}_2(p\text{-cymene})]_2$ with adamantylphosphine oxide as additive [114], or the diarylation of aldimines with aryl bromides in the presence of a catalytic system containing $[\text{RuCl}_2(p\text{-cymene})]_2/\text{KOAc}/\text{PPh}_3$ in a 1:4:2 ratio operating in water [115]. Arylation of aromatic aldimines by arylboronates has been achieved under neutral conditions with $\text{Ru}_3(\text{CO})_{12}$ as pre-catalyst in the presence of benzylidene acetone as hydrogen acceptor followed by hydrolysis with HCl to give biarylaldehydes [116]. Another example is furnished by the *meta*-alkylation of aromatic ketamines by alkyl bromides catalyzed by $[\text{RuCl}_2(p\text{-cymene})]_2$ in combination with 1-adamantylcarboxylic acid and potassium carbonate to give *meta*-decorated acetophenones [117].



Scheme 42. One-pot ruthenium-catalyzed C-H bond functionalization/hydrolysis of imine directing group.

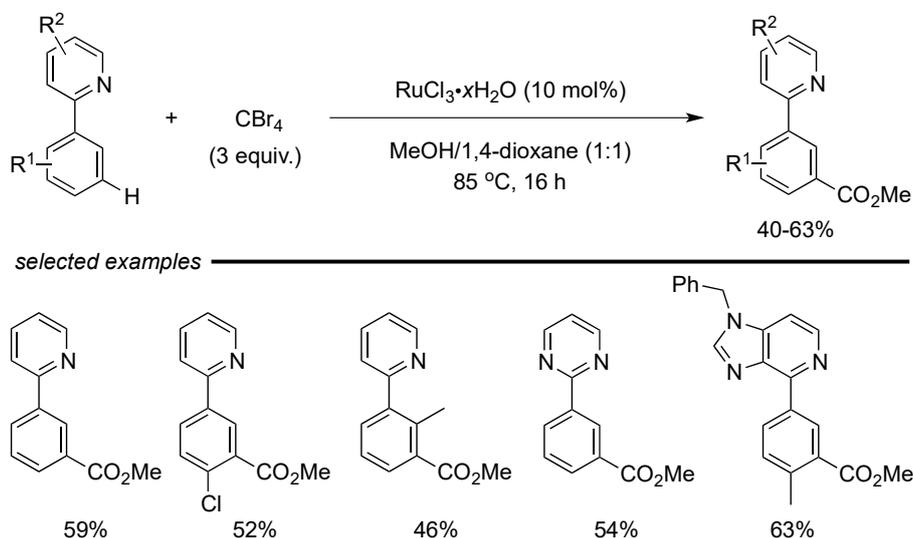
5.3. *In situ* post-functionalization

The nitrogen-directed $\text{sp}^3\text{C-H}$ bond functionalization/silylation of heterocycles such as 8-methylquinolines or 2-*o*-tolylpyridines by triethylsilane catalyzed by the ruthenium(0) complex $\text{Ru}_3(\text{CO})_{12}$ was first carried out at 150 °C in toluene in the presence of norbornene for 20 h. After changing the solvent by evaporation of toluene and addition of DMF, the fluoride-mediated carboxylation under 1 atm of carbon dioxide followed by esterification by methanol in the presence of Cs_2CO_3 afforded the expected esters (**Scheme 43**) [118]. Altogether, this one-pot sequential protocol corresponds to a $\text{sp}^3\text{C-H}$ bond carboxylation. The first step could also be achieved with $[\text{Ir}(\text{cod})\text{Cl}]_2$ under milder conditions in refluxing toluene with an excess of silane limited to only 5 equivalents and in the absence of norbornene.



Scheme 43. One-pot carboxylation of sp³C-H bonds of *N*-heterocycles merging a ruthenium-catalyzed C-H bond functionalization and a fluoride-mediated carboxylation.

