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Ruthenium(II)-Catalysed Functionalisation of C–H Bonds with Alkenes: Alkenylation versus Alkylation

Christian Bruneau and Pierre H. Dixneuf

Dedicated to the memory of Guy Lavigne

Abstract This chapter describes the recent achievements since 2011 of ruthenium(II)-catalysed transformations of sp^2C–H bonds of a variety of functional arenes, heterocycles, alkenes and ferrocene derivatives on their reaction with alkenes, either via oxidative dehydrogenation to produce functional alkenes or via formal insertion of alkene into C–H bonds to afford alkylated products. The regioselectivity of *ortho* C–H bond alkenylation or alkylation is shown to be directed by both strongly and weakly coordinating functional groups from N-heterocycles and bidentate groups to carbonyl-containing groups such as ketone, ester, amide, carbamate and sulfonic acid derivatives. The ruthenium(II) catalysts often based on $[RuCl_2(p\text{-cymene})]_2$ or $RuCl_2(PPh_3)_3$ derivatives sometimes require the presence of a halide abstractor and an oxidant. The alkenylation of heterocycles will be shown to occur in the presence of base and their alkylation in the presence of proton source to give branched or linear alkylated isomers. Discussion of catalytic mechanism will involve the initial formation of a cyclometallate via C–H bond deprotonation and that of an intermediate resulting from alkene insertion into the Ru–C bond before its evolution to alkenylation or alkylation.

Keywords Alkenylation · Alkylation · Alkene hydroarylation · C–C bond cross coupling · Directing groups · Ruthenium(II) catalysis · sp^2C–H bond activation

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1 Introduction

Metal-catalysed regioselective functionalisation of C–H bonds for the cross-coupling formation of C–C and C–heteroatom bonds has brought a revolution in synthetic methods, by providing atom- and step-economical processes, for the production of complex pharmaceutical molecules, industrial intermediates or molecular materials [1–8].

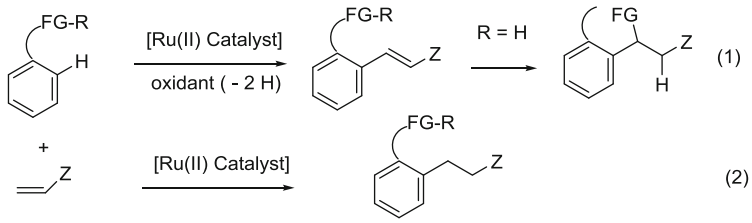
Besides successful C–C bond cross couplings from sp^2C–H bonds promoted by palladium [7, 9–14] and rhodium [14–20] catalysts, the Murai group since 1993 has shown that lower-cost ruthenium(0) catalysts offer the direct access to functional arenes, heterocycles and alkenes, via initial directed ruthenium(0) insertion into the sp^2C–H bond [21–26].

More recently, stable ruthenium(II) catalysts have been shown to promote the directed sp^2C–H bond activation and functionalisation, initiated by the pioneer work since 2001 of Oi and Inoue [27, 28]. Some applications, even in water as solvent, have been presented in several reviews especially for arylations and heteroarylations of (hetero)aromatic compounds [29–35]. It was actually shown that the ruthenium(II) activation of arene sp^2C–H bond is *ortho*-directed by the functional group and easily takes place at room temperature via C–H bond deprotonation by cooperative action of the Ru(II) site and carbonate [36] or external carboxylate [37, 38], initially leading to a cyclometallated intermediate on coordination of the functional group and C–Ru bond formation.

The easy ruthenium(II) activation of C–H bond by carboxylate deprotonation has been applied to the oxidative dehydrogenation of two sp^2C–H bonds as an alternative route to polyfunctional alkenes, by cross coupling of a (hetero)arene and an alkene, a reaction which was previously discovered using Pd(II) catalysts and oxidant by Moritani and Fujiwara [1, 39, 40]. A general method of ruthenium(II)-catalysed alkenylation of arene and heterocycle directly on reaction with alkenes was demonstrated only recently in 2011. First, Satoh and Miura showed the alkenylation of heteroarylcarboxylic acids [41], Ackermann alkenylated

arylcarboxylic acids in water, [42] Bruneau and Dixneuf performed the alkenylation of heteroaryl arenes with catalytic amount of Cu(II) [43] and Jeganmohan demonstrated that ketone could direct alkenylation [44].

Since 2011, many applications of this Ru(II)-catalysed *alkenylation* reaction have shown that a variety of weakly bonding functional groups (FG) could direct this *ortho* C–H bond functionalisation with alkenes of arene and heterocycle derivatives, thus offering a low-cost, general route to multifunctional alkenes, some of them were profitably used for sequential oxa- or aza-Michael addition (Eq. 1).



More importantly, the Ru(II)-catalysed reaction of functional (hetero)arenes with alkenes can also lead to the formal *alkylation* at the *ortho*-position of the functional directing group. It was first observed for the hydroarylation of ethylene with Ru(II) catalyst by Gunnoe et al. [45]. This Ru(II)-catalysed alkylation corresponds to the formal insertion of the alkene into the *ortho* C–H bond (Eq. 2) as it was previously observed to be the main product in the Murai reaction but with Ru(0) catalyst [21, 23]. Thus, it becomes crucial to understand how to orientate the reaction of alkenes with (hetero)arenes towards alkylation or alkenylation with ruthenium(II) catalytic systems and explore the role of additional oxidant. Only a few examples of ruthenium(II)-catalysed alkenylations have appeared in recent reviews [32, 46–49].

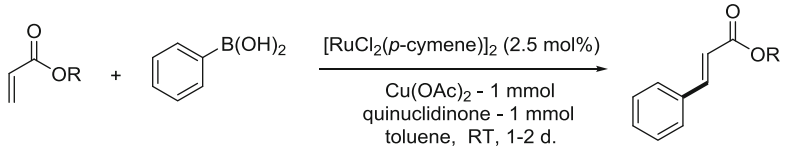
The objective of this chapter is to show the regioselective *alkenylation or alkylation*, on reaction with alkenes of functional arenes, heteroarenes and alkenes promoted by simple ruthenium(II) catalysts, as new routes to promote sp^2C–H bond activation for C–C cross coupling. This chapter will cover the literature since the first direct alkenylations in 2011 till the end of 2014 even if a few 2015 crucial reports will be cited. This chapter will provide opportunities to discuss the ruthenium(II) sp^2C–H bond activation mechanism leading to cyclometallate intermediates and their further functionalisation of the (C–H) carbon leading to C–C cross couplings.

2 Ruthenium(II)-Catalysed Alkenylation of sp^2C–H Bonds with Alkenylboronic Acids

Ruthenium-catalysed alkenylation of sp^2C–H bonds directly with alkenes has been initially performed by the Murai group mostly using ruthenium(0) catalyst precursors such as $RuH_2(CO)(PPh_3)_3$ or $Ru_3(CO)_{12}$ [21–26]. However, it was often in competition with preferential alkylation by formal insertion of alkene into the same *ortho* C–H bond [26, 50–52] as also shown by Genet with $[RuCl_2(p\text{-cymene})]_2$/$MO_2CH$ catalyst [53, 54]. It is noteworthy that Chatani and Kakiuchi have recently succeeded to perform *ortho*-alkenylation of arenes, linked to a variety of heterocycles as directing groups, with another Ru(0) species Ru(COD)(COT), and this catalyst allows alkenylation with functional alkenes such as alkenyl esters [55] and alkenyl carbonates [56].

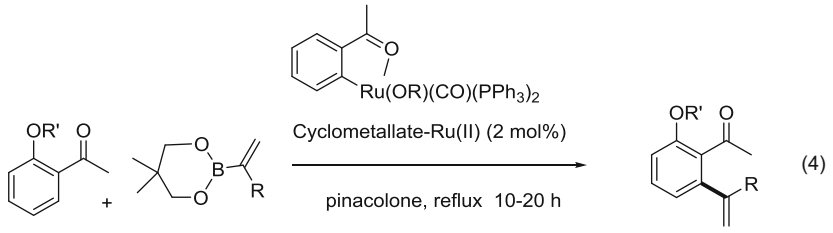
Ruthenium-catalysed regioselective alkenylations of aromatic sp^2C–H bonds have been easily performed first with alkenylboron derivatives and since 2011 more generally simply by oxidative dehydrogenation with alkenes with ruthenium(II) catalysts. These two approaches will be successively presented.

Alkenylarenes have been produced by reaction of arylboronic acids with alkenes in the presence of ruthenium(II) catalysts with a Cu(II) oxidant by Brown [57, 58] (Eq. 3). This reaction corresponds to the functionalisation of alkene C–H bonds, and by contrast to palladium catalysts, it tolerates arene carbon–halide bonds.



(3)

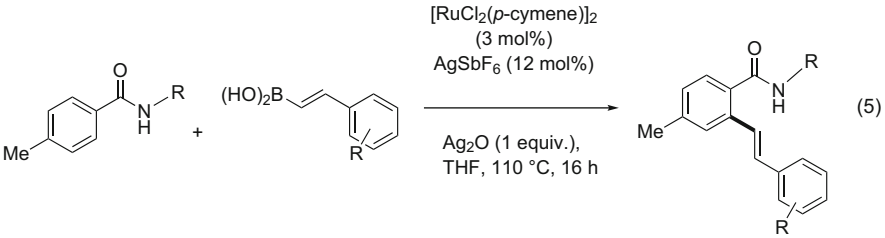
Chatani and Kakiuchi have demonstrated that a ruthenium(II) cyclometallate catalysed the selective monoalkenylation of aromatic ketones, containing a tolerated ether group, at the *ortho* C–H bond of the ketone group. A related cyclometallate was demonstrated to be formed on reaction of the ketone with the Ru(0) species arising from $RuH_2(CO)(PPh_3)_3$ (Eq. 4) [59].



(4)

Recently, Jeganmohan has developed the *ortho*-alkenylation of *N*-alkylbenzamides with alkenylboronic acids in the presence of a simple $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ catalytic system, with 1 equiv. of Ag_2O in THF. The reaction leads, via a

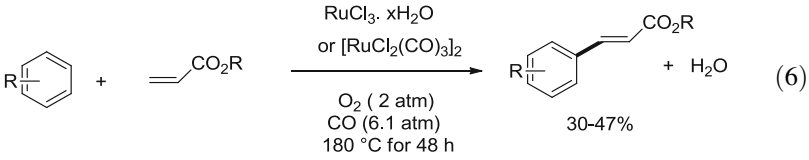
five-membered Ru(II) cyclometallate, to the clean functionalisation of *ortho* C–H bond via C–C bond cross coupling (Eq. 5) [60]. Ag_2O accelerates the transmetallation of the alkenyl group from boron to the ruthenium(II) centre.



3 Alkenylation of sp^2C–H Bonds with Alkenes and Ruthenium(II) Catalysts

The synthesis of functional olefins has made a tremendous improvement with the discovery of the Mizoroki–Heck reaction by combination of an alkene with an aromatic halide, catalysed by palladium(0) catalysts [61]. The Fujiwara–Moritani alkenylation has made another decisive step for the formation of Heck-type products, but via the cross oxidative dehydrogenation of alkene and (hetero)aromatic C–H bonds, catalysed by palladium(II) catalysts in the presence of an oxidant [39]. These discoveries have motivated the search for simple and cheaper catalysts based on ruthenium(II) precursors for the dehydrogenative coupling of an alkene with arene or heterocycle sp^2C–H bonds.

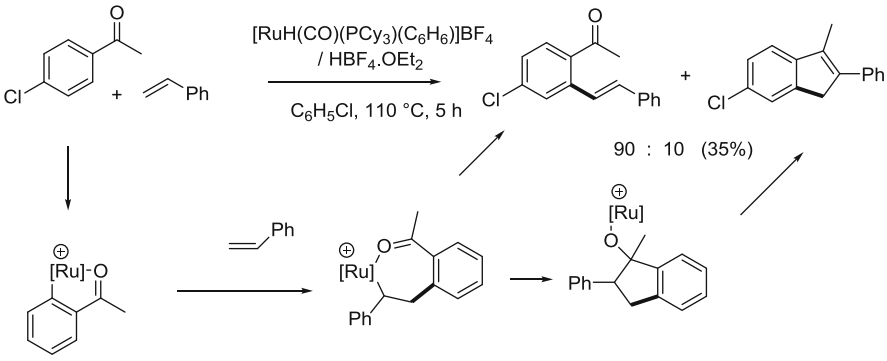
The first example of alkenylation of an arene with ruthenium (II or III) catalysts was actually presented by Milstein in 2001 [62], for the oxidative coupling of acrylate with an arene without directing group. The reaction was catalysed by either $RuCl_3.xH_2O$, $[RuCl_2(CO)_3]_2$ or $[RuCl_2(C_6H_6)]_2$ but under weak pressure of carbon monoxide and using oxygen as the only oxidant. Ruthenium(0) catalyst such as $Ru_3(CO)_{12}$ was less efficient (Eq. 6).



Then the cross coupling of two sp^2C–H bonds between an alkene and an arene has been achieved first by Yi in 2009 using of Ru(II) hydride precursor and recently since 2011 by a variety of groups using the simple $[RuCl_2(p\text{-cymene})]_2$ catalyst precursor with an oxidant. These two processes will be successively presented.

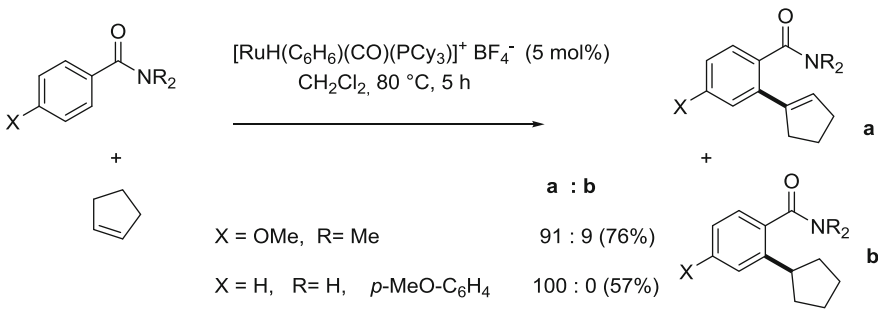
3.1 Ruthenium Hydride-Catalysed Alkenylation of Arenes with Functional Alkenes

Chae S. Yi has shown that the ruthenium(II) hydride catalyst [RuH(CO)(PCy_3)(C_6H_6)][BF_4] in the presence of a strong acid $HBF_4.OEt_2$ could perform the alkenylation at the *ortho*-position of an aromatic ketone or amide with a rather good selectivity. He first succeeded the alkenylation with styrene of an aromatic ketone at the *ortho* C–H bond [63]. The directed activation of the *ortho* C–H bond is demonstrated by the alkenylation of the naphthylketone. The reaction is believed to generate a metallacycle which inserts the alkene and leads either to the alkenylated ketone by β-elimination or to indene after carbonyl insertion into the Ru–C bond (Eq. 7) [63].



(7)

Chae S. Yi also explored, in the presence of the same [RuH(CO)(PCy_3)(C_6H_6)][BF_4] catalyst, the reaction of arylamides with cyclic and disubstituted alkenes under mild conditions. Cyclopentene and cycloheptene led to the preferential alkenylation at the *ortho*-position of the $CONR_2$ or CONHR directing group, with a small amount of the alkylated product corresponding to the formal alkene insertion into the *ortho* C–H bond (Eq. 8) [64]. The alkenylation product may arise from the initial formation of a cyclometallate by *ortho* C–H bond cleavage as for acetophenone, followed by alkene double bond insertion into Ru–C bond followed by β-elimination.



(8)

The same catalyst also promotes the reaction of arylamides with 1,1-disubstituted terminal alkenes to preferentially afford the *ortho*-alkylated products at the expenses of the *ortho*-alkenylated arylamides [64].

3.2 *Dehydrogenative Alkenylation of Arenes with Ruthenium(II) Catalysts According to Directing Groups*

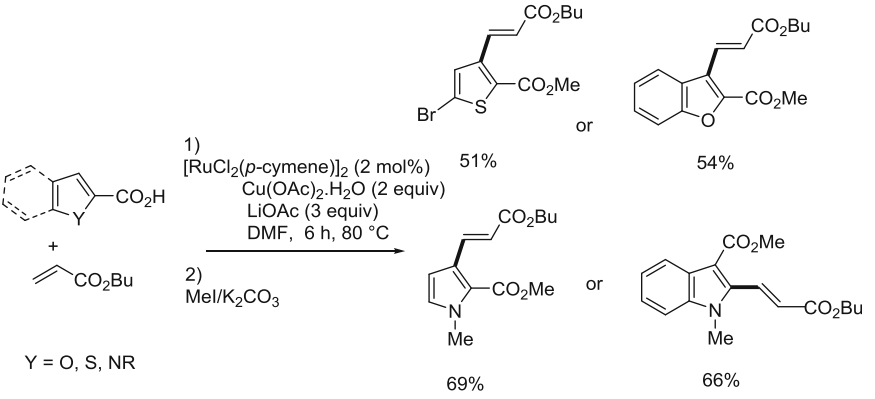
The high potential of the dehydrogenative cross coupling of alkenes with (hetero) aromatic C–H bonds has initiated efforts to open synthetic routes to multifunctional alkenes using stable and low-cost catalysts. The understanding of the mechanism of activation of sp^2C–H bond with ruthenium(II) catalysts [37, 38], via C–H bond deprotonation with the help of carbonate or especially carboxylates, which can take place at room temperature has attracted interest to attempt further oxidative couplings with alkenes. Whereas the first attempts of ruthenium(II)-catalysed reactions of ethylene with arenes have led to hydroarylation of ethylene, e.g. the alkylation of benzene with ethylene [45], alkenylations with functional olefins of arenes and heteroarenes with ruthenium(II) catalysts but in the presence of an oxidant have emerged since 2011 and were shown to be regioselectively directed by a variety of functional groups including weakly coordinating ones.

The first examples of ruthenium(II)-catalysed alkenylation with alkenes were shown within a few months of 2011 first by Satoh and Miura with (hetero)aromatic carboxylic acids [41], then by Ackermann who could perform successive alkenylation of carboxylic acids and oxa-Michael reaction in water [42], then Bruneau and Dixneuf who used nitrogen-containing heterocycle groups to direct alkenylation with catalytic amount of Cu(II) in air [43] and Jeganmohan who showed that a simple weakly bonding ketone could direct the activation/alkenylation at *ortho*-position [44]. Since 2012, a general method of ruthenium(II)-catalysed alkenylation has been developed, via ruthenium(II)-catalysed dehydrogenative cross coupling of functional arenes or heterocycles and alkenes which will be presented now. It will be shown that a variety of functional groups direct the C–H bond alkenylation

such as carboxylate, heterocycles, ketone, aldehyde, amides, esters, carbamates, free amine or alcohol and sulfonic acid derivatives.

