Topics in Heterocyclic Chemistry 42
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Xiao-Feng Wu
Matthias Beller *Editors*

Transition Metal Catalyzed Carbonylative Synthesis of Heterocycles

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42
Topics in Heterocyclic Chemistry

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Editors

Transition Metal Catalyzed Carbonylative Synthesis of Heterocycles

With contributions by

J.-B. Feng · T. Fukuyama · F. Li · W. Li · Z. Lian · A.T. Lindhardt · D.U. Nielsen · I. Ryu · T. Skrydstrup · X.-F. Wu · Q. Xing

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Preface

Heterocyclic compounds are prevailing in a huge number of organic compounds and holding utmost important applications in many fields such as pharmaceuticals, agrochemicals, and materials. Hence, the development of new methodologies for heterocycles' synthesis is in the center of organic chemistry in the past and present and will definitely be in the future as well. Not surprisingly, numerous methodologies have been established for the preparation of all kinds of heterocyclic compounds. Among them, the merger of carbonylations in heterocycles synthesis is remarkable. Through transition metal-catalyzed carbonylative transformations, CO, one of the cheapest C1 sources, can be installed into the parent molecules. Considering the high value of heterocyclic compounds, carbonylative synthesis of heterocycles is like "transforming stone into gold." This concept has been also well accepted by our synthetic community, and various carbonylative procedures have been established, which raised the possibility to breed this book.

In this book, we summarized and discussed the achievements on Ru-, Rh-, and Pd-catalyzed carbonylative synthesis of heterocycles. The successes in Pd-catalyzed carbonylative synthesis of large membered heterocycles from aryl halides have been discussed by Prof. Skrydstrup and his coworkers in chapter "Pd-Catalyzed Carbonylative Synthesis of Other-Membered Heterocycles from Aryl Halides". Based on their own experience, Prof. Ryu and Prof. Fukuyama discussed the applications of radical carbonylation in heterocycle preparation in chapter "Synthesis of Heterocycles via Radical Carbonylation". The last chapter on applying oxidative carbonylation in heterocycle synthesis is provided by Prof. Fuwei Li and his coworker from Lanzhou Institute of Chemical Physics, China.

With the support from all our authors, this book finally comes into reality. We have to give appreciation to all our authors and thank them for their support and understanding. Hopefully, I did not pressure them too much!

We would like also to thank our series editors: Profs. Bert U.W. Maes, Janine Cossy, and Slovenko Polanc, for providing us this valuable opportunity to join their book series *Topics in Heterocyclic Chemistry*.

The chemists who have performed the scientific works are also thanked. Without their works, we see no chance for this book.

If any related works are not included here or if there are mistakes, which is most likely the case, we wish to take this chance to apologize in advance!

Rostock, Germany Xiao-Feng Wu
4 August 2015

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Ruthenium-Catalyzed Carbonylative Synthesis of Heterocycles

Jian-Bo Feng and Xiao-Feng Wu

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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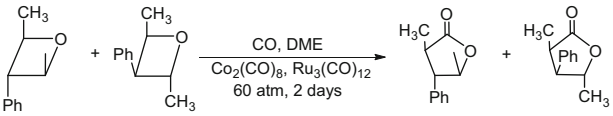
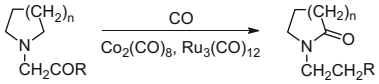
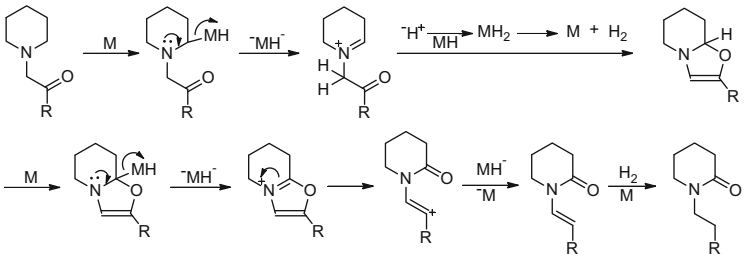


Scheme 1 Regiospecific carbonylative ring expansion catalyzed by Ru/Co carbonyls



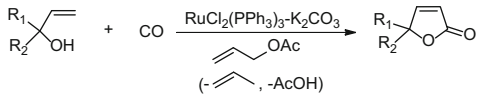
Scheme 2 Ru/Co carbonyls catalyzed ring-expansion carbonylation



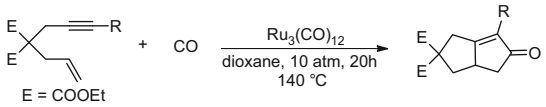
Scheme 3 Mechanism for Ru/Co carbonyls catalyzed rearrangement and cyclization

(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.

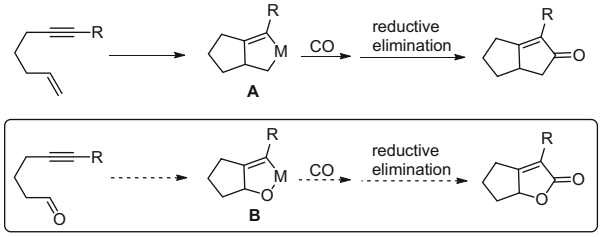
In 1994, a new route direct to 2(5*H*)-furanones via ruthenium-catalyzed oxidative cyclocarbonylation of allylic alcohols was reported by Watanabe and coworkers (Scheme 4) [4]. In the presence of catalytic amount of $RuCl_2(PPh_3)_3$, several 2(5*H*)-furanones were obtained in moderate to highly yields 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

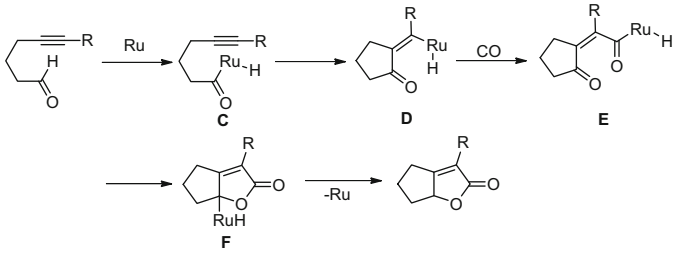


Scheme 6 Metal-catalyzed carbonylative synthesis lactones

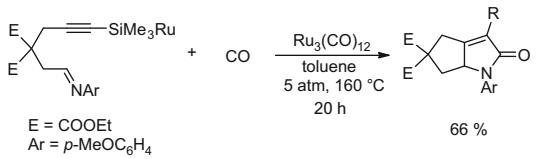
as the carbonyl source initially, while based on the controlled experiment of ^{13}C-labelled K_2CO_3, it only act as a base for trapping acetic acid generated by the hydrogenolysis of allyl acetate.

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



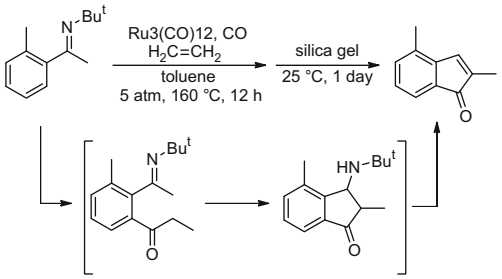
Scheme 8 Ru-catalyzed yne-imine with CO leading to bicyclic α,β-unsaturated lactam

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.

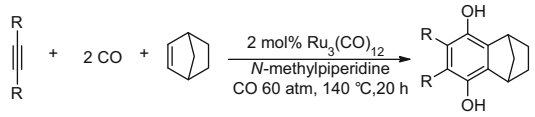
Solvents, catalyst complexes and the pressure of CO were screened; different substituted yne-aldehyde gave moderate to excellent yields under optimized conditions. From the obtained results, it can be found that when R is a small group, such as a methyl group, a reductive elimination from **D** can take 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.

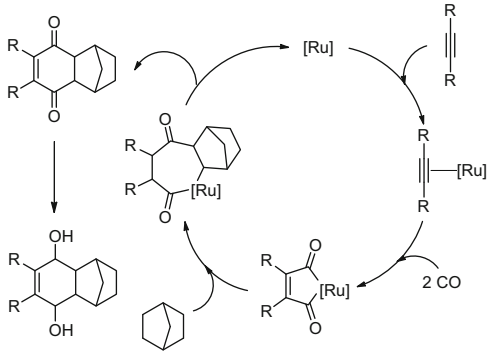
In 1997, Murai and coworkers reported a new synthetic method for the preparation of indenones based on the Ru-catalyzed carbonylation of aromatic imines at an *ortho* C–H bond (Scheme 9) [17]. This reaction involves the effective carbonylation at a C–H bond in the benzene ring [18, 19]. Notably, no reaction 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

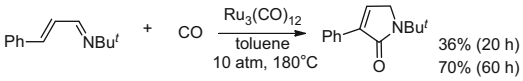


Scheme 10 Ru-catalyzed cross-carbonylation of alkyne and 2-norbornene to hydroquinone

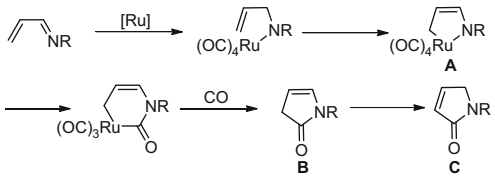


Scheme 11 Mechanism of Ru-catalyzed cross-carbonylation of alkynes and norbornenes to hydroquinones

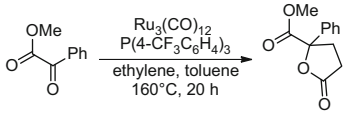
Mitsudo and his research group developed a novel ruthenium-catalyzed cross-carbonylation of alkynes and alkenes [20]. It was the first example about the selective synthesis of unsymmetrically substituted hydroquinones from alkynes, 2-norbonenes, and carbon monoxide (Scheme 10). A series of different 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



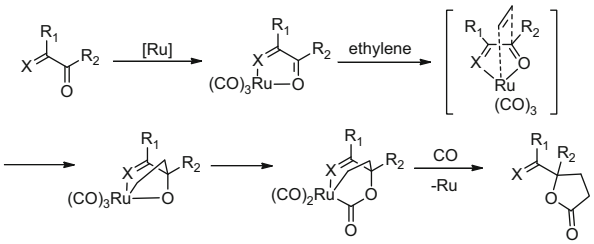
Scheme 13 Mechanism for Ru-catalyzed [4 + 1] cycloaddition of α,β-unsaturated imine with CO



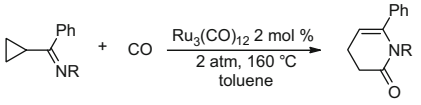
Scheme 14 Ru-catalyzed [2 + 2 + 1] cycloaddition of ketones, olefins, and CO

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

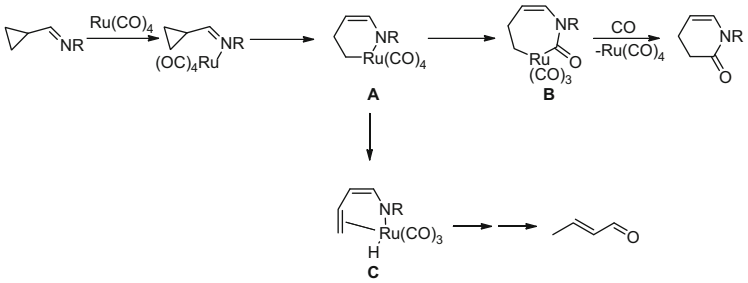


Scheme 16 Ru-catalyze carbonylative [5 + 1] cycloaddition of cyclopropyl imines

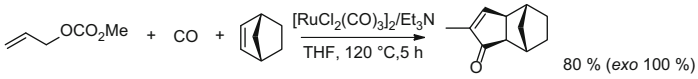
transformed in 23% isolated yield without further optimization. In the substrate testing, the reactions were clean and no by-product was detected. It should be noted that when the carbonyl group was replaced with a C=N unit, the reaction also works well. In this system, the heteroatom in α-position to 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].

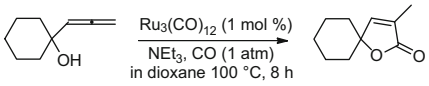
With a variety of different factors being examined, the optimal reaction conditions is 160°C under 2 atm of CO and in the presence of $Ru_3(CO)_{12}$. After that, different substituted imines were examined; in all cases, the corresponding products can be formed in moderate to good yields, while there 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

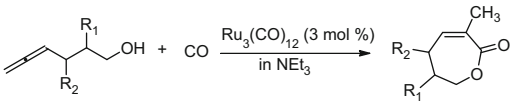


Scheme 19 Ru-catalyzed cyclic carbonylic of allenyl alcohols

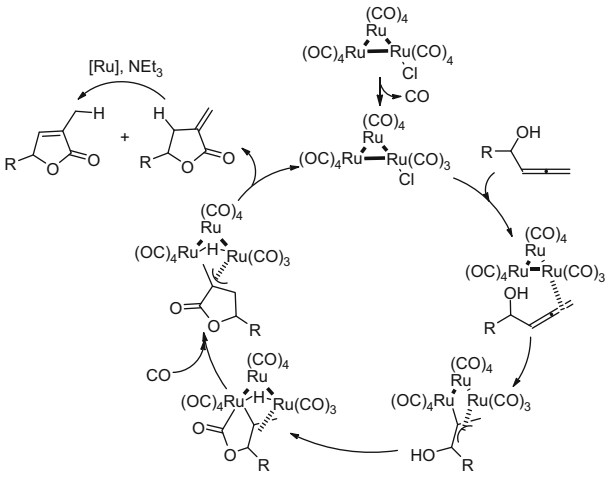
2-position on the cyclopropane ring that can facilitate the β-hydride elimination from **A** (Scheme 17).

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

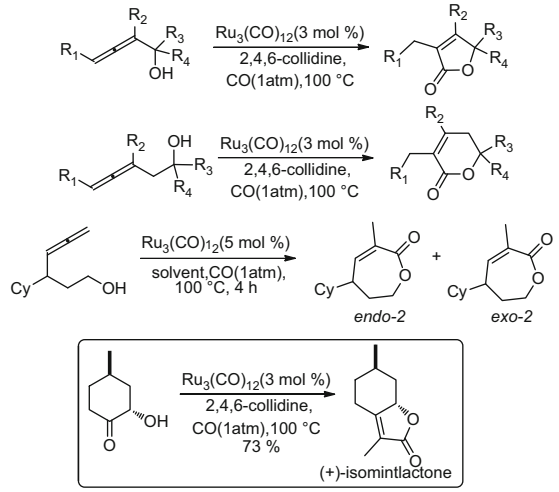


Scheme 21 Mechanism of Ru-catalyzed cyclocarbonylation of allenyl alcohols

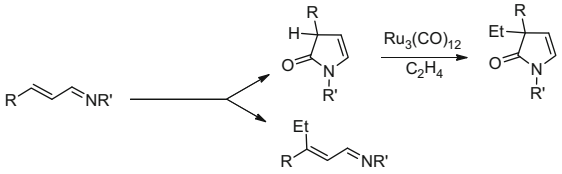
Later on, based on this research, Takahashi and coworkers succeeded in applying carbonylation reaction to the synthesis of medium-ring lactones. Based on previous reports, transition metal-catalyzed carbonylation of unsaturated compounds is strongly depending on the use of the solvent [5, 27]. They found 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



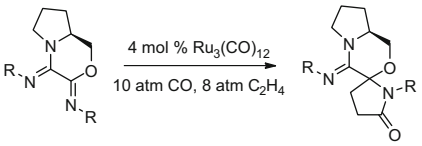
Scheme 23 Ru-catalyzed synthesis dihydro-pyrrol-2-one from α,β-unsaturated imines



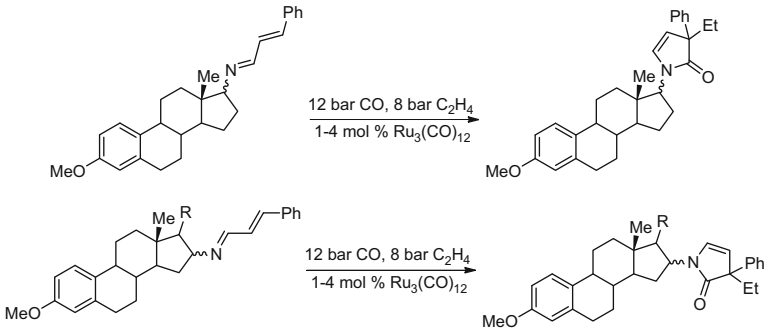
of five-, six-, and seven-membered heterocycle compounds (Scheme 22) [30]. (+)-Isomintlactone was synthesized as well.

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).

