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Ruthenium-Catalyzed Carbonylative Synthesis of Heterocycles

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Abstract The main achievements on ruthenium-catalyzed carbonylative synthesis of heterocycles have been summarized and discussed.

Keywords Carbon monoxide • Carbonylation • Heterocyclic compounds • Organic synthesis • Ruthenium catalyst

Content

Ruthenium catalysts are more known as catalysts in metathesis which have been verified by the Nobel Prize in Chemistry in 2005 as well. And the achievements of ruthenium catalysts in other organic transformations are somehow ignored. In this chapter, we summarized the applications of ruthenium catalysts in carbonylation reactions. Heterocycles were prepared with carbon monoxide as the C1 source.

In 1989, Alper and coworkers reported a method for the formation of γ-butyrolactone transformed from oxetane (Scheme 1) [1]. They found that $Ru_3(CO)_{12}/Co_2(CO)_8$ is the best catalytic system for carbonylative transformation of thietane and related analogues. Moreover, the ring-expansion process is regiospecific for both classes of heterocycles with carbonyl insertion occurring into the less steric carbon-heteroatom of the two bonds.

Later, Wang and Alper utilized these Ru/Co carbonyls to catalyze rearrangement and cyclization reactions to produce lactams from heterocyclic nitrogen ketones

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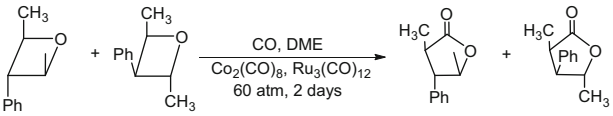
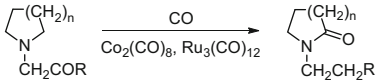
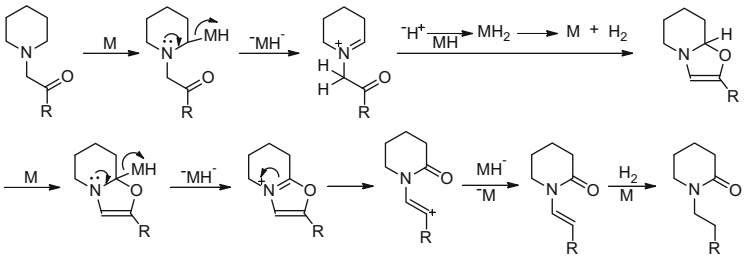


Scheme 1 Regiospecific carbonylative ring expansion catalyzed by Ru/Co carbonyls



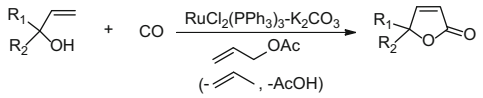
Scheme 2 Ru/Co carbonyls catalyzed ring-expansion carbonylation



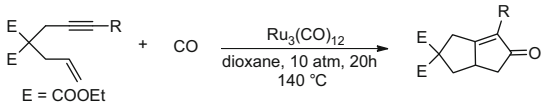
Scheme 3 Mechanism for Ru/Co carbonyls catalyzed rearrangement and cyclization

(Scheme 2) [2]. The reaction is regiospecific in most cases; moreover, when the ruthenium carbonyl acted as a co-catalyst, the yield of the product can be increased significantly, while there was no reaction occurred with $Ru_3(CO)_{12}$ as the only catalyst. In addition, the novel rearrangement reaction can be applicable to heterocycles containing either aliphatic or aromatic ketone side-chain groups which may involve a net oxidation at a ring carbon bonded to nitrogen. Several labeling experiments were taken to elucidate the reaction pathway (Scheme 3) [3]. It was demonstrated that five- to eight-membered ring nitrogen heterocycles are applicable as substrates and afford the corresponding products in excellent yields.

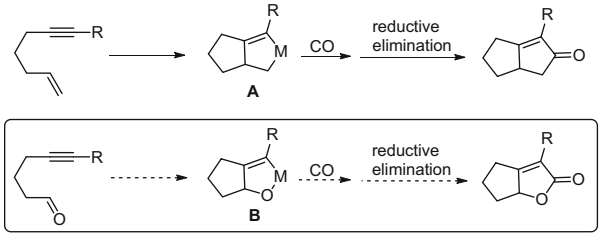
In 1994, a new route direct to 2(5*H*)-furanones via ruthenium-catalyzed oxidative cyclocarbonylation of allylic alcohols was reported by Watanabe and coworkers (Scheme 4) [4]. In the presence of catalytic amount of $RuCl_2(PPh_3)_3$, several 2(5*H*)-furanones were obtained in moderate to highly yields from the 1,1-disubstituted allylic alcohols. However, when monosubstituted allylic alcohols were treated under the same reaction condition, there were no desired products occurred. Catalysts like $NiBr_2(PPh_3)_3$, $RhCl(PPh_3)_3$, $PdCl_2(PPh_3)_2$, and $PtCl_2(PPh_3)_2$ were also taken into consideration; all of them were totally ineffective and no carbonylation were taken place. The addition of allylic acetate seems to be essential for the selective synthesis of 2(5*H*)-furanones. There was no carbonylated product formed in the absence of allyl acetate or other hydrogen acceptors such as acetone, cyclohexene, and diphenylacetylene. In addition, K_2CO_3 was considered



Scheme 4 Ruthenium-catalyzed oxidative cyclocarbonylation of allylic alcohols



Scheme 5 $Ru_3(CO)_{12}$ catalyzed cyclocarbonylation of 1,6-enynes to bicyclo[3,3,0]octenones

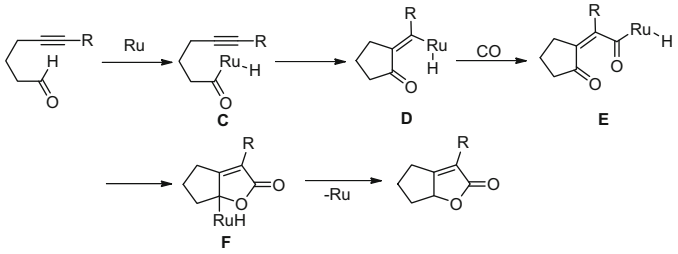


Scheme 6 Metal-catalyzed carbonylative synthesis lactones

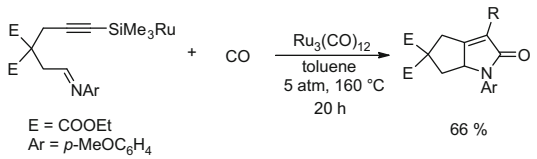
as the carbonyl source initially, while based on the controlled experiment of ^{13}C-labelled K_2CO_3, it only act as a base for trapping acetic acid generated by the hydrogenolysis of allyl acetate.

Three years later, Murai and coworkers presented the cyclocarbonylation of enynes to cyclopentenones with $Ru_3(CO)_{12}$ as the catalyst (Scheme 5) [5]. Trimethylsilyl-substituted enynes can be transformed with 2 mol% of $Ru_3(CO)_{12}$ under 20 atm of CO in toluene, and the silyl group can be converted into other functional groups in a variety ways [6–8]. When the reaction was run at 160°C, 72% isolated yield can be obtained. However, when it was treated at 140°C, the yield decreased to 61% and there was no reaction when the temperature was set at 100°C.