3.2.1 Alkenylation with Carboxylic Acid as a Directing Group

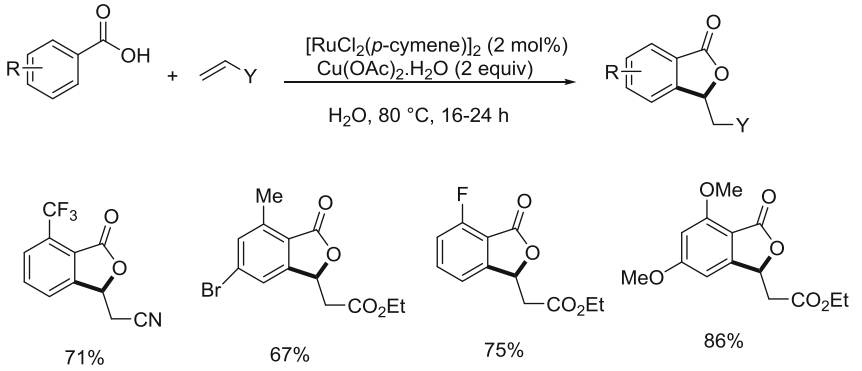
Carboxylate groups have been shown to easily coordinate to Ru(II) complexes without decarboxylation, and they lead to weakly bonded ligands that easily dissociate from the Ru(II) centre and deprotonate neighbour C–H bonds [37, 65]. Satoh and Miura reported in 2011 the first example of ruthenium(II)-catalysed alkenylation with acrylates. The selected substrates were *heterocycles* such as benzothiophene, benzofuran, pyrrole and indole derivatives, but containing a carboxylate group as a directing group. The reaction was performed with $[RuCl_2(p\text{-cymene})]_2$ catalyst and required a stoichiometric amount of $Cu(OAc)_2.H_2O$ as oxidant with LiOAc as a base (Eq. 9) [41]. It was demonstrated before that carboxylic acids did favour the C–H bond activation by Ru(II) systems, but the tremendous advantage of ruthenium(II) catalysts was that they tolerated this functional group, whereas useful palladium(II) catalysts for similar reaction undergo decarboxylation of the aromatic carboxylate directing group [66]. The thiophene-3-carboxylic acid could lead to its dialkenylation at both C2 and C4 positions thus demonstrating the directing ability of the carboxylate directing group [41].



(9)

Ackermann showed that the carboxylic group could direct the alkenylation with Ru(II) catalyst at the *ortho*-position of benzoic acid derivatives with alkyl acrylates or acrylonitrile with 2 equiv. of oxidant $Cu(OAc)_2.H_2O$ (Eq. 10) [42]. This reaction took place efficiently in *water as solvent*, and the alkenylation was followed by oxa-Michael addition, thus leading to a variety of lactones. The reaction with Ru(II) catalysts was shown to tolerate a bromide linked to the arene. This constitutes a

new example of the stability and efficiency in water of ruthenium(II) catalysts for functionalisation of sp^2C–H bonds [33, 67].

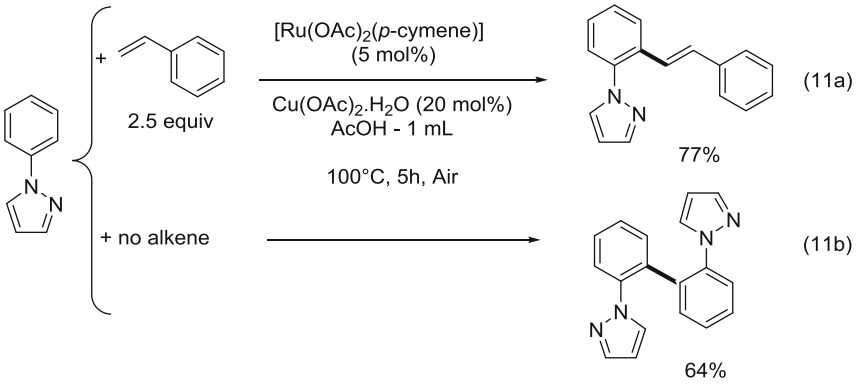


(10)

3.2.2 Heterocycles as Directing Groups for Alkenylation

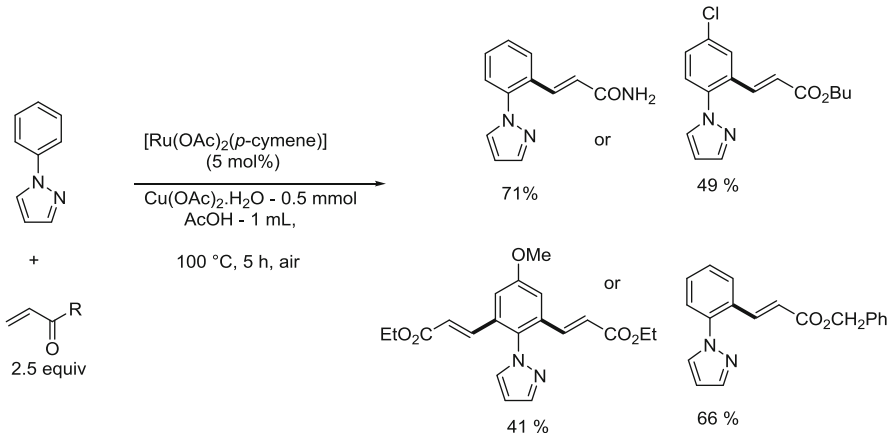
Evidence for Directed C–H Bond Alkenylation

Nitrogen-containing heterocycles are known to give strong N–Ru bond with Ru(II) complexes, and several of them can be isolated [65]. Then, oxidative alkenylation of arenes, directed by a heterocycle in *N*-arylpyrazoles, with nonactivated alkenes such as styrene was shown by Bruneau and Dixneuf (Eq. 11a) [43]. The reaction was performed by $Ru(OAc)_2$(*p*-cymene) catalyst, but with only catalytic amount of $Cu(OAc)_2.H_2O$ (20 mol%) in air at 100°C. A key of the success was the use of a simple $Ru(OAc)_2$(*p*-cymene) catalyst in acetic acid which together allows easy C–H bond cleavage [37, 38].



It is noteworthy that in the absence of styrene, the catalytic system performed easy *ortho* C–H bond cleavage of *N*-arylpyrazole and *ortho* C–C homocoupling leading to bidentate ligand (Eq. 11b) [43].

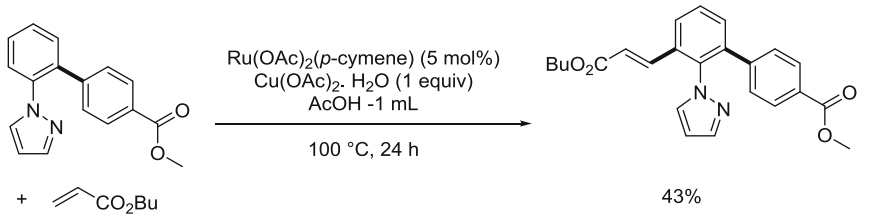
This alkenylation of arylpyrazoles can be applied to electrophilic acrylamides or acrylates under similar conditions, but the reaction is slower. However, good yields can be obtained using 1 equiv. of $Cu(OAc)_2.H_2O$ in acetic acid. The *ortho*-dialkenylation with acrylate of N-*p*-methoxy-substituted phenylpyrazole can also be achieved (Eq. 12) [43].



(12)

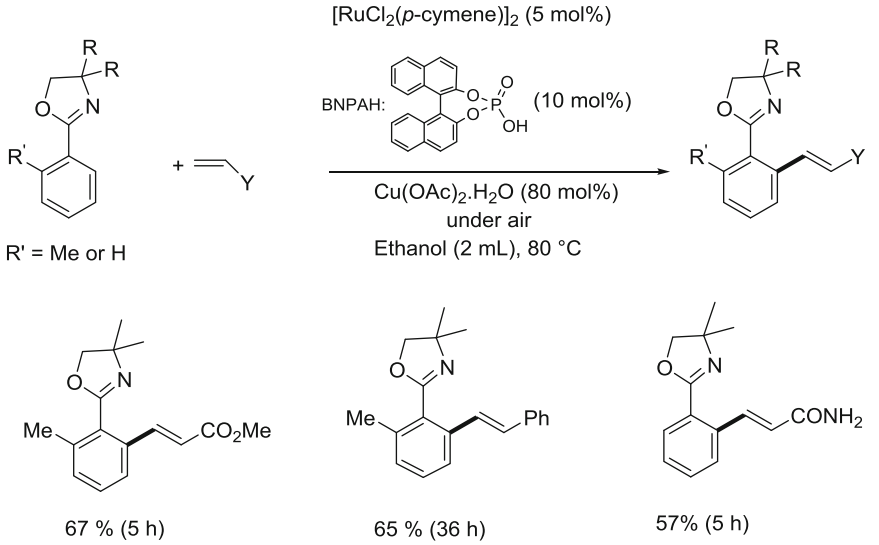
The selective monoalkenylation of 1-phenylpyrazoles has also been performed by Satoh and Miura with $[RuCl_2(p\text{-cymene})]_2$ catalyst and 2 equiv. of $Cu(OAc)_2.H_2O$ in DMF under nitrogen atmosphere at 100°C. The reaction was shown to tolerate various substituents on the arene ring such as Cl, Me, CO_2R and CN groups [68].

The alkenylation directed by pyrazole has been applied to illustrate the successive functionalisations of two *ortho* C–H bonds of the *N*-phenylpyrazole aryl group. After selective monoarylation of *N*-phenylpyrazole with ruthenium(II) catalyst in water, the new *N*-phenylpyrazole derivative was *ortho*-alkenylated with *n*-butyl acrylate with catalyst $Ru(OAc)_2(p\text{-cymene})$ in acetic acid using 1 equiv. of oxidant $Cu(OAc)_2.H_2O$ (Eq. 13) [69].



(13)

The oxazoline ring has been shown to be an efficient directing group for *ortho*-alkenylation of aryl C–H bonds with acrylates, acrylamides in toluene. However, the usual carboxylic acids such as AcOH or $PhCO_2H$ were not efficient partners, and the 1,1′-binaphthyl-2,2′-diyl hydrogen phosphonate (HMPAH) appeared to be an excellent Ru(II) partner for a reaction performed in simple ethanol as solvent, with less than 1 equiv. of $Cu(OAc)_2.H_2O$ under air (Eq. 14) [70].

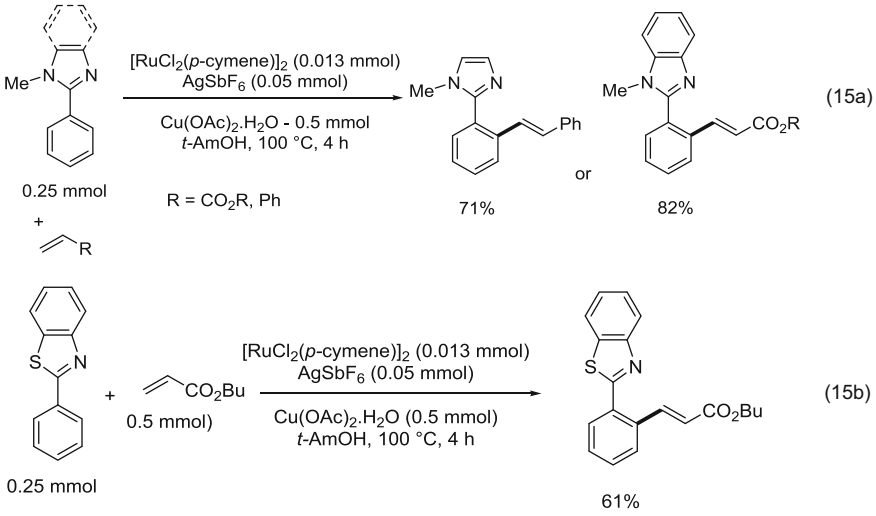


(14)

This transformation shows that a variety of C–H bond deprotonation partners have to be selected according to both the substrate and directing group nature, and phosphate derivatives such as $(alkylO)_2P(O)OK$ are now commonly used for catalytic monoarylation of arene C–H bonds directed by a tetrazole unit for the production of industrial intermediates [71].

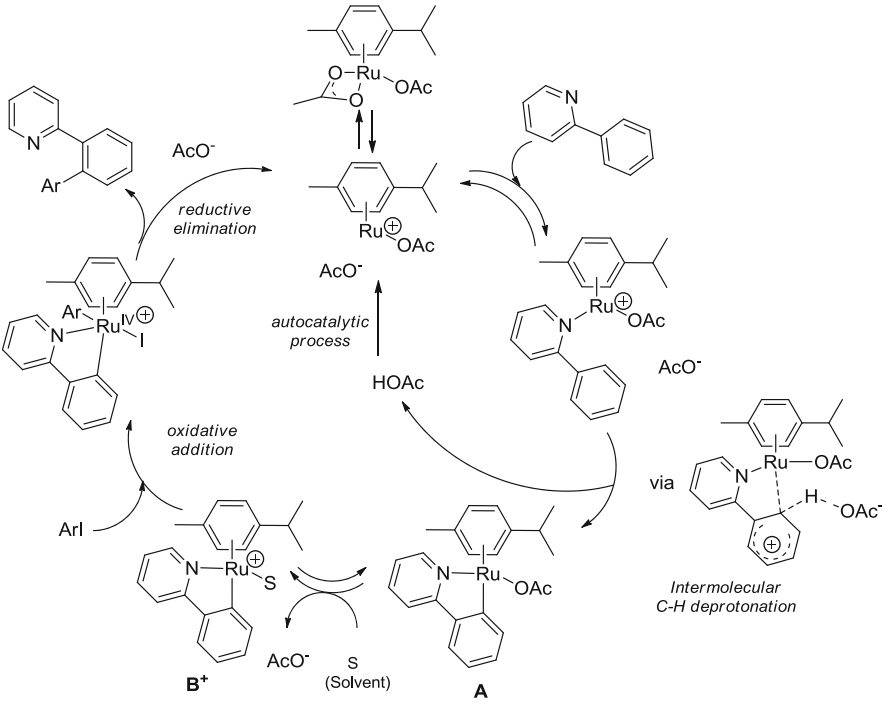
Azole has also been used as a heterocycle directing group in the ruthenium(II) alkenylation of phenylazoles by Miura [72]. The catalytic system is based on Jeganmohan's catalyst discovered for alkenylation of aromatic ketones [44], with $[RuCl_2(p\text{-cymene})]_2/4AgSbF_6$ also with 2 equiv. of $Cu(OAc)_2.H_2O$ in *t*-AmOH solvent at 100°C under nitrogen (Eq. 15a) and under conditions presented later with

amides as directing groups. The reaction with acrylate of phenylbenzothiazole with only $[RuCl_2(p\text{-cymene})]_2$ led to 20% only of the alkenylated product [68]. By contract with $AgSbF_6$, the same catalyst afforded 61% of the *ortho*-alkenylated product (Eq. 15b) [72]. $AgSbF_6$ favours halide abstraction and formation of Ru(II)–OAc bond.



First Approach of Mechanism for C–H Bond Activation and Alkenylation

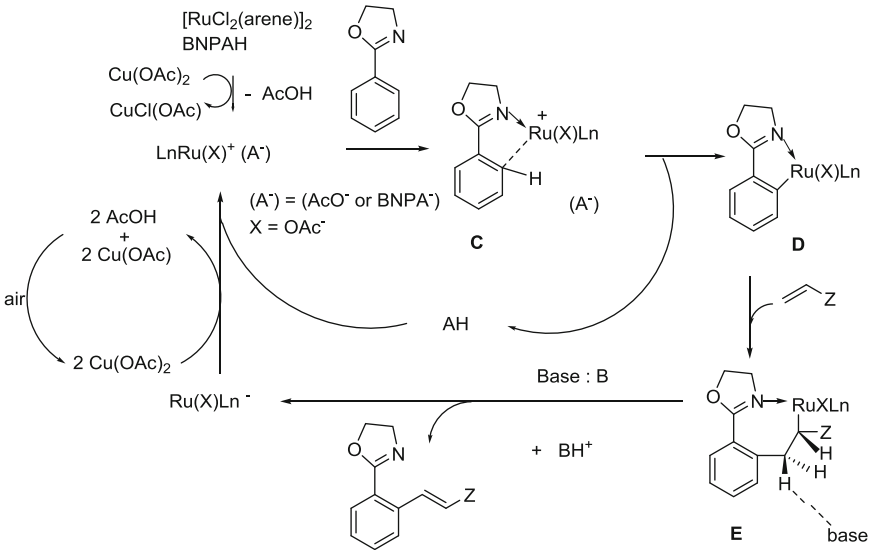
At this stage, a mechanism for the alkenylation of functional arenes can be proposed as exemplified by that of phenyloxazoline (Eq. 14). It is based on the first step of the mechanism established with the help of kinetic studies for C–H bond activation and arylation at 27°C of functional arene: 2-phenylpyridine [37], 2-phenyl-2-oxazoline and 1-phenylpyrazole [38], using $Ru(OAc)_2(p\text{-cymene})$ catalyst (Scheme 1). The Ru(II)–OAc bond of $Ru(OAc)_2(p\text{-cymene})$ is weak [65], and acetate dissociation from an 18-electron complex takes place first to allow the coordination of the heterocycle nitrogen. The formation of the cyclometallate **A** is first produced by acetate C–H bond deprotonation and accelerated by additional KOAc, thus supporting an intermolecular deprotonation of C–H bond by external acetate. This cyclometallate formation is strongly accelerated by the freed AcOH, likely to keep the Ru(II) site coordinatively unsaturated, and this phenomenon reveals an *autocatalytic process*. This will be reflected in most C–H bond activation/deprotonation processes observed with Ru(II) catalysts, and the crucial role of carboxylic acids and carboxylates partners will be shown. More importantly, the kinetic studies of C–H bond activation process with phenylpyridine by $Ru(OAc)_2(p\text{-cymene})$ and $Pd(OAc)_2$, leading in both cases to a cyclometallate complex, show that the reaction of $Pd(OAc)_2$ is faster than with the ruthenium(II) catalyst, but that it is not affected at all by the addition of acetic acid or acetate [38]. Thus, $Pd(OAc)_2$ proceeds via an



Scheme 1 Proposed mechanism for Ru(II)-OAc assisted C–H bond activation and arylation

intramolecular non-autocatalysed concerted metallation–deprotonation (CMD) mechanism, whereas $Ru(OAc)_2L_n$ catalysts proceed via an *intermolecular deprotonation favoured by carboxylate or phosphate via an autocatalytic process* [37, 38].