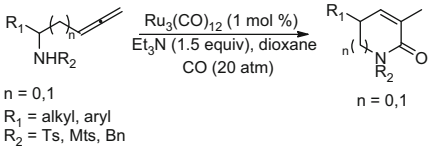
The formation of the pyrrole ring proceeds via a nucleophilic attack of the imine nitrogen toward the carbonyl carbon atom which was introduced into the molecule by the catalytic CO insertion reaction. The migration of hydrogen atom from the aldehyde function toward C_3 of the pyrrole system leads to 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

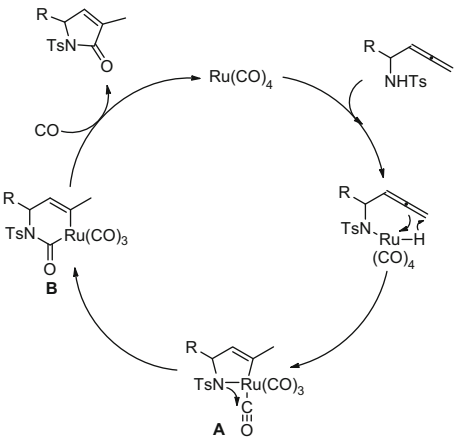


Scheme 26 Ru-catalyzed cyclocarbonylation of α-allenic sulfonamides

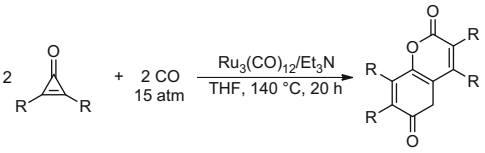
of the imine moieties of the starting material reacted and the cycloaddition only takes place at the C–N double bond neighboring the oxazine oxygen atom. Moreover, from their later research on the synthesis of the 2-pyrrolone derivatives from α,β-unsaturated imines, which took place stepwise by first 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

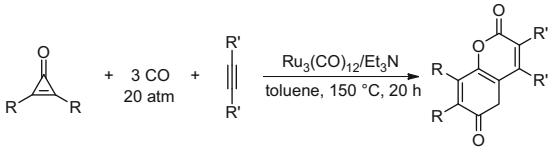
Scheme 27 Mechanism for Ru-catalyzed carbonylation of allenic sulfonamide



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

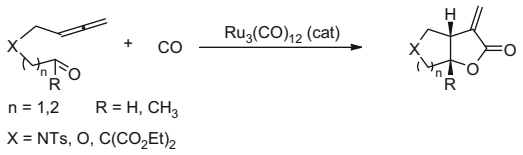


Scheme 29 Ru-catalyzed cross-carbonylation of cyclopropenones with internal alkynes

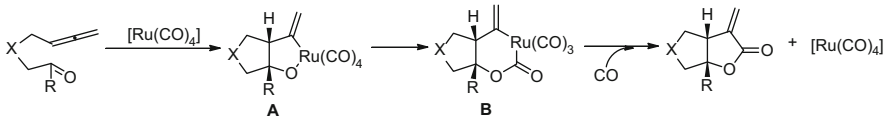


different substituted sulfonamide derivatives can also be transformed and gave the desired products in good to excellent yields. Deuterium-substituted α-allenic sulfonamide was employed as well and it was found that the deuterium was totally transferred to the product lactam. Hence, it is presumed that 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

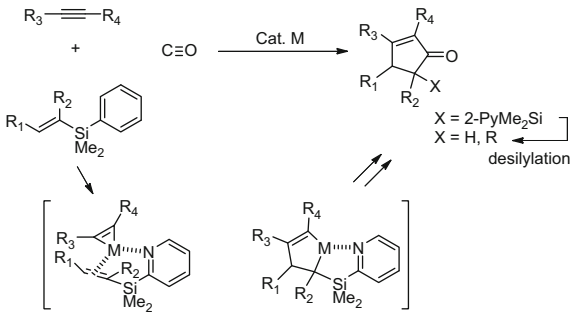


Scheme 31 Proposed mechanistic pathway for the Ru-catalyzed [2 + 2 + 1] cycloaddition

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

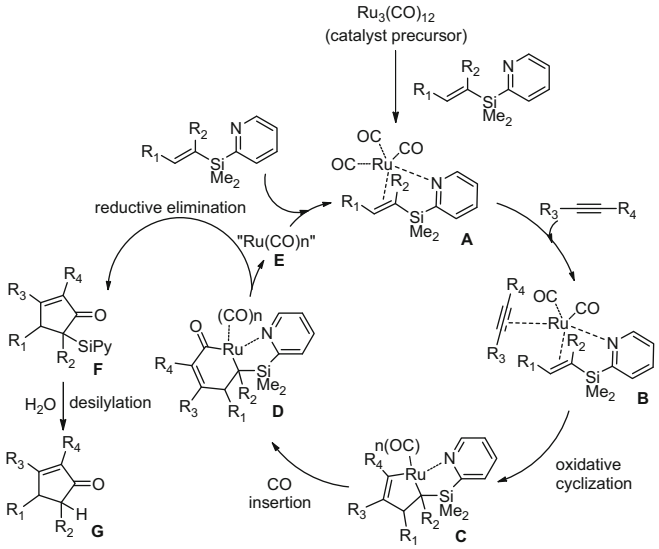


Scheme 32 Catalytic intermolecular Pauson–Khand reaction directed by a pyridylsilyl group

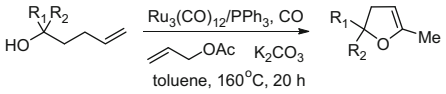
5- or 4-position, respectively. Moreover, the substituted vinylsilanes not only serve as surrogates for terminal alkenes but also enable the complete regioselective incorporation of the alkene subunit into the cyclopentenone skeleton.

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).

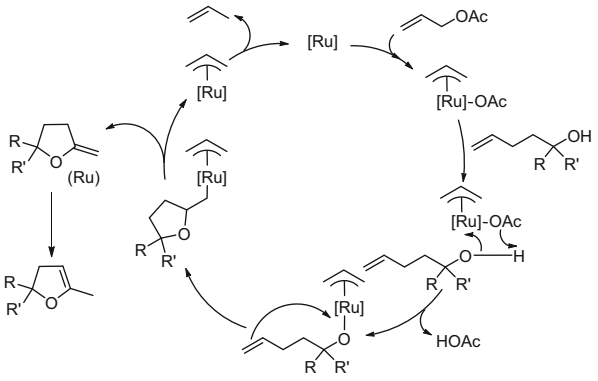
In 2003, based on the previous researches [4, 38], Mitsudo and coworkers reported a oxidative cyclization of 4-penten-1-ols in the presence of $Ru_3(CO)_{12}$ and PPh_3 ligand with allyl acetate and K_2CO_3 in toluene under 20 atm of CO. 2,5-Dimethyl-2-phenyl-2,3-dihydrofurans can be produced in quantitative 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



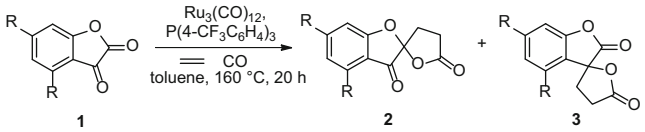
Scheme 34 Ru-catalyzed oxidative cyclization of 4-penten-1-ol



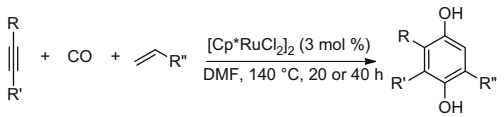
Scheme 35 Mechanism for Ru-catalyzed oxidative cyclization of 4-penten-1-ols

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



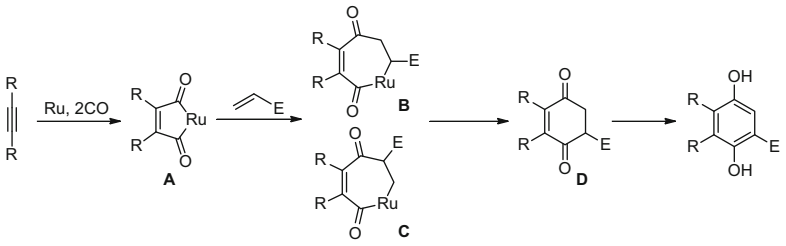
Scheme 36 Ru-catalyzed carbonylative cycloaddition of α-keto lactones with alkenes



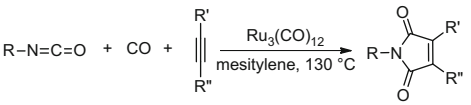
Scheme 37 Ru-catalyzed cocyclization of alkynes, alkenes, and CO

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).



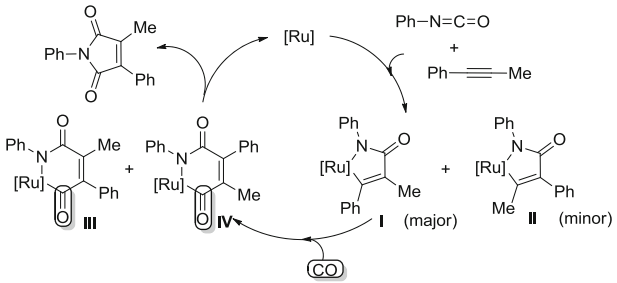
Scheme 38 Mechanism of Ru-catalyzed cyclization of alkynes to hydroquinones



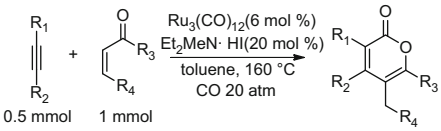
Scheme 39 Synthesis of polysubstituted maleimides in the presence of $Ru_3(CO)_{12}$

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,



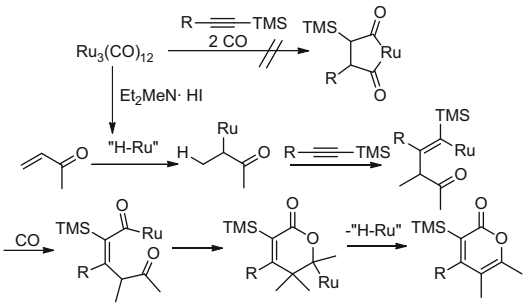
Scheme 40 Mechanism for Ru-catalyzed [2 + 2 + 1] cyclization to polysubstituted maleimides



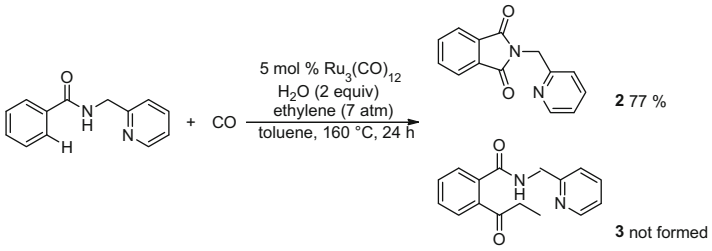
Scheme 41 Ru-catalyzed [3 + 2 + 1] cycloaddition of vinyl ketones, silylacetylenes, and CO

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

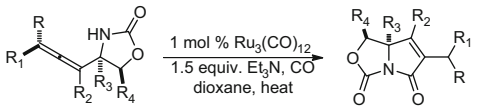


Scheme 43 Ru-catalyzed carbonylation at *ortho* C–H bond to phthalimides

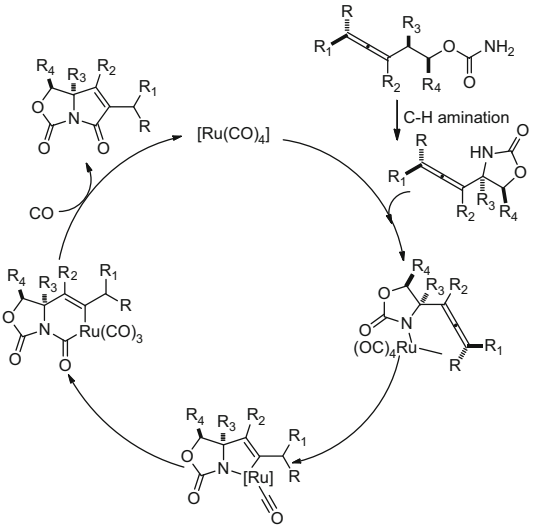
order to achieve high conversion. Finally, ethylene was found as the best H_2 acceptor (Scheme 43). After then, a variety of *para*-substituted aromatic amides were examined; from the obtained result, all the *para*-substituted phthalimides were formed in high yields. It can be concluded that the electronic 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

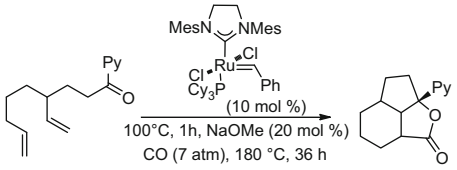
Scheme 44 Ru-catalyzed cyclocarbonylation to α,β-unsaturated γ-lactams



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



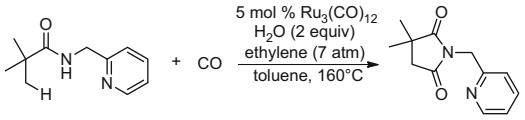
Scheme 46 Ru-catalyzed cycloaddition to polycyclic lactones



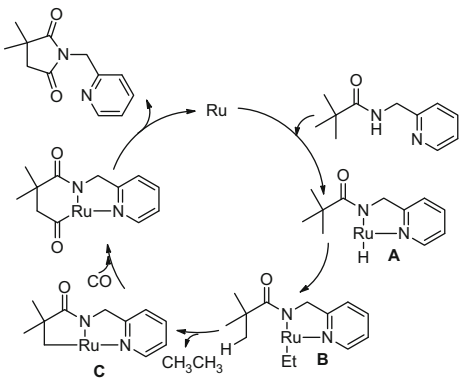
effectively dictate the stereochemistry of subsequent manipulations of these scaffolds (Scheme 45).

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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Rhodium-Catalyzed Carbonylative Synthesis of Heterocycles

Jian-Bo Feng and Xiao-Feng Wu

Abstract The main achievements in rhodium-catalyzed carbonylative synthesis of heterocycles are summarized and discussed.

Keywords Carbon monoxide · Carbonylation · Heterocyclic compounds · Organic synthesis · Rhodium catalyst

Contents

Nowadays, rhodium catalysts are 'star catalysts' in C–H activation reactions. Numerous synthetic systems have been developed based on Rh(I) or Rh(III) precursors. Compared with the achievements in C–H activation, the application of rhodium catalysts in carbonylation are less explored, except for the well-known Monsanto process which can transform methanol to acetic acid. In this chapter we summarize the established carbonylation procedures for the synthesis of heterocycles.

The carbonylation of acetylenes has received much attention because of its scientific and industrial importance. Various mono- and dicarboxylic acids, cyclic ketones, hydroquinones, butenolides, and other derivatives can all be produced from acetylenes [1]. Procedures for the synthesis of furanones catalyzed by Co [2, 3] and Pd [4] have been developed. In 1981, Mise and co-workers succeeded in developing a rhodium-catalyzed procedure for the synthesis of 5-alkyl-2(5*H*)-

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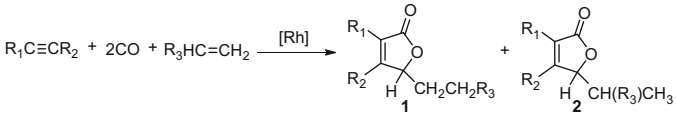


Scheme 1 General synthesis of furanones by carbonylation of acetylenes

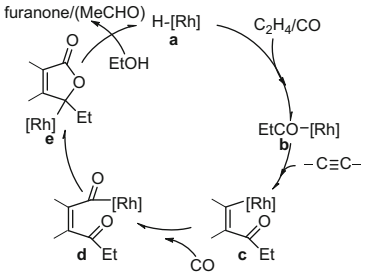
furanones from acetylenes. Rhodium carbonyl complexes and their precursors were tested in the presence of olefins and proton donors (Scheme 1) [5].

In this work, $Rh_4(CO)_{12}$ showed the best catalytic activity with different solvents acting as proton donors such as methanol, ethanol, propanol, and water. The formation of 5-ethyl-3,4-diphenyl-2(5*H*)-furanone and by-products indicated that the ethanol acted as both hydrogen donor and solvent medium in this reaction. Furthermore, 5-ethyl-3,4-dimethyl-2(5*H*)-furanone can also be produced from 2-butyne. Unfortunately, terminal acetylenes such as phenylacetylene and 1-hexyne did not give the desired products. Moreover, several mono-substituted olefins were used in the catalytic system with formation of the corresponding products in low yields. For the purpose of suppressing by-product formation, the influence of temperature was studied, results showing that a temperature of about 150°C is sufficient for maintaining yields and suppressing by-products. Finally, a possible mechanism was proposed by the authors and is shown in Scheme 2. It seems that the acyl complex **b** acted as an important intermediate given by stepwise insertion of ethylene and CO into the Rh-H intermediate. Then the subsequent addition of complex **b** to the acetylene and CO could give intermediate **d** and be converted to **e**, providing the final furanone.

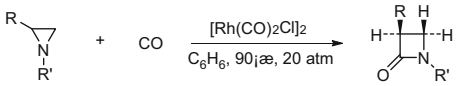
In 1983, Mise's group used $Rh_4(CO)_{12}$ as the catalyst to synthesize 5-ethoxy-3,4-diphenl-2(5*H*)furanone, and 72% yield of the corresponding product was formed. Interestingly, the addition of alkali metal salt to $Rh_4(CO)_{12}$ or its precursors can greatly improve the yield. A $Rh_4(CO)_{12}$/NaOAc system was found to be the best combination and gave the 5-ethoxyl-2(5*H*)-furanone in 87% yield [6]. Reasonable results could also be obtained by using Na_2CO_3 and $NaHCO_3$. Unfortunately, stronger bases such as NaOH and NaOEt gave no product. All of these results were dependent on the stability of $Na[Rh_6(CO)_{15}(COOR)]$ under the basic conditions [7]. Meanwhile, different rhodium catalysts such as Rh_2O_3, $RhCl_3{\cdot}3H_2O$, and $RhCl(PPh_3)_3$ were screened instead of $Rh_4(CO)_{12}$. The catalytic activities of the Rh_2O_3 and $RhCl_3{\cdot}3H_2O$ were nearly the same as the $Rh_4(CO)_{12}$ whereas the activity of $RhCl(PPh_3)_3$ was very low. All the results indicated that it was easy to obtain an (ethoxycarbonyl)rhodium intermediate by Rh_2O_3, $RhCl_3{\cdot}3H_2O$, and $Rh_4(CO)_{12}$, the triphenylphosphine ligand suppressing nucleophilic attack of an alkoxide ion on the coordinated carbon monoxide.

Later, Alper and Urso published a paper on the metal-catalyzed carbonylative ring expansion of aziridines to β-lactams [8]. To start with, they used the catalytic amount of $Pd(PPh_3)_4$ but, unfortunately, no β-lactams were formed. Then they used Rh salts as catalyst which can lead to the carbonylation of aziridines to β-lactams directly and regioselectively. It was found that when *N*-*tert*-butyl-2-phenylazirdine

Scheme 2 Proposed mechanism for the formation of furanone



Scheme 3 Carbonylation of *N-tert*-butyl-2-phenylaziridine



was treated with carbon monoxide in benzene with chlorodicarbonylrhodium (I) dimer as the catalyst at 90°C and 20 atm, the corresponding β-lactams can be produced in quantitative yield (Scheme 3).

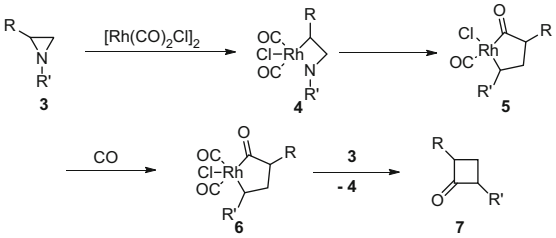
Other rhodium complexes were also taken into account, such as the 1,5-cyclo-octadienerhodium(I) chloride dimer, which is also an effective catalyst, whereas the dimers of 1,5-hexadiene-rhodium chloride and rhodium acetate were incapable of catalyzing this transformation. In this research, a mechanism was proposed whereby the oxidative addition of multi-substituted C–N bonds to Rh(I) afforded the corresponding Rh complex, then, followed by the migration of ligand and CO insertion, gave the desired product after reductive elimination (Scheme 4).

In 1989, Alper's group used 1,5-cyclo-octadienerhodium(I) chloride as catalyst and D- or L-menthol as an added chiral agent to study the asymmetric synthesis of β-lactams from aziridines [9]. To examine the ring-expansion process, *cis*-1-iso-propyl-3-methyl-2-phenylaziridine was subjected to benzene with $[Rh(CO)_2]Cl_2$ as the catalyst and the corresponding *cis*-3,4-disubstituted β-lactams was isolated in 81% yield, indicating that the carbonylation had taken placed with retention of the stereochemistry of the substituent groups (Scheme 5). Moreover, the remarkable regio-, stereo-, and enantiospecificity of the β-lactam synthesis suggested that it might be a promising route to synthesize corresponding asymmetric compounds from racemic aziridines in the presence of an appropriate chiral ligand.

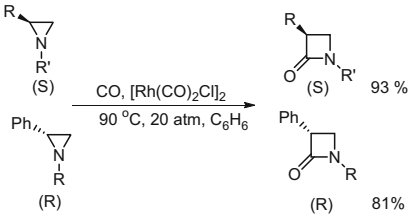
In 1990, Matsuda and co-workers synthesized β-lactones by rhodium-catalyzed cyclocarbonylation of substituted propargyl alcohols [10]. Because of the catalytic efficiency of Rh [11], an elegant cyclocarbonylation of acetylenic alcohols to form lactones with the assistance of an appropriate base and a catalytic amount of $Rh_4(CO)_{12}$ was demonstrated (Scheme 6).