Based on this research, it can be found that the reaction of 1,6-enynes with a transition metal gives rise to bicyclic metallocyclopentene **A** or related complexes which may undergo insertion of CO followed by reductive elimination to give cyclopentenones [9]. Additionally heteroatom containing metallocyclopentenes **B** has been reported that with Ti and Zr [10–15]. If the metallocyclopentene **B** is formed from the reaction of yne-aldehyde with a late transition metal under CO atmosphere, it would be expected that **B** could undergo the insertion of CO and the resultant carbonylated metallacycle could then undergo reductive elimination to give bicyclic α,β-unsaturated lactones (Scheme 6). Murai's group employed yne-aldehyde and treated with CO in toluene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ at 160°C. The desired bicyclic lactone was formed in 82% isolated yield. This represents the first catalytic transformation of yne-aldehydes to bicyclic α,β-unsaturated lactones. Moreover, it also represents the first report of the



Scheme 7 Mechanism of Ru-catalyzed cyclocarbonylation of yne-aldehyde to lactone



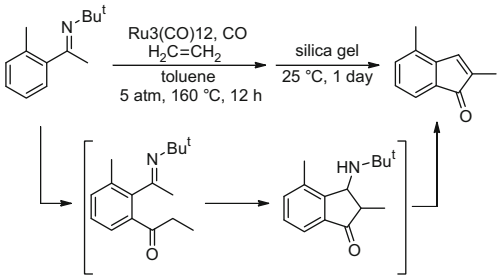
Scheme 8 Ru-catalyzed yne-imine with CO leading to bicyclic α,β-unsaturated lactam

synthesis of five-membered lactones via a [2 +2 +1] cyclization reaction, incorporating the aldehyde π-bond, the alkyne π-bond, and the carbon atom of CO into a five-membered ring.

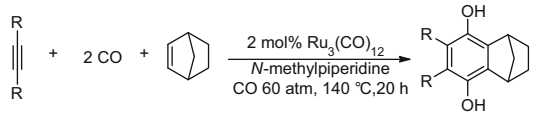
Solvents, catalyst complexes and the pressure of CO were screened; different substituted yne-aldehyde gave moderate to excellent yields under optimized conditions. From the obtained results, it can be found that when R is a small group, such as a methyl group, a reductive elimination from **D** can take place. The more bulky R group facilitates the insertion of CO and gives the final product (Scheme 7).

Another Ru-catalyzed carbonylation reaction to synthesize bicyclic α,β-unsaturated lactam form yne-imines was also developed by Murai' s group (Scheme 8) [16]. In this procedure, the cyclocarbonylation of 1,6- and 1,7-yne-imines was realized in the presence of catalytic amount of $Ru_3(CO)_{12}$. A variety of substituents like alkyl, aryl, and silyl on the acetylenic terminal carbon are tolerated and provide the bicyclic α,β-unsaturated lactams in good yields. In all cases, yields of this reaction were somehow lower than those in the case of yne-aldehyde.

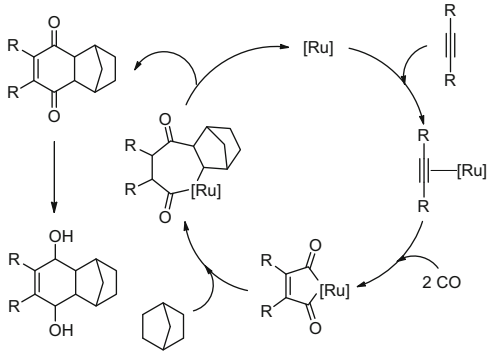
In 1997, Murai and coworkers reported a new synthetic method for the preparation of indenones based on the Ru-catalyzed carbonylation of aromatic imines at an *ortho* C–H bond (Scheme 9) [17]. This reaction involves the effective carbonylation at a C–H bond in the benzene ring [18, 19]. Notably, no reaction occurred in the absence of ethylene and CO. In addition, it was found that olefins such as 1-hexene, styrene, and methylacrylate couldn't react with the imine, while *tert*-butylethylene can give the corresponding indenone in 41% yield. Different substituted aromatic imines were tested as well; electron-withdrawing group on the aromatic ring will decrease the yield significantly and carbonylation always takes place at the less sterically hindered C–H bond.



Scheme 9 Ru-catalyzed carbonylation of the aromatic imine

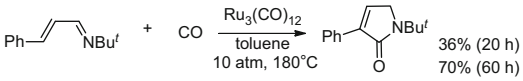


Scheme 10 Ru-catalyzed cross-carbonylation of alkyne and 2-norbornene to hydroquinone

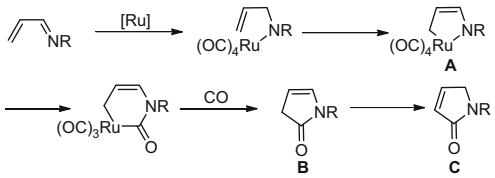


Scheme 11 Mechanism of Ru-catalyzed cross-carbonylation of alkynes and norbornenes to hydroquinones

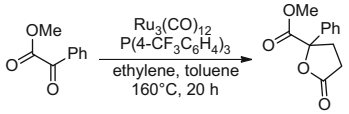
Mitsudo and his research group developed a novel ruthenium-catalyzed cross-carbonylation of alkynes and alkenes [20]. It was the first example about the selective synthesis of unsymmetrically substituted hydroquinones from alkynes, 2-norbonenes, and carbon monoxide (Scheme 10). A series of different substituted alkynes were tested and the corresponding hydroquinones were produced in high yields. It should be noted that the norbornene skeleton is essential for the present reaction, which indicates that the reaction selectively occurred on the olefinic moiety in the norbornene skeleton rather than on the ethylidene moiety. Moreover, there was no reaction occurred with the terminal alkyne. Finally, a proposed mechanism was presented that a maleoylruthenium complex would be obtained by the reaction between an alkyne and two molecules of carbon monoxide, which acted as a key intermediate for the follow-up reactions (Scheme 11).



Scheme 12 Ru-catalyzed carbonylative [4 + 1] cycloaddition to γ-lactam from α,β-unsaturated imine



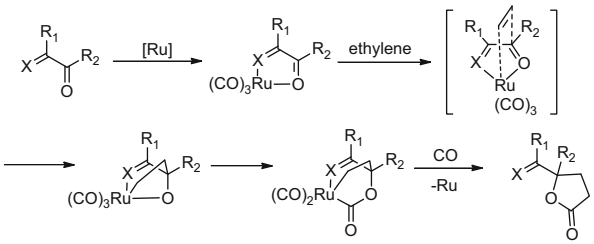
Scheme 13 Mechanism for Ru-catalyzed [4 + 1] cycloaddition of α,β-unsaturated imine with CO



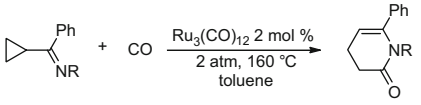
Scheme 14 Ru-catalyzed [2 + 2 + 1] cycloaddition of ketones, olefins, and CO

In 1999, Murai and coworkers reported a new procedure for the transformation of α,β-unsaturated imines to the corresponding unsaturated γ-lactams via Ru-catalyzed carbonylative [4 + 1] cycloaddition [21, 22]. Initially, the α,β-unsaturated imine which was derived from the reaction of *trans*-cinnamaldehyde with *tert*-butylamine, with toluene as the solvent in the presence of a catalytic amount of $Ru_3(CO)_{12}$ at 180°C for 20 h, 36% of 1,5-dihydro-1-(1,1-dimethylethyl)-3-phenyl-2*H*-pyrrol-2-one, can be formed. When the reaction time to 60 h is prolonged, the isolated yield can be increased to 70% (Scheme 12). However, when the substituents on the nitrogen atom were changed into *i*-Pr, *n*-Bu, or *p*-$MeOC_6H_4$, no desired product can be detected; when the aldimino group was changed into a ketimino group, the efficiency of this transformation improved. To the mechanism, it was considered that the coordination of nitrogen to ruthenium allows the complex to be easily converted to metallacycle **A** via an oxidative cyclization of the α,β-unsaturated imine. Subsequently, the insertion of CO and reductive elimination of ruthenium initially produce the β,γ-unsaturated γ-lactam **B**. For the reaction of imines which contain a β-hydrogen, **B** is transferred to the more stable α,β-unsaturated isomer **C** (Scheme 13).