Thus, for Ru(II)-catalysed alkenylation of functional arenes such as phenyloxazoline (see (Eq. 14) [70]), the first step of C–H bond activation is expected to be analogous to that observed for arylation of phenylpyridine (Scheme 2). The reaction of $[RuCl_2(p\text{-cymene})]_2$ catalyst and $Cu(OAc)_2.H_2O$ gives easily $Ru(OAc)_2(p\text{-cymene})$ which, in the presence of the phosphonate BNPAH, can lead to a ruthenium(II) cation, with counter-anion (A^-) = (AcO^- or $BNPA^-$). The coordinatively unsaturated Ru(II) centre is able to coordinate the functional group and favours the interaction of the ruthenium(II) site with the *ortho* (C–H) carbon **C**, increasing its C–H bond acidity. The C–H bond deprotonation by external $BNPA^-$ is expected to afford the five-membered cyclometallate **D**, which via coordinative insertion of alkene leads to cyclometallate **E**. When the N–Ru bond is stable, then classical β-elimination cannot take place due to the rigidity of the seven-membered cyclometallate **E**, avoiding the coplanarity of both Ru–C and Cβ–H bonds. Then, the deprotonation of a β-hydrogen in *anti*-position to the Ru–C bond should take place to give the alkenylated product and a Ru(0) species $Ru(X)Ln^-$. The latter is oxidised into Ru(II) species with the Cu(II) salt in the presence of air. If the Ru–N



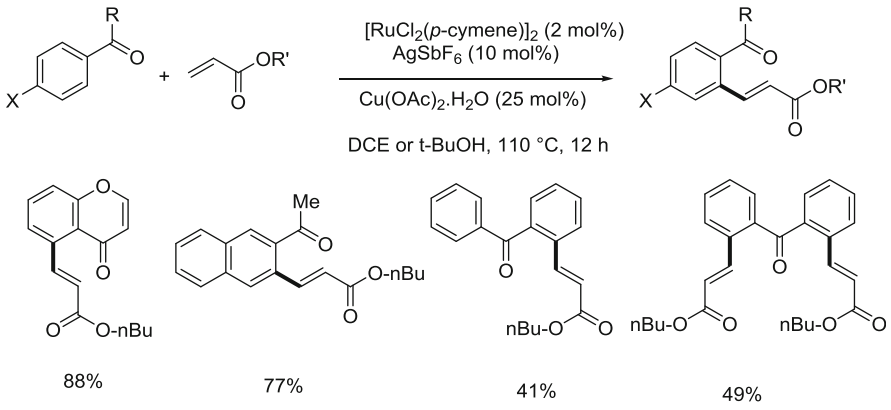
Scheme 2 Possible mechanism for alkenylation of ortho C–H bond of phenyloxazoline

bond can easily dissociate, then β-elimination takes place to generate a Ru(H)(X)Ln species leading, on reaction with $Cu(OAc)_2$, to the catalytic species.

3.2.3 Ketone as a Directing Group for Alkenylation

With the help of ruthenium(0) catalysts, the Murai group showed that ketone groups could direct *ortho*-arylation, with arylboronates, of aromatics, and with alkenes, they direct alkylation preferentially to alkenylation [21–26]. However, ketones with Ru(II) catalysts could not direct arylation with aryl halides or Fujiwara–Moritani alkenylation, whereas their corresponding imines could make direct arylation possible with aryl halides [28, 73–76].

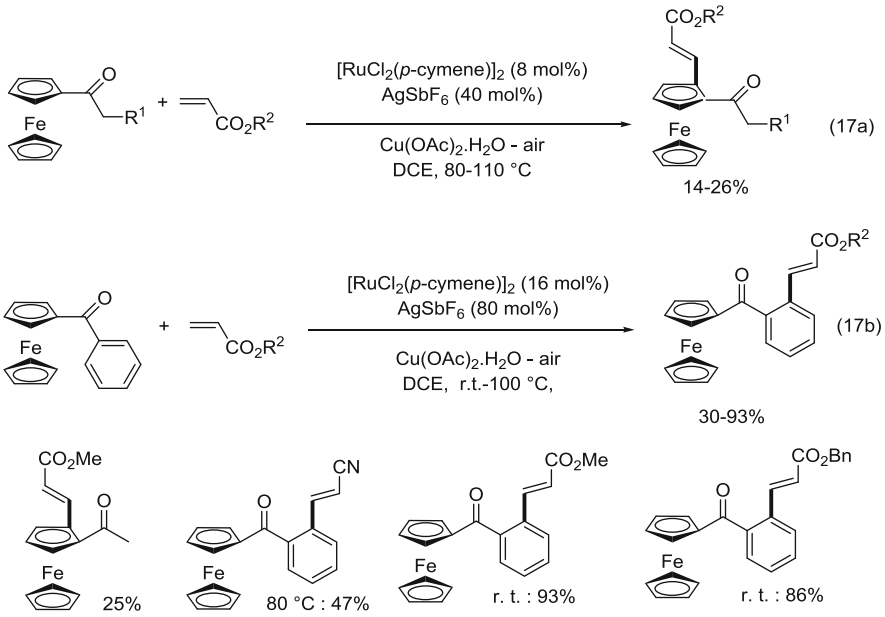
A very useful modification of the Ru(II) catalysts was brought by Jeganmohan et al. at the end of 2011 which allowed the selective, efficient dehydrogenative alkenylation of aromatic ketones (Eq. 16) [44]. Thus, by reacting the catalyst $[RuCl_2(p\text{-cymene})]_2$ with more than 4 equiv. of $AgSbF_6$ to abstract the chlorides from the ruthenium(II) complex, in the presence of $Cu(OAc)_2.H_2O$ as an acetate provider and as oxidant, they succeeded to perform the *ortho*-alkenylation of a large variety of substituted aryl methyl ketones (X=F, I, MeO, CO_2Me) (Eq. 16). The reaction of benzoketone can lead either to *ortho*-mono- or dialkenylation.



(16)

This Jeganmohan catalytic system, based on the abstraction of chlorides by Ag^+ SbF_6^- salt, which favours the formation of Ru–OAc bond in the presence of $Cu(OAc)_2$, has contributed to further establish general methods of alkenylation of a variety of arylketones, but also of arenes and heteroarenes containing a carbonyl bond for weak interaction with the Ru(II) centre, such as formyl, ester, amide, amidine and carbamate directing groups of which applications will be presented later.

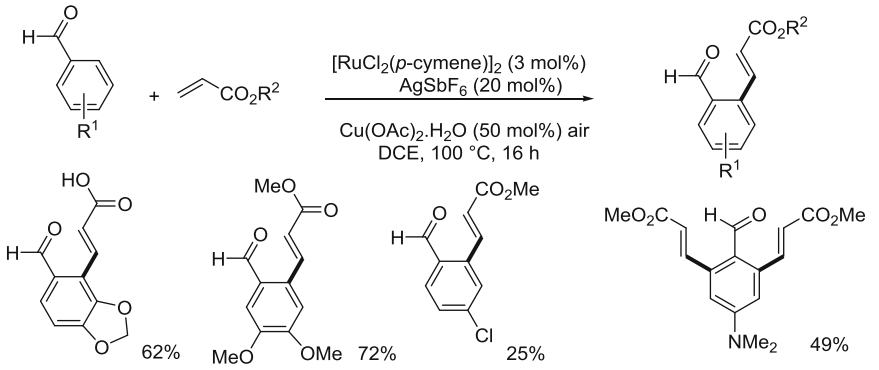
The ketone group has also been used to directly alkenylate ferrocene derivatives which could not be arylated before. This functionalisation directed to *ortho*-position of the ketone would open the direct access to compounds with planar chirality. Using a similar catalytic system as Jeganmohan for alkenylation of aromatic ketones (Eq. 16) [44], Singh and Dixneuf have reported the catalytic alkenylation with acrylates of ferrocenyl ketones, with COMe and COEt directing group, using 8 mol% of $[RuCl_2(p\text{-cymene})]_2$, 40 mol% of $AgSbF_6$ and 2 equiv. of $Cu(OAc)_2.H_2O$ in DCE. The C2-alkenylation product was selectively produced at 80–100°C but was obtained in moderate yields (<30%) (Eq. 17a) [77].



Then, in order to evaluate the easiness of activation and functionalisation of (Fc)C–H versus (Ph)C–H bonds, the reaction was applied to ferrocenyl phenyl ketone. Surprisingly in that case, the alkenylation selectively took place by functionalisation of the *ortho* (Ph)C–H bond only and not at the electron-rich ferrocenyl cyclopentadienyl group. With acrylates, alkenylation occurred *at room temperature* and in quantitative yields (Eq. 17b) [77]. The same alkenylation was performed at the phenyl group with acrylonitrile and styrene derivatives but at 80–100°C. These reactions show that the FcCO acyl group actually favours *ortho* aryl C–H bond activation for alkenylation.

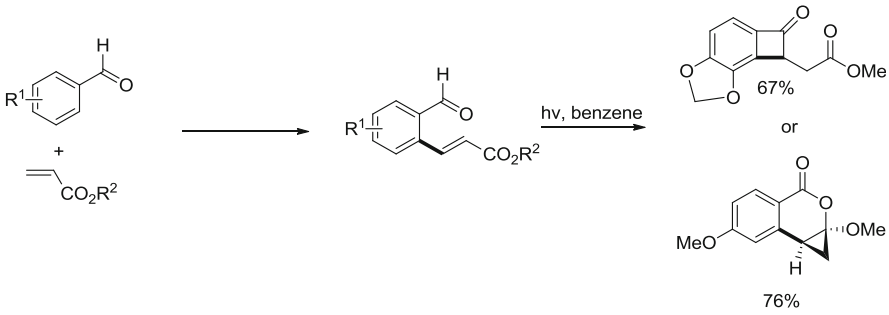
3.2.4 Formyl as a Directing Group for Alkenylation

Soon after, in 2012, Jeganmohan used his catalytic system $RuCl_2(p\text{-cymene})]_2$/6 $AgSbF_6$ with $Cu(OAc)_2.H_2O$ under air to show that the formyl group also directed the alkenylation at its *ortho*-position of aromatic aldehydes. He showed that the electron-withdrawing substituents such as Cl, CN and CO_2Me on the aryl groups disfavour the reaction; by contrast, electron-rich substituents such as OMe, Me, NMe_2 and dioxole led to good yields (Eq. 18) [78]. The directing ability is likely due to the weak coordination of the carbonyl oxygen to the Ru(II) site. It is noteworthy that with Ru(0) catalysts, the Murai alkylation with olefins of aromatic aldehydes was disfavoured. The formation of the alkenylated products is suggested to take place via initial activation with a Ru(II)–OAc species leading to the five-membered cyclometallate by *ortho* C–H bond cleavage.



(18)

Jeganmohan showed the interest of the produced *ortho*-alkenylated aromatic aldehydes, as under irradiation in benzene they afforded the four-membered cyclic ketones or the polysubstituted isochromanone derivatives (Eq. 19) [78].

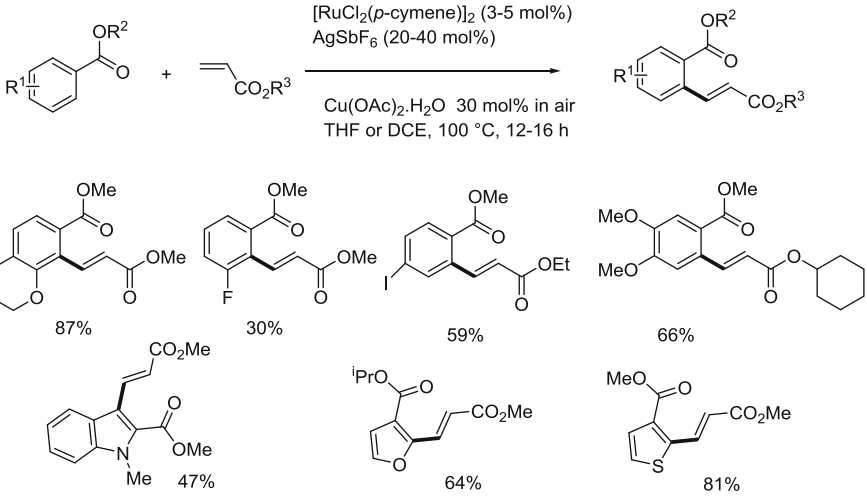


(19)

3.2.5 Ester as a Directing Group for Alkenylation

As for ketone and formyl groups, it was shown soon after first by Jeganmohan [79] and by Ackermann [80] that the weakly coordinating ester function could also direct the alkenylation of arenes with acrylates on action of the catalyst $[RuCl_2(p\text{-cymene})]_2$/n $AgSbF_6$. Under air atmosphere, $Cu(OAc)_2.H_2O$ in 1,2-dichloroethane could be used this time in a catalytic amount of 30 mol%. A variety of aromatic and heteroaromatic esters could be alkenylated by acrylates (Eq. 20) [79, 80]. It is shown in the two reports, especially by cross experiments, that the reaction is favoured by electron-rich substituents on the aryl groups. The reaction tolerates the presence of iodide substituent.

The reaction appears quite general and can be applied to thiophene, furan and indole derivatives, but an electron-withdrawing group on aromatic esters disfavours this cross-coupling reaction (Eq. 20) [79, 80].

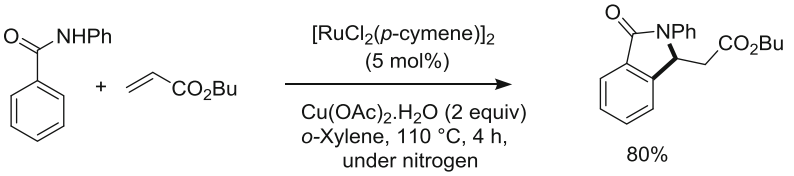


(20)

It is noteworthy that Loh used the ester group of acrylates to direct the alkene C–H bond activation to give functional dienes in the presence of another alkene (see Sect. 3.4) [81].

3.2.6 Amides CONHR and NHCOR as Directing Groups for Alkenylation

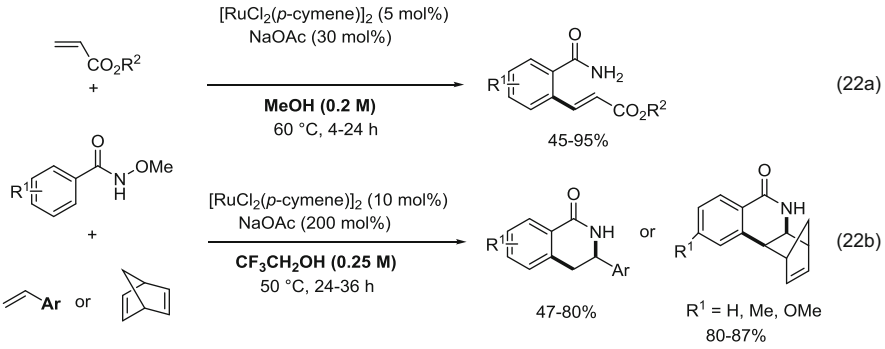
At the same time as the alkenylation of *N*-phenylpyrazoles, Miura et al. [68] have also found in 2011 that an amide group CONHR could direct the *ortho*-alkenylation of a phenyl ring with $[RuCl_2(p\text{-cymene})]_2$ catalyst and 2 equiv. of $Cu(OAc)_2.H_2O$ in *o*-xylene. The reaction of benzylanilide and *n*-butyl acrylate led first to *ortho*-alkenylation followed by intramolecular aza-Michael addition and the production of the lactam (Eq. 21) [68]. Thus, they showed for the first time that both *ortho* C–H and N–H bonds could be easily functionalised with ruthenium(II) catalyst.



(21)

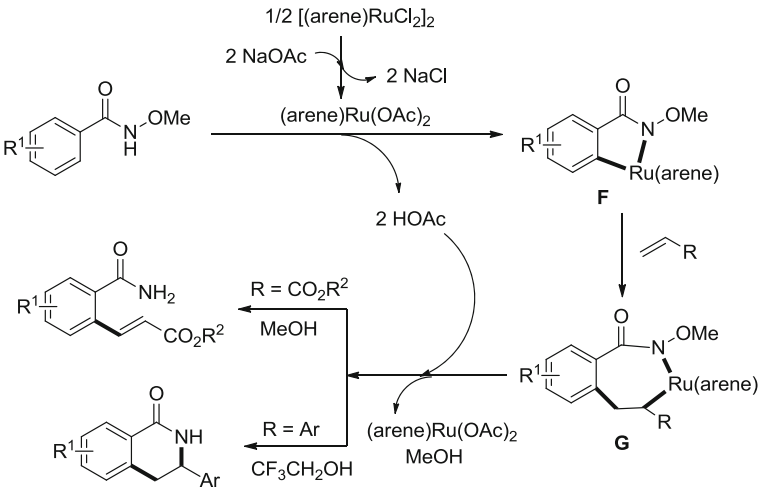
Bin Li and Baiquan Wang, in the beginning of 2012, reported that the amide group CONH(OMe) could direct *ortho*-alkenylation and behave as an oxidising reagent. They showed that $[RuCl_2(p\text{-cymene})]_2$, without $Cu(OAc)_2$ this time, allowed the general catalysed oxidative alkenylation with acrylates, simply in the presence of NaOAc (30 mol%) in methanol at 60°C (Eq. 22a) [82].

The similar reaction with unactivated alkenes, with styrene and norbornadiene, but in CF_3CH_2OH as solvent, allows the formation of 3,4-dihydroisoquinolinones via initial *ortho*-alkenylation of *N*-methoxybenzamides followed by intramolecular nucleophilic addition of the nitrogen to the formed C=C bond (Eq. 22b) [82].