The selectivity between the two products **9** and **10** can be tuned by the addition (or absence) of NEt_3. Preliminary research indicated that the propensity of β-lactones formation depended on both steric and electronic factors.

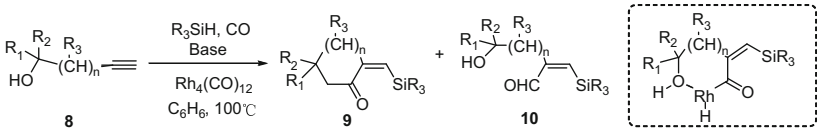
In 1990, Takahashi and co-workers found that the use of water instead of molecular hydrogen can give cyclocarbonylated products, 2(5*H*)-furanones, in excellent yield [12–14]. Later on, a novel rhodium-catalyzed carbonylation of



Scheme 4 Possible mechanism for the formation of β-lactams

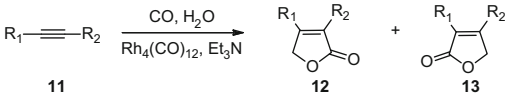


Scheme 5 Enantioselectivity of the carbonylation reaction

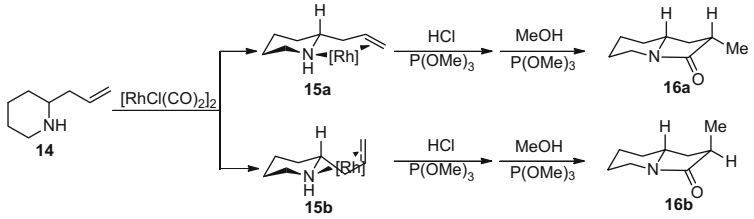


Scheme 6 Cyclocarbonylation of propargyl alcohols by the catalyst of rhodium

acetylenes was developed [15]. Under water-gas shift reaction conditions, internal acetylenes were selectively carbonylated to 3,4-disubstituted 2(5*H*)-furanones (Scheme 7). In addition, the reaction of D_2O instead of water gave the desired product 5,5-dideuteriofuran-2(5*H*)-one, indicating that the hydrogen came from water. Among the transition metal complexes, $Rh_4(CO)_{12}$ and $Rh_6(CO)_{16}$ were found to be the best catalysts. The effect of additives, solvents, the amount of H_2O in ethanol, and the pressure of CO were also examined. Thereby, the reactions can proceed with satisfactory yields by means of internal acetylenes bearing alky, alkenyl, and aryl substitutes. However, monosubstituted acetylenes such as phenylacetylene were of no use, possibly because the terminal acetylene has an active C–H bond. What should be pointed out is that, by employing a cyano group at the *para* position of one of the phenyl group of the acetylene, the reactivity was increased noticeably and the isomer **13** became the dominant product. In contrast, electron-donating groups could increase the isomer ratio of **12/13**. All of these results show that the electron density on the acetylene carbons have a strong effect on the product and that the carbonyl group of furanones is preferred to carbon atoms with lower electron densities.



Scheme 7 Carbonylation of acetylene to furanone by rhodium catalyst



Scheme 8 Synthesis of a bicyclic lactam through cyclocarbonylation of 2-allylpiperidine

A few years later, in 1993, Zhang and Ojima reported the synthesis of nitrogen heterocycles by direct hydrocarbonylation [16–21]. Based on previous research by Krafft et al. [22–24], Ojima and co-workers developed the diastereoselective annulation of 2-allylpiperidine **14** which it was thought could give a bicyclic lactam **16** (Scheme 8). During the process, it was found that the 2-allylpiperidine was processed highly stereoselectively and **16a** was given as the sole product in 43% isolated yield.

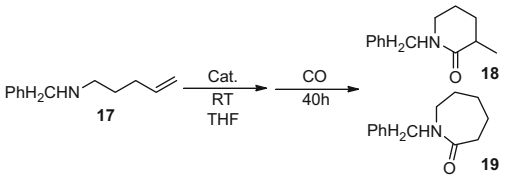
In addition, 5-benzylamino-1-pentene **17** was taken to examine catalytic and regioselective factors with a variety of rhodium complexes in the presence of hydrogen chloride. 1-Benzyl-3-methyl-2-piperidinone **18** and 1-benzyl-azepan-2-one **19** in ratios from 82:18 to 95:5 indicated that the amine-directed chelation control is effectively processed and is in favor of the formation of six-membered ring products (Scheme 9). However, the reactions gave lower conversion without hydrogen chloride, although good to excellent regioselectivities can be obtained with $HRh(CO)(PPh_3)_3$ or $Co_2Rh_2(CO)_{12}$.

In 1994, Khumtaveeporn and Alper used 1,3-thiazolidine as the substrate in the presence of catalytic amounts of chloro(1,5-cyclooctadiene)rhodium(I) dimer and potassium iodide to afford a thiazolidinone (Scheme 10) [25]. However, in the absence of KI, the six-membered ring thiazin-3-one becomes the primary product. Quantitative conversion was achieved and a ketene was produced as the by-product. Hence, the reaction involved a novel regiospecific insertion of carbon monoxide into one of two ring carbon–nitrogen bonds and a metal-catalyzed ketene elimination process. In this work, a serious of N-substituted thiazolidine derivatives were synthesized in dry benzene under 65 bar of carbon monoxide at 180°C for 48 h. In this catalytic system, complete conversion and good to excellent yields could be obtained.

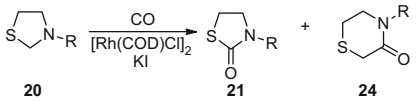
Under standard conditions, **21** was obtained in quantitative yield when **24** was used as the start material. All of this indicates that rhodium(I) not only catalyzed the ring expansion but also the subsequent ring contraction (Scheme 11).

In 1994, Joh and co-workers improved the reaction conditions for internal alkynes and extended the substrates to terminal alkynes. 3- and 4-substituted 2 (5*H*)-furanones were selectively produced (Scheme 12) [26].

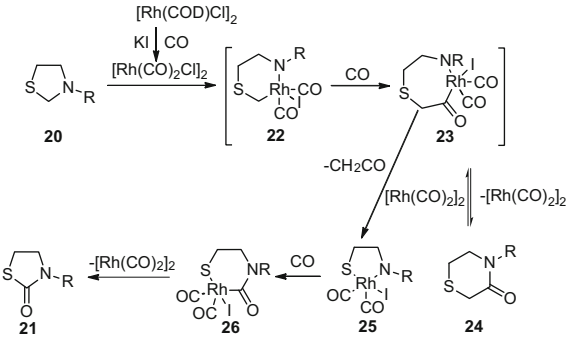
Scheme 9 Cyclocarbonylation of 5-benzylamino-1-pentene



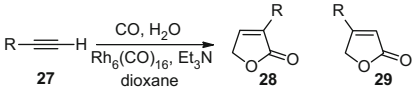
Scheme 10 Rhodium(I)-catalyzed carbonylation of 1,3-thiazolidines



Scheme 11 Mechanism of the rhodium-catalyzed carbonylation of 1, 3-thiazolidines



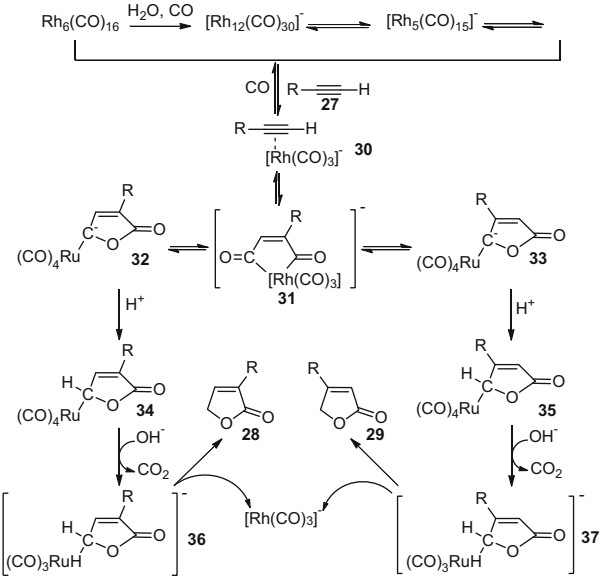
Scheme 12 Rhodium-catalyzed carbonylation of terminal alkynes



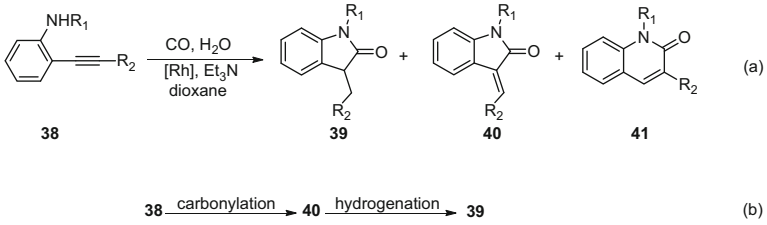
In the optimization process, the effect of solvent, concentration of Et_3N, alkyne, catalyst, and amount of water were all tested. Based on the observations described above, a new reaction pathway was given in detail (Scheme 13). Because there was no furanonyl product when the countercation of the intermediate was replaced with a cation with no hydrogen, it was considered that the most important step was the attack of a proton on the intermediate (**32**/**33**). Moreover, the amine may not only have promoted the attack of the OH^- anion but also have contributed to the stabilization of the anionic complex and transferred the proton to give the furanonyl complex.

In 1995, Takahashi and co-workers used 2-alkynylaniline as the start material to synthesize 1,3-dihydroindol-2-ones using the rhodium-catalyzed carbonylation process [27]. The typical experiment was performed under 100 bar of carbon monoxide in 1,4-dioxane containing water and triethylamine at 175°C for 14 h in the presence of $Rh_6(CO)_{16}$ (Scheme 14).

From the data obtained, it can be seen that the temperature affected the product distribution over a wide range. At low temperature, the main product was not **39** but



Scheme 13 Mechanism for rhodium-catalyzed carbonylation of terminal alkynes

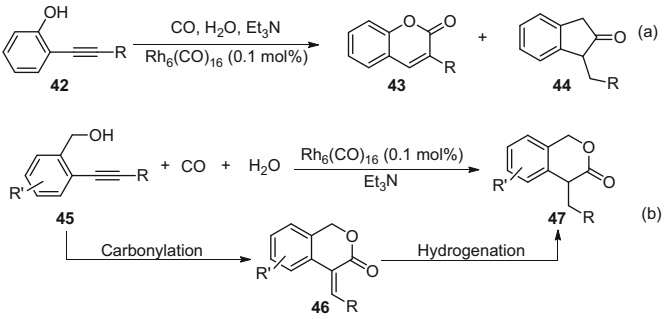


Scheme 14 Rhodium-catalyzed carbonylation of 2-alkynylaniline to dihydroindo-2-ones

40, which suggested that **40** was initially produced and then hydrogenated to **39** at higher temperature (Scheme 14b) and this was confirmed experimentally.

Later on, Takahashi's group succeeded in using *ortho*-substituted phenols as substrates to synthesize benzofuranones and coumarins also under water-gas shift reaction conditions [28]. The hydroxyl group adjacent to the carbon–carbon triple bond participates in the cyclic carbonylation with high yields up to 96% (43:44 = 65:35; Scheme 15a). The effects of solvent and additives were also investigated and 1,4-dioxane was found to be the best solvent for product selectivity, and both water and amines were compulsory for this system.

Taking the reaction mechanism into consideration, the hydroxy group of 2-alkynylbenzylalcohol may participate more effectively in the cyclic carbonylation of alkynes, and 2-alkynylbenzylalcohol was used in the presence of rhodium as catalyst to synthesize 3-isochromanone. The reaction proceeded via cyclic carbonylation under water-gas shift reaction conditions with highly selectivity and good yields (Scheme 15b) [29]. Interestingly, when 1,3,5-trimethylphenyl was used as a



Scheme 15 Rhodium-catalyzed carbonylation of 2-alkynyphenols

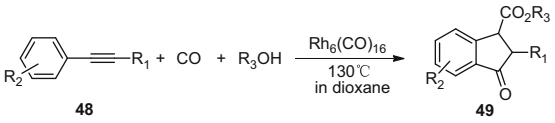
substitute group, no desired product was obtained but 71% yield of the intermediate. Hence the reaction involved two steps – carbonylation and hydrogenation.

In 1999, da Rosa and co-workers first reported the effects of chelating diphosphines on the rhodium-catalyzed carbonylation of allylamines [30]. The catalytic system was prepared in situ by mixing $RhCl_3 \cdot 3H_2O$ and equimolar amounts of the diphosphine ligands in THF. All the systems were tested and showed high conversion although, unfortunately, the selectivity decreased when the diphosphine carbon chain length increased. Hence there is a strong influence of the bite angle on both conversion and selectivity. The steric hindrance of the group attached to the allylamines nitrogen atom is also critical for the reaction.

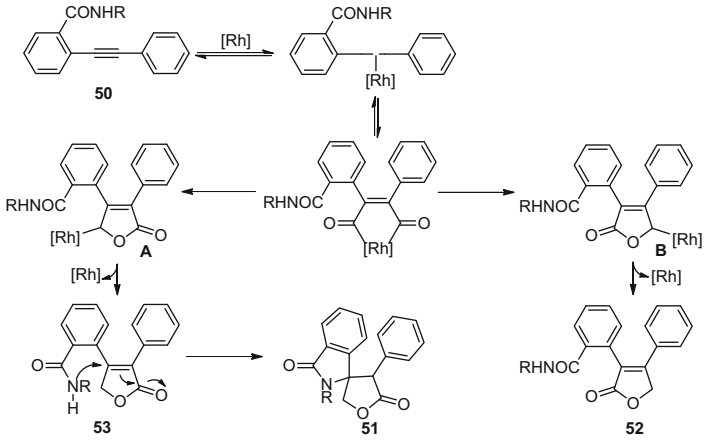
Carbonylation of alkynes under water-gas shift reaction conditions to give furan-2(5*H*)-ones in the presence of rhodium catalyst was reported. In 1999, the group of Takahashi used alcohol instead of water, and the corresponding 3-alkoxycarbonylindanones were obtained in good yield (up to 93%; Scheme 16) [31].

In the absence of methanol, the carbonylation of alkyne did not occur and the substrate was quantitatively recovered. The addition of 0.4 equiv. of methanol (based on the substrate) resulted in 52% conversion and a lower yield of about 32% when 1.0 equiv. of methanol was added, the reaction proceeding smoothly and completely. Rhodium complexes such as $[Rh(CO)_2Cl]_2$ and $RhCl_3$ showed almost the same activity as $Rh_6(CO)_{16}$ under the same reaction conditions. Moreover, study of the substrates indicated that primary alcohols gave higher yields of the corresponding indanone derivatives than secondary alcohols, possibly because of the acidity of the alcohols. It was found that alcohols with higher acidity gave better yields of the desired products.

Another example of rhodium-catalyzed cyclic carbonylation under water-gas reaction conditions was presented in 1999 by Takahashi's group. In this case, 2-phenylethynybenzamide was taken as the start material and treated with carbon monoxide in the presence of $Rh_6(CO)_6$, NEt_3, and H_2O in 1,4-dioxane at 80°C for 3 days. Two kinds of products **51**/**52** were obtained (Scheme 17) [32]. Normally, the amide group of the product was on the C=O side of the furanone ring. However, in the reaction of *N*,*N*-dimethyl-2-phenylethynylbenzamide, no further cyclization



Scheme 16 Rhodium-catalyzed carbonylation of alkynes in the presence of alcohol

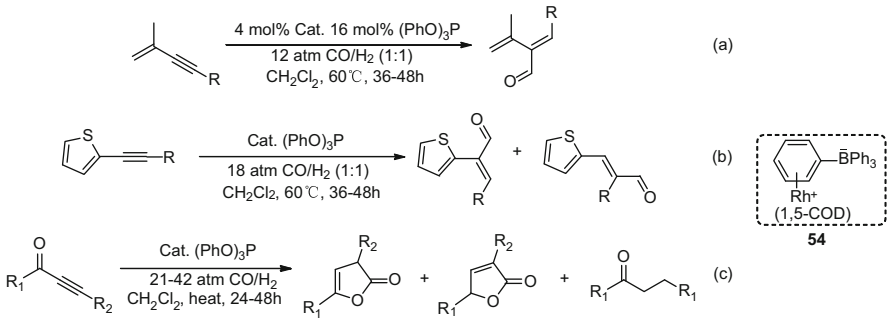


Scheme 17 Rhodium-catalyzed carbonylation of 2-phenylethynybenzamide

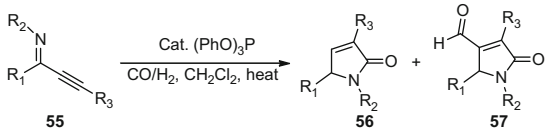
occurred and no spiro product was detected. All these results suggested that spiro compounds would be formed via a furanone intermediate with a structure similar to **53**, but it should have an N–H bond at the amide group.

In 1999, Alper and co-workers used the zwitterionic rhodium complex $(\eta^6\text{-}C_6H_5BPh_3)^-Rh^+(1,5\text{-COD})$ **54** as catalyst and triphenyl phosphite as ligand at moderate temperature and low pressure to study the hydroformylation of both enynes [33] and acetylenic thiophenes [34] (Scheme 18a, b). They used this catalyst system for the cyclohydrocarbonylation of multifunctionalized α-ketoalkynes in 2000. Good to excellent yield and good chemo- and regioselectivities could be obtained (Scheme 18c). The temperatures and pressures required were milder than those previously reported. In addition, good chemo- and regioselectivity were observed for a variety of multifunctionalized alkynones to give 2-, 2(3*H*)- and 2(5*H*)-furanones as the dominant products.

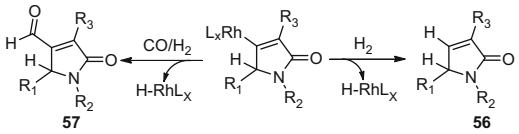
In 2001, Alper and co-workers described a novel chemo- and regioselective route to synthesize 4-carbaldehydepyrrolin-2-ones in the presence of zwitterionic rhodium complex **54** [35]. When the oxygen atom was replaced with nitrogen and under the same reaction conditions, 4-carbaldehydepyrrolin-2-ones **57** could be prepared in good yield (Scheme 19). R_1, R_2, and R_3 were replaced by different substitutes to investigate the electronic and steric effect in detail. Moreover, with some controlled experiments, together with the data obtained, the conversion of α-imino alkynes to 4-carbaldehydepyrrolin-2-ones was shown to be the minor route to **57** (Scheme 20).