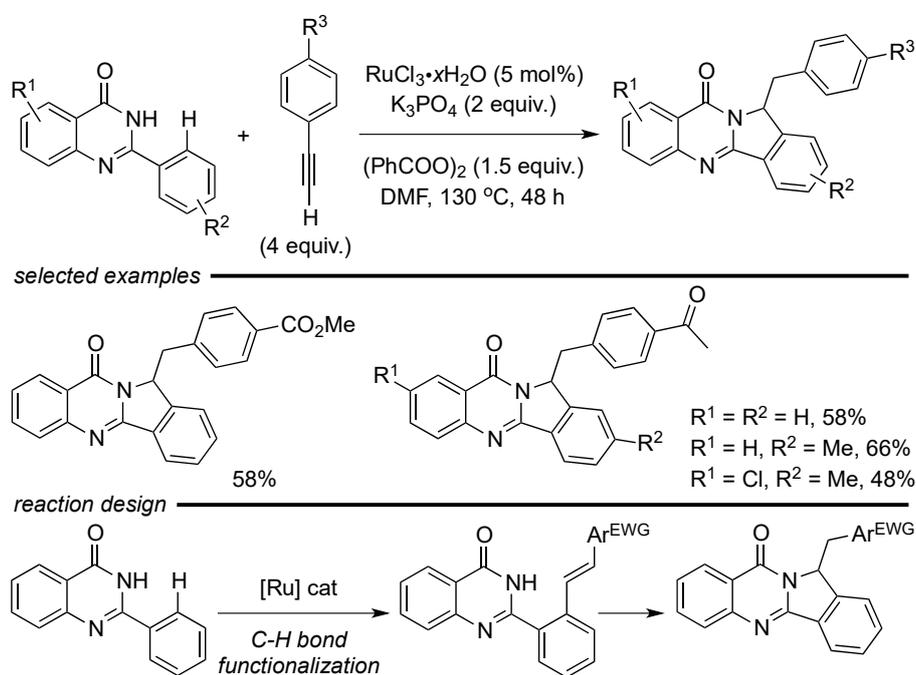
A related carboxylation taking place upon methanolysis of a CBr₃ group has been reported. In this case, the ruthenium-catalyzed reaction was a *meta*-tribromomethylation of 2-phenylpyridine derivatives. The reaction was promoted by RuCl₃·*x*H₂O and proceeded *via* a single electron transfer to generate the CBr₃ radical leading to regioselective functionalization of the phenyl group in *meta*-position after formation of a five-membered ruthenacycle *via* C-H activation at the *ortho*-position. As the solvent contained methanol, the brominated intermediate was not detected due to fast methanolysis into the corresponding carboxylic methyl ester (**Scheme 44**) [119]. Phenyl groups substituted in *para*-position by electron-donating or -withdrawing groups as well as halides provided suitable substrates, and other *N*-heterocycles were also compatible for directing the first cyclometalation step.



Scheme 44. Ruthenium-catalyzed *meta*-C-H bond carboxylation resulting from one-pot tribromomethylation/methanolysis sequence.

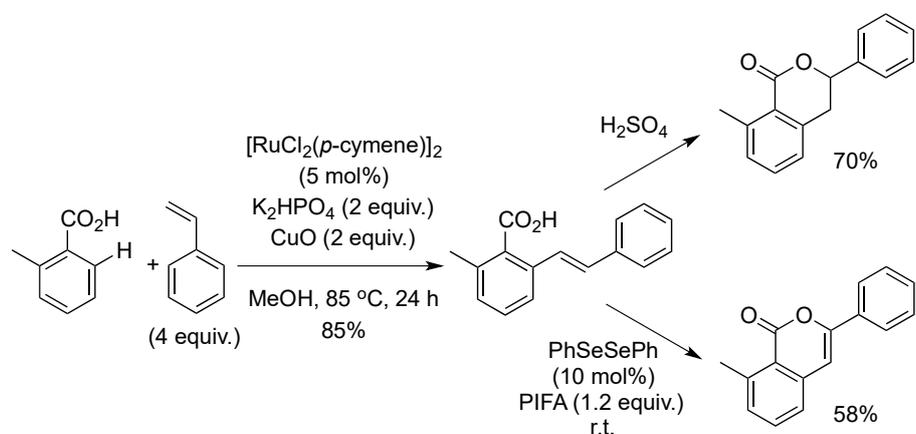
The reaction of 2-arylquinazolin-4(3*H*)-one with terminal arylacetylene in the presence of the ruthenium catalyst RuCl₃·*x*H₂O, K₃PO₄ as a base and dibenzoyl peroxide as an oxidant in NMP at 120 °C led to the regioselective *mono*- or *ortho*-C-H bond alkenylation of the aryl group of the quinazolinone moiety depending on the substitution pattern of this phenyl group [120]. A further

intramolecular hydroamidation of the newly formed carbon-carbon bond with formation of a fused five-membered ring was possible at higher temperature (130 °C) and longer reaction time when the arylacetylene substrate was substituted by an electron-withdrawing group such as a ketone or an ester group (Scheme 45) [120].



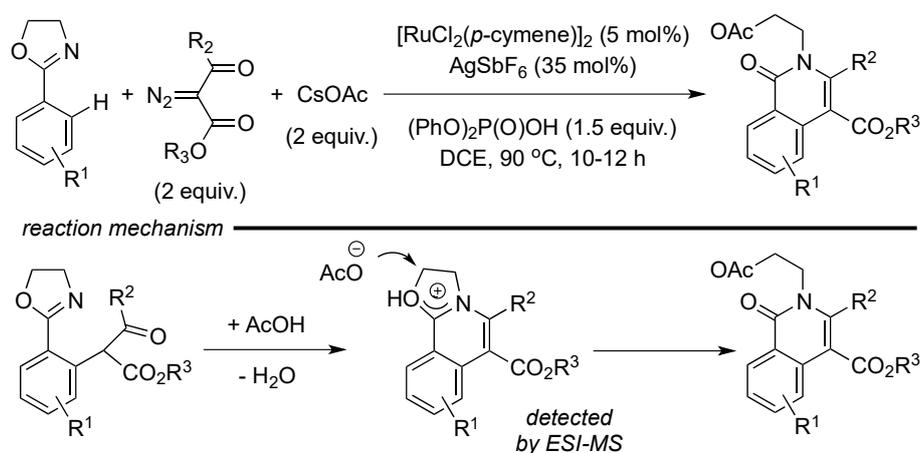
Scheme 45. Ruthenium-catalyzed one-pot C-H bond alkenylation/hydroamidation from terminal alkynes and 2-arylquinazolinones.