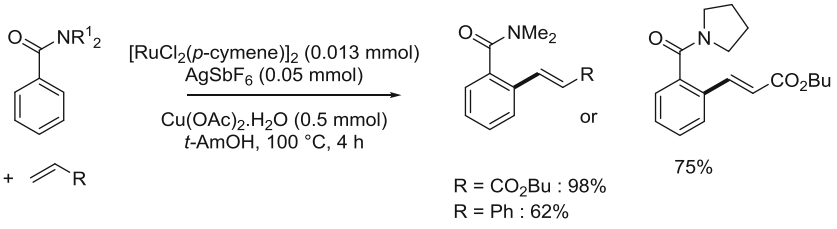


The authors proposed a realistic mechanism based on initial formation of Ru $(OAc)_2$(*p*-cymene) catalyst shown in Scheme 3 [82]. The cyclometallated intermediate **F** is likely to be formed from *N*-methoxybenzamide on acetate deprotonation of both *ortho* C–H and N–H bonds. The intermediate **G** should result from coordinative insertion of the alkene. The alkenylated product is produced via β-elimination from the intermediate **G**, or by deprotonation with copper freed acetate, in the case of acrylate in methanol. By contrast, the alkyl and aryl group in **G** arising from styrene or norbornadiene in CF_3CH_2OH should favour reductive elimination. These processes lead to the release of MeOH with the regeneration of the Ru$(OAc)_2$(*p*-cymene) catalyst.

Miura and co-workers, as they did for the alkenylation of phenylazole and phenylthiazole (Eq. 15) [72], used the [$RuCl_2$(*p*-cymene)]$_2$/4 $AgSbF_6$ catalytic system and 2 equiv. of $Cu(OAc)_2.H_2O$ under nitrogen, in *t*-AmOH for the regioselective *ortho*-alkenylation with alkyl acrylates of *N*,*N*-dialkylbenzamides (Eq. 23) [72].

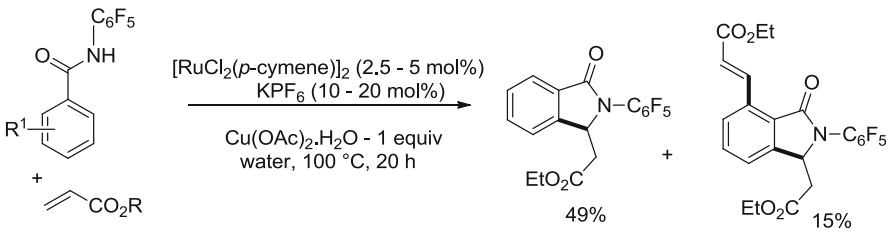


Scheme 3 Proposed mechanism for alkenylation of *N*-methoxybenzamides



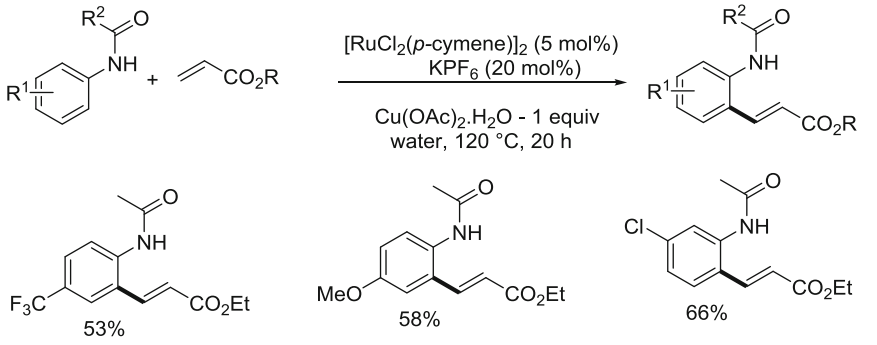
(23)

All the previous ruthenium(II)-catalysed directed alkenylations with alkenes of functional arenes were performed in organic solvents except that of arylcarboxylic acids performed in water as soon as 2011 by Ackermann's group (Eq. 10) [42]. Ackermann's group succeeded to perform this catalytic monoalkenylation of benzamides *in water* using the $[RuCl_2(p\text{-cymene})]_2$ catalyst with the non-coordinating salt KPF_6 (20 mol%) in the presence of $Cu(OAc)_2.H_2O$ as the oxidant. The *N*-(pentafluorophenyl)benzamides were first monoalkenylated and further led to intramolecular aza-Michael addition to form the expected lactams (Eq. 24) [83].



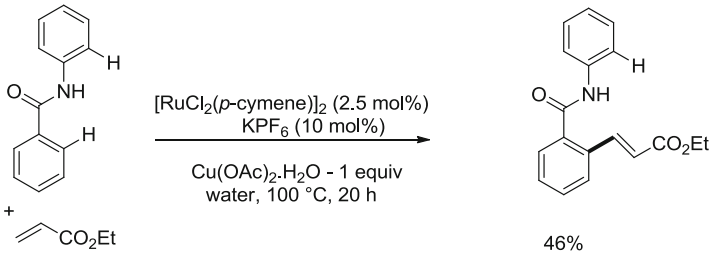
(24)

They showed that the NHCOR group of anilides, more generally than the CONHR group, directed the *ortho*-alkenylation with acrylates and *in water as solvent*. This catalytic system $[RuCl_2(p\text{-cymene})]_2/KPF_6$ (20 mol%) in the presence of $Cu(OAc)_2.H_2O$ is more active in water than in DMF, NMP, *t*-AmOH. The reaction is general and favoured by electron-rich anilides (Eq. 25) [83].



(25)

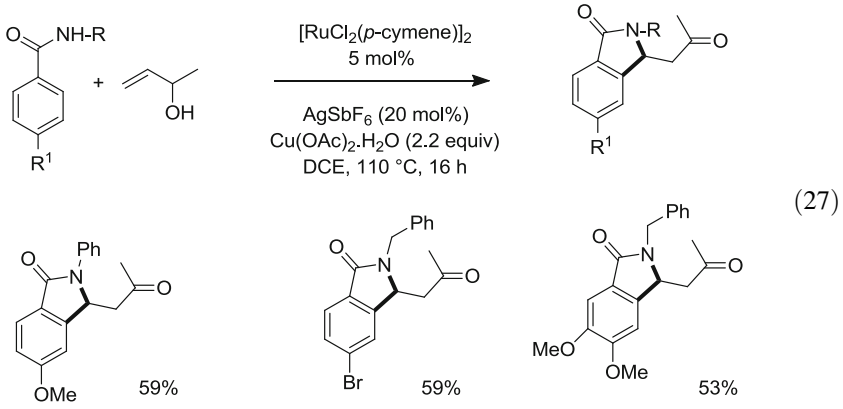
The alkenylation of N-benzoyl aniline took place only at the *ortho* C–H bond of the aromatic ring linked to the amide carbonyl showing the preferential activation/alkenylation by the -CONHPh than the -NHCOPh group. It is consistent with the activation of the more acidic C–H bond of the phenyl linked to the carbonyl group (Eq. 26) [83].



(26)

Ackermann also demonstrated that the CONHR group could efficiently direct the alkenylation of heterocycles such as indole, thiophene, benzothiophene and benzofuran [83].

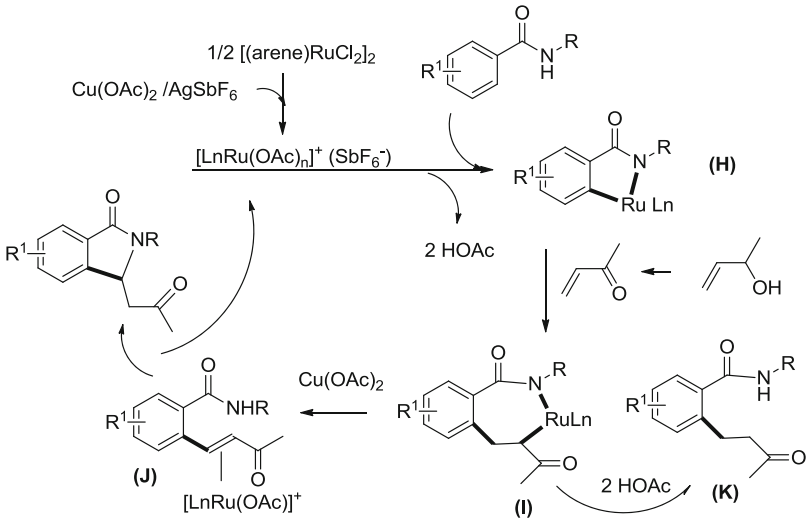
The amide group $CONR_2$ has first been used in 2013 by Huanfeng Jiang to direct the ruthenium(II)-catalysed *ortho*-alkylation of arenes and heterocycles with allylic alcohols [84] (see alkylation part of Sect. 4.1). Now Jeganmohan has profitably used the amide group CONHR to direct *ortho*-alkenylation of arenes, directly with allylic alcohols, followed by isoindolinone formation via intramolecular Michael addition. The alkenylated intermediate offers the direct access to a variety of isoindolinones (Eq. 27) [85]. The catalyst is similar to that used for acrylates, $[RuCl_2(p\text{-cymene})]_2$/4 $AgSbF_6$, that is only effective with $Cu(OAc)_2.H_2O$ (2 equiv). With the $CONH^tBu$ group, a mixture of isoindolinones and *ortho*-alkenylated product with a 1:0.4 ratio was obtained in 45% yield, suggesting an initial formation of alkenylated intermediate.



(27)

The reaction occurs for a variety of allylic alcohols in DCE at 110°C. It is shown that under the catalytic conditions, (1) allylic alcohol is dehydrogenated into the α,β-unsaturated ketone and (2) the unsaturated ketone with arylamide leads to isoindolinone. Thus, the suggested mechanism of the reaction is presented on Scheme 4. It involves the formation of the cyclometallate **H** that was isolated in one example: the insertion of the α,β-unsaturated ketone, arising from allylic alcohol, leads to the cyclometallate **I** and then to the alkenylated intermediate **J**. The latter double bond is activated by the ruthenium(II) catalyst to form the isoindolinone via intramolecular addition. It is also shown that the *ortho*-alkylated product **K** can be obtained in small quantity in one example and that *in the presence of AcOH its formation is increased*. This formation of **K** is expected to result from protonation of the inserted product Ru–C bond of **I**, before β-elimination.

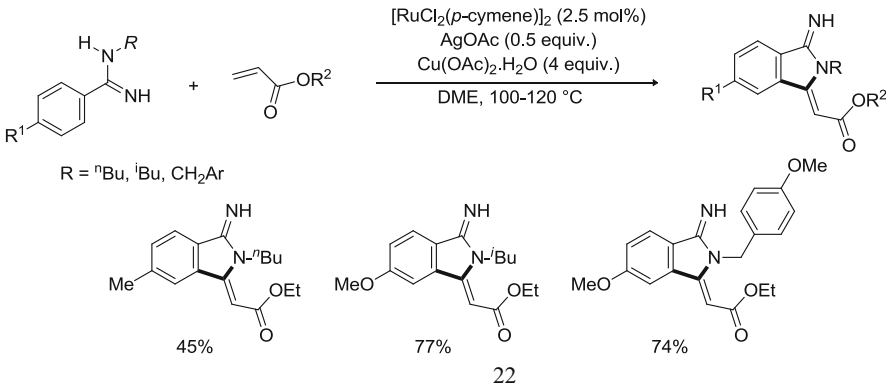
It is noteworthy that Loh used the $CONR_2$ amide group of acrylamides to direct this alkene C–H bond activation towards alkenylation in the synthesis of (*Z*,*E*)-dienamides (see Sect. 3.4) [86].



Scheme 4 Proposed mechanism for alkenylation of benzamides with allyl alcohol

3.2.7 Amidines as Directing Groups

One of the *ortho* C–H bonds of benzylamidines was efficiently and selectively activated by ruthenium catalyst generated from $[RuCl_2(p\text{-cymene})]_2$ in the presence of silver acetate and copper acetate, owing to the excellent directing properties of the amidine functionality [87]. The dehydrogenative coupling with acrylates took place at 100–120°C to give 3-alkylidene-1-iminoisoindolines. Two types of products were formed depending on the steric hindrance of the *N*-substituent of the benzamidine. With the less sterically hindered *iso*- and *n*-butyl or benzylic groups, the amino group was involved in the C–N bond formation (Eq. 28). A variety of functional groups on the benzyl group of benzamidine were tolerated in this reaction.



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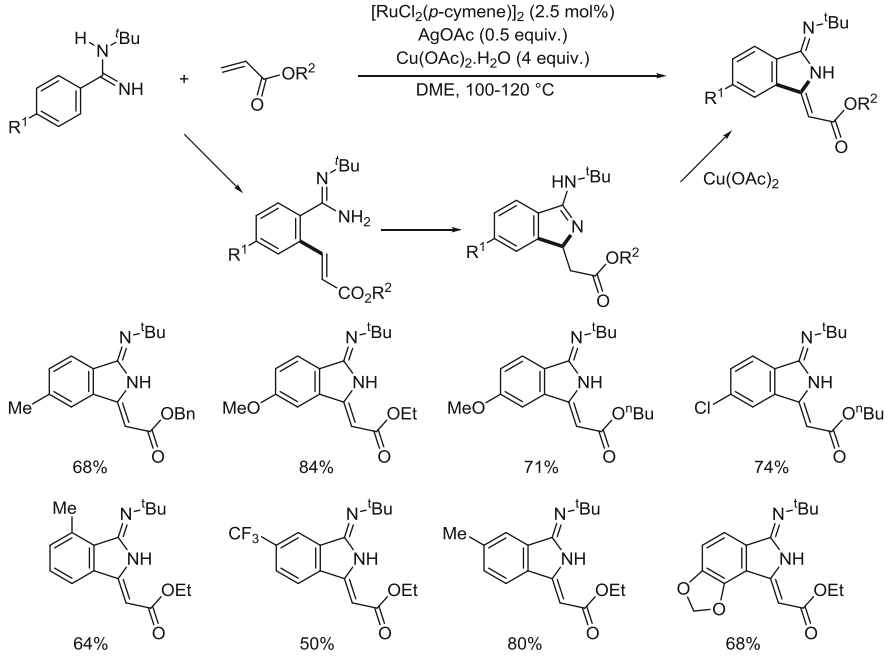
(28)

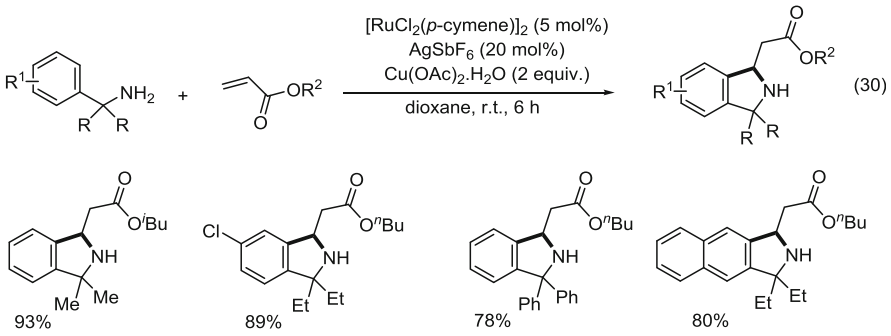
By contrast with the bulky *t*-butyl group, the imino group was incorporated in the five-membered ring of the isoindoline (Eq. 29). Mechanistic studies indicated that the transformation resulted from a sequence of oxidative alkenylation followed by intramolecular aza-Michael reaction and then by copper-catalysed dehydrogenation to generate the acrylic system (Eq. 29).



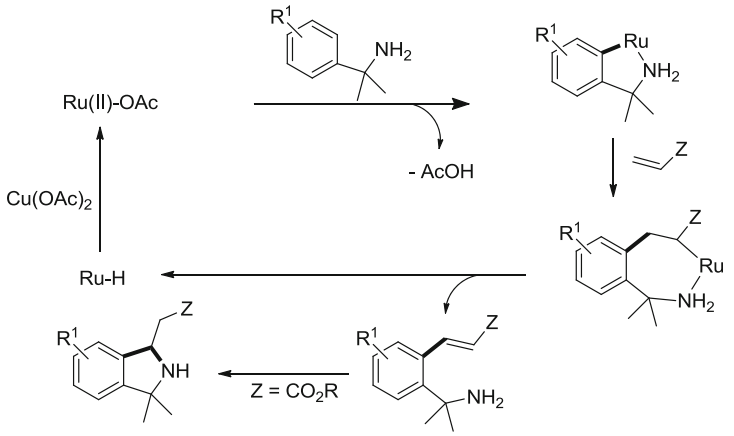
(29)

3.2.8 Free Amine as a Directing Group for Alkenylation

The coordinating ability of the free primary amino group of benzylamines was shown by Miura and Satoh to be strong enough to direct the *ortho* C–H bond activation of the phenyl group and to allow alkenylation. α,α-Disubstituted benzylamines, in the presence of catalytic amounts of $[Cp^*RhCl_2]_2$, or with the low-cost $[RuCl_2(p\text{-cymene})]_2$ and $AgSbF_6$, and 2 equiv. of copper(II) diacetate, led to the direct coupling with electron-deficient acrylates and the selective formation of isoindolines *at room temperature* in dioxane (Eq. 30) [88]. The reaction is supposed to produce first an *ortho*-alkenylated benzylamine, which is prone to cyclise via aza-Michael addition. The formation of the five-membered ring was favoured when the starting benzylamine was disubstituted at the benzylic position, whereas the α-unsubstituted benzylamine only gave aza-Michael addition to the electron-deficient olefin. This is the first example of ruthenium(II)-catalysed C–H bond functionalisation directed by a free NH_2 group. An intermediate situation leading to a mixture of isoindoline and secondary linear benzylamine was observed when acrylonitrile was used as coupling partner. This catalytic system based on ruthenium was not active for the alkenylation with styrene. On the other hand, a catalytic system based on $[Cp^*RhCl_2]/AgSbF_6$ and $Cu(OAc)_2$ was also able to achieve this alkenylation/cyclisation at 80°C from acrylate and also the simple *ortho*-alkenylation from styrene.