In 1999, Murai and coworkers employed α-dicarbonyl compounds as substrates for the synthesis of methyl benzoylformate (Scheme 14). $Ru_3(CO)_{12}$ was used as the catalyst in the presence of ethylene (3 atm) at 25°C in toluene for 20 h. Tetrahydro-5-oxo-2-phenyl-2-furancarboxylic acid methyl ester can be



Scheme 15 Mechanism for Ru-catalyzed [2 + 2 + 1] cyclocoupling of ketones, ethylenes, and CO

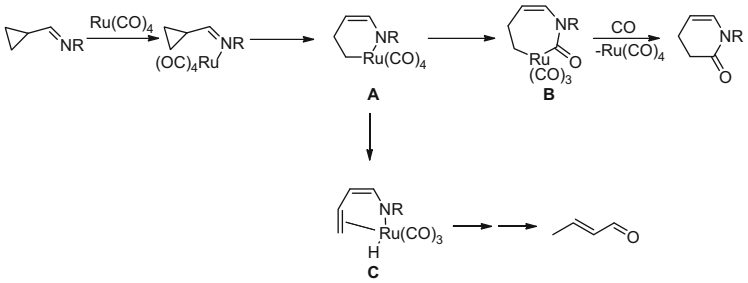


Scheme 16 Ru-catalyze carbonylative [5 + 1] cycloaddition of cyclopropyl imines

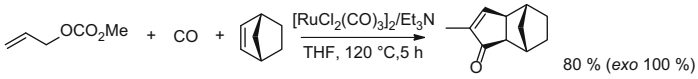
transformed in 23% isolated yield without further optimization. In the substrate testing, the reactions were clean and no by-product was detected. It should be noted that when the carbonyl group was replaced with a C=N unit, the reaction also works well. In this system, the heteroatom in α-position to with ruthenium leading a chelate ruthenium carbonyl complex or the related metallacycles would be a key step for the cyclocoupling reaction, which was examined later in detail (Scheme 15) [23].

Based on the Murai's previous work about Ru-catalyzed carbonylative [4 + 1] cycloaddition of the α,β-unsaturated imines to synthesize the unsaturated γ-lactams, they presented another type of Ru-catalyzed carbonylative [5 + 1] cycloaddition of cyclopropyl imines in 2000. The reaction involved ring opening of cyclopropane, and six-membered carbonyl compounds were constructed effectively (Scheme 16) [24].

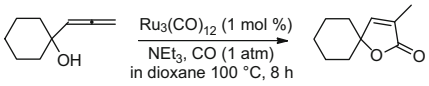
With a variety of different factors being examined, the optimal reaction conditions is 160°C under 2 atm of CO and in the presence of $Ru_3(CO)_{12}$. After that, different substituted imines were examined; in all cases, the corresponding products can be formed in moderate to good yields, while there was no effect on the yield when the *tert*-butyl group was replaced by a cyclohexyl group. To the reaction mechanism, the coordination of a nitrogen to ruthenium facilitated the conversion to metallacycle **A** via an oxidative cyclization of the cyclopropyl imine. The insertion of CO in **A** gives the acyl complex **B**, which undergoes a reductive elimination to give the final lactam. Compared to the former carbonylative [4 + 1] cycloaddition of imines, the efficiency of the present reaction is relatively low which might be due to the formation of aldehyde as the by-product. The alkene complex **C** is more stable than that derived from the non-substituted substrate at the



Scheme 17 Mechanism for Ru-catalyzed carbonylative [5 + 1] cycloaddition of cyclopropyl imines



Scheme 18 Ru-catalyzed carbonylative cyclization of allylic carbonates with alkenes

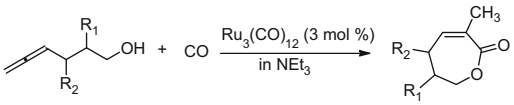


Scheme 19 Ru-catalyzed cyclic carbonylic of allenyl alcohols

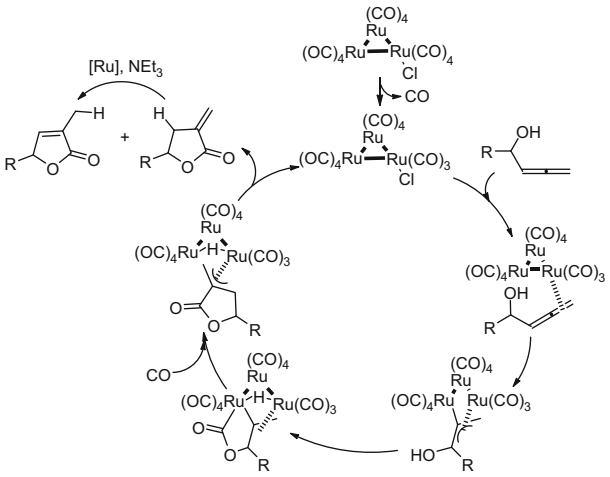
2-position on the cyclopropane ring that can facilitate the β-hydride elimination from **A** (Scheme 17).

At the same time, Mitsudo and coworkers reported a new route to build cyclopentenones via Ru-catalyzed carbonylative cyclization of allylic carbonates with alkenes (Scheme 18) [25]. $[RuCl_2(CO)_3]_2/Et_3N$ and $(\eta^3\text{-}C_3H_5)RuBr(CO)_3/Et_3N$ proved as highly effective catalytic systems for this carbonylative cyclization reaction to give the corresponding cyclopentenones in high yields with high stereoselectivity. Different catalysts and amine ligands were taken into account as well as the carbon monoxide pressure; the carbon monoxide pressure had a dramatic effect on the carbonylative cyclization; the best result was obtained under 3 atm of carbon monoxide and either an increase or decrease of it can decrease the yield rapidly. This may be explained that higher carbon monoxide pressure would suppress coordination of 2-norbornene and lower carbon monoxide pressure would prevent the insertion of CO.

Selective synthesis of γ- and δ-lactones by Ru-catalyzed carbonylation of allenyl alcohols was presented by Takahashi and coworkers in 2000 (Scheme 19) [26]. A variety of allenyl alcohols, such as mono-, di-, and trisubstituted alcohols, were transformed into the desired 3- and 4-substituted γ-lactones. Similarly, the cyclic carbonylation of 3,4-pentadien-1-ol and 2-methyl-4,5-hexadien-2-ol can give corresponding δ-lactones in high yield with excellent selectivity.