2-Styrylbenzoic acids have been produced from aryl carboxylic acids and styrene under Ru(II) catalysis conditions. In a sequential procedure, involving elimination of methanol used in the catalytic step without purification of the product and addition of the appropriate reagent, isochromanone and isocoumarin resulting from cyclization were obtained in good yields. Thus, after production of the stilbene arising from *o*-toluic acid and styrene in 85% yield, treatment with sulfuric acid for 5 min gave the saturated isochromanone in 70% yield, and reaction with bis(trifluoroacetoxy)iodobenzene (PIFA) in the presence of a catalytic amount of diphenyl diselenide in acetonitrile for 1 h afforded the isocoumarin in 58% yield (Scheme 46) [121].



Scheme 46. Sequential ruthenium-catalyzed C-H bond alkenylation/cyclization of benzoic acids and styrene derivatives.

Finally, the synthesis of isoquinolinones arising from a three-component cascade cyclization involving a 2-aryloxazoline, 2-diazo-3-oxobutanoate and cesium acetate represents an excellent example of cascade transformation including a C-H bond activation promoted by a ruthenium catalyst. It has been shown that the catalytic cycle started with the C-H bond activation followed by carbene migratory insertion. Cyclization resulting from nucleophilic attack of the nitrogen onto the ketonic group of the diazo substrate and then oxazoline ring opening led to the final isoquinolinone (**Scheme 47**) [122]. A large scope of products were thus produced in good yields from *ortho*, *meta*- and *para*-substituted phenyloxazolines ($R^1 = \text{Me, OMe, } i\text{Pr, Br, F, CF}_3, \text{CN, NO}_2$) and diverse diazoketoesters with $R^2 = \text{Me, Et, } n\text{Pr, } p\text{-methoxyphenyl}$, and $R^3 = \text{Me, Et}$.



Scheme 47. One-pot three-component cascade formation of isoquinolinones by means of ruthenium catalysis involving one C-H bond functionalization.

Conclusion

It is obvious that the last decades have witnessed the power of ruthenium complexes to behave as excellent catalysts far beyond C-H bond functionalization. In this review, we have summarized key successes for ruthenium-catalyzed C-H bond functionalizations compatible with other transformations in a one-pot fashion or in a sequential manner without the requirements for purification/isolation of intermediates. As such, a high degree of molecular complexity has been achieved with more sustainable approaches. In particular, the fact that ruthenium-catalyzed C-H bond functionalizations are compatible with isomerizations, oxidations, hydrogenations, hydroaminations, annulations, cross-coupling reactions and uncatalyzed organic transformations should still lead to fast and improved methodologies for the future synthesis of fine chemicals. Most of the examples surveyed are based on the readily available $[\text{RuCl}_2(p\text{-cymene})]_2$ dimer as the *golden* pre-catalyst for the C-H bond functionalization that occurs before or after another chemical transformation. The fact that this metal complex is rather stable in the presence of air, moisture and other chemicals could explain its high compatibility with other transformations. Unfortunately, the loading of the ruthenium catalyst in the reviewed reactions is high, typically in the range of 2-10 mol%. For sustainability purposes it would be highly desirable to find systems enabling these transformations at ppm (or ppb!) levels as it has been shown with other types of transition-metal catalysts, or to recover the ruthenium catalyst at the end of the reactions. For that, the use of unconventional media or techniques such as nanoparticles,

micelles, sonochemistry (ultrasounds, microwaves), mechanochemistry (ball milling, magnetic filtration/recovery) or flow chemistry could be interesting directions to explore.

The examples herein reviewed rely mainly on ruthenium-catalyzed C-H bond functionalization steps with *ortho* selectivity in the arene rings, however, given the current interest in the design of directing group enabling distal (*meta* or *para*) C-H bond functionalization [123-127], novel methodologies following one-pot or tandem transformations are expected in the near future. To our knowledge, merging ruthenium-catalyzed C-H bond functionalization with organocatalytic or enzymatic transformations has not met success yet [128]. Besides the fact that important attention needs to be paid for the careful design of reaction conditions, one could expect that ruthenium-catalyzed C-H bond functionalizations might reach a level of reaction compatibility analogous to that found nowadays for ruthenium-catalyzed olefin metathesis, which is well-implemented in one-pot multiple transformations (with other olefin metathesis, hydrogenation, isomerization sequences) [129-132], and thus still enlarge the scope of applications of ruthenium catalysts. For environmental reasons, one-pot or tandem transformations with more benign and available first row transition metal catalysts such as those derived from Co, Ni, Fe and others, which have already shown remarkable reactivities in the functionalization of C-H bonds, might be an interesting research direction to follow in the coming years.

Acknowledgements

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