Scheme 18 Hydrocarbonylation catalyzed by zwitterionic rhodium complex



Scheme 19 Rhodium-catalyzed cyclohydrocarbonylation/CO insertion of α-imino alkynes

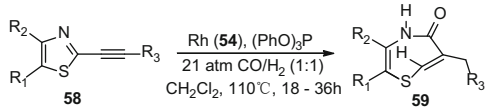


Scheme 20 Possible route to **56** and **57**

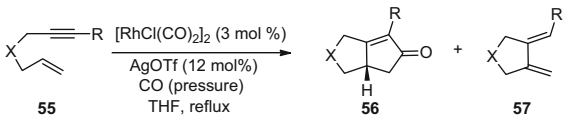
Another example of the application of a zwitterionic rhodium catalyst is the synthesis of 2-(*Z*)-6-(*E*)-4*H*-[1,4]-thiazepin-5-ones by cyclohydrocarbonylative ring expansion of acetylenic thiazoles (Scheme 21) [36], in the presence of 2 mol% Rh complex as the catalyst, 8 mol% ligand, 10 mL of CH_2Cl_2 in a 45-mL autoclave, at 110°C. In addition, a 1:1 ratio of CO/H_2 at a total pressure of 14 and 21 atm resulted in selectivity for the desired product of 89% and 90%, respectively.

In the substrates testing of this transformation, it is found that all the reactions can produce good to excellent isolated yields. Moreover, the reactions of thiazoles with different substitutes in the acetylenic unit seemed to proceed in a significantly temperature-dependent fashion.

Based on previous investigations, rhodium catalysts bearing bidentate phosphine ligands were also found to be effective for cyclization by tuning phosphine ligands [37]. Jeong and co-workers used $RhCl(CO)_2$ to study a rhodium-catalyzed asymmetric intramolecular Pauson–Khand-type reaction with (*S*)-BINAP as the ligand (Scheme 22) [38]. Even though using toluene as the solvent was more efficient, better enantioselectivity can be obtained in a coordinating solvent such as THF. In addition, the CO pressure was quite critical for the enantioselectivity and for the chemical yield. More Pauson–Khand reaction (PKR) products were favored under



Scheme 21 Zwitterionic rhodium-catalyzed cyclohydrocarbonylation of acetylenic thiazoles



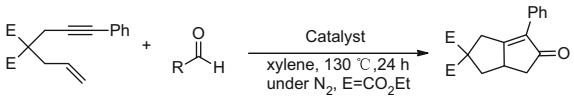
Scheme 22 Rh(I)-catalyzed enantioselective Pauson–Khand-type reaction

higher pressure, but better enantioselectivities might be obtained under lower CO pressure because the unfavorable equilibrium between potential catalysts is suppressed. In most cases, this transformation proceeded nicely to PKR products with good to excellent enantioselectivities in reasonable reaction times (4–6 h) under 1 atm of CO. Moreover, aryl-substituted acetylenes provided better chemical yields of PKR products but lower *ee* than alkyl-substituted acetylenes.

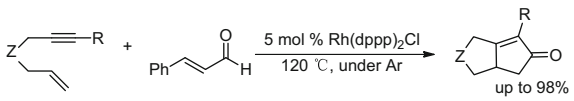
In 2002, Kakiuchi and co-workers used aldehydes as a source of carbon monoxide and investigated the Pauson–Khand-type reaction of enynes [39–42]. The reaction of enyne and benzaldehyde in the presence of catalytic amounts of [RhCl(cod)]$_2$ and dppp in xylene at 130°C for 24 h can afford the carbonylated product in 33% isolated yield although 66% of the starting material remains unreacted (Scheme 23). Additionally, a variety of aldehydes were examined and all the aromatic aldehydes were able to act as a carbon monoxide source. Aldehydes which contain electron-withdrawing substituents can donate CO moieties better [43]. Various enynes have been converted into the corresponding products with good to excellent yields. In addition, when two such groups were positioned on contiguous carbons of a ring system, the cyclocarbonylation proceeded diastereoselectively and tricyclic cyclopentenones were transformed in excellent yields.

Another example of carbonylation of alkene–alkyne using aldehyde as CO source and in the presence of Rh(dppp)$_2$Cl catalyst was reported by Shibata and co-workers in 2002 (Scheme 24) [44]. Among a variety of aldehydes, cinnamaldehyde showed the best efficiency as the CO source. It should be noted that the process was carried out under solvent-free conditions.

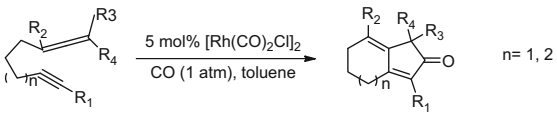
In 2002, Brummond and co-workers found that when alkynyl allenes were treated with [Rh(CO)$_2$Cl]$_2$ and processed via [2+2+1] cycloaddition reaction, a variety of 4-alkylidene cyclopentenones can be produced without α-alkylidenecyclopentenones (Scheme 25). The scope and limitations of the rhodium-catalyzed allenic Pauson–Khand-type reaction were examined in detail. All the result demonstrated that the ring system can be transformed from the distal double bond of the allene with highly regioselectivity. Another rhodium-catalyzed Pauson–Khand-type reaction was reported by Mukai and co-workers [45, 46]. 1-Phenylsulfonylallenes with a hexynyl appendage were treated with catalytic



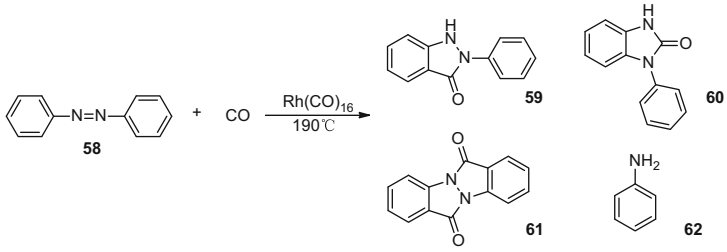
Scheme 23 Catalytic Pauson–Khand-type reaction of enyne with aldehyde as CO source



Scheme 24 Rhodium-catalyzed carbonylation of alkene-alkyne using aldehyde as CO source



Scheme 25 Rhodium-catalyzed carbonylation of alkynyl allenes



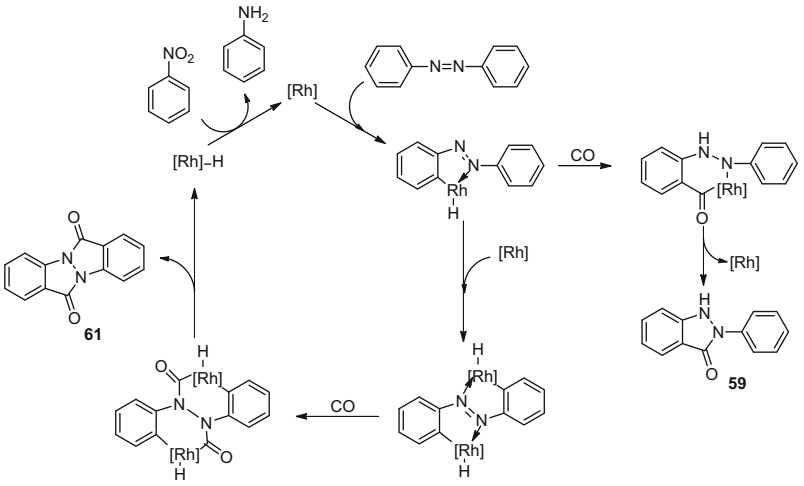
Scheme 26 Rhodium-catalyzed cyclocarbonylation of azobenzene

amounts of rhodium catalyst ($[RhCl(CO)_2]_2$ or [RhCl(CO)dppp]) in a carbon monoxide atmosphere and produced the corresponding bicyclo[5.3.0]dec1,7-dien-9-one via regioselective [2+2+1]-cycloaddition. Different substrates were also examined and produced acceptable yields.

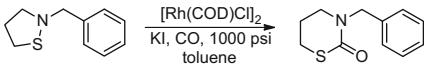
Later, Saito's group published relevant works on rhodium-catalyzed Pauson–Khand-type reactions for the synthesis of pyrrolo-indolones, pyrrolo-pyrrolinones [47], and pyrrolo[2,3-*b*]quinones [48]. As there are many research items and reviews published on the Pauson–Khand-type reaction, we do not discuss it extensively here [49–53].

Carbonylation of azobenzene derivatives catalyzed by rhodium carbonyls in the presence of nitrobenzenes was reported by Takahashi and co-workers [54]. Indazolo[2,1-*a*]indazole-6,12-dione was transformed from this novel cyclocarbonylation with C–H activation and CO insertion at each benzene nucleus of azobenzene (Scheme 26).

In this work, different carbonyl complexes and solvents were examined in detail, and it was found that the $[Rh(CO)_2Cl]_2$/nitrobenzene system showed the best



Scheme 27 Proposed mechanism for rhodium-catalyzed cyclocarbonylation of azobenzene

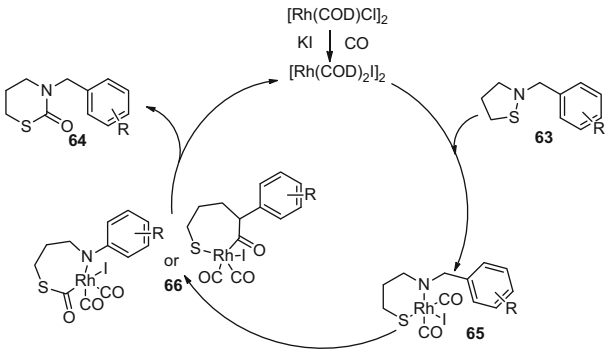


Scheme 28 Rhodium-catalyzed carbonylation of *N*-benzylisothiazolidine

selectivity for **61** synthesis. In addition, an Rh-H species is postulated as an active intermediate in this reaction, which it was also thought may cause the reductive cleavage of N=N bond to give aniline. Hence, the addition of nitrobenzene can depress the consumption of the azobenzene. After that, several azobenzene derivatives were used in this new type of cyclocarbonylation. Based on the result obtained and the previous literature, a tentative cyclocarbonylation mechanism was proposed as shown in Scheme 27.

In 2004, Dong and Alper used the carbonylation of *N*-alkylisothiazolidines in the presence of rhodium complex to produce the tetrahydro-2*H*-1,3-thiazin-2-ones [55], based on previous work on the rhodium-catalyzed carbonylation of isoxazolidines with regioselective insertion of CO into the N–O bond affording tetrahydro-1,3-oxazin-2-ones [56]. When *N*-benzylisothiazolidine is reacted with 5 mol% of (1,5-cyclooctadiene)rhodium(I) dimer in benzene in the presence of 1,000 psi of carbon monoxide at 130°C for 24 h, a 58% yield of 2*H*-1,3-thiazin-2-one can be achieved, and the addition of 5 mol% of potassium iodide can increase the yield to 70% (Scheme 28).

This reaction tolerates various substrates and can afford the corresponding products in 35–85% yields. Considering the isothiazolidines which contain one more CH_2 unit between the N atom and the phenyl ring, *N*-(2-phenylethyl) isothiazolidine was used and afforded 85% yield of the corresponding product. The mechanism of this carbonylation of *N*-alkylisothiazolidines as depicted consisted of three steps – oxidative addition, CO insertion, and reductive elimination (Scheme 29).



Scheme 29 Proposed mechanism of rhodium-catalyzed carbonylation of *N*-alkylisothiazolidines

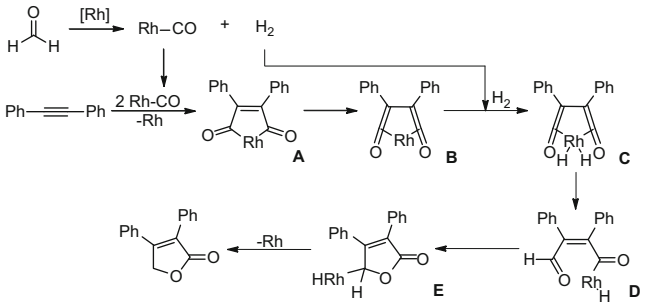
Later, in 2005, Kakiuchi and co-workers published a communication on rhodium-catalyzed cyclocarbonylation of alkynes to α,β-butenolides with formaldehyde [57–60]. In the presence of 5 mol% of $[RhCl(cod)]_2$ and 10 mol% of dppp in xylene, a variety of substrates were transformed with up to 95% yields. Generally, there are always two isomers produced because of the different locations of the of carbonyls. The mechanism of this reaction has been proposed (Scheme 30). In addition, the possibility of a lactonization process via **D** was demonstrated with *o*-phthalaldehyde, which was treated under the same reaction conditions, and 91% of benzolactone was transformed.

In 2006, an efficient and straightforward method to synthesize 5-aryl-2(5*H*)-furanones under the same conditions as for rhodium-catalyzed carbonylation of alkynes with aryl boronic acids was presented by Artok and co-workers (Scheme 31) [61].

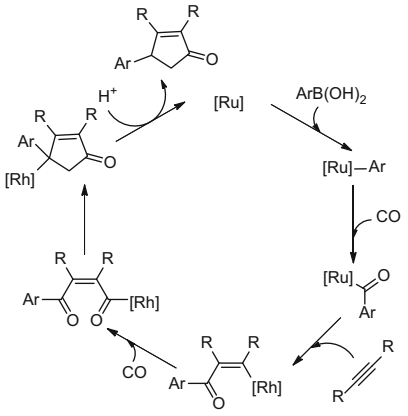
In the presence of 1 mol% of $[RhCl(COD)]_2$ in 1,4-dioxane under 20 atm of CO at 80°C for 16 h, 3,4,5-triphenylfuran-2(5*H*)-one can be obtained in 78% yield. The reaction proceeds efficiently when the aryl boronic acid contains an electron-donating functional group. A higher yield can also be obtained by increasing the amount of Rh catalyst to 3 mol%. Although moderate to excellent yields can be obtained under these conditions, no reaction occurs with terminal alkyne.

Chatani and co-workers used $[RhCl(cod)]_2$ as the catalyst in the reaction of alkynes with 2-bromophenylboronic which gave indenones in up to 97% yield (Scheme 32) [62]. In this reaction, it is found that some Rh complexes such as $[RhCl(CO)_2]_2$ and Rh(0) complexes such as $Rh_4(CO)_{12}$ show similar activities and give the corresponding product in good yield whereas rhodium phosphine complexes such as $RhCl(PPh)_3$ and $RhH(CO)(PPh_3)_3$ produce no activity. Moreover, alkenes were also examined with 2-bromophenylboronic. Unfortunately the styrene and cyclopentene showed no carbonylated products whereas norbornene gave the corresponding ketone in 80% yield.

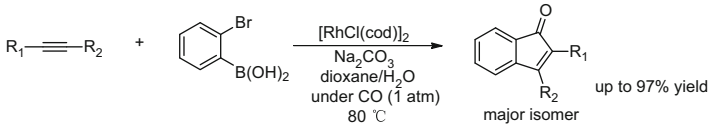
Regarding the reaction mechanism, a vinylrhodium intermediate could be generated by the addition of arylrhodium species to 2-bromophenyl(trimethylsilyl) acetylene followed by olefin isomerization to form the indenone as the sole product



Scheme 30 Mechanism for rhodium-catalyzed cyclocarbonylation of alkynes with formaldehyde



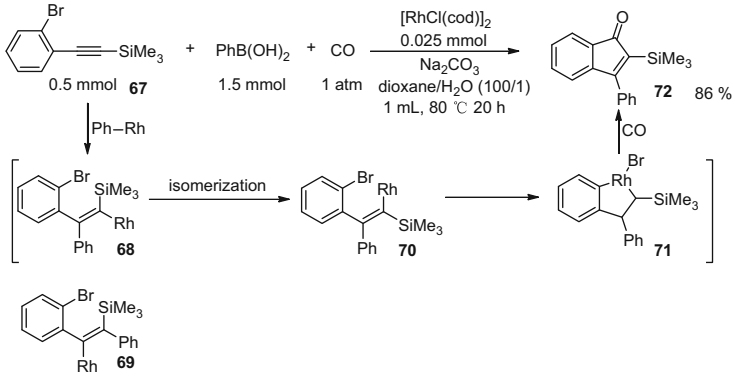
Scheme 31 Rhodium-catalyzed carbonylation of boronic acid to alkyne



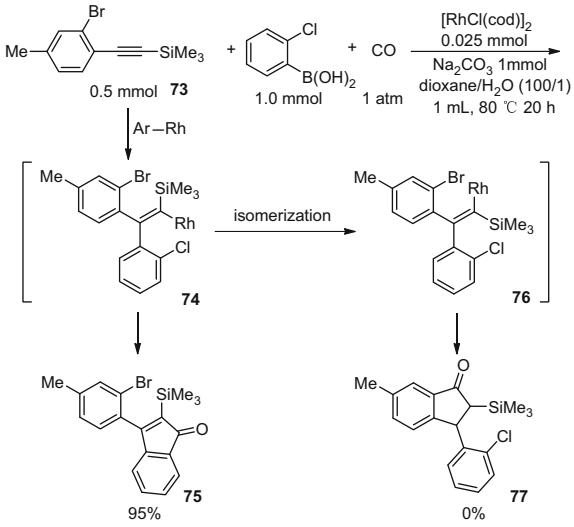
Scheme 32 Rhodium-catalyzed carbonylation of alkynes with 2-bromophenylboronoic acid

(Scheme 33). There were no regioisomeric indenones formed because the isomer **69** cannot be converted to indenones even if they were formed. Moreover, when trimethylsilyl was replaced with a *tert*-butyl, ester, and phenyl group, the corresponding product was not detected. All these indicated that a silyl group at the terminal acetylenic carbon is essential for the isomerization.

During this work, the *E*/*Z* isomerization of vinylrhodium complex was considered to act as a key step in the synthesis of indenone. Hence, to examine the isomerization, 2-bromo-4-methylphenyl(trimethylsilyl)acethylane was reacted with 2-chlorophenylbononic acid (Scheme 34). Theoretically, it forms two isomers with the oxidative addition of a C–Cl bond and a C–Br bond leading to two different



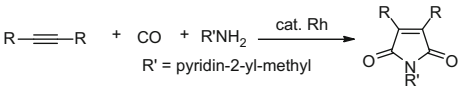
Scheme 33 Reaction of 2-bromophenyl(trimethylsilyl)acetylene with phenylboronic acid/CO



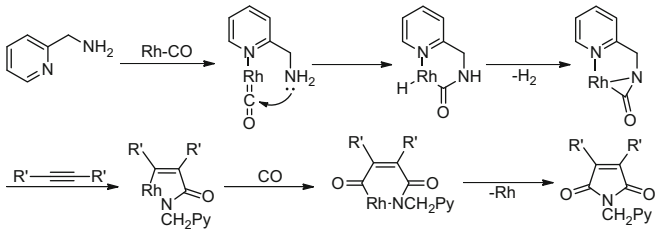
Scheme 34 Carbonylation of 2-bromo-4-methylphenyl(trimethylsilyl)acethylane with 2-chlorophenylbononic acid

products. Unfortunately, **77** was not detected although **75** was formed in 95% yield. All of these indicate that the isomerization of a vinylrhodium complex is not facile. In addition, the reaction of 1-(2-bromophenyl)-hept-2-yn-1-one with $PhB(OH)_2$ under similar conditions gave the carbonylative cyclization product indan-1,3-dione derivative in good yield. Finally, the rhodium-catalyzed regioselective addition of an arylrhodium(I) species to alkynes, followed by the oxidative addition of C–Br bonds in the adjacent phenyl ring afforded vinylrhodium(I) as the key step.