Scheme 20 Direct synthesis of seven-membered lactones by Ru-catalyzed cyclocarbonylation of allenyl alcohols

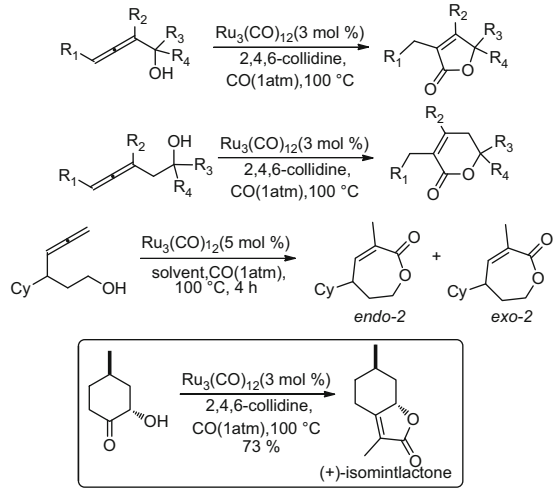


Scheme 21 Mechanism of Ru-catalyzed cyclocarbonylation of allenyl alcohols

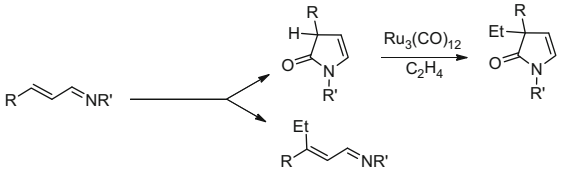
Later on, based on this research, Takahashi and coworkers succeeded in applying carbonylation reaction to the synthesis of medium-ring lactones. Based on previous reports, transition metal-catalyzed carbonylation of unsaturated compounds is strongly depending on the use of the solvent [5, 27]. They found that the use of a tertiary amine such as triethylamine and *N*-methylpiperidine as a solvent enables the formation of seven-membered lactones by in good yields from allenyl alcohols via $Ru_3(CO)_{12}$-catalyzed cyclocarbonylation [28]. 6-Hydroxyhexa-1,2-diene was tested in the presence of $Ru_3(CO)_{12}$ (3 mol%) at 100°C under 5 atm of carbon monoxide for 4 h; 71% yield of the corresponding product can be isolated (Scheme 20). 7-Hydroxyhepta-1,2-diene was also treated under the similar reaction condition, but the corresponding eight-membered lactone can be transformed but with lower selectivity.

Regarding the mechanism, they attempted to isolate intermediates via stoichiometric reactions of the substrate with the catalyst. On the basis of the obtained data, a possible reaction mechanism was proposed (Scheme 21) [29]. Moreover, the amine was considered may enhance the nucleophilicity of the hydroxyl group and accelerate intramolecular attack of an alkoxy anion to the Ru-COR intermediate in the cyclization. Recently, a similar Ru-catalyzed cyclocarbonylation of allenyl alcohols to α,β-unsaturated lactones was presented in detail including the synthesis

Scheme 22 Ru-catalyzed cyclocarbonylation of allenyl alcohols to α,β-unsaturated lactones



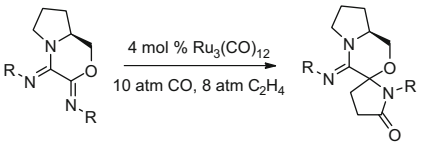
Scheme 23 Ru-catalyzed synthesis dihydro-pyrrol-2-one from α,β-unsaturated imines



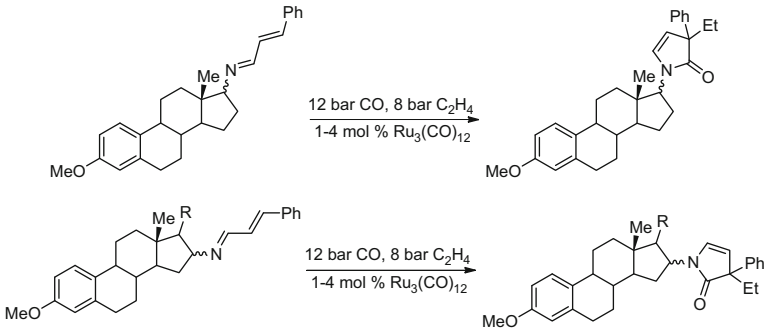
of five-, six-, and seven-membered heterocycle compounds (Scheme 22) [30]. (+)-Isomintlactone was synthesized as well.

It has been shown that the aromatic imines or ketones are treated with CO and/or olefins in the presence of catalytic amounts of $Ru_3(CO)_{12}$ to yield the respective cyclized products. Berger and Imhof have shown that 1,3-dihyro-pyrrol-2-one derivatives can be synthesized from α,β-unsaturated imines [31]. They reported a catalytic synthesis of pyrrol-2-one derivatives from α,β-unsaturated imines, CO, and ethylene in the presence of $Ru_3(CO)_{12}$ [32]. From the obtained results, it is obvious that the variation of the organic substituent at nitrogen (R′) determines the product distribution. If R′ is an electron-withdrawing substituent, ethylene is inserted into the activated C–H bond leading to ethyl substituted imines as their *Z* and *E* isomers (Scheme 23).

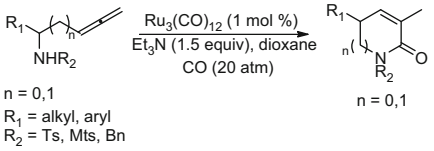
The formation of the pyrrole ring proceeds via a nucleophilic attack of the imine nitrogen toward the carbonyl carbon atom which was introduced into the molecule by the catalytic CO insertion reaction. The migration of hydrogen atom from the aldehyde function toward C_3 of the pyrrole system leads to 1,3-dihydro-pyrrol-2-one. The 1,3-dihydro-pyrrol-2-one is a thermodynamically less stable compound and it will be rearranged to 1,5-dihydro-pyrrol-2-one [21]. After then, Imhof and coworkers synthesized spiro[pyrrolidin-2-one] derivatives by a [2 + 2 + 1] cycloaddition of ketimines, CO, and ethylene (Scheme 24) [33]. Interestingly, only one



Scheme 24 Ru-catalyzed synthesis of spiro[pyrrolidin-2-one] by cycloaddition of ketimines, CO, and ethylene



Scheme 25 Synthesis of steroidal cinnamaldehyde imines and pyrrolones

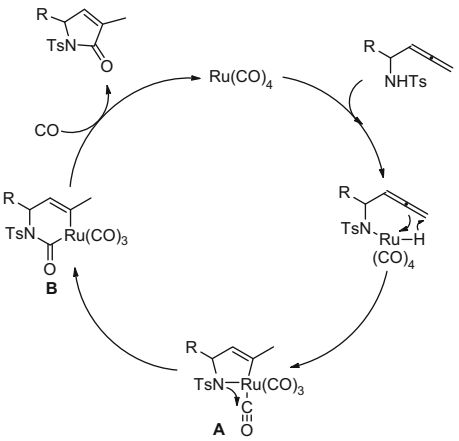


Scheme 26 Ru-catalyzed cyclocarbonylation of α-allenic sulfonamides

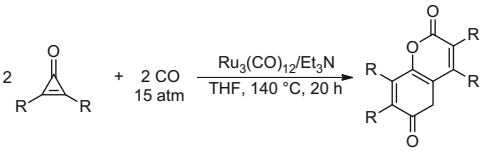
of the imine moieties of the starting material reacted and the cycloaddition only takes place at the C–N double bond neighboring the oxazine oxygen atom. Moreover, from their later research on the synthesis of the 2-pyrrolone derivatives from α,β-unsaturated imines, which took place stepwise by first inserting one carbon monoxide into the C–H bond of the imine chain in the β-position with respect to the imine double bond followed by the formation of the pyrrolone ring (Scheme 25) [34]. The observed diastereoselectivities may be rationalized by the assumption of an intramolecular hydrogen bond leading to a stereoselective formation of the new stereogenic center at C_3 of the pyrrolone system.