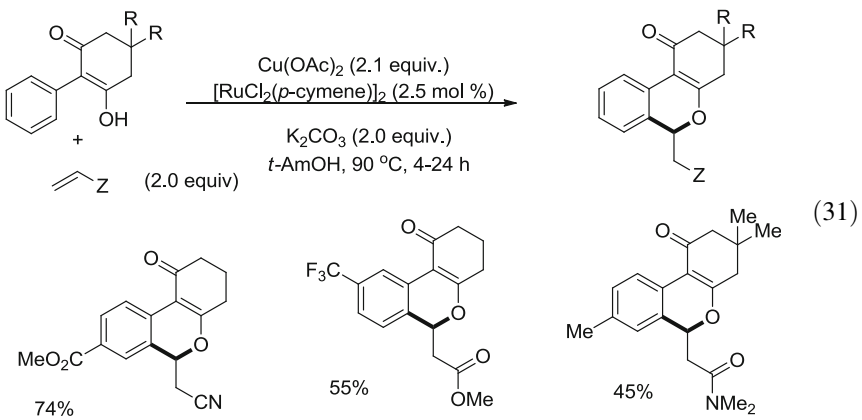
The mechanism is suggested to involve the initial formation of a Ru(II)–OAc species leading to a five-membered cyclometallate, the regioselective coordinative insertion of the acrylate double bond into the Ru–C bond, the β-elimination with metal hydride formation and the intramolecular Michael addition. Reoxidation of the metal hydride species with $Cu(OAc)_2$ is proposed to release the Ru(II) catalyst (Scheme 5) [88].



Scheme 5 Proposed mechanism for the alkenylation of benzylamines directed by free amine

3.2.9 Free Hydroxy Directing Group for Alkenylation

The directing ability of a hydroxy group has been revealed by Lam during the alkenylation of 2-aryl-3-hydroxy-2-cyclohexenones with acrylate, acrylonitrile or acrylamide using simply the catalyst $[RuCl_2(p\text{-cymene})]_2$ with 2 equiv. of $Cu(OAc)_2.H_2O$. The reaction leads to the formation of benzopyrans via oxa-Michael-type addition of the enol oxygen atom to the alkenylated intermediate (Eq. 31) [89].

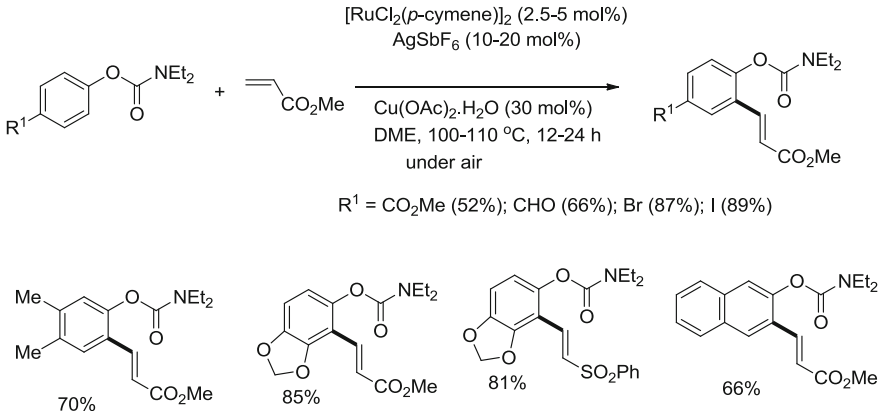


(31)

3.2.10 Carbamate, Carboxylate and 2-Pyridyl as Phenol Protecting and Directing Groups for Alkenylation

The hydroxy group of phenols does not direct ruthenium(II) C–H bond activation, but their protecting groups such as carbamates or carboxylates and the strongly coordinating 2-pyridyl group have been shown to direct the alkenylation of thus protected phenols, and the further deprotection allows to reach

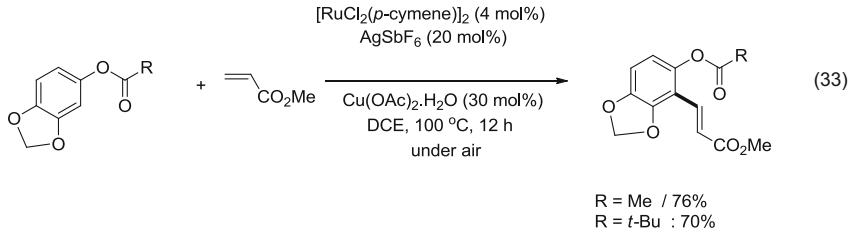
ortho-alkenylated phenols. Ackermann first [90] and then Jeganmohan [91] and Baiquan Wang [92] have shown that carbamate derivatives of phenols easily direct *ortho*-alkenylation with acrylates in a general way (Eq. 32), using the usual catalyst $[RuCl_2(p\text{-cymene})]_2$/4 $AgSbF_6$ with 2 equiv. of $Cu(OAc)_2.H_2O$ or better only 30 mol% but under air in 1,2-dimethoxyethane (Eq. 32) [91].



(32)

The reaction was successful with less reactive alkenes such as styrenes, alkenyl sulfone or acrylonitrile. With a weakly coordinating functional directing group at the *para*-position of carbamate, it was revealed that the carbamate is a stronger directing group than the CO_2Me or CHO directing group (Eq. 32) [91]. The carbamate directing group was easily removed and led to *ortho*-alkenylated phenol using $LiOH{\cdot}H_2O$ in THF/MeOH/H_2O (4:1:1) solvent at 80°C [91] or NaOH in EtOH at 80°C [90, 92].

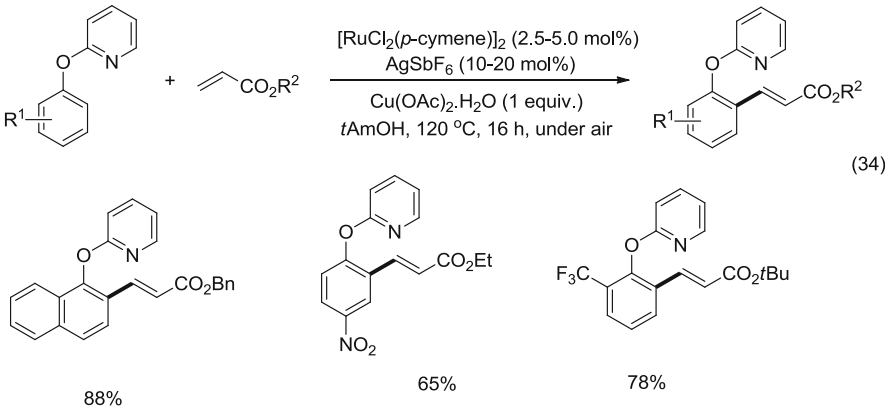
Carboxylate groups have also been shown to direct *ortho*-alkenylation of their phenol derivatives, with alkyl acrylate. Thus, sesamol acetate and pivalate, in the presence of similar ruthenium–silver catalyst, lead to regioselective alkenylation at the C–H bond between both carboxylate and alkoxy groups (Eq. 33) [91].



(33)

Ackermann et al. have shown that removable 2-pyridyl group of O-protecting phenols could direct *ortho*-alkenylation of the phenol derivatives, after he demonstrated their *ortho* C–H bond activation for C–C cross-coupling arylation [93].

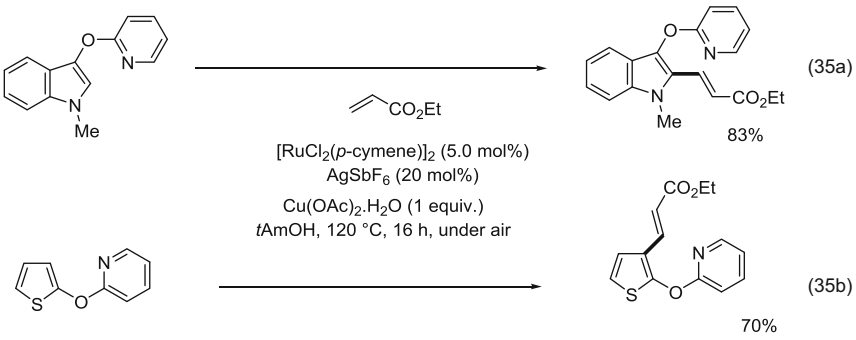
A similar Ru(II)/$AgSbF_6$ catalytic system was used for general alkenylation with alkyl acrylates and with $Cu(OAc)_2.H_2O$ in aerobic atmosphere (Eq. 34) [94].



(34)

It is noteworthy that the intermediate is a six-membered cyclometallate that is usually more difficult to generate than the previous five-membered metallacycles. The 2-pyridyl protecting group is easily removed from alkenylated products with MeOTf and sodium in methanol without modification of phenol and alkene functional group.

This 2-pyridyl directing/protecting group has been used by Ackermann to functionalise heterocycles with alkenes. *N*-Methylindole containing an O-2-pyridyl group at C_3 led to alkenylation at C_2 only (Eq. 35a) [94]. The strong directing power of the O-2-pyridyl group was revealed by the reaction of acrylate with thiophene containing an O-Py group at C_2, which led to selective alkenylation at C_3 position and not at C_5 (Eq. 35b) [94].

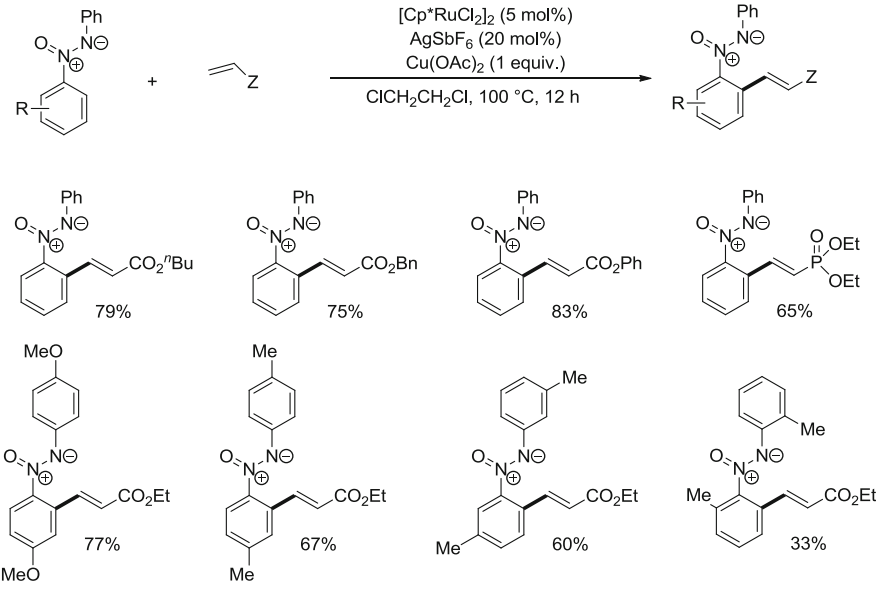


(35a)

(35b)

3.2.11 Azoxy Directing Group for Alkenylation

The azoxy group was shown by Wang to be another efficient directing group for sp^2C–H bond activation. The activation of the *ortho* sp^2C–H bond of azoxybenzenes has been completed with high selectivity in the presence of a new type of C–H bond activation ruthenium catalyst, a Ru(III) precursor $[Cp^*RuCl_2]_n$ associated to $AgSbF_6$ and $Cu(OAc)_2$, and alkenylations have been achieved with electron-deficient olefins such as acrylates and vinylphosphonates at 110°C in DCE (Eq. 36) [95]. Competition experiments have revealed that azoxybenzenes substituted by a methoxy electron-donating group reacted faster than by a neutral or electron-deficient analogue. With this azoxy directing group, the formation of cyclic products was not possible.

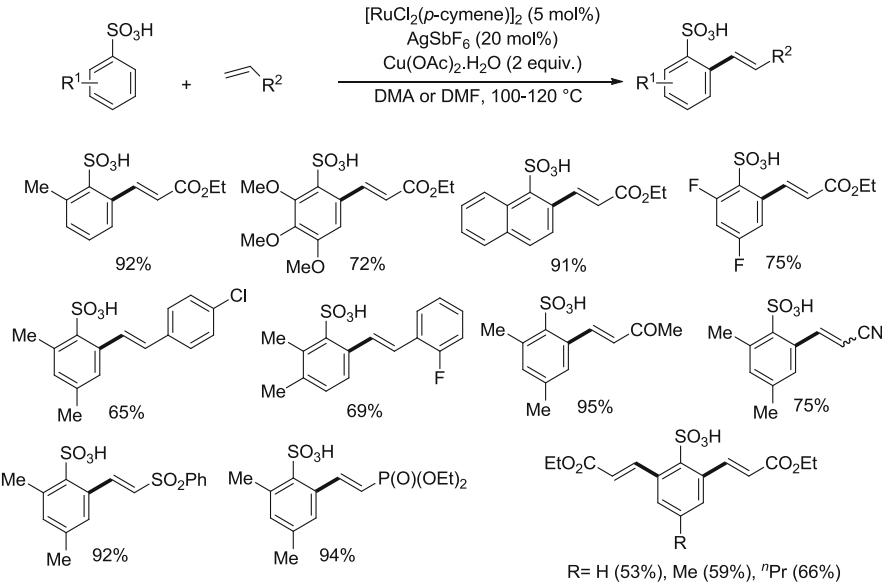


(36)

3.2.12 Sulfonic Acid, Sulfonamide and Sulfoximine Directing Groups for Alkenylation

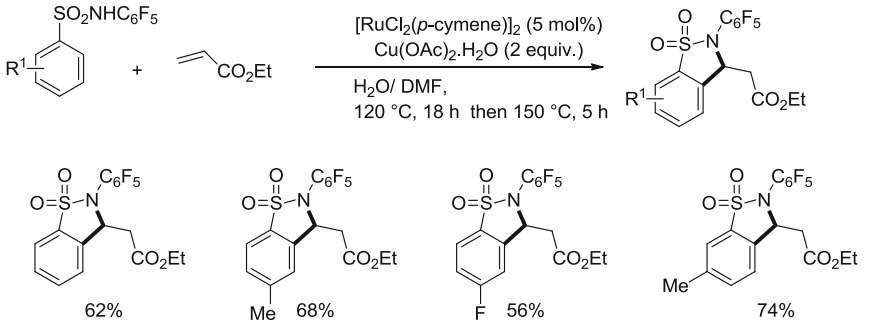
Ackermann showed that the sulfonyl moiety arising either from *sulfonic acid or sulfonyl chloride* generated a five-membered bidentate *ortho*-phenylsulfonate ligand coordinated to the ruthenium(II) centre. Subsequent regioselective insertion of an alkene into the C–Ru bond followed by a type of β–H elimination process led to *ortho*-alkenylated sulfonic acids (Eq. 37) [96]. Interestingly, not only electron-poor olefins were suitable for this reaction, such as acrylates, α,β-unsaturated ketones, vinylsulfones or vinylphosphonates, but styrenes could also be efficiently used. Electron-rich and electron-deficient, as well as hindered *ortho*-substituted,

sulfonic acids were reactive. This allowed the 2,6-bis(alkenylation) to take place in the presence of a threefold excess of alkene.



(37)

Sulfonamides, which also contain a NH in β-position with respect to the aromatic ring, have been shown by Ackermann to be excellent directing groups for alkenylation reaction with acrylates promoted by the same type of in situ generated ruthenium carboxylate catalyst from $[RuCl_2(p\text{-cymene})]_2$ with 2 equiv. of $Cu(OAc)_2.H_2O$. The alkenylation is followed by intramolecular aza-Michael addition leading to cyclisation into sultams in good yields (Eq. 38) [96].



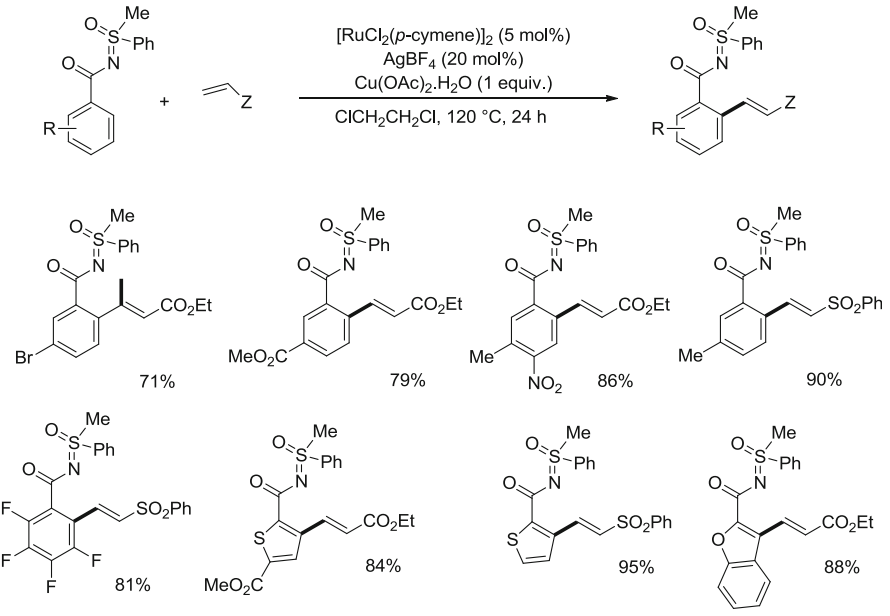
(38)

The Sahoo group has revealed that *sulfoximine* is an excellent directing group for ruthenium-catalysed alkenylation of aromatic and heteroaromatic substrates with electron-deficient olefins such as acrylates, α,β-unsaturated ketones and vinylsulfones

[97]. A variety of substituted arenes bearing either electron-donating or electron-attracting groups have been alkenylated in the presence of $[RuCl_2(p\text{-cymene})]_2$/$AgBF_4$ and $Cu(OAc)_2$ as catalyst precursor (Eq. 39) [97].

It is noteworthy that heteroaromatic substrates including thiophenes, indoles and benzofurans equipped with a *sulfoximine* at carbon C_2 were alkenylated at C_3 with excellent regioselectivity and yields. It is demonstrated that the *sulfoximine prevails over the ester* as directing group for this alkenylation (Eq. 39) [97].

This directing group could be removed under basic treatment with NaOH in $MeOH/H_2O$ at 60°C to give the corresponding aromatic carboxylic acid and regenerate methyl phenyl sulfoximine that could be recycled to prepare the substrates.