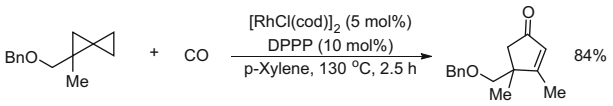
In the same year, Chatani and co-workers presented another report that on using $Rh_4(CO)_{12}/P(OEt)_3$ as the catalytic system to catalyze the carbonylation of alkynes with pyridin-2-ylmethylamine (Scheme 35) [63]. It is different from former



Scheme 35 Rh-catalyze carbonylation of alkynes with pyridin-2-yl-methylamine



Scheme 36 Proposed reaction mechanism of rhodium-catalyzed carbonylation of alkynes with pyridin-2-yl-methylamine



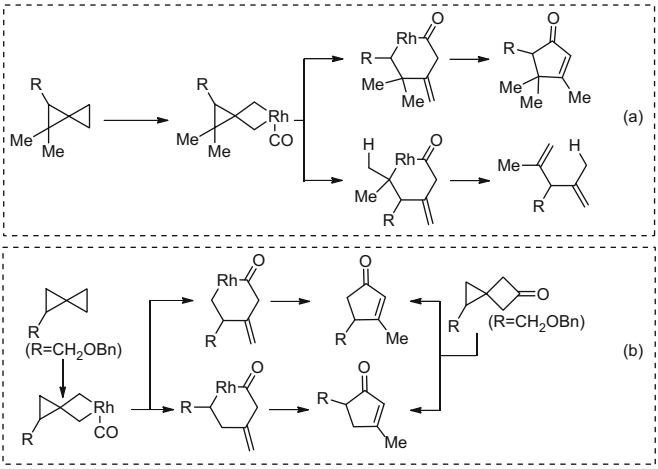
Scheme 37 Rhodium-catalyzed carbonylation of spiropentanes

literature on the carbonylation of alkynes with amines affording α,β-unsaturated amides [15, 64].

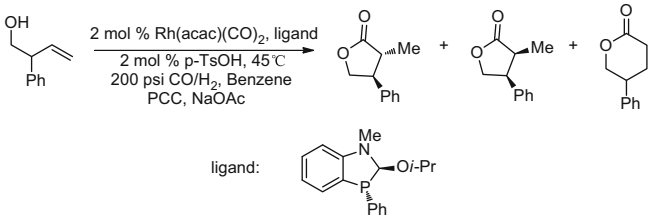
First, when 4-octyne was treated with pyridin-2-ylmethylamine under CO (3 atm) in toluene (1 mL) at 100°C in the presence of $Rh_4(CO)_{12}$ for 20 h, it afforded the corresponding product 3,4-dipropyl-1-(pyridin-2-ylmethyl)pyrrole-2,5-dione in 39% isolated yield. With increased temperature the yields of the corresponding products also increased. However, because the $Rh_4(CO)_{12}$ was decomposed there was no desired product when the reaction was carried out at 130°C. When the reaction was carried out at 120°C or lower, the color of the reaction mixture was red, whereas it would be black when the temperature was 130°C or higher. The yield can be significantly increased by the addition of P $(OEt)_3$. Both aliphatic and aromatic internal alkynes gave the corresponding products in good yield. Control experiments were performed and showed that the nitrogen of the pyridine is essential because the coordination of the pyridine nitrogen to the rhodium center facilitated the intramolecular attack of the amine on the coordinated carbon monoxide to give a rhodium hydride species (Scheme 36).

Later, Murakami and co-workers used 5 mol% of $[RhCl(cod)]_2$ and described a catalytic carbonylation reaction of spiropentanes to synthesize a series of 3-methylcyclopent-2-enones (Scheme 37) [65].

Various disubstituted spiropentanes were used under catalytic reaction conditions and afforded good yields. Trisubstituted spiropentanes were also examined, and the corresponding cyclopentenones were obtained with diene (Scheme 38a). However, when monosubstituted spiropentane was subjected to the reaction



Scheme 38 Rhodium-catalyzed carbonylation of tri- and 1; mono-substituted spiropentane

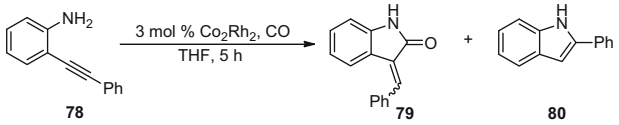


Scheme 39 Rhodium-catalyzed hydroformylation of terminal olefin

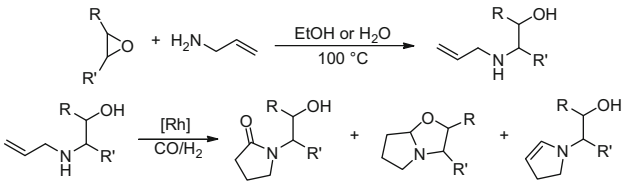
conditions, an isomeric mixture of cyclopentenones was transformed (Scheme 38b). This all indicates that the carbonylation of spiropentanes forming cyclopentenones also involves two successive carbon–carbon bond cleavage processes which were discussed in the former research [66].

In 2007, based on previous studies on hydroformylation [67–74], it seemed that the application of supramolecular catalysts could solve the problems with low regio-, diastereo-, and enantioselectivity [75–77]. Tan and co-workers synthesized a series of scaffolding ligands and tested them in the hydroformylation of terminal olefin (Scheme 39) [78]. With a range of substrates, the direct hydroformylation of them with an electron-rich and electron-deficient aromatic ring at the allylic position afforded good regio- and diastereoselectivities.

Cobalt/rhodium nanoparticles were also used as catalyst in the carbonylative cycloaddition of 2-alkylanilines to prepare oxindoles [79]. With the development of transition metal nanoparticles, they have been widely used as catalysts for organic synthesis because of their high catalytic activity and recyclability [80–85]. Chung and co-workers found that cobalt/rhodium nanoparticles derived from $Co_2Rh_2(CO)_{12}$ were useful as a catalyst in carbonylation reactions [86]. Co_2Rh_2-catalyzed carbonylative cyclization of 2-akynylanilines can form oxindoles



Scheme 40 Co_2Rh_2 catalyzed synthesis of oxindoles from 2-alkynylanilines

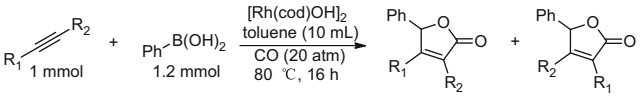


Scheme 41 Aminolysis of epoxides followed by carbonylation

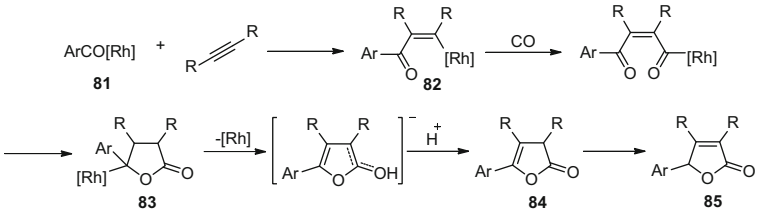
successfully and without any need for additives or promoters. The catalyst can be recycled several times without any significant loss of activity (Scheme 40). Various 2-alkynylanilines were screened under optimized conditions and gave the desired oxindoles in satisfactory yields. However, there was no desired product detected in the reaction of terminal alkynes.

In 2008, da Rosa and co-workers synthesized *N*-(2-hydroxy-alkyl)-γ-lactams and bicyclic oxazolidines by carbonylation of allylaminoalcohols in the presence of rhodium catalyst (Scheme 41) [87]. In this work, allylaminoalcohols from the aminolysis of cyclohexene oxide, styrene oxide, (*R*)-(+)-limonene oxide, and ethyl-3-phenyl-glicidate were used as the substrates. $RhClCO(PPh_3)_2$ was used as the catalyst, and moderate to excellent yields were obtained. The selectivity of the isomers can be optimized by controlling the CO/H_2 ratio. Excess CO provided a lactam selectivity of up to 90% although a higher quantity of H_2 gas can increase the selectivity of oxazolidines resulting from hydroformylation/cyclization. The kinetic studies indicated that oxazolidines and γ-lactams were formed through parallel routes. Moreover, two mechanisms for the two products were ascertained in detail, and the X-ray crystal structure of an iridium-carbamoyl complex prepared under the same reaction conditions was obtained which directly supported the assumption that the key step of the mechanism was the formation of a metal-carbonyl intermediate.

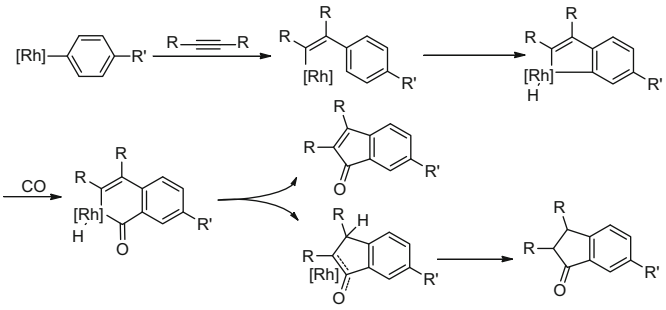
Aryl boronic reagents can be carbonylated with rhodium catalysts to give acyl rhodium species that are amenable to the addition of unsaturated C–C bonds [88–94]. In 2009 Artok and co-workers investigated a carbonylative reaction of various alkynes with aryl boronic acids in the presence of Rh complex and afforded 5-aryl-2(5*H*)-furanones (Scheme 42) [95]. In this catalytic system, the selectivities of the products were tunable by varying the reaction conditions and gave the desired 5-aryl-2(5*H*)-furanones in up to 90% yield. From the results obtained it can be seen that the relative formation of isomeric products was influenced by electronic and steric properties effects on the alkyne substrate. The acyl rhodium species **81** formed was considered subsequently to undergo 1,2-addition to the carbon–carbon



Scheme 42 Rhodium-catalyzed carbonylation of phenylboronic acid with alkynes



Scheme 43 Proposal mechanism of the formation of 2(5*H*)-furanone

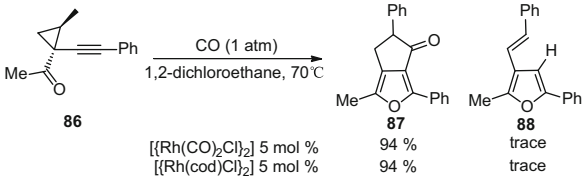


Scheme 44 Mechanism of indenone and indanone formation

triple bond, followed by the insertion of CO into the resulting β-aroyl alkenylrhodium(I) complex **82** and then by ring closure to form a *σ*-furanoyl complex **83**. Displacement of Rh from the cyclic complex and subsequent protonation leads to a 5-aryl-2(3*H*)-furanone molecule **84** which should undergo isomerization to a more stable structure, 5-aryl-2(5*H*)-furanone molecule **85** (Scheme 43).

Artok and co-workers also used the reaction to synthesize indanones by the reaction of alkynes and organoboranes under a CO atmosphere in the presence of 1.5 mol% of $Rh(cod)_2BF_4$ (Scheme 44).

A rhodium-catalyzed regio- and stereospecific carbonylation of 1-(1-alkynyl) cyclopropyl ketones to highly substituted 5,6-dihydrocyclopental[c]furan-4-ones was presented by Zhang and co-workers in 2009 [96]. Highly substituted furans as the key structure in bioactive natural compounds and pharmaceuticals, methodologies based on allenyl ketones [97–117], 3-alkyl-1-ones [111, 112, 118, 119], (*Z*)-2-en-4-yn-1-ols [120] and 2-(1-alkynyl)-2-alkens-1-ones [121–126], alkylidenecyclopropyl ketones [127–129], cyclopropenyl ketones [130, 131], etc., have been developed. The versatile compound 1-(1-alkynyl)cyclopropyl ketone has been



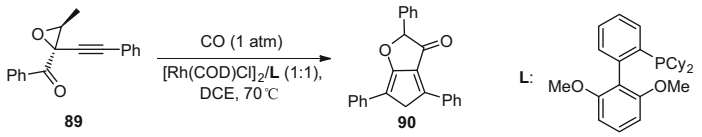
Scheme 45 Carbonylation of 1-(1-alkynyl)cyclopropyl ketones in the presence of Rh

successfully developed by Schmalz [132, 133] and Zhang [134, 135] as substrate for the production of highly substituted furans and other cyclic compounds using gold(I) complexes as catalyst. Based on previous research, it was thought that 1-(1-alkynyl)cyclopropyl ketones might undergo transformations initiated by rhodium(I) catalyzed activation of the carbon–carbon σ-bond of the cyclopropane ring [65, 136–142]. Hence, in the presence of 1 atm of CO and 5 mol% of [{Rh$(CO)_2Cl\}_2$] or [{Rh(cod)$Cl\}_2$], 1-methyl-3,5-diphenyl-5,6-dihydrocyclpenta[c]furan-4-one **87** can be detected in excellent yield in 1,2-dichloroethane at 70°C as the desired product by carbonylation of 1-(1-alkynyl)cyclopropyl ketones **86**. At the same time, (*E*)-2-methyl-5-phenyl-3-styrylfuran **88** as the sole and major by-product was formed (Scheme 45).

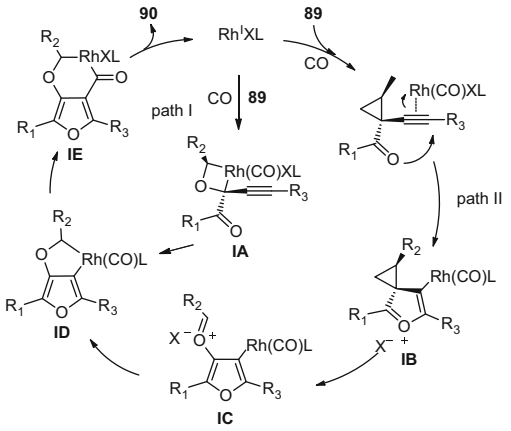
With 1-(1-alkynyl)oxiranyl ketone **89** as the substrate, formal [4+1] cycloaddition can occur in the presence of rhodium catalyst and finish with highly substituted furo[3,4-*b*]furan-3-(2*H*)-ones **90** as the products in good to excellent yields (Scheme 46) [143]. Two plausible reaction pathways were suggested by the authors (Scheme 47). In path **I**, it was considered that there was an oxidative addition of the C–C bond of epoxy motif of **89** and generated rhodaoctane **IA**, which would undergo rapid cycloisomerization to form intermediate **ID**. Then the insertion of CO and **90** was produced by reductive elimination of **IE**. In path **II**, the rhodium (I) coordination of the triple bond of **89** enhanced the electrophilicity of alkynes. The nucleophilic attack of the carbonyl oxygen on the rhodium(I)-activated alkyne would subsequently form the oxonium-containing vinyl-rhodium intermediate **IB**. Then the cleavage of C–C bond of **IB** would lead to intermediate **ID** and undergo the same process to afford **90**.

In 2011, a simple and highly efficient rhodium-catalyzed tandem heterocyclization and carbonylative [(3+2)+1] cyclization reaction that can afford furan scaffold **92** to be easily converted to highly substituted bicyclic phenols **93** was presented by Zhao and Zhang (Scheme 48) [144]. Based on previous research, the metallacycle intermediate **91** has been proposed which can afford fused tricycloheptadienes [145]. It was also considered that it can be trapped by CO, leading to a tricyclic scaffold. Different solvents, rhodium-complexes, and the amount of CO were examined. DCM was found to be the best solvent and this reaction can produce a better yield with a lower pressure of CO in the presence of 5 mol% $[RhCl(cod)]_2$.

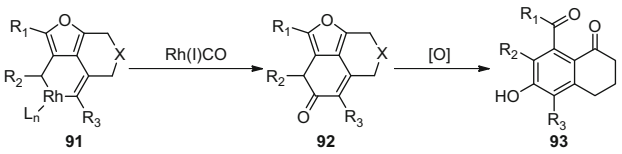
Rh(III)-complex-catalyzed formation of phthalimides by oxidative carbonylation of aromatic amides via C–H/N–H activation was developed by Rovis and co-workers in 2001 [146]. This was based on previous reports of coupling of



Scheme 46 Rhodium-catalyzed cycloaddition of 1-(1-alkynl)oxiranyl ketones

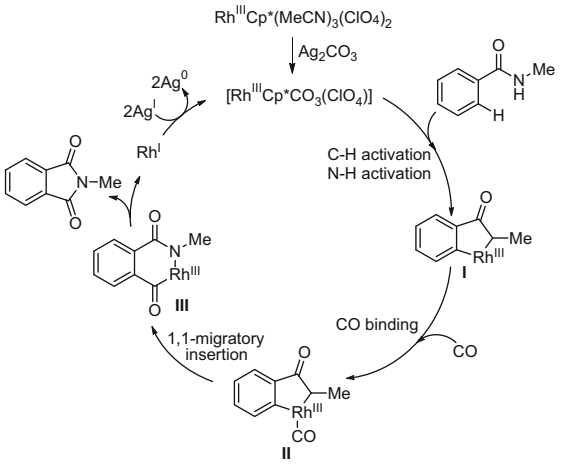


Scheme 47 Plausible mechanism of rhodium-catalyzed cycloaddition of 1-(1-alkynl)oxiranyl ketones



Scheme 48 Rhodium-catalyzed carbonylative [(3+2)+1] cyclization

benzamide and α,β-unsaturated amides with alkynes to produce isoquinolones and pyridones utilizing Rh(III)-catalyzed C–H activation [147–155]. It was considered that it could provide unique phthalimides via an analogous approach when the alkyne was replaced with CO. With a screening of different catalysts, solvents, and oxidants, the best results were obtained in the presence of 5 mol% RhCp* $(MeCN)_3(ClO_4)_2$, Ag_2CO_3 2 equiv., KH_2PO_4 2 equiv., and CO 1 atm. A number of different amides were tested under optimized conditions and indicated that the reactions of amides bearing alkyl groups at the nitrogen atom proceeded smoothly to deliver phthalimides in excellent yields of up to 95%. On the basis of the results obtained, a plausible mechanism for this RhCp*$(MeCN)_3(ClO_4)_2$-catalyzed oxidative carbonylation was proposed in detail (Scheme 49). It should be noted that the generated rhodium(I) species after reductive elimination is reoxidized by Ag_2CO_3 to close the catalytic cycle.



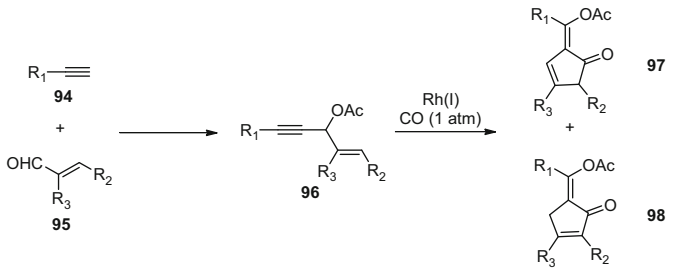
Scheme 49 Mechanism of rhodium-catalyzed oxidative carbonylation of benzamides with CO

In 2012, Tang and co-workers reported an efficient procedure for the synthesis of highly functionalized cyclopentenones **97** and **98** from 3-acyloxy-1,4-enyne **96** via a Rh(I)-catalyzed carbonylation reaction (Scheme 50) [156].