As an extension of the utilization of allenic sulfonamides in carbonylation, Kang and coworkers attempted and presented a $Ru_3(CO)_{12}$-catalyzed cycloaddition of α- and β-allenic sulfonamides to form γ- and δ-unsaturated lactams [35]. To find the optimal conditions, a series of catalysts, bases, and solvents were examined. From the obtained data, the use of $Ru_3(CO)_{12}$ or $[RuCl_2(CO)_3]_2/Et_3N$ as the base and 1,4-dioxane as the solvent under 20 atm of carbon monoxide was found to be the best condition and can afford γ-unsaturated lactam in 85% yield (Scheme 26). The

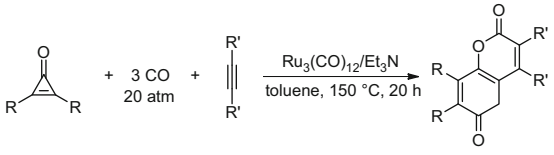
Scheme 27 Mechanism for Ru-catalyzed carbonylation of allenic sulfonamide



Scheme 28 Ru-catalyzed synthesis of pyranopyrandiones by carbonylation of cyclopropenones

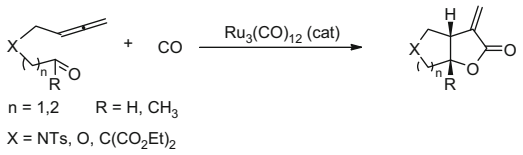


Scheme 29 Ru-catalyzed cross-carbonylation of cyclopropenones with internal alkynes

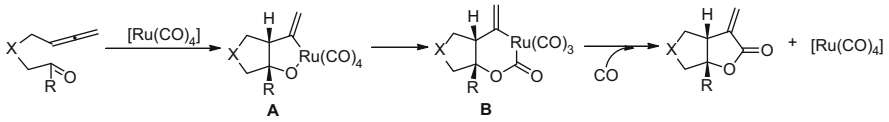


different substituted sulfonamide derivatives can also be transformed and gave the desired products in good to excellent yields. Deuterium-substituted α-allenic sulfonamide was employed as well and it was found that the deuterium was totally transferred to the product lactam. Hence, it is presumed that oxidative insertion of $Ru(CO)_4$ to the N–H bond of the NHTs group in the starting compound followed by syn-addition of the Ru–H bond to the terminal allene produces the intermediate **A**. Then carbonyl insertion to the N–Ru bond gives the intermediate **B**, which reacts with CO to form the product lactam and liberate $Ru(CO)_4$ (Scheme 27).

In 2002, Mitsudo and coworkers reported a rapid Ru-catalyzed synthesis of pyranopyrandiones by carbonylation of cyclopropenones [36] (for lead references, see [37–44]). Based on their previous research on the unusual Ru-catalyzed coupling of cyclobutenediones with alkenes, they found that 3.3 mol% of $Ru_3(CO)_{12}$ and 10 mol% of NEt_3 in THF under 15 atm of CO at 140°C for 20 h are the best conditions with cyclopropenone as substrate. A novel carbonylative dimerization product can be formed in high isolated yield with high selectivity (Scheme 28). Furthermore, unsymmetrically substituted pyranopyrandiones were generally obtained in good to high yields under this catalytic system with internal alkynes (Scheme 29).



Scheme 30 Ru-catalyzed [2 + 2 + 1] cycloaddition of allenyl aldehydes and ketones with CO

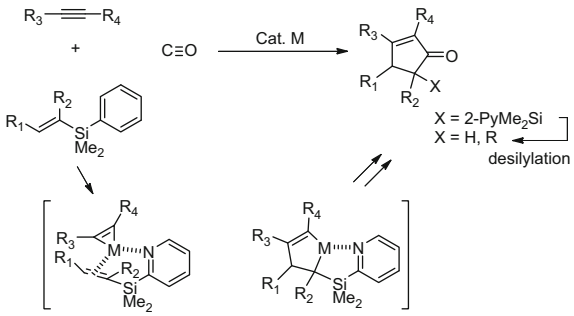


Scheme 31 Proposed mechanistic pathway for the Ru-catalyzed [2 + 2 + 1] cycloaddition

Ruthenium-catalyzed carbonylation has also been applied in the carbonylative synthesis of α-methylene-γ-butyrolactones which was considered as a skeleton of biologically active natural product [45–48]. Kang and coworkers described a Ru-catalyzed [2 + 2 + 1] cycloaddition of allenyl aldehydes and ketones with carbon monoxide to α-methylene-γ-butyrolactones in 2002 (Scheme 30) [49]. Initially, δ-allenyl aldehyde was used to evaluate the feasibility to find the optimal reaction conditions. A variety of ruthenium complexes were examined and $Ru_3(CO)_{12}$ acted as the best catalyst. Finally, the optimum reaction condition was found to react with 20 atm of CO in dioxane at 120°C for 12 h as the best condition (75% yield). Moreover, under the same reaction condition, the δ-allenyl ketone can afford the corresponding product in 82% yield. To the mechanism, intermediacy of metallocyclopentene **A** was considered to undergo the insertion of CO to form the carbonylated metallacycle **B**. Reductive elimination then gives the product (Scheme 31). In addition, they explored the cyclocarbonylation of δ-allenyl imine and the stereochemistry of the resulting products; *cis*-fused α-methylene-γ-butyrolactam was detected as the sole product, which supports a [2 + 2 + 1] cycloaddition.

Dimethyl(2-pyridyl)silyl(2-PyMe_2Si) group was demonstrated as an excellent, removable directing group in a number of metal-catalyzed reactions that were presented by Yoshida in recent works [50–58]. Alkenyldimethyl(2-pyridyl)silane as a substrate for a catalytic intermolecular Pauson–Khand reaction. It has been accepted that the oxidative cyclization of alkyne, alkene, and metal can be regarded as a carbometalation of an (alkyne)metal complex across an alkene [59–61]. Therefore, the facile and regioselective formation of a metallocyclopentene intermediate owing to the coordination effect of the pyridyl group on silicon was expected, and they have already established the high reactivity of alkenyldimethyl(2-pyridyl) silanes in several carbometalation processes (Scheme 32) [62].