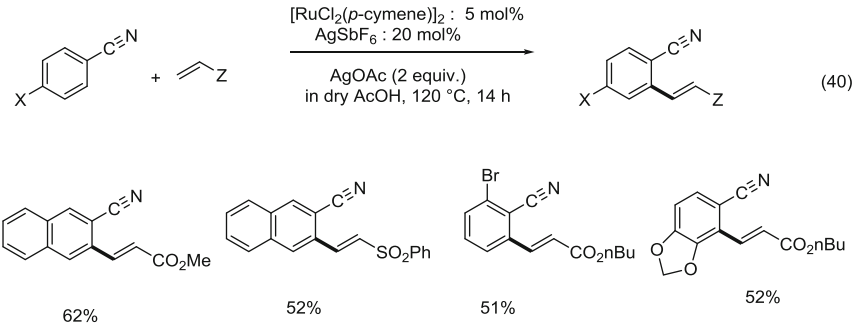


(39)

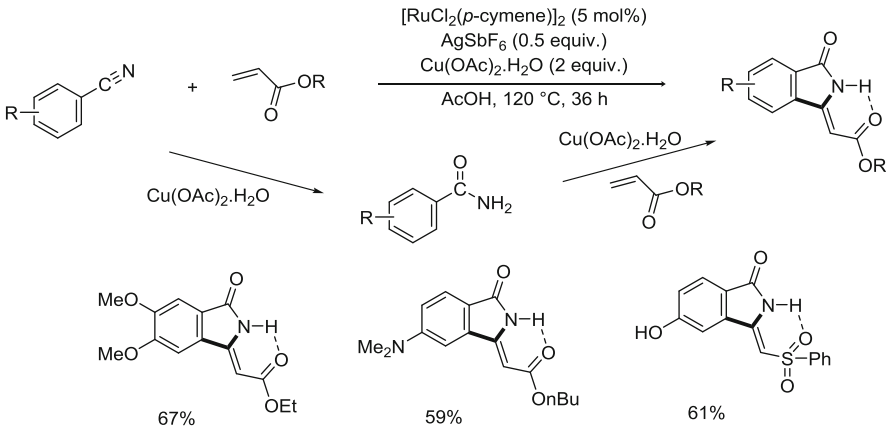
3.2.13 Nitrile as a Directing and Reactive Group for Alkenylation of Arenes

Jeganmohan has just shown that a nitrile group directly linked to a phenyl ring could direct *ortho*-alkenylation by acrylate, thus by π-interaction with the ruthenium(II) catalyst. The success was brought by the cooperative action of both $AgSbF_6$ (20 mol%) and AgOAc (2 equiv.) in addition to $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in dry acetic acid. Thus, a large variety of *ortho*-alkenylated arylnitriles were directly obtained in excellent yields on reaction with acrylates or alkenyl sulfones (Eq. 40) [98]. The proposed mechanism involves the formation of a cyclometallate containing a CN group π-bonded to the Ru(II) centre.

This reaction can be easily extended to heteroaromatic nitriles such as 2-nitrile and 3-nitrile thiophenes [98].



Previously, Jeganmohan also showed that the nitrile group could orientate alkenylation at the *ortho*-position of functional arenes but that in the presence of water the nitrile is hydrolysed into amide and can lead to the synthesis of (*Z*)-3-methyleneisoindilin-1-ones (Eq. 41) [99]. These cascade transformations were promoted by $[RuCl_2(p\text{-cymene})]_2$ catalyst with $AgSbF_6$ (20 mol%) but with $Cu(OAc)_2.H_2O$ (2 equiv.) in acetic acid. Thus, the only difference with the sole alkenylation step in dry medium (Eq. 40) is the introduction of $Cu(OAc)_2.H_2O$, instead of AgOAc, as an oxidant and acetate provider in the presence of water.

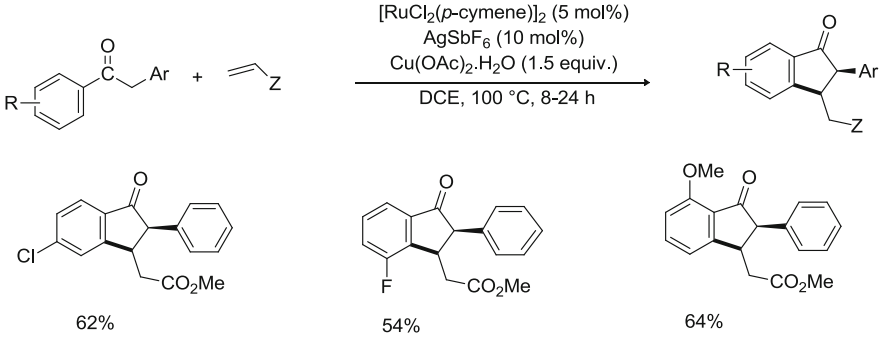


(41)

The mechanism is based on initial hydrolysis of the nitrile group into the amide group $CONH_2$ which becomes the directing group for *ortho*-alkenylation, followed by Ru(II)-assisted addition of the amide NH_2 group to the Ru(II)-coordinated double bond and finally β-elimination [99].

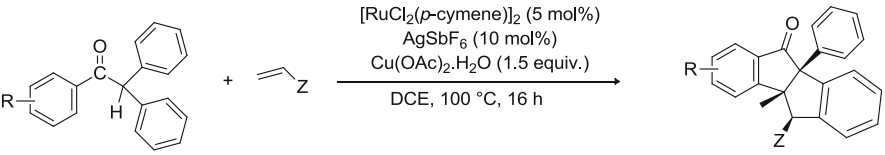
3.2.14 Enolisable Ketone as a Directing and Reactive Group in Alkenylation of C–H Bonds

Greaney has recently shown that ruthenium(II)-catalysed alkenylation of arylacetophenone C–H bonds with acrylates could further lead via cascade transformations to synthesis of heterocycles. First 1-indanones were selectively obtained as a major *trans*-isomer using $[RuCl_2(p\text{-cymene})]_2$ (5 mol%)/$AgBF_4$ (20 mol%) with $Cu(OAc)_2.H_2O$ (2 equiv.). The reaction is demonstrated to lead first to *ortho*-alkenylation and then the presence of $Cu(OAc)_2.H_2O$, and thus, free acetate allows the enolate formation and its Michael addition to the acrylic double bond (Eq. 42) [100].



(42)

By using diarylated acetophenones, the similar catalytic reaction led to the formation of tetracyclic compounds: indenoindenes (Eq. 43) [100]. This transformation is proposed to take place via radical formation promoted by $Cu(OAc)_2.H_2O$ [100].



(43)

3.3 *Alkenylation of Heterocycles with Ruthenium(II) Catalysts and Copper(II)*

3.3.1 The First Examples

Several examples of ruthenium(II)-catalysed alkenylation of heterocycles have just been presented above. The first example of alkenylation of heterocycles with functional alkenes was performed by Miura and Satoh using the carboxylic acid directing group with $[RuCl_2(arene)]_2$ catalyst with stoichiometric amount of

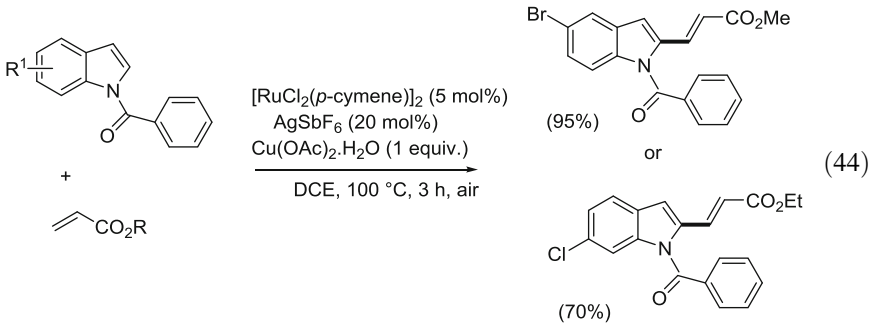
$Cu(OAc)_2$ as oxidant. They especially showed that Ru(II) catalyst did not decarboxylate heterocycles such as furan, thiophene or indole derivatives as did previously Pd catalysts (Eq. 9) [41].

Then, both Jeganmohan [79] and Ackermann [80], by showing the directing ability of the ester group for ruthenium-catalysed alkenylation, also reported a few examples of direct alkenylation of thiophene, furan and indole derivatives (Eq. 20) [79, 80].

Ackermann et al. also showed that the O-2-pyridyl group linked to thiophene or indole, in the presence of $[RuCl_2(arene)]_2$/4 $AgSbF_6$ with 1 equiv. of oxidant $Cu(OAc)_2$, could direct alkenylation of heterocycles (Eq. 35) [94].

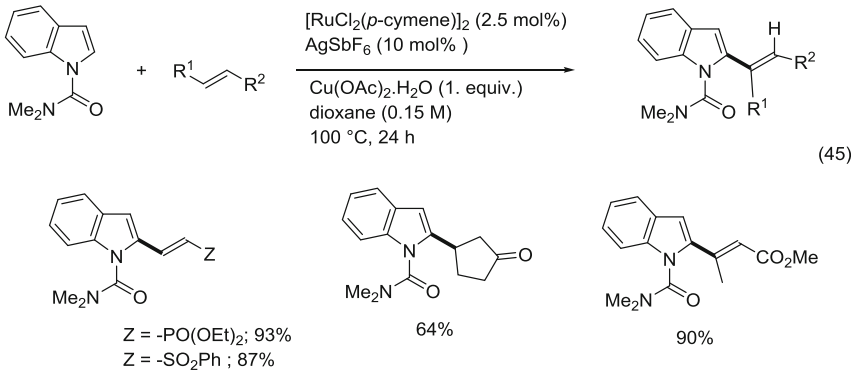
3.3.2 The Directing Ability of N-$CONR_2$ Groups of N-Containing Heterocycles

These pioneer examples of Ru(II)-catalysed alkenylation of heterocycles were directed by functional groups (FG): CO_2H, CO_2R and O-2-Py. In 2013, Prabhu demonstrated that a *N*-benzoyl group of indole could direct the alkenylation by acrylate at C_2 using the usual Ru(II)/$AgSbF_6$ catalytic system in the presence of $Cu(OAc)_2$ as oxidant (Eq. 44) [101]. It is noteworthy that with Pd(II) catalyst the alkenylation of indole takes place at C_3 and that the amide carbonyl does not direct alkenylation at *ortho*-positions of the phenyl group of the benzoyl or of the indole. The reaction tolerates a Cl or a Br group on the indole.

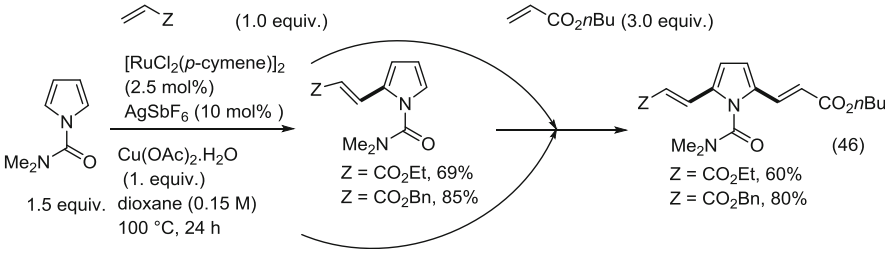


(44)

At the same time, by using the same type of Ru(II) catalytic system, Li and Wang have performed the alkenylation of indole containing a *N*,*N*-dimethyl amide group with a variety of functional alkenes: acrylate, styrene, *E*-methyl crotonate, vinylphosphonate and vinylsulfone. Cyclopentenone by contrast led to the addition product featuring a formal alkylation by alkene (Eq. 45) [102]. Competition experiments show that an electron-donating group on indole arene favours the reaction. This $CONMe_2$ directing group has the advantage of being easily removed with 6 equiv. of *t*BuOK at room temperature or with NaOH at 80°C in ethanol.

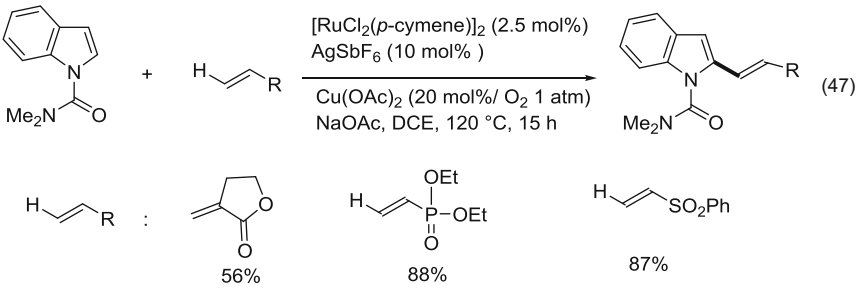


Analogously, under similar conditions with the same catalyst, the reaction of acrylate with N-protected dimethylamidopyrrole shows that the alkenylation successively takes place at C_2 and then C_5 positions thus leading to unsymmetrically dialkenylated pyrroles (Eq. 46) [102].



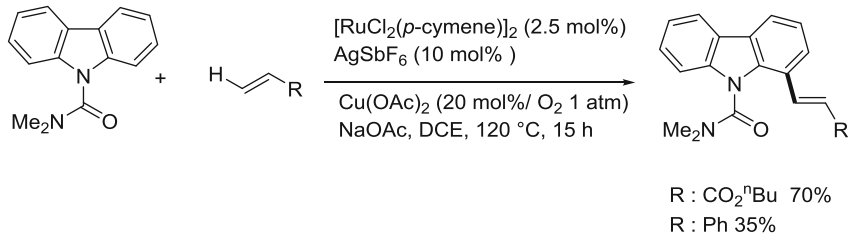
Song has also performed the direct alkenylation of indoles containing a removable *N*,*N*-dimethylcarbamoyl group, with acrylate derivatives, but also with unsaturated esters, phosphonates or sulfonyl derivatives and functional styrenes. The reaction is performed with $[RuCl_2(p\text{-cymene})]_2$/4 $AgSbF_6$ catalyst and catalytic amount (only 20 mol%) of $Cu(OAc)_2.H_2O$ in the presence of air. The profitable influence of NaOAc is surprisingly shown.

The direct alkenylation always takes place at the C_2–H carbon atom of the heterocycle, not at the *ortho* phenyl C–H bond adjacent to the Me_2NCO-N directing group (Eq. 47) [103].



(47)

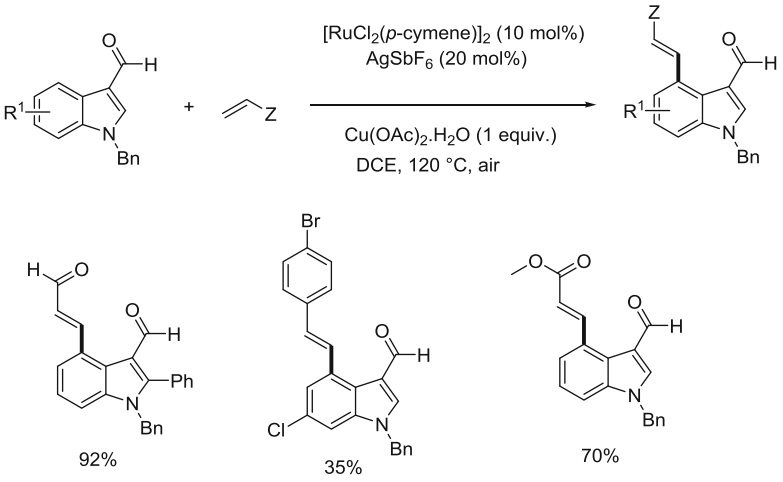
Under the same conditions, monoalkenylation or dialkenylation with acrylates of pyrrole can be selectively performed. More importantly, monoalkenylation of carbazole was achieved with either alkyl acrylates or styrene (Eq. 48) [103].



(48)

3.3.3 The Formyl Directing Group Ability in Heterocycles

Whereas most of the previous modifications of heterocycles took place at the heterocycle ring, in 2013, Prabhu showed the selective functionalisation of the C_4–H bond with no alkenylation at the C_2 position of *N*-protected indoles by introducing a formyl directing group at the C_3 position and by using the usual Ru (II)/$AgSbF_6$ catalytic system with $Cu(OAc)_2.H_2O$, (Eq. 49) [104]. These experiments, compared to the previous alkenylation of *N*-amide indole (Eq. 45), confirm that the *N*-amide group really directs alkenylation of indole at C_2 position. A cross experiment between *N*-benzoyl indole and the C_3-formyl *N*-amide-indole (Eq. 44) showed the preferential formation of the C_4-alkenyl C_3-formyl indole [104].

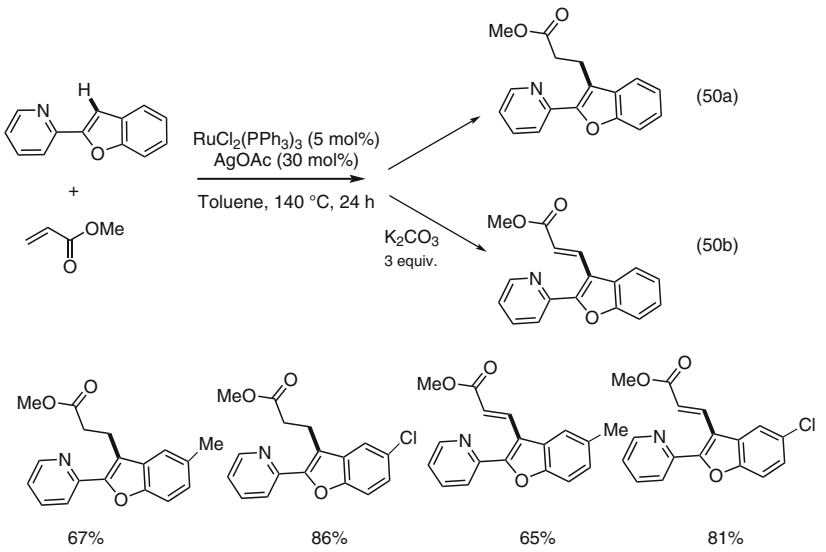


(49)

3.3.4 The Kommagalla–Ramana Alkenylation of Benzofurans: Evidence for Alkenylation Versus Alkylation

Alkenylation of furan and benzofuran derivatives with alkenes has been performed in several occasions with the Ru(II) catalyst and a Cu(II) salt as an oxidant, as for the C_3-alkenylation directed by C_2-CO_2Me group (Eq. 9) [41], or C_2-alkenylation directed by a C_3-CO_2Me group (Eq. 20) [79]. Kommagalla and Ramana have recently demonstrated crucial aspects of Ru(II)-catalysed alkenylation of benzofuran C–H bonds directly with alkene. They showed that changing the directing group to C_2-2-pyridyl group also favoured C_3–H bond activation but, more importantly, that only the presence or absence of base can tune the *alkenylation versus alkylation* of the C–H bond (Eq. 50) [105].