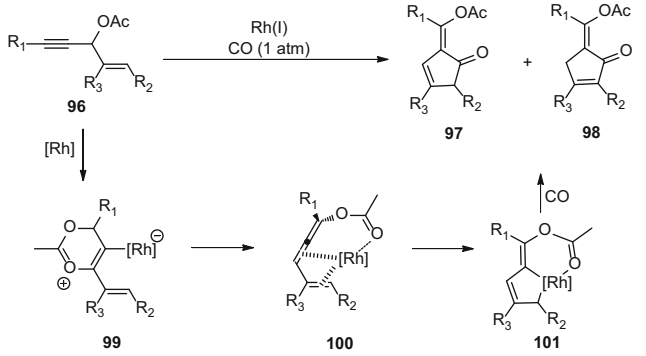
It has been demonstrated that 3-acyloxy-1,4-enynes with a terminal alkyne can serve as a five-carbon building block for [5+1] [157] and [5+2] [158] cycloadditions with CO and alkynes, respectively. Moreover, both of these cycloadditions involve a rhodium-catalyzed 1,2-acyloxy migration of propargyl esters which was reported in 1984 [159, 160]. With some elegant work in this field [161–163], cyclopentenones can also be produced with the use of rhodium catalyst $[Rh(COD)Cl]_2$ (Scheme 51). Here, the acyloxy group in the propargyl ester starting material not only eliminates the need for the preformation of allenes but also provides a useful handle for further selective functionalization of the cyclopentenone products.

In the same year, Tang and co-workers developed two different types of tandem reactions for the synthesis of highly functionalized cyclohexenones from cyclopropyl substituted propargyl esters (Scheme 52) [164]. First, different catalysts such as Au, Rh, Ag, and Pd were tested, but no reaction occurred or only the formation of enone. After this, it was found that alkylidene cyclohexenone was formed as a mixture of *E*/*Z* isomers (ratio = 1:1) in about 30% yield when in the presence of 20 mol% $[Rh(CO)_2Cl]_2$ in toluene (Scheme 53). However, the addition of different ligands (e.g., PPh_3, $P(OMe)_3$, $P(OPh)_3$, and pyridine) either decreased the conversion of the reaction or shut down the reaction completely. It should be noted that no reaction occurred for the secondary propargyl acetate although it can work well when replaced by pivalate.

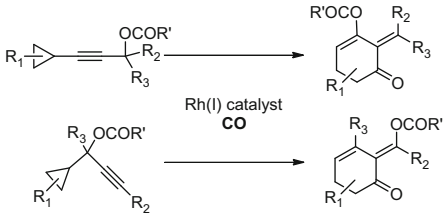
In 2015, Yu and co-workers first reported a rhodium-catalyzed benzo/[7+1] cycloaddition of cyclopropyl-benzocyclobutenes (CP-BCBs) and CO to benzocyclooctenones (Scheme 54) [165]. An appropriate R group in CP-BCBs can facilitate the ring opening of benzocyclobutene; more specifically, an electron-donating group could promote BCB's ring opening [166]. It should also



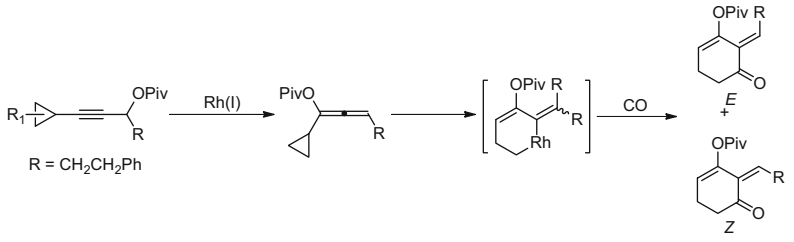
Scheme 50 Carbonylation of 3-acyloxy-1,4-enyne for the synthesis of cyclopentenones



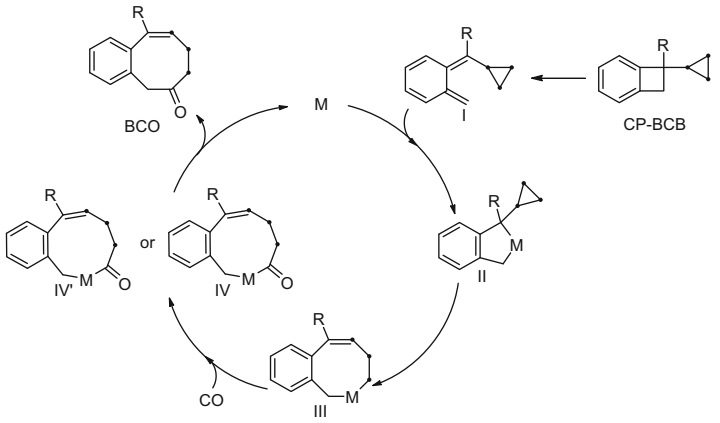
Scheme 51 Carbonylation of 3-acyloxy-1,4-enyne for the synthesis of cyclopentenones



Scheme 52 Rhodium-catalyzed carbonylation of cyclopropyl substituted propargyl esters



Scheme 53 Proposed mechanism for the formation of alkylidene cyclohexenone from cyclopropyl substituted propargyl ester



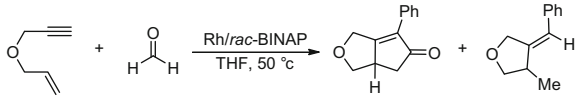
Scheme 54 Proposed benzo/[7+1] reaction pathway of CP-BCB with CO

be pointed out that the TBS protecting group is necessary for the success of the present reaction.

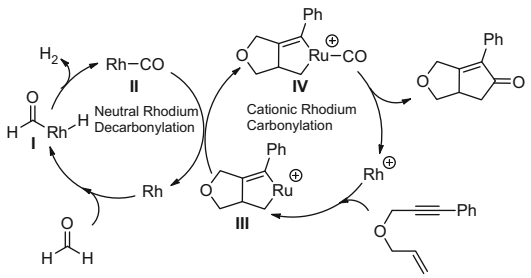
Under optimal reaction conditions, the reaction showed good tolerance with functional groups and substitution patterns on the phenyl ring. Moreover, substitutes on the cyclopropane ring can be tolerated and gave the corresponding products in moderate yields. The substrate with a methyl group at the nonfunctional position on the cyclopropane ring can also be tolerated with a little selectivity favoring the cleavage of the less-hindered C–C bond of the cyclopropane ring. However, when the methyl group was substituted on the four-membered ring there was no corresponding product, probably because of unfavorable steric hindrance.

Recently, Morimoto and co-workers reported an asymmetric Pauson–Khand-type reaction of 1,6-enynes that formaldehyde used as a carbonyl source in the presence of rhodium catalysts [167]. Initially, 1,6-enynes were treated with formaldehyde in the presence of $[RhCl(cod)]_2$ and *rac*-BINAP at 50°C; 18% conversion and 4% yield of the corresponding cyclocarbonylation product were the result (Scheme 55). After optimization, it was found that the cyclocarbonylation can occur even at 30°C. Other aldehydes were also examined although none of them can work as a carbonyl source. Then the role of each neutral and cationic Rh catalyst was examined. The result of ^{31}P NMR indicated that $[RhCl((R)\text{-binap})]_2$ is an effective catalyst for the carbonylation reaction at room temperature. Under the best reaction conditions, different substituted 1,6-enynes with oxygen tethers were converted into the corresponding bicyclic cyclopentenones in moderate yields with high enantioselectivities. However, when there was a sterically bulky substituent at the terminal alkyne, those containing a carbon(malonate)-tether were less reactive under the standard reaction condition. A proposed reaction pathway was that formaldehyde reacts with neutral rhodium to generate the carbonyl rhodium species **II** via the formation of a formyl rhodium complex **I**. Then the carbonyl moiety is directly transferred to the cationic rhodacycle **III**, followed by carbonylation to give the final product (Scheme 56).

Scheme 55 Rhodium-catalyzed cyclocarbonylation of 1,6-enyne



Scheme 56 Proposed mechanism of rhodium-catalyzed cyclocarbonylation of 1,6-enyne



In summary, the main contributions on rhodium-catalyzed carbonylative synthesis of heterocycles have been summarized and discussed. The related achievements have also been included, even though no heteroatom was involved. Most of the work is still limited with alkenes and alkynes, and the use of organohalides as substrates is still rare.

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Palladium-Catalyzed Carbonylative Synthesis of Six-Membered Heterocycles from Aryl Halides

Wanfang Li and Xiao-Feng Wu

Abstract The main achievements on palladium-catalyzed carbonylative synthesis of six-membered heterocycles based on aryl halides as the substrates have been summarized and discussed.

Keywords Aryl halides • Carbon monoxide • Carbonylation • Heterocyclic compounds • Palladium catalyst

Contents

1 Introduction

Six-membered ring system is widely present in many natural products, pharmaceuticals, agrochemicals, and functional materials [1, 2]. Specifically, the oxygen-, nitrogen-, and sulfur-containing six-membered fused ring scaffolds are of great

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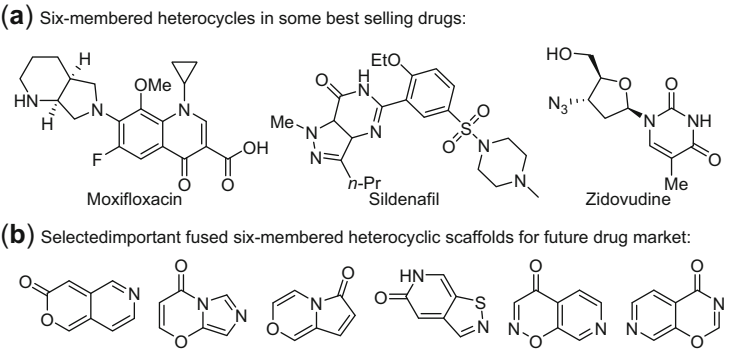


Fig. 1 Six-membered heterocycles in important drugs/their candidate structures

interest for the drug industry. For example, quinolones, pyrimidines, and quinazolines are present in many of the best-selling drugs (Fig. 1a) [3]. In 2009, in the highly cited paper titled Heteroaromatic Rings of the Future, Pitt el al. described a virtual exploratory heterocyclic library based on a learning computer program, which would be a powerful tool in drug discovery [4]. Many fused six-membered heterocyclic scaffolds are found in the library (Fig. 1b). Owing to their great importance for the human beings, the chemists have tried a lot to devise various methods to obtain these heterocyclic compounds. Look at the structures in Fig. 1, one could find that all the compounds contain a carbonyl group (-CO-). These types of carbonyl-incorporated six-membered rings are widely present in numerous other pharmaceutically interesting molecules. In the past decades, catalytic carbonylation reactions have found many applications in the synthesis of such type of six-membered heterocycles [5]. In this chapter, we mainly review the palladium-catalyzed formation of oxygen- and nitrogen-containing rings from organo halides. Some closely related ring formation from non-halide starting materials will also be mentioned.

2 Chromone and Flavonoid Derivatives

Chromones and flavones (flavonoids) are an important class of biologically and pharmacologically interesting heterocycles (Fig. 2) [6–9]. For example, flavones have many activities such as antioxidant, antitumor, antimicrobial, and anti-inflammatory, and they could affect the behavior of some mammalian enzymes [10–16]. In clinical setting, flavonoid drugs have been used in the treatment of cancer, diabetes, cardiovascular disease, neurodegenerative disorders, etc. [17–20]. Although more than 4,000 naturally occurring flavonoids have been reported, chemists are still trying to synthesize more structurally versatile ones to explore their therapeutic applications. Besides the traditional procedures for their synthesis

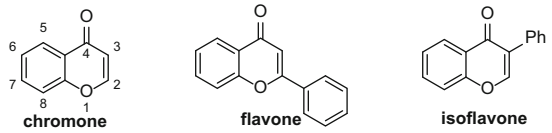
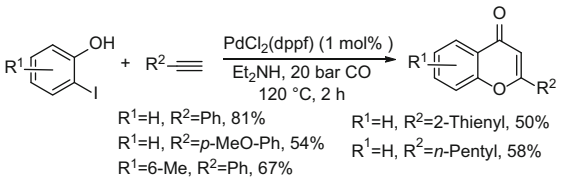
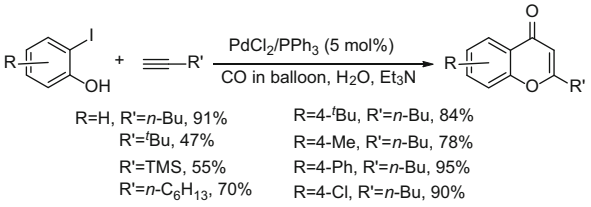


Fig. 2 Structure of chromone and flavonoids



Scheme 1 First synthesis of chromones and flavones by Pd-catalyzed carbonylation



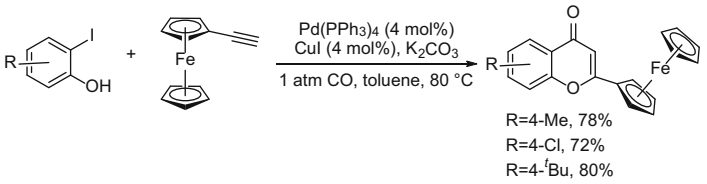
Scheme 2 Pd-catalyzed carbonylative synthesis of flavones in water

[8, 21], palladium-catalyzed carbonylations have provided a more straightforward route to flavonoid derivatives.

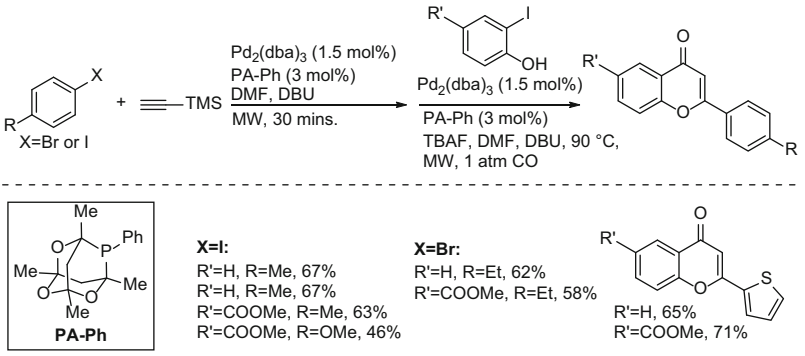
The first synthesis of chromones and flavones using palladium-catalyzed carbonylation reaction was reported in 1990 by Kalinin and coworkers [22]. In their report, 2-iodophenols and two equivalents of alkynes were converted into substituted chromone derivatives catalyzed by 1 mol% of $PdCl_2$(dppf). However, only five examples were provided and the yields were moderate to good (Scheme 1). One drawback of this earliest procedure is the employment of diethylamine both as the solvent and base. The yields were much lower in other solvents like THF, DMF, benzene, and anisole (46–55%). In 1993, the substrate scope of this reaction was extended under the same reactions by the same group [23].

In 2005, Yang and coworkers developed a $PdCl_2/PPh_3$-catalyzed carbonylative Sonogashira cross-coupling with the same starting materials at room temperature [24]. The key feature of this reaction was that water was used as the green solvent and the atmospheric pressure of CO. They used this new procedure to synthesis several flavones in good to excellent yields (Scheme 2). By using 4 mol% of Pd $(PPh_3)_4$ as the catalyst, several 2-ferrocenyl flavones were synthesized in 72–80% yields (Scheme 3) [25]. In their procedure, 4 mol% of CuI was needed as the cocatalyst and with K_2CO_3 as the base.

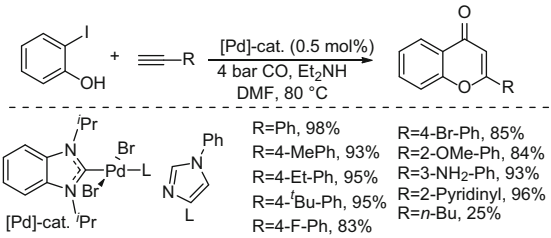
In 2009, Awuah and Capretta developed a microwave-assisted synthesis of flavones through one-pot Sonogashira–carbonylation–annulation reaction [26]. Starting from commercially available aryl bromides or iodides and trimethylsilylacetylene, flavones were obtained without isolation of the Sonogashira



Scheme 3 Carbonylative synthesis of 2-ferrocenyl flavones



Scheme 4 Microwave-assisted synthesis of flavones

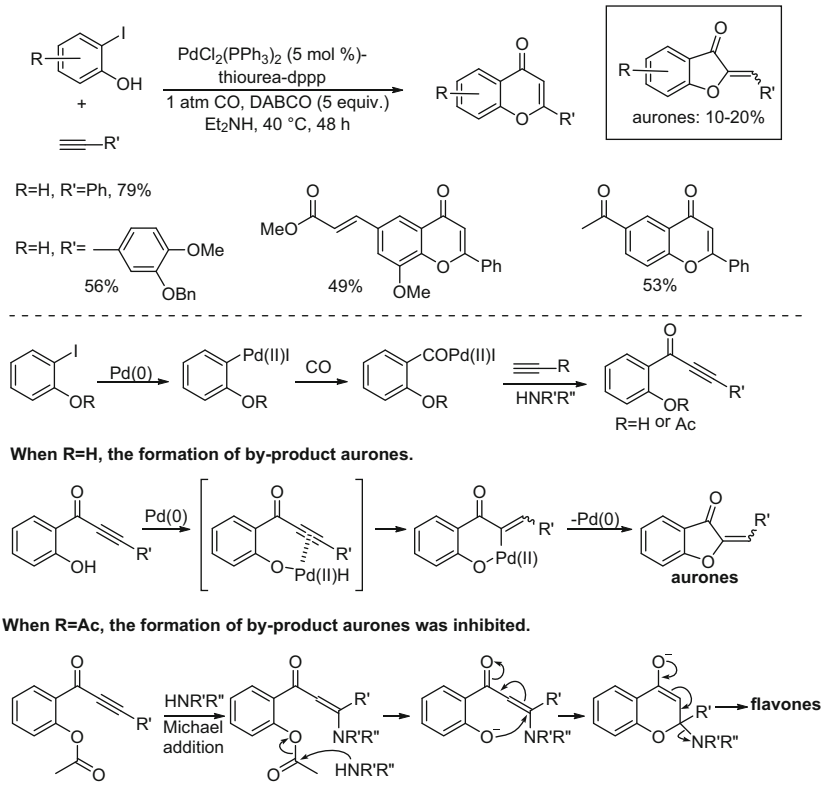


Scheme 5 Pd–NHC-catalyzed carbonylation of 2-iodophenols

coupling intermediates. In their procedure, 1.5 mol% of $Pd_2(dba)_3$ was used as the catalyst, and PA–Ph (1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane) was used as the ligand (Scheme 4).

In 2010, Yang and Alper reported a ligand-free carbonylative synthesis of flavones from 2-iodophenols and alkynes in phosphonium salt ionic liquids [27]. They used 5 mol% of $PdCl_2$ as the sole catalyst and triethylamine as the base. Under atmospheric CO pressure, 64–96% yields of various substituted flavones were obtained. One drawback of this procedure was that the reaction must be performed at 110°C, and the catalyst loadings were high (5 mol%).

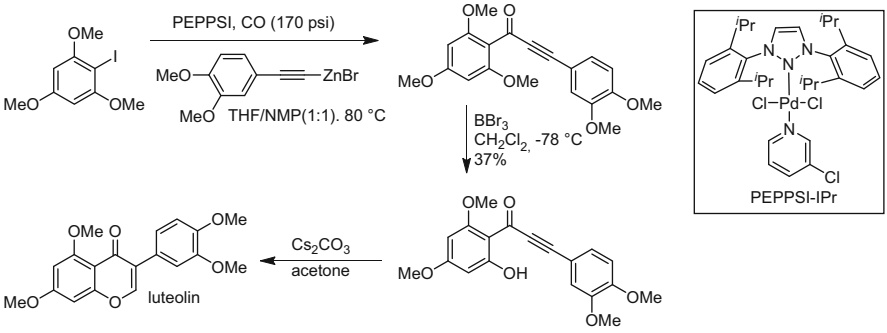
In 2011, Li and coworkers reported a Pd–carbene-catalyzed carbonylations of 2-iodophenols. Using 0.5 mol% [$PdBr_2$(^{i}Pr_2-bimy)L] (L=*N*-phenyl imidazole) as the catalyst and diethylamine as the base, a series of flavones were synthesized in good yields (Scheme 5).



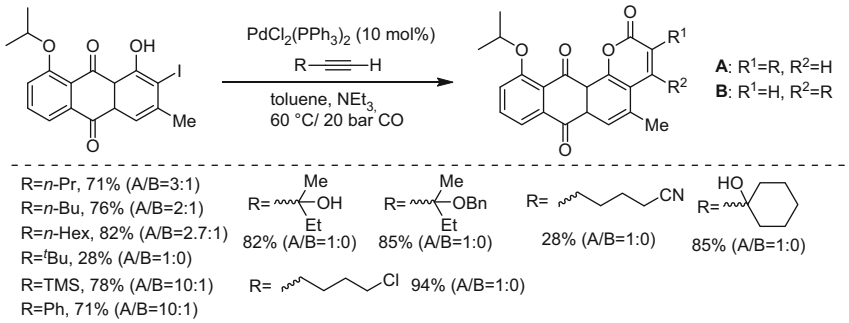
Scheme 6 Carbonylative annulation of 2-iodophenol acetates with high regioselectivity

Using a new type of palladium–thiourea–dppp complex as the catalyst, Miao and Yang reported a regiospecific carbonylative annulation of 2-iodophenol to form flavones in moderate yields (Scheme 6) [28]. The authors found that significant amount of aurone **3** was observed in all cases (10–20%). Besides, the conversion of 2-iodophenols remained 80–90% even though the reaction time was extended to more than 2 days. To overcome these problems, acetylated 2-iodophenols were used as the substrates to afford the flavonoid products in 70–92% yields. The formation of aurones resulted from the oxidative addition of phenol O–H bond to Pd(0), which could not happen when the hydroxyl was protected by acetyl group.

The construction of flavones from 2-iodophenols also found many applications in total synthesis. Martin and coworkers reported the total synthesis of luteolin in 2011 (Scheme 7) [29]. Using $PdCl_2(PPh_3)_2$ as the catalyst, Rixson et al. [30] realized a facile synthesis of some novel anthrapyran-2-ones by the carbonylative cross-coupling between 1-hydroxy-2-iodo-dihydroanthrancene and terminal alkynes. These structures may have been reported with antibacterial or antitumor activities (Scheme 8).



Scheme 7 Carbonylation of 2-iodophenol as key step in total synthesis of luteolin

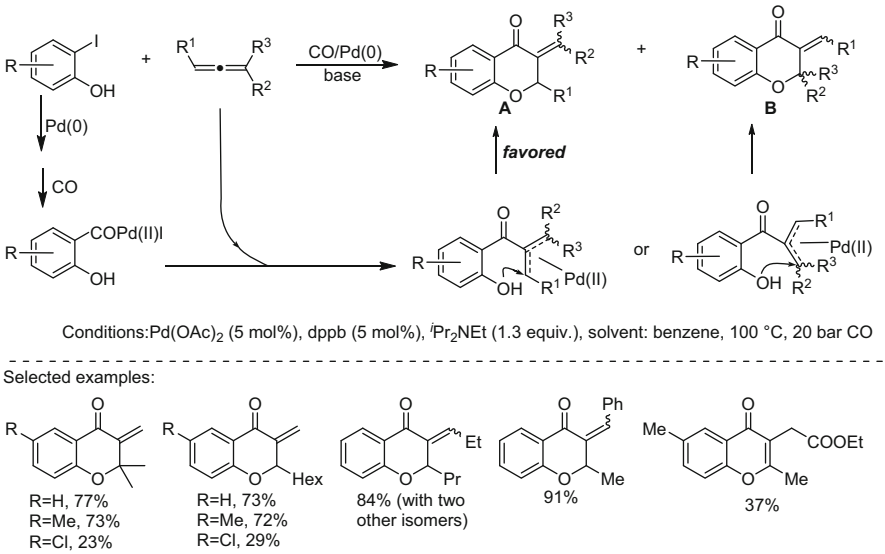


Scheme 8 Pd-catalyzed carbonylative synthesis of anthrapyran-2-ones

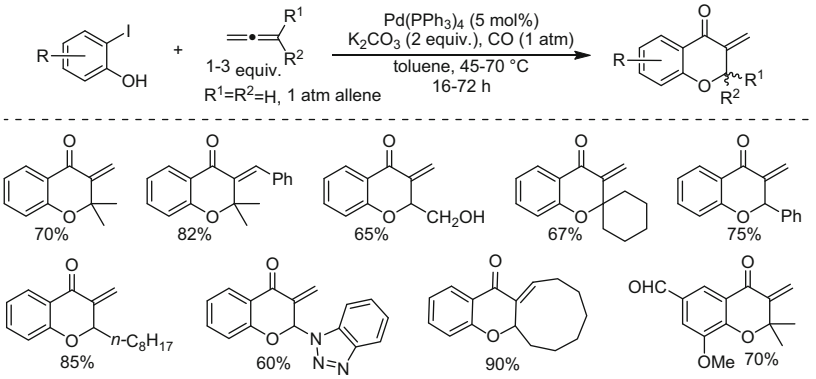
Alper and coworkers reported the first carbonylation reaction with 2-iodophenols and allenes [31]. Using 5 mol% of $Pd(OAc)_2$/dppb as the catalyst and $^{i}Pr_2NEt$ as the base, the reaction favored isomer **A** in high regioselectivity, especially when terminal allenes (R^1=H) were employed. The regioselectivity resulted from the more favorable OH attacking on the less hindered terminus of the π-allyl palladium intermediate (Scheme 9).

Also started from 2-iodophenols and allenes, Grigg and coworkers performed the reaction under atmospheric CO pressure [32]. Using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base, various functionalized chroman-4-ones were obtained in good to excellent yields (Scheme 10). Besides, 2-iodoanilines were also converted to quinol-4-ones under the same conditions.

In 2000, Kadnikov and Larock reported the carbonylation of 2-iodophenols and internal alkynes (Scheme 11) [33]. A variety of substituted coumarins were synthesized in good yields in the presence of 5 mol% of $Pd(OAc)_2$ under 1 atm of CO. Owing to the large over amount of alkynes (5 equiv.) and low CO pressure, the insertion of the internal alkyne occurs in preference to the insertion of CO. When asymmetric internal alkynes were used, two regioisomers were obtained in moderate selectivity. In 2014, Zhao, Cai et al. used a highly efficient and reusable



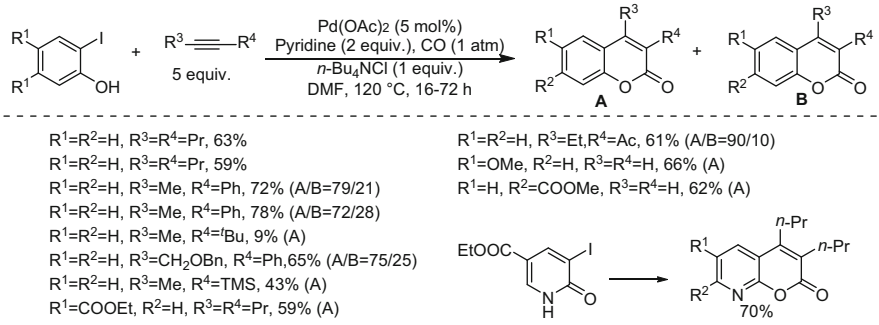
Scheme 9 Pd-catalyzed carbonylation of 2-iodophenols with allenes



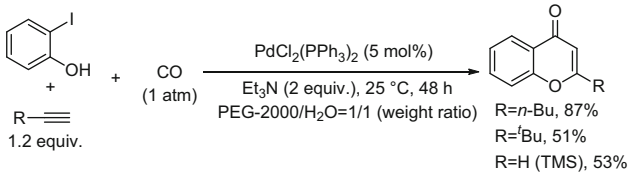
Scheme 10 Chroman-4-ones via Pd-catalyzed carbonylation–allene insertion

$PdCl_2(PPh_3)_2$/PEG-2000/H_2O system for the carbonylative Sonogashira coupling (Scheme 12) [34]. This system could also been used for the synthesis of flavone under very mild conditions (1 atm CO and 25°C). In 2005, Cao and Xiao performed this reaction using $Mo(CO)_6$ as the CO source under microwave irradiation, and a series of chromen-2-one derivatives was obtained (Scheme 13) [35].

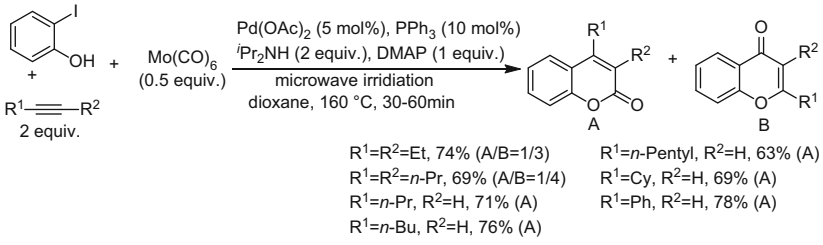
In 2012, Gøgsig, Skrydstrup et al. reported a palladium-catalyzed synthesis of 1,3-diketones through carbonylative α-arylation in a two-chamber reactor using 9-methyl-9*H*-fluorene-9-carbonyl chloride as the solid CO source [36]. Starting from MOM-protected 2-iodophenol, the ^{13}C-labeled 1,3-diketone was obtained in a



Scheme 11 Pd-catalyzed synthesis of coumarins from 2-iodophenols and internal alkynes



Scheme 12 Pd-catalyzed carbonylative synthesis of coumarins in aqueous system

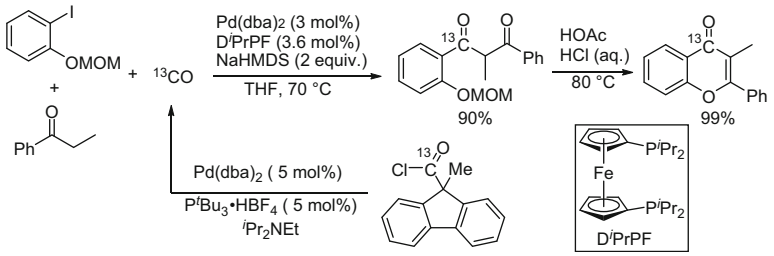


Scheme 13 Microwave-promoted carbonylative synthesis of chromen-2-ones using $Mo(CO)_6$ as CO source

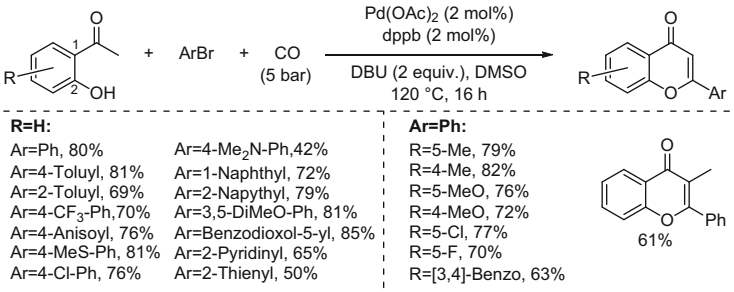
90% yield. Subsequent hydrolysis of the ethoxymethyl ether protecting group and dehydrative cyclization formed the 3-methyl-flavone in 99% yield (Scheme 14).

All the above carbonylative procedures toward flavones started from expensive iodophenols and terminal alkynes or allenes. In 2012, Wu et al. reported a carbonylative synthesis of flavones from 2-hydroxyacetophenones and aryl bromides (Scheme 15) [37]. This alternative procedure employed only 2 mol% Pd $(OAc)_2$/dppb as the catalyst and two equivalent UBU as the base, which allowed for the convenient synthesis of various 2-(hetero)aryl-substituted flavones in moderate to good yields. Besides, when 2-propenyl phenol was used as the substrate, 3-methyl-flavone could be obtained in 61% yield.

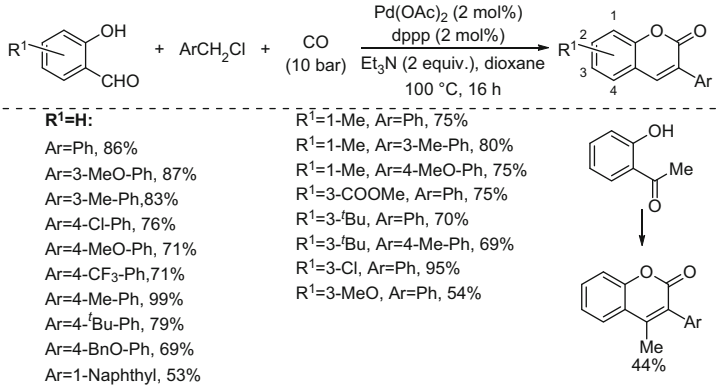
In the next year, Wu and coworkers developed a palladium-catalyzed carbonylative synthesis of chromenones from salicylic aldehydes and benzyl



Scheme 14 CO-free carbonylative synthesis of 3-methyl-flavone using two-chamber reactor

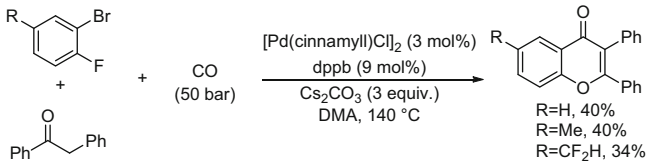


Scheme 15 Pd-catalyzed synthesis of flavones from 2-hydroxyacetophenones and aryl bromides



Scheme 16 Carbonylative synthesis of chromenones from salicylic aldehydes and benzyl chlorides

chlorides in good to excellent yields (Scheme 16) [38]. Regarding the reaction pathway, the benzyl chloride firstly underwent phenoxycarbonylation with salicylic aldehydes to form 2-formylphenyl 2-phenyl-acetate, which led to the products through intramolecular condensation. 2-Hydroxyacetone could also afford methyl-substituted chromenone but the yield was much lower.



Scheme 17 Pd-catalyzed synthesis of chromenones from 2-bromofluorobenzenes

In 2014, Wu and coworkers provided three examples of palladium-catalyzed synthesis of chromenones starting from 2-bromofluorobenzenes and 1,2-diphenylethan-1-one under 50 bar of CO [39]. The combination of carbonylation and nucleophilic substitution afforded the desired product in 30–40% yields (Scheme 17).

3 Valeralactone, Pyran-2-One, and Their Derivatives

As early as 1980, Cowell and Stille reported the synthesis of γ-lactones by palladium-catalyzed carbonylation of halo alcohols [40] (Fig. 3). In this paper, one example of δ-lactone, 1*H*-2-benzopyran-3(4*H*)-one, was also synthesized from (2-(bromomethyl)phenyl)methanol in the presence of 1.6 mol% $PdCl_2(PPh_3)_2$ (Scheme 18). Owing to the industrial interest as a precursor for various pharmaceuticals and plant protection agents, Lindsell et al. reinvestigated this reaction in 2005 [41]. Although they failed to reproduce Stille's procedure, they obtained near-quantitative yield of the same product under different reaction conditions. In 2006, Preston et al. patented a palladacycle catalyst to realize this reaction [42]. CO was bubbled through the reaction mixture under mild conditions, and quantitative yield of isochroman-3-one was obtained.

In 1983, Brunet et al. described $Co_2(CO)_8$-catalyzed SRN_1 carbonylations of the same substrates under sunlamp-irradiated phase-transfer conditions [43]. Two benzolactones were synthesized in excellent yields (Scheme 19). In this procedure, $Co_2(CO)_8$ was used as both the catalyst and the CO source. When the amines were used instead of alcohols, the corresponding benzolactam was obtained albeit in somewhat lower yields.

In 2004, Alterman and coworkers reported a palladium-catalyzed carbonylation of 2-(*o*-bromophenyl)ethanol using molybdenum hexacarbonyl as the CO source [44]. At high temperature (180°C), isochroman-1-one was obtained in 74% yield (Scheme 20).