From the obtained result, the use of α- or β-substituted vinylsilanes results in the regioselective production of substituted cyclopentenones with the substituent at the

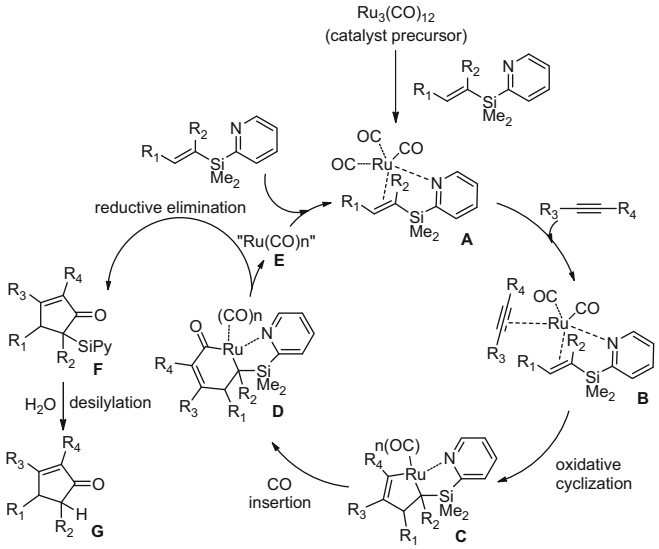


Scheme 32 Catalytic intermolecular Pauson–Khand reaction directed by a pyridylsilyl group

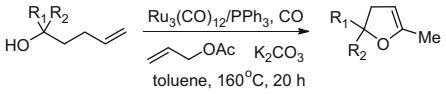
5- or 4-position, respectively. Moreover, the substituted vinylsilanes not only serve as surrogates for terminal alkenes but also enable the complete regioselective incorporation of the alkene subunit into the cyclopentenone skeleton.

The comprehensive research of this kind reaction was presented later and a possible mechanism was discussed in detail, which was proposed that the reaction is begun with the formation of Ru(alkenylsilane) complex **A**. The coordination of alkyne leads to the formation of Ru(alkyne)(alkenylsilane)complex **B**, which undergoes a typical oxidative cyclization process to produce ruthenacyclopentene intermediate **C**. Then migratory insertion of a carbon monoxide ligand into the C (sp)–Ru bond produces the six-membered ruthenacycle intermediate **D**. Although an alternative mechanism that involves a migratory insertion into the C(sp^2)–Ru bond may also be plausible, they preferred the former case as it retains the strong pyridyl-to-ruthenium complexation. Later, the reductive elimination gives the silylated cyclopentenone **F** and "$Ru(CO)_n$" complex **E**, which be trapped by alkenyl(2pyridyl)silane to regenerate Ru(alkenylsilane) complex **A**. At the end, the desilylation of **F** produces **G** as the final product (Scheme 33).

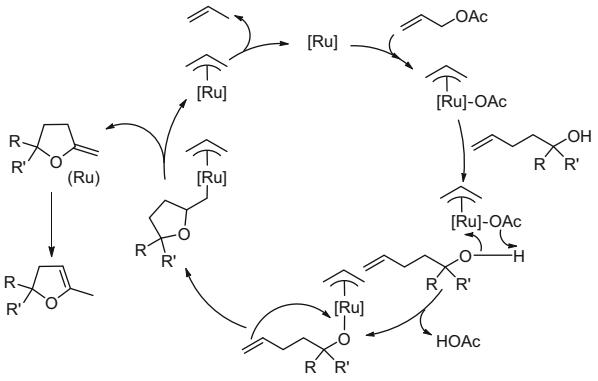
In 2003, based on the previous researches [4, 38], Mitsudo and coworkers reported a oxidative cyclization of 4-penten-1-ols in the presence of $Ru_3(CO)_{12}$ and PPh_3 ligand with allyl acetate and K_2CO_3 in toluene under 20 atm of CO. 2,5-Dimethyl-2-phenyl-2,3-dihydrofurans can be produced in quantitative yield (Scheme 34) [63]. Both allyl acetate and K_2CO_3 as well as carbon monoxide pressure are essential for the success of this reaction. Allyl acetate operates as an effective hydrogen acceptor, while with other hydrogen acceptors, such as styrene, 3,3-dimethyl-1-butene, and vinyl acetate, there was no reaction occurred at all. Under the optimized reaction conditions, several substituted 4-penten-1-ols were smoothly converted into the corresponding 2,3-dihydrofurans. From the obtained result, only allyl acetate can operate as an effective hydrogen acceptor. Initial step of the present reaction might be oxidative addition of allyl acetate to a low-valent active ruthenium species (for chemistry of π-allylruthenium complexes, see [64–66]). The generated π-allylruthenium intermediate may undergo ligand exchange reaction or σ-bond metathesis between an acetoxyl group and a hydroxyl group to give an (alkoxy)(π-allyl)ruthenium intermediate. Then the intramolecular insertion



Scheme 33 Mechanism for Ru-catalyzed intermolecular Pauson–Khand Reaction



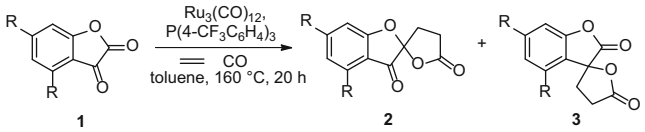
Scheme 34 Ru-catalyzed oxidative cyclization of 4-penten-1-ol



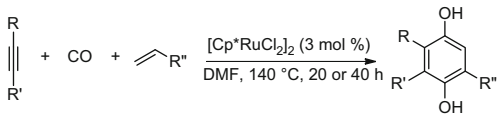
Scheme 35 Mechanism for Ru-catalyzed oxidative cyclization of 4-penten-1-ols

of an alkene moiety into the O-[Ru] bond, followed by β-hydride elimination/ isomerization, gave 2,3-dihydrofuran and propene (Scheme 35).

Ester–carbonyl group participated in a carbonylative cycloaddition reaction was firstly reported by Murai and coworkers in 2003 [67]. Benzofuran-2,3-dione and its



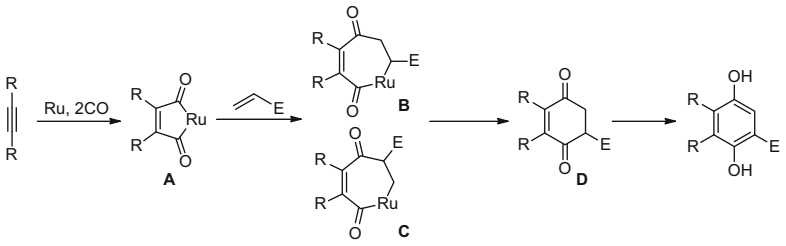
Scheme 36 Ru-catalyzed carbonylative cycloaddition of α-keto lactones with alkenes



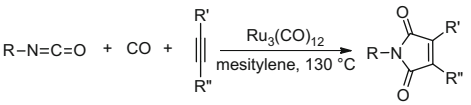
Scheme 37 Ru-catalyzed cocyclization of alkynes, alkenes, and CO

derivatives were reacted with CO in the presence of ruthenium catalyst to give lactone via carbonylative [2 + 2 + 1] cycloaddition. The ester–carbonyl group was considered incorporated into a two-atom assembling unit to give the corresponding spirolactone and its derivatives. From the previous reports, the use of an ester–carbonyl function as a two-atom assembling unit is rare for its reduced reactivity compared with aldehydes and ketones. On the basis of their success in carbonylative cycloaddition of ketones [23], initially, $Ru_3(CO)_{12}$ was employed as the catalyst and ethylene as the coupling partner, and 2-pyridinecarboxylates or α-diesters were employed as the substrates. And the desired product can be formed in 85% yield from 4,6-dimethylbenzofuran-2,3-dione, ethylene, and CO in toluene in the presence of a catalytic amount of $Ru_3(CO)_{12}$ and P(4-$CF_3C_6H_4$) at 160°C (Scheme 36). From the obtained result of different substituted substrates, the electronic nature has a slight effect on the product distribution, such as a bulky substituent *t*-Bu, it just gave the corresponding **2** derivative as the sole product. Moreover, other alkenes and alkynes were also applicable in this reaction [68, 69]. All of these indicate that cycloaddition reaction with esters will be useful in organic chemistry and merit further investigations.