Thus, 2-pyridyl C_2-substituted benzofuran and methyl acrylate with $RuCl_2(PPh_3)_3$ (5 mol%)/AgOAc (30 mol%) catalyst react in toluene at 140°C for 24 h and lead to unique *alkylation* at C_3 (Eq. 50a) [105], thus corresponding to a formal insertion of alkene double bond into the C_3–H bond. More importantly under the same conditions except the addition of 3 equiv. of K_2CO_3, only the *C_3-alkenylation* was observed (Eq. 50b), thus demonstrating that carbonate is crucial for alkenylation and that the AgOAc acetate alone is not performing alkenylation. However, when $Cu(OAc)_2$ was used instead of AgOAc without K_2CO_3, the C_3-alkenyl (43%) and C_3-alkylated (31%) products were obtained, showing that $Cu(OAc)_2$ acetate is also operating as a base. These simple results bring crucial information for the first time to understand the mechanism.

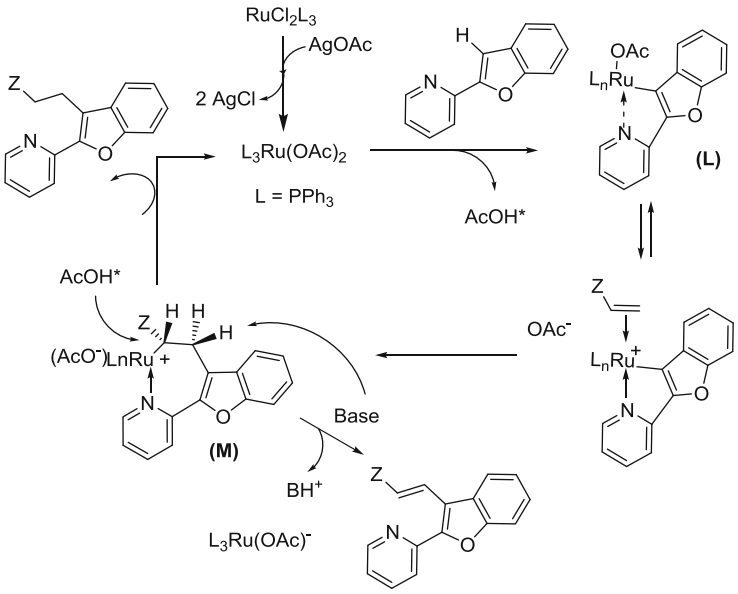


Kommagalla and Ramana [105] have proposed that the five-membered cyclometallate **L** is first produced via C–H bond deprotonation with AgOAc acetate, followed by coordinative insertion of the alkene (Scheme 6). The addition of the nucleophilic (Ru–C) carbon to the alkene electrophilic carbon to form the seven-membered cyclometallate **M** is thus expected. As the pyridine is strongly coordinating the Ru(II) site, further classical β-elimination is not possible from this rigid ruthenacycle, as the Ru–Cα and Cβ–H bonds cannot be coplanar and in *syn* position. Thus, AcOH protonation of the Ru–Cα bond takes place to form the alkylated product (Scheme 6).

In the presence of carbonate, this seven-membered cyclometallate **M** is deprotonated at the Cβ–H bond, at the *anti*-position of the Ru–Cα bond to give the alkenylated product and a Ru(0) species that can be reoxidised into a Ru(II) species with the available silver salt in the presence of acetic acid (Scheme 6). This mechanism brings light to the general Ru(II)-catalysed reaction of the C–H bond with alkene leading to either alkenylation or alkylation.

Each time a strong rigid metallacycle is formed via alkene insertion, the β-elimination will not take place and thus lead to the alkylated product when acid such as AcOH is present. By contrast with weakly bonding directing group (DG), the dissociation of this DG group may allow β-elimination and formation of the LnRu(H)(OAc) intermediate, even in the absence of a base. However, in the presence of large amount of base, the Cβ–H bond deprotonation should be favoured.

It is noteworthy that recently the nitrile ability to direct alkenylation of aromatic nitriles with ruthenium catalyst (Eq. 40) has been used by Jeganmohan to reach

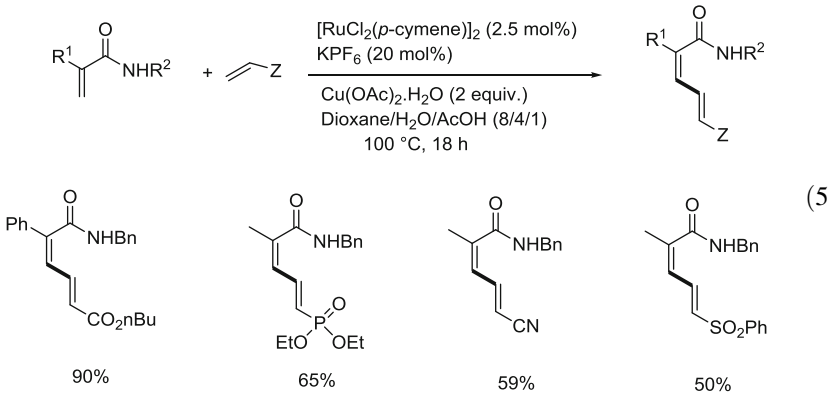


Scheme 6 Proposed mechanism for the alkenylation versus alkylation with alkenes

mono C_3-alkenylation of 2-nitrile thiophene, whereas 3-nitrile thiophene led easily to C_2- and C_4-dialkenylation [98].

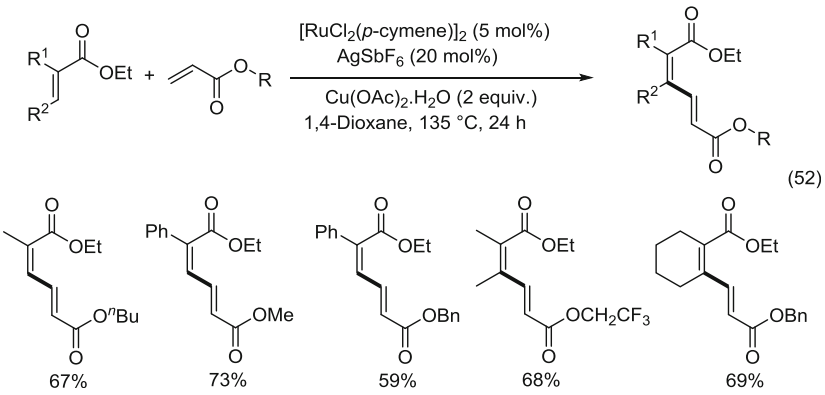
3.4 Alkenylation of Alkene C–H Bonds with Ruthenium(II) and Copper(II)

The ruthenium(II) alkenylation of functional alkenes has been performed for the first time by Loh [86]. He demonstrated the successful synthesis of (*Z*,*E*)-dienamides upon alkenylation of acrylamides with electron-deficient alkenes in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) and 20 mol% of KPF_6, with 2 equiv. of oxidant $Cu(OAc)_2.H_2O$ and a small amount of acetic acid. Thus, substituted acrylamides reacted with various functional alkenes containing the CO_2R, CONHBn, $PO(OEt)_2$, CN, SO_2Ph or 4-Cl phenyl group to lead to the (*Z*,*E*)-dienamides, and the reaction of *N*-aryl methacrylamides with acrylate gave the desired products in 31–39% yield (Eq. 51) [86].



(51)

Loh also showed the cross coupling of two acrylate derivatives leading stereoselectively to (*Z*,*E*)-muconates which was achieved at 135°C with a closely related catalytic system involving an additional amount of $AgSbF_6$ (20 mol%) as additive. The self-alkenylation of unsubstituted acrylates was possible, but due to steric hindrance, 2-substituted propenoic acid esters were not self-alkenylated, which made the heterocoupling of diversely substituted acrylate derivatives with simple acrylates very effective in the presence of an excess of the latter (Eq. 52) [81].



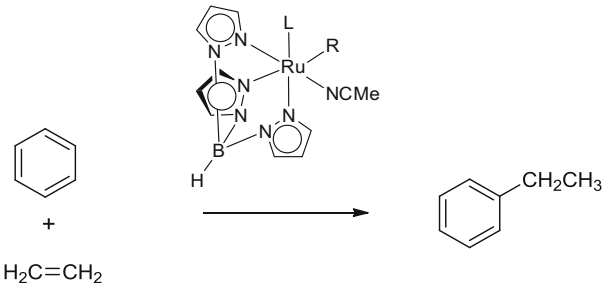
(52)

4 Alkylation with Alkenes of Arene and Heterocycle sp^2C–H Bonds with Ruthenium(II) Catalysts

4.1 Alkylation of Arenes with Alkenes

The formal insertion of an alkene into a sp^2C–H bond of arene, or hydroarylation of olefins, corresponds to an atom economy reaction. This alkylation of functional arenes by alkenes, rather than alkenylation, was first observed as the preferential

reaction with Ru(0) catalysts in the Murai reaction [21–26]. It involves the oxidative addition of the arene C–H bond to Ru(0) species. Gunnoe has reported first that ruthenium(II) catalysts promote the addition of benzene C–H bond to ethylene C=C bond to form ethylbenzene. The ruthenium(II) catalysts used are of type TpRu-R(L)(NCMe) (Tp=hydrotris(pyrazolyl)borate) (Eq. 53) [45, 106–110].



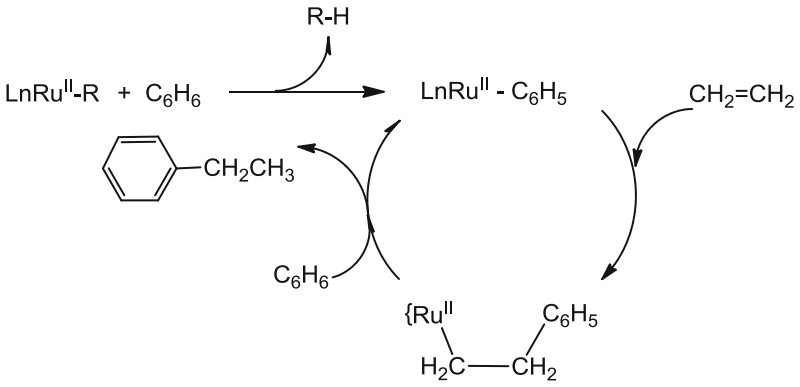
(53)

Kinetic studies and calculations have shown that the mechanism does not involve an oxidative addition of C–H bond and a ruthenium(IV) species, but undergoes the formation of Ru(II)–C_6H_5 species resulting from benzene coordination to the TpRu-R(L) intermediate and alkane R–H elimination. The insertion of ethylene into the Ru(II)–C_6H_5 bond leads to a Ru(II)–$CH_2CH_2C_6H_5$ species, which reacts with benzene to produce ethylbenzene (Scheme 7) [106–111].

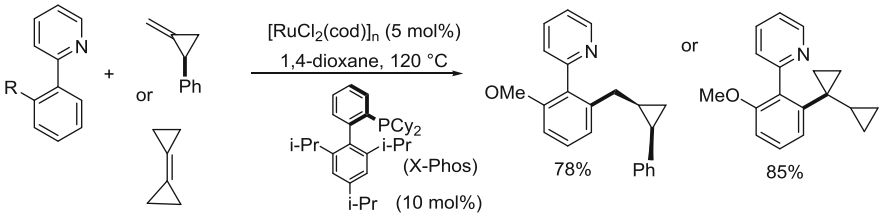
The rate-determining step, favoured by electron-donating ligands L, is the C–H bond activation of the coordinated benzene by TpRu-R(L). By contrast, the withdrawing ligand L=CO decreases the energy barrier of the olefin insertion [111].

The catalyst TpRu-Me(L)(NCMe) similarly promotes the alkylation of heterocycles, thiophene and furan, via the formation of isolated intermediates TpRu(CO)(NCMe)(2-thienyl) and TpRu(CO)(NCMe)(2-furyl). The TpRu(CO)(NCMe)(2-thienyl) does catalyse the insertion of ethylene into the C_2–H bond of thiophene [112].

Ackermann has shown as early as 2008 the direct ruthenium(II)-catalysed intermolecular hydroarylation of highly strained methylenecyclopropanes using the $[RuCl_2(cod)]_n$ catalyst in the presence of the bulky electron-donating monophosphine XPhos. The hydroarylation of phenyl-substituted methylenecyclopropane and bicyclopropylidene was produced at the *ortho* C–H bond of phenylpyridine. The hydroarylation leads to the formation of *cis*-disubstituted cyclopropanes (Eq. 54) [113].



Scheme 7 Proposed mechanism for the TpRu-R(L) catalyzed hydroarylation of ethylene

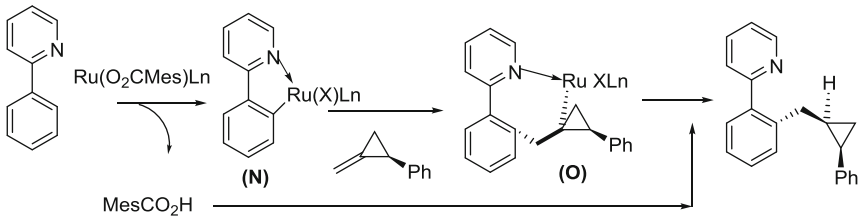


(54)

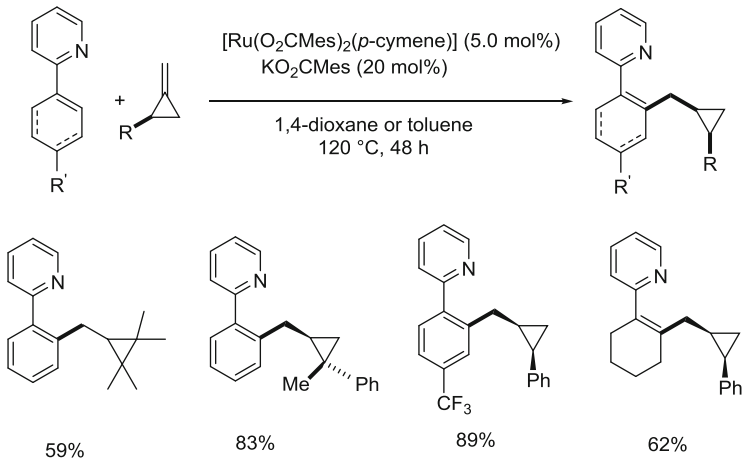
Recently, Ackermann extended this ruthenium(II)-catalysed hydroarylation of methylenecyclopropanes to a variety of *ortho* C–H bonds of 2-arylheterocycles directed by pyridine, oxazoline, diazole, pyrimidine, etc., using the same catalytic system [$RuCl_2$(cod)]$_2$/(XPhos). In some examples, an *anti*-Markovnikov addition was observed, or a ring opening occurred leading to Diels–Alder products [114].

The use of C_6D_5-Py showed a partial deuterium retention in the resulting alkyl group, and the authors suggest an oxidative addition of the C–H bond to the ruthenium(II) site, alkene insertion into the Ru–H bond and C–C bond formation via reductive elimination. However, this mechanism taking place previously with Ru(0)-catalysed Murai-type reaction [21–26] may not take place with a ruthenium(II) species even enriched by basic phosphine, and an alternative mechanism can be suggested later (Scheme 8).

Ackermann has now shown that a catalyst containing carboxylate ligand Ru(O_2CMes)$_2$(*p*-cymene) with 20 mol% of KO_2CMes is more efficient than the previous [$RuCl_2$(cod)]$_2$/phosphine catalyst to perform the same reaction (Eq. 55) [115]. This reaction is now highly regioselective and stereoselective without ring opening and can be applied to alkylation of cyclohexene C–H bond directed by a 2-pyridyl group.



Scheme 8 Alternative mechanism for the alkylation of phenylpyridine with methylidenecyclopropane

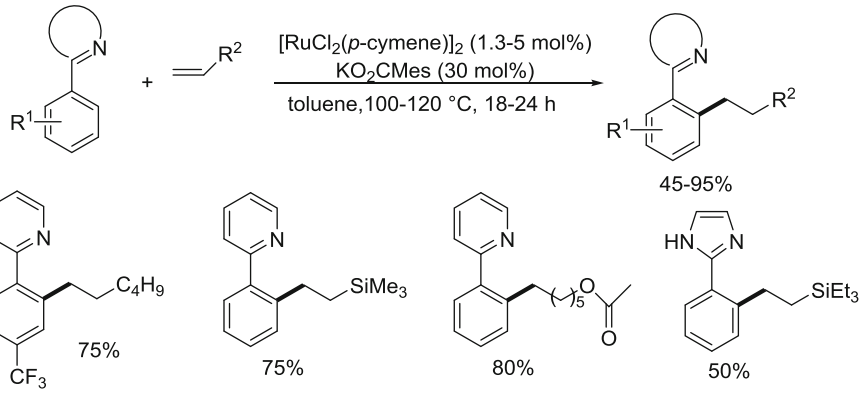


(55)

The authors suggest the initial insertion of the Ru(II) centre into the C–H bond and insertion of the alkene bond into the Ru–H bond [114, 115]; however another possible mechanism (Scheme 8) involves the classical Ru(II) activation of the *ortho* C–H bond via C–H deprotonation with carboxylate and cyclometallate **N** formation from phenylpyridine and formation of carboxylic acid [37]. The insertion of the C=C bond into the Ru–C bond corresponds to the *cis*-addition of the Ru–C bond to the less hindered face of the alkene, opposite to the substituent, to give the intermediate **O**. The protonation of the Ru–C(cyclopropyl) bond by the freed $MesCO_2H$ acid affords the alkylated product (Scheme 8). It is noteworthy that this alkylation occurs with strongly coordinating directing group pyridine, e.g. when rigid metallacycles are disfavouring β-elimination to form the corresponding alkene (see Scheme 6).

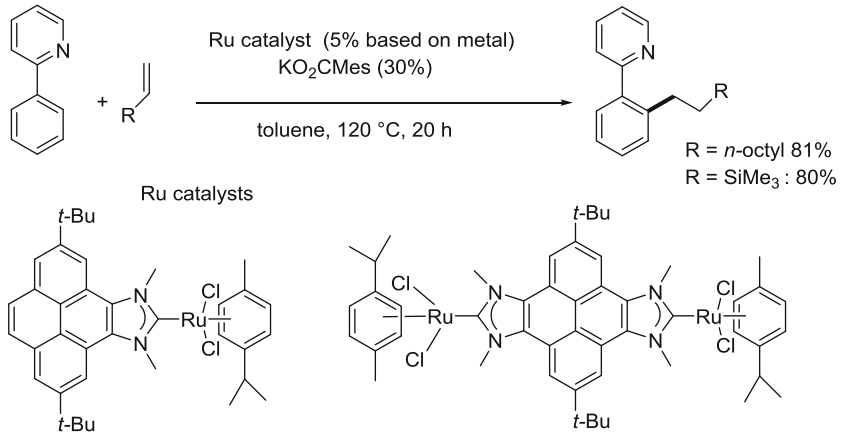
With the in situ generated carboxylate–Ru(II) catalyst $Ru(O_2CMes)_2(p\text{-cymene})$ from $[RuCl_2(p\text{-cymene})]_2$ and KO_2CMes, the alkylation of arene C–H bonds with unactivated and unstrained alkenes was performed by Ackermann in toluene and even in H_2O. Unactivated alkenes with a distant functional group such as ether, ketone, hydroxyl, ester and fluorine groups led to *ortho*-monoalkylated products (Eq. 56) [116]. The *ortho* C–H bond activation is directed by strongly coordinating

nitrogen-containing heterocycles which also disfavour the alkenylation from the seven-membered cyclometallate. No alkenylation was observed.