In 2007, Alper and coworkers reported an interesting synthesis of highly substituted endocyclic enol lactones (Scheme 21) [45]. In this method, 3 mol% of $PdCl_2(PPh_3)_2$ and 6 mol% dppp were used as the catalyst, and ionic liquid [bmim][Tf_2N] was used as the reaction medium. Under 200 psi of CO, a series of β-diketones and alkynes were converted to the desired products in reasonably good regioselectivity and yields. More importantly, the system could be recycled five times with only modest loss of its catalytic activity. The authors also proposed a

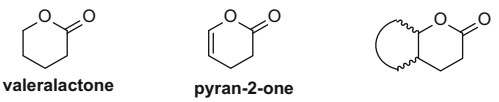
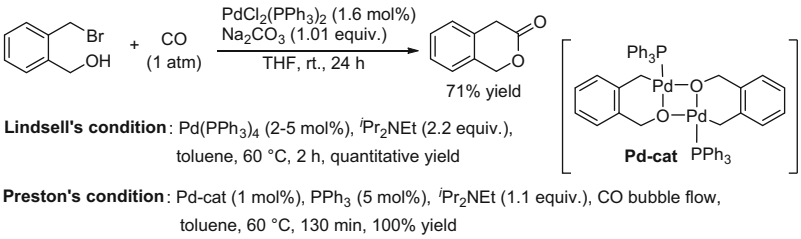
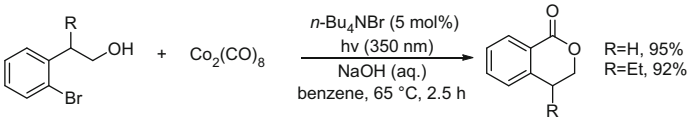


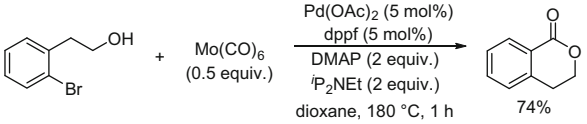
Fig. 3 Structure of six-membered lactones



Scheme 18 Synthesis of γ-lactones by Pd-catalyzed carbonylation



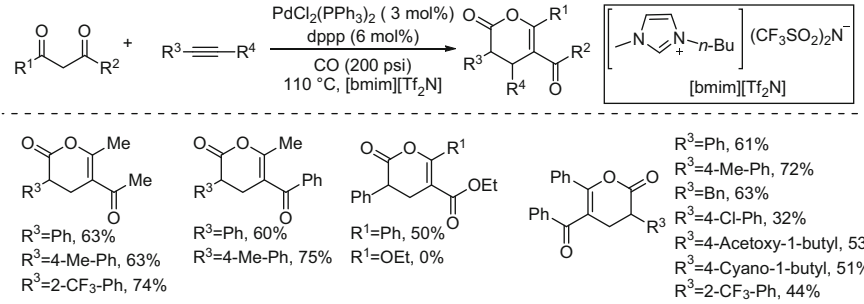
Scheme 19 $Co_2(CO)_8$-catalyzed radical carbonylative synthesis of benzolactones



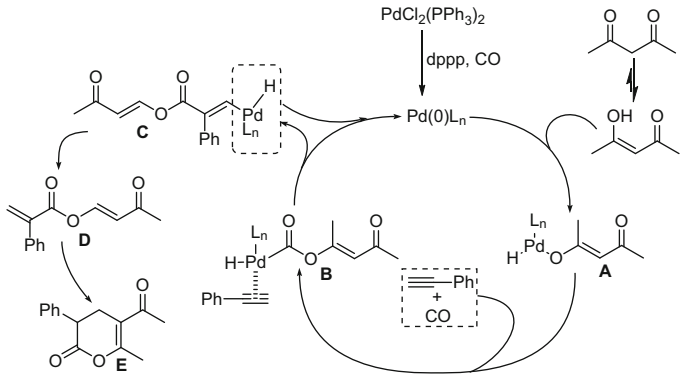
Scheme 20 CO-free carbonylative synthesis of isochroman-1-one

mechanism for this transformation. In the first step, $PdCl_2(PPh_3)_2$ was reduced to Pd (0) species in the presence of CO. The in situ formed $Pd(0)L_n$ oxidatively added into the enol –OH of the β-diketone to give Pd-hydride intermediate **A**. Then the alkyne would coordinate to **A** and CO insertion to form the intermediate **B**. Next, the alkyne was regioselectively inserted to the Pd–acyl bond to form **C**, which easily underwent reductive elimination to form **D** and regenerated Pd(0). **D** is rearranged through intramolecular cyclization of the vinyl acetate on the activated double bond to give the final product **E** (Scheme 22).

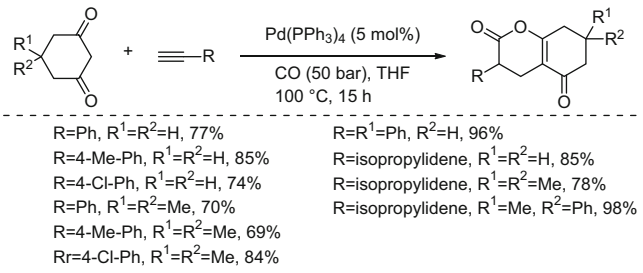
Based on the similar strategy, Wu and Hua described an efficient synthesis of 3,4,7,8-tetrahydro-2*H*-chromene-2,5(6*H*)-dione derivatives via a [3+2+1] cyclocarbonylative coupling of 1,3-cyclohexanediones, terminal alkynes, and CO (Scheme 23) [46]. Using 5 mol% $Pd(PPh_3)_4$ as the catalyst and THF as the solvent, the products were obtained in excellent selectivity. The route for the formation of chromene-2,5-dione derivatives was proposed to involve the similar steps in Scheme 22.



Scheme 21 Pd-catalyzed carbonylative synthesis of substituted endocyclic enol lactones



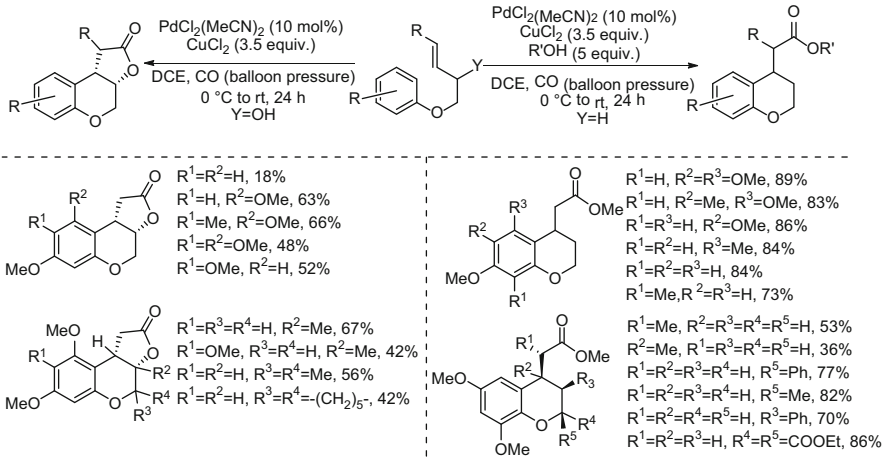
Scheme 22 Proposed mechanism for the transformation in Scheme 21



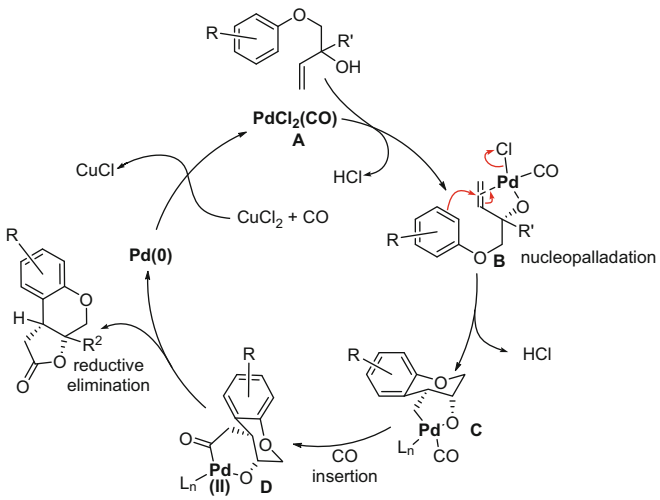
Scheme 23 Pd-catalyzed cyclocarbonylative synthesis of chromene-2,5-dione derivatives

4 Saturated Oxygen-Containing Six-Membered Rings

In 2015, Yang and coworkers [47] described a Pd(II)-catalyzed intramolecular carbonylative cyclization reaction of aryl alkenes and aryl alkenols (Scheme 24). Using 10 mol% of $PdCl_2(PPh_3)_2$ as the catalyst and 3.5 equiv. of $CuCl_2$ as the oxidant, chromane derivatives were obtained under atmospheric CO pressure.



Scheme 24 Pd-catalyzed intramolecular carbonylative cyclization toward chromanes



Scheme 25 Proposed mechanism for the Pd-catalyzed carbonylative cyclization of aryl alkenols

When external alcohols were added as nucleophiles, α-(chroman-4-yl) acetate esters were obtained in high yields and stereoselectivity. When aryl alkenols were used as the substrates, five-membered lactone rings were constructed by intramolecular alkoxycarbonylation. It was noticeable that the only electron-rich aromatic rings led to the products in good yields. The authors also propose a mechanism to explain the formation of the fused ring products (Scheme 25). At the first step, the allylic alcohol reacted with palladium carbonyl complex to form complex **B**. Next, a *cis*-intramolecular nucleopalladation led to an intermediate palladacycle **C**. The

migratory CO insertion led to complex **D**, which released the product by reductive elimination. The resultant Pd(0) was then reoxidized by $CuCl_2$.

5 Quinolinone Derivatives

Quinolinone and its derivatives have diverse chemical and pharmacological properties and thus attracted much interest of both synthetic and pharmaceutical chemists [48–53] (Fig. 4). Palladium-catalyzed carbonylative construction of these structures has become a very unique method because it employed some readily available starting materials and CO as the carbonyl source.

In 1990, Torii et al. reported an efficient synthesis of 3-substituted 3-(2-haloarylamino)prop-2-enoates catalyzed by 5 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 under CO pressure (Scheme 26) [54]. When lactone substrates were employed, the desired products were obtained in very good yields.

Two years later, Kalinin and coworkers synthesized 2-substituted quinolin-4-ones from 2-iodoanilines and terminal alkynes (Scheme 27) [55]. They used 5 mol % $PdCl_2(PPh_3)_2$ as the catalyst and diethylamine as the solvent. Under 20 bar CO pressure, 61–95% yields of the products were isolated. As a synthetic application, Haddad et al. accomplished convergent synthesis of the key quinolone intermediate for protease inhibitor BILN 2061 by using 1.5 mol% $PdCl_2$(dppf) as the catalyst [56]. In 2015, Larhed's group reported a similar carbonylative synthesis of 4-quinolones using $Co(CO)_6$ as the carbonyl source (Scheme 28) [57]. Under microwave conditions, this method yielded the products after only 20 min of microwave heating at 120°C. Using $Pd(OAc)_2/P^tBu_3{\cdot}HBF_4$ as the catalytic system, the reaction could run in a one-pot two-step sequence at room temperature, and some sensitive substituents in the substrates could be well tolerated.

In 2005, Alper and coworkers developed an intramolecular carbonylation procedure with recyclable palladium-complexed dendrimers on silica for the synthesis of some fused ring system [58]. In this report, they gave one example of six-membered ring synthesis. Starting from 2′-iodo-[1,1′-biphenyl]-2-amine, 6(5*H*)-phenanthridinone was obtained in 97% yield catalyzed by G1-palladium dendrimer (Scheme 29).

In 2007, Alper's group synthesized a series of methylene-2,3-dihydro-1*H*-quinolin-4-ones through the carbonylative cross-coupling between *o*-iodoanilines and allenes in ionic liquid. They used only 2 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and dppb as the catalyst, and both terminal and internal allenes were applicable as the substrates

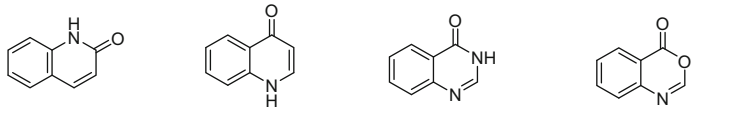
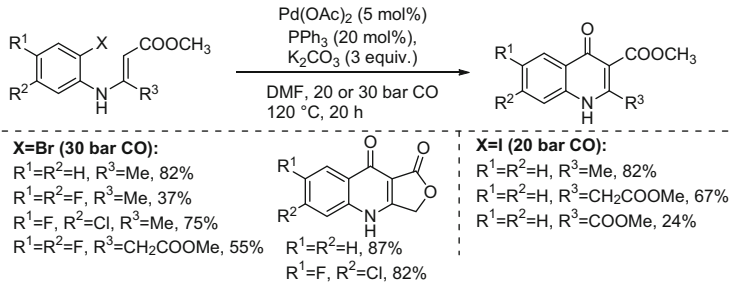
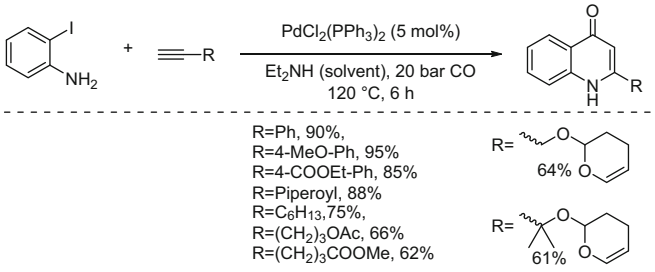


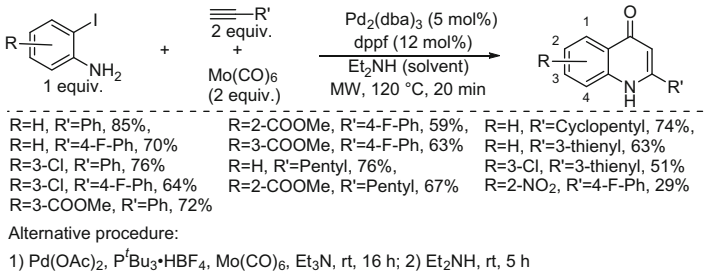
Fig. 4 Structure of quinolinones



Scheme 26 First example of carbonylative synthesis of quinolin-4(1*H*)-ones



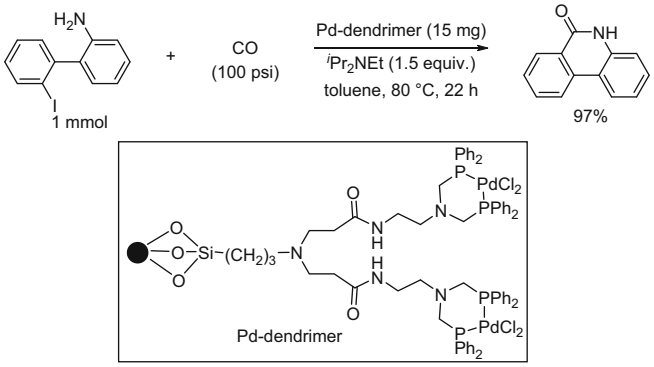
Scheme 27 Carbonylative synthesis of 2-substituted quinolin-4-ones from 2-iodoanilines and terminal alkynes



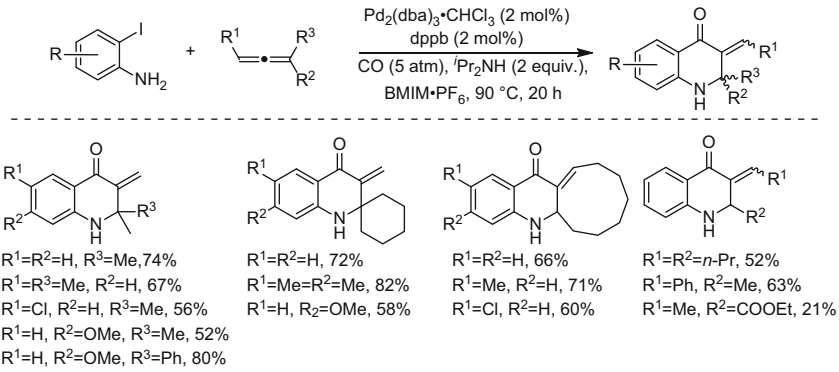
Scheme 28 Synthesis of 4-quinolones using $Mo(CO)_6$ as the carbonyl source

(Scheme 30). Under relatively mild conditions (5 bar of CO and 90°C), up to 82% yield of the products was obtained. When the asymmetric enteral allenes were used, two region isomers were isolated in a ca. 2:1 to 7:1 ratio. Notably, cyclononene could be incorporated into the dihydro-1*H*-quinolin-4-one ring system.

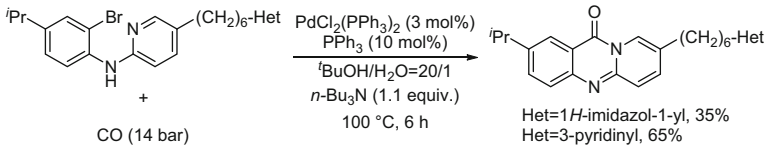
Quinazolinones are another important class of six-membered heterocyclic compounds containing two isolated nitrogen atoms. Until now, many methods had been reported for their synthesis [59–61]. As early as in 1987, Tilley and coworkers reported a carbonylative synthesis of pyrido[2,1-*b*]quinazoline derivatives starting



Scheme 29 Recyclable carbonylation palladium catalyst for the phenanthridinone synthesis



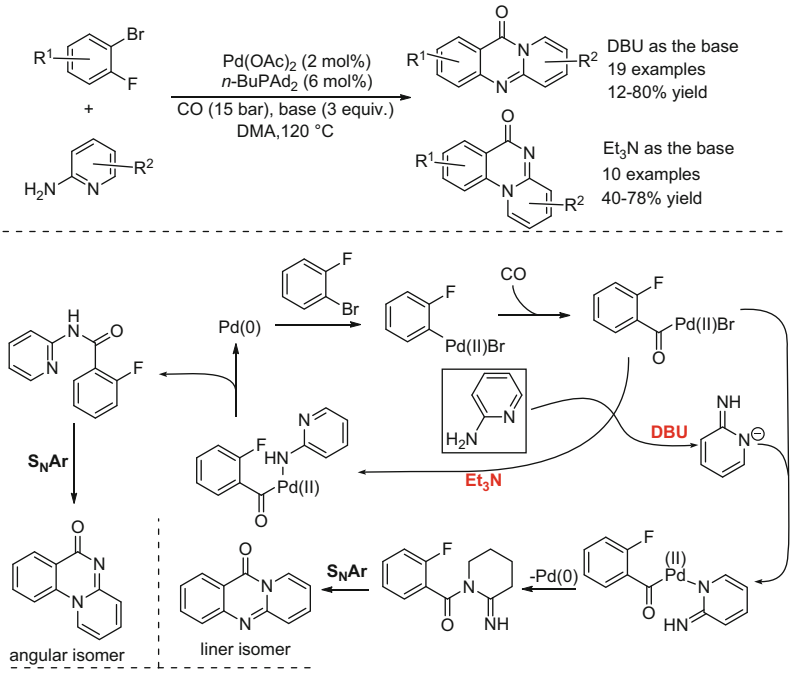
Scheme 30 Pd-catalyzed carbonylative cross-coupling between *o*-iodoanilines and allenes



Scheme 31 Pd-catalyzed aminocarbonylation of *N*-(2-bromophenyl)pyridin-2-amines

from *N*-(2-bromophenyl)pyridine-2-amines (Scheme 31) [62]. The authors proposed that this reaction initialized with the oxidation of *N*-(2-bromophenyl)pyridine-2-amine onto Pd(0) to form the aryl-palladium bond. Then CO insertion and nucleophilic attack by the pyridine nitrogen afforded the desired product.

Inherently, 2-aminopyridine ($pK_a = 6.86$) exists s as a mixture of tautomeric amino and imino isomers with the predominance of the amino form over the imino form (1000:1). By utilization of this unique tautomerization nature of 2-aminopyridine, several syntheses of nitrogen heterocycles were reported through

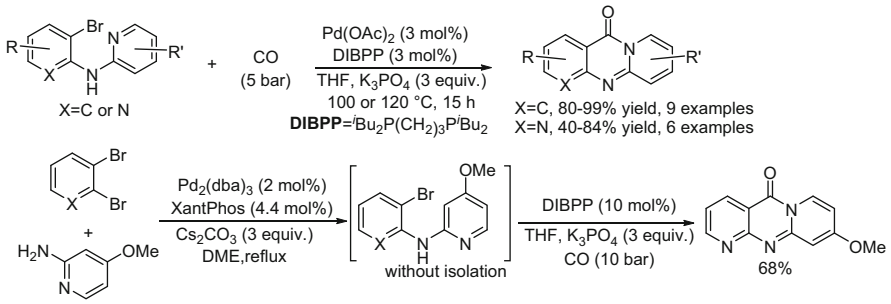


Scheme 32 Regio-switchable procedure toward linear and angular fused quinazolinones