In 2005, Mitsudo and coworkers synthesized functionalized hydroquinones via $[Cp^*RuCl_2]_2$-catalyzed cyclization of alkynes, α,β-unsaturated carbonyl compounds, and carbon monoxide [70]. After screening a variety of reaction conditions, with $[Cp^*RuCl_2]_2$ as the catalyst in DMF can effectively catalyze the reaction and gave the corresponding product in 79% yield (Scheme 37). Moreover, from the substrate scope, a variety of electron-deficient alkenes can be employed as coupling partner to give the corresponding hydroquinones. Also, a maleoylruthenium complex **A** was considered to be formed by the reaction of ruthenium with an alkyne and two molecules of carbon monoxide, which would then react with an electron-deficient alkene to give seven-membered ruthenacycles **B** and/or **C**. The seven-membered ruthenacycles **B** and/or **C** will go reductive elimination to give **D**, which will give the substituted hydroquinones by enolization (Scheme 38).



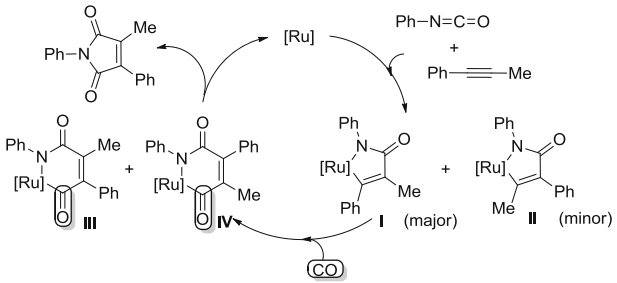
Scheme 38 Mechanism of Ru-catalyzed cyclization of alkynes to hydroquinones



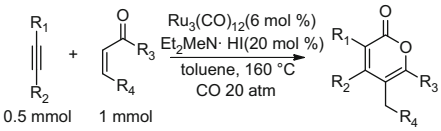
Scheme 39 Synthesis of polysubstituted maleimides in the presence of $Ru_3(CO)_{12}$

In 2006, Kondo and coworkers developed a novel and rapid procedure for the synthesis of polysubstituted maleimides by the Ru-catalyzed intermolecular [2 + 2 + 1] cyclization of isocyanates, alkynes, and carbon monoxide (Scheme 39) [71]. It is different from the traditional process that gives only non-substituted and/or symmetrically substituted maleimides [72]. In the optimization process, the effects of catalysts and other parameters were examined with phenyl isocyanate and 4-octyne as the model system under 1 atm of CO. $Ru_3(CO)_{12}$ showed the highest catalytic activity and mesitylene proven to be the best solvent. In the substrates testing under the optimum conditions, excellent yields of the products can be achieved. From the obtained results, terminal alkynes just give a trace amount of the desired product, and no significant effect was observed in electron-donating or electron-withdrawing substituents on a phenyl ring in aryl isocyanates. Long reaction time was required in order to complete the conversion when bulky alkyl isocyanate was applied. For the mechanism, it was considered that the reaction started with the formation of azaruthenzacylopentenones by oxidative cyclization on an active ruthenium center [73–75]. Moreover, to the aryl-substituted alkynes, the oxidative cyclization process is thought to proceed significantly faster than that with alkyl-substituted alkynes. After then, the insertion of CO into a Ru–C(sp^2) bond rather than a Ru–N bond predominantly occurred to give azaruthenacyclohexenediones, followed by reductive elimination to give maleimides in an excellent yield with high selectivity. At the same time, it also regenerates an active low-valent ruthenium species to finish the cycle (Scheme 40).

Recently, a few catalytic systems for the synthesis of α-pyrones based on carbonylation have been reported [76–78]. Among these methods, only a limited range of substrates can be tolerated. Moreover, during the former research on the synthesis of hydroquinones, when silylacetylenes were used as alkynes, no such cycloaddition took place but α-pyrones were formed as the major products. Hence,



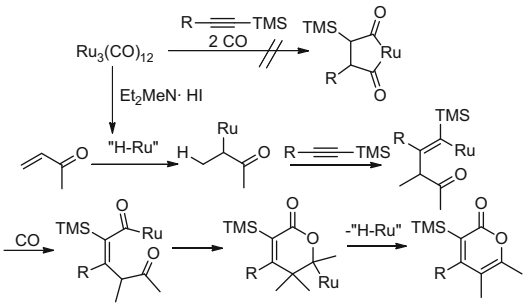
Scheme 40 Mechanism for Ru-catalyzed [2 + 2 + 1] cyclization to polysubstituted maleimides



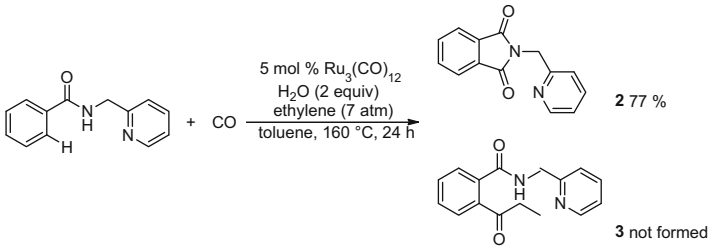
Scheme 41 Ru-catalyzed [3 + 2 + 1] cycloaddition of vinyl ketones, silylacetylenes, and CO

a novel procedure for the synthesis of α-pyrones by the Ru-catalyzed carbonylative [3 + 2 + 1] cycloaddition of vinyl ketones, silylacetylenes, and CO was presented (Scheme 41). Here, vinyl ketones were incorporated as a three-atom assembling unit into the products. When 1-(trimethylsilyl)-2-phenylacetylene reacts with methyl vinyl ketone under 20 atm of CO in the presence of catalytic amount of $Ru_3(CO)_{12}$ at 140°C for 20 h, a [3 + 2 + 1] cycloaddition reaction took place and gave the corresponding α-pyrones in 20% yield. In addition, when the reaction was carried out in the presence of H_2O, the yield was slightly improved and the addition of $Et_2MeN{\cdot}HI$ can give an increased yield to 40%. Hence, under the catalytic system of $Ru_3(CO)_{12}/Et_2MeN{\cdot}HI$, different substituted silylacetylenes and alkenes were carried out and products were obtained in good to moderate yields. Firstly, a ruthenium hydride species generated from the ruthenium carbonyl complex with an amine·HI salt or water was considered to react with methyl vinyl ketone to give a ruthenium enolate. Later, carboruthenation of the enolate to silylacetylene gives a vinyl ruthenium complex, which undergoes CO insertion to give an acyl ruthenium complex. Then the cyclization followed by β-hydride elimination would give the final product α-pyrones and generate the ruthenium hydride species (Scheme 42).