(56)

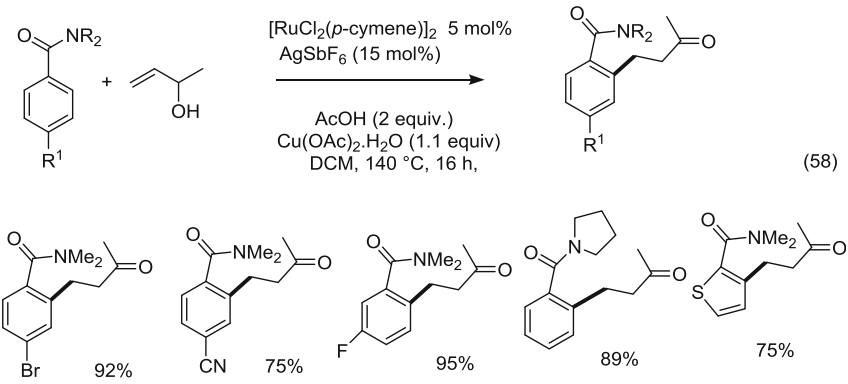
Peris has recently prepared mono- and di-*N*-heterocyclic carbenes based on pyrene and their related ruthenium(II) complexes and evaluated them for catalytic arylation and alkylation with alkenes of phenylpyridine. With nonactivated alkenes in the presence of KO_2CMes, both catalysts lead to only mono *ortho*-alkylation and show the same activity (Eq. 57) [117], with similar efficiency as the previous system $Ru(O_2CMes)_2(p\text{-cymene})$ [116]. However, these catalysts allow two cross *ortho* C–H bond functionalisations sequentially: alkylation with alkene and then arylation with phenyl bromide [117].



(57)

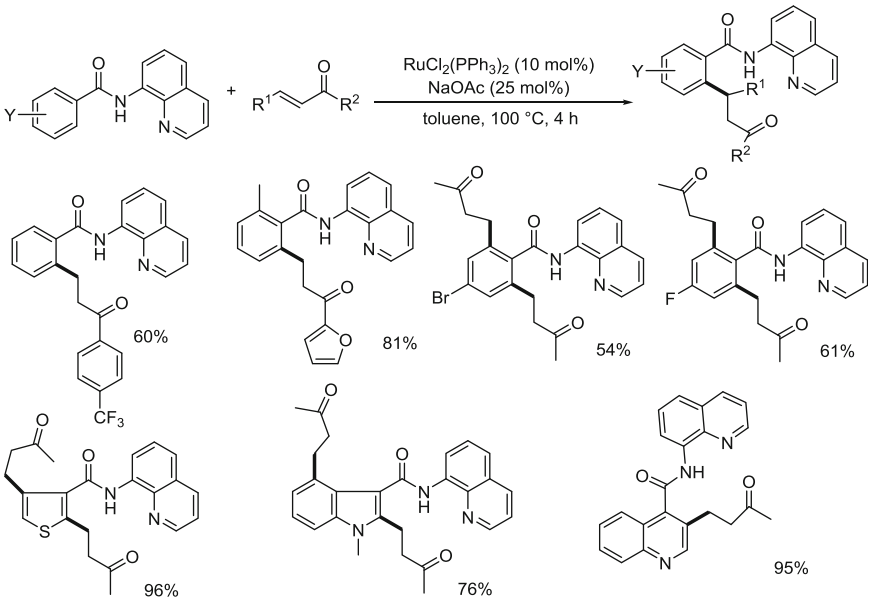
In 2013, Huanfeng Jiang used the amide group $CONR_2$ to direct the ruthenium(II)-catalysed *ortho*-alkylation of arenes on reaction of arylamides but with *allylic alcohols* [84]. The reaction was performed with $[RuCl_2(p\text{-cymene})]_2$ catalyst in

the presence of $AgSbF_6$ and 1 equiv. of $Cu(OAc)_2.H_2O$ but also in the presence of 2 equiv. of AcOH. Thus, the reaction allows the selective formation of β-aryl ketones (Eq. 58) [84] and tolerates arene functional groups such as Br, CN, NO_2 and F. The alkylation occurs at the less sterically hindered *ortho* C–H bond, as shown from *meta*-substituted arylamide. It can be extended to thiophene derivative containing the C_2-$CONMe_2$ group directing the alkylation only at C_3. Jiang also showed that this reaction can be catalysed with $[RhCl_2Cp^*]_2$ with $AgSbF_6$ (7.5 mol %) and 1 equiv. of $Cu(OAc)_2.H_2O$, which allowed *ortho*-dialkylation of arylamides in *t*-butanol/water solvent, without the addition of AcOH [84]. In that case, the $CONR_2$ group is a weakly coordinating group, but the reaction is made in the presence of AcOH which favours both C–Ru bond cleavage and alkylation.



The mechanism is not described, but a realistic proposal can be made based on the recent reported ruthenium(II)-catalysed *ortho*-alkenylation, by Jeganmohan (Eq. 27) [85] of aryl-CONHR derivatives also with allylic alcohols, followed by isoindolinone formation and the recent demonstration by Kommagalla and Ramana on the *alkenylation versus alkylation* of benzofuran (Eq. 50) [105]. Thus, Jeganmohan showed that allyl alcohol is first dehydrogenated into unsaturated ketone leading to alkylation under acidic conditions, and Kommagalla and Ramana demonstrated that alkenylation takes place in the presence of base. Thus, it is expected that the Ru(II) catalyst generates the unsaturated ketone by hydrogen transfer, the enone double bond inserts into the Ru–C bond of the cyclometallate intermediate to give a seven-membered cyclometallate for which the β-elimination is disfavoured and, thus, protonation with AcOH of the Ru–C bond is expected to give the alkylated product (see Scheme 6 mechanism).

In 2013, Chatani has reported the ruthenium(II)-catalysed *ortho* C–H bond alkylation of aromatic amides with a variety of α,β-unsaturated ketones using the 8-aminoquinoline bidentate directing group. The best catalyst was based on $RuCl_2(PPh_3)_3$/NaOAc system (Eq. 59) [118]. The reaction of 2-substituted aromatic amides afforded monoalkylated products, whereas for *para*-substituted arylamides, the *ortho*-dialkylated amides were preferentially produced.



(59)

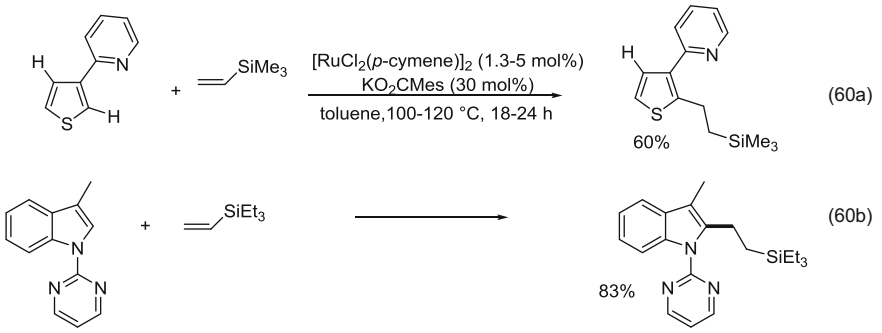
It is noteworthy that unsaturated ketones containing an electron-withdrawing C=O group facilitate this reaction by contrast to styrene and 1-hexene. The H/D exchange occurred in the cleavage of the *ortho* C–H bond, even in the absence of the alkene, and of the N–H bond indicating that the N–H bond is also involved in the reaction. The mechanism is not clear for this transformation, but the catalytic conditions are closely related to those giving cyclometallate intermediate by C–H bond deprotonation by acetate. Then, the insertion of the ketone double bond into the Ru–C bond could be postulated leading to a rigid strong seven-membered metallacycle, due to strong coordination of the chelating group, from which the β-elimination is not possible. Protonation of the Ru–C bond by the formed AcOH would then release the alkylated product.

4.2 Alkylation of Heteroarenes with Alkenes

4.2.1 Alkylation of Heterocycles with $Ru(O_2CR)_2L_n$ Catalyst

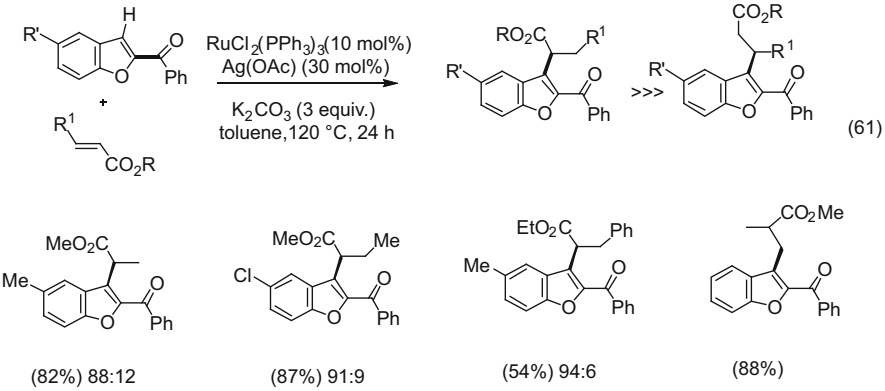
Ackermann has reported that the in situ generated carboxylate–Ru(II) catalyst $Ru(O_2CMes)_2$(*p*-cymene), for the alkylation of arene C–H bonds with unactivated and unstrained alkenes (Eq. 56) [116], could be profitably used for alkylation with vinylsilanes of heterocycles. This alkylation was applied to indole and thiophene derivatives and proceeded in site-selective manner, but it is noteworthy that

they were directed by strongly coordinating nitrogen-containing groups such as 2-pyridyl for thiophene (Eq. 60a) and *N*-2-pyrimidyl for indole (Eq. 60b) [116].



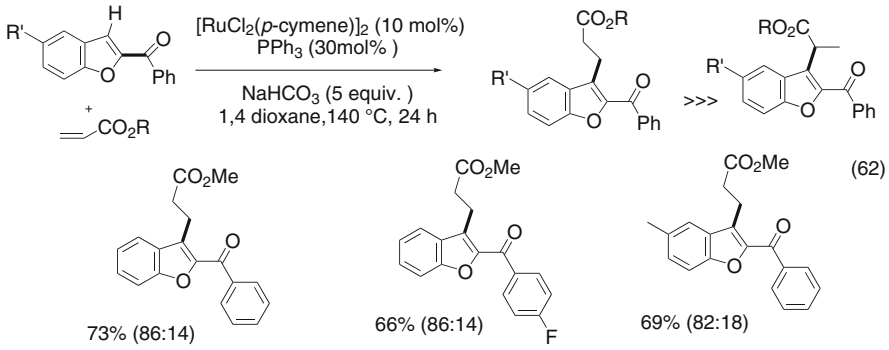
4.2.2 First Branched Alkylations Observed for Benzofuran

Kommagalla and Ramana have shown a unique way of Ru(II)-catalysed alkylation with acrylates applied to benzofuran directed by a C_2-benzoyl group. They showed that the COPh group does favour the alkylation at carbon C_3, but more importantly they found for the first time the formation of the branched alkylated isomer via hydroarylation of acrylates (Eq. 61) [119]. The catalyst is based on $RuCl_2(PPh_3)_3$ (5 mol%) with 30 mol% of additive $PivCO_2H$ or $MesCO_2H$ with K_2CO_3 (3 equiv.) as a base, but better efficiency was found with AgOAc (30 mol%) as additive. However, with methyl methacrylate, only the linear product was formed; thus, the substituent at alkene C_2 carbon disfavours the alkene C_2-(furan)–C bond formation.

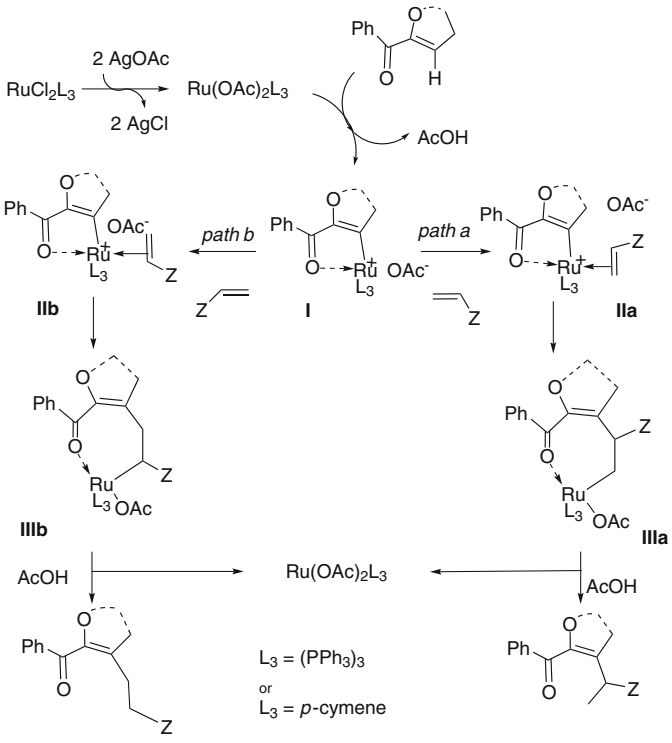


However, the linear alkylation of the same benzofuran with acrylate can be restored using the $[RuCl_2(p\text{-cymene})]_2$ catalyst (10 mol%) with 30 mol% of PPh_3 with

no other additive but with $NaHCO_3$ (5 equiv.) as base and proton source as well (Eq. 62) [119].



The rational mechanism (Scheme 9) proposes the initial formation of $Ru(OAc)_2L_3$ catalytic species leading to cyclometallate **I**, accepting the coordination of the olefin that can insert either from conformation **IIa** or **IIb** according to the nature of L_3 being $(PPh_3)_3$ and *p*-cymene, respectively.



Scheme 9 Proposed mechanism for branched versus linear alkylation with alkenes

It is thus proposed that the steric hindrance of the $(PPh_3)_3$ ligands favours the insertion of alkene with its terminal carbon forming the C–Ru bond in **IIIa** and that its protonation with AcOH leads to the branched alkylated product. Alternatively, with L_3 ligand being *p*-cymene, the electrophilic β-carbon of the acrylate binds preferentially to the carbon of the more polar Ru–C bond in **IIb** than in **IIa** to give **IIIb**, which on protonation by AcOH or $NaHCO_3$ leads to the linear alkylated product (Scheme 9) [119].

5 Conclusion

The direct ruthenium(II)-catalysed oxidative dehydrogenative reaction of simple alkenes with functional arenes, heterocycles and even alkenes and ferrocene derivatives has become in a few years since 2011 a straightforward and inexpensive method to produce multiple functionalised alkenes, and new applications are reported every month [120–123]. Ruthenium(II) catalysts not only offer the advantages of their low-cost metal source, easiness of preparation and stability even in the presence of water which allows their use in water as solvent, but they have been shown efficient actors for innovations in synthesis. Most of the time for alkenylation, the ruthenium(II) catalytic reaction requires $AgSbF_6$, a halide abstractor, plus an oxidant such as $Cu(OAc)_2$ or sometimes Ag(OAc), and these oxidants can be used in catalytic amount but in the presence of air.

The activation of the *ortho* sp^2C–H bond is directed by a variety of strongly coordinating functional groups such as 2-pyridyl or other nitrogen-containing heterocycles. Recently, a variety of weakly coordinating groups, which were not efficient for direct arylation of the same *ortho* C–H bonds, have been shown to direct very efficiently *ortho*-alkenylation. These include ketone, formyl, ester, amide of type CONRR' or NHCOR, amidine, azoxy, sulfonic acid, sulfonamide and sulfoximine, carbamate or carboxylate as phenol protecting groups and even a few examples of free amine, free alcohol and nitrile.

The presence of acetate linked to the oxidant is not innocent as carboxylates are crucial partners of the Ru(II) centre to activate the *ortho* sp^2C–H bond via deprotonation with external carboxylate to produce very easily a five-membered cyclometallate able to insert into its Ru–C bond a variety of functional alkenes from acrylate derivatives to styrenes or non-electrophilic alkenes.

It is shown especially with strongly coordinating directing groups that the formation of the alkenylated product requires the presence of a base, such as carbonate, but sometimes, carboxylate can operate alone. This has been demonstrated in the case of heterocycles. This chapter supports that this observation results from the formation of a rigid stable seven-membered cyclometallate which cannot lead easily to β-elimination, and thus, the alkenylation product arises from β-C–H deprotonation by the base.

The ruthenium(II)-catalysed reaction of similar functional arenes and heteroarenes with alkenes can also lead to *ortho-alkylation* instead of alkenylation, via

hydroarylation of the alkene. The first example of formation of the branched alkylation product has been shown with heterocycles. This alkylation is shown to occur with strained alkenes such as methylidene cyclopropanes, but also with strongly coordinating functional groups such as nitrogen-containing heterocycles, and strongly chelating 8-aminoquinoline bidentate groups. It also occurs with amide directing group but in the presence of proton source AcOH, or $NaHCO_3$ with heterocycles. It is demonstrated with heterocycle C–H bond that alkylation product is formed in the absence of base. This chapter supports the point that this observation results from the formation of a rigid stable seven-membered cyclometallate, which cannot lead to β-elimination, and thus, the presence of acid or proton source favours the protonation of Ru–C bond of the metallacycle and releases the C-alkylated product.

The easy ruthenium(II)-catalysed activation of C–H bond offers many challenges to overcome. No doubt that simple or new ruthenium catalysts will be evaluated as an attempt to favour the difficult functionalisation of the Ru–C carbon of the cyclometallate intermediate, and no doubt that future investigations and developments of ruthenium(II)-catalysed activation of C–H bond will deal more with the functionalisation of sp^3C–H bonds.

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