In 2009, Chatani and coworkers presented a Ru-catalyzed carbonylation at *ortho* C–H bonds in aromatic amides leading to phthalimides [79]. A variety of functional groups, such as ketone, ester, amide, pyridine, oxazoline, imine, and cyano groups, can be tolerated here. A bidentate system has been used for the catalytic activation of C–H bond before [80], as the bidentate system is expected to bind tighter to the catalyst. In the reaction of amide with CO and ethylene in the presence of $Ru_3(CO)_{12}$ in toluene at 160°C, there was no desired product **3** formed; instead, the phthalimide **2** was detected. The conversion of **1** to **2** requires the release of two hydrogen atoms which indicates that the reaction requires a hydrogen acceptor in



Scheme 42 Mechanism for Ru-catalyzed [3 + 2 + 1] cycloaddition of vinyl ketones, silylacetylenes, and CO

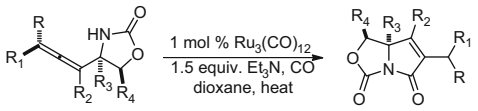


Scheme 43 Ru-catalyzed carbonylation at *ortho* C–H bond to phthalimides

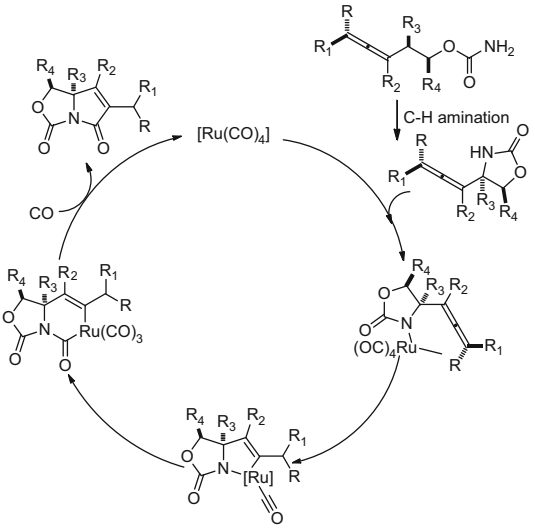
order to achieve high conversion. Finally, ethylene was found as the best H_2 acceptor (Scheme 43). After then, a variety of *para*-substituted aromatic amides were examined; from the obtained result, all the *para*-substituted phthalimides were formed in high yields. It can be concluded that the electronic effects are not a dominant factor but that the steric nature of the substituents has a significant effect on the regioselectivity of the reaction.

Two years later, Grigg and coworkers reported C–H amination/cyclocarbonylation of allene carbamates which seems as a versatile platform for the synthesis of α,β-unsaturated γ-lactams (Scheme 44) [81]. Despite their utility as building blocks for the construction of a variety of nitrogen-containing heterocyclic scaffolds, the preparation of allenic amines via the direct C–H amination of allenes of the general structure has not been well explored. In this work, either bicyclic methylene aziridines or the desired allenic amines can be produced by Ru-catalyzed aminations of allenes. A variety of metal carbonyls were tested to promote the reaction, and 1 mol% of $Ru_3(CO)_{12}$ was found to be the most effective with an optimal temperature of 80°C. Higher temperature resulted in a greater overall conversion but also greater amounts of decarboxylated by-products. In addition, at least 1 equiv. of a tertiary amine base was necessary to get good conversion. Here, the bicyclic nature of the unsaturated lactam produced as a result of cyclocarbonylation means that the stereochemistry of R_3 group could be used to

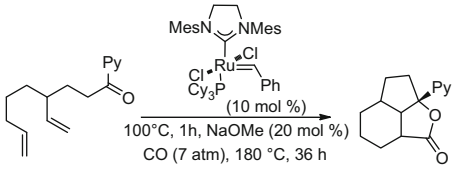
Scheme 44 Ru-catalyzed cyclocarbonylation to α,β-unsaturated γ-lactams



Scheme 45 C–H amination/ cyclocarbonylation of allenic carbamates as a route to γ-lactams



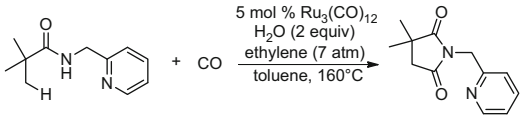
Scheme 46 Ru-catalyzed cycloaddition to polycyclic lactones



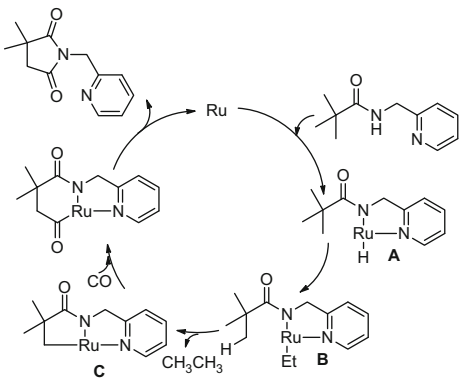
effectively dictate the stereochemistry of subsequent manipulations of these scaffolds (Scheme 45).

In 2011, Finnegan and Snapper reported the formation of polycyclic lactones through Ru-catalyzed ring-closing metathesis/hetero-Pauson–Khand reaction sequence (Scheme 46) [82]. In this reaction, a pyridine group in the substrate might cause problems in the metathesis step. Coordination of the pyridine nitrogen to the ruthenium catalyst can block a necessary coordination site on the metal and inhibit metathesis activity [83, 84]. Under the optimal reaction conditions, the starting compound was treated with 10 mol% of catalyst, CO and NaOMe; the corresponding product can be obtained in 72% yield by this tandem process. After then, different substituted substrates were prepared and examined. From the obtained results, it can be concluded that the cycloaddition step is sensitive to the Lewis basicity of the chelating functionality adjacent to the carbonyl group.

Scheme 47 Ru-catalyzed carbonylation of unactivated C(sp^3)–H bond in amide



Scheme 48 Mechanism for Ru-catalyzed carbonylation of unactivated C(sp^3)–H bond



At the same year, Chatani and coworkers presented a highly regioselective carbonylation of unactivated C(sp^3)–H bonds in the presence of ruthenium carbonyl (Scheme 47) [85]. With the optimization of different conditions, a variety of different amides were treated under the standard reaction conditions. All the reactions were highly regioselective and tolerated functional groups like MeO, Cl, CF_3, CN, and even Br. Electron-withdrawing substituents gave better results, and a sterical bulkyl aryl group has no effect on the efficiency of the reaction. Next, the effect of directing group was examined and the presence of 2-pyridinylmethylamine moiety in the amide is crucial and necessary for a successful reaction, while other directing groups whether they are with pyridine moiety or not and with shorter or longer carbon chains couldn't give the corresponding product.

To explore the mechanism of this reaction, deuterated reaction was also performed and the result indicated that the cleavage of C–H bond is irreversible and it is the rate-determining step. Moreover, the coordination of the amide followed by N–H bond activation gives the ruthenium hydride complex **A**. The insertion of ethylene followed by irreversible C–H bond activation gives metallacycle **C** with the concomitant generation of ethane. The insertion of CO and subsequent reductive elimination afford the final product with regeneration of the ruthenium catalyst. Furthermore, having no carbonylation products in the absence of ethylene suggests that no direct cleavage of a C–H bond takes place in complex **A** and that ethylene acts as a hydrogen acceptor (Scheme 48).

In conclusion, the main achievements on ruthenium-catalyzed carbonylative synthesis of heterocycles have been summarized and discussed. Their reaction mechanisms have been considered as well.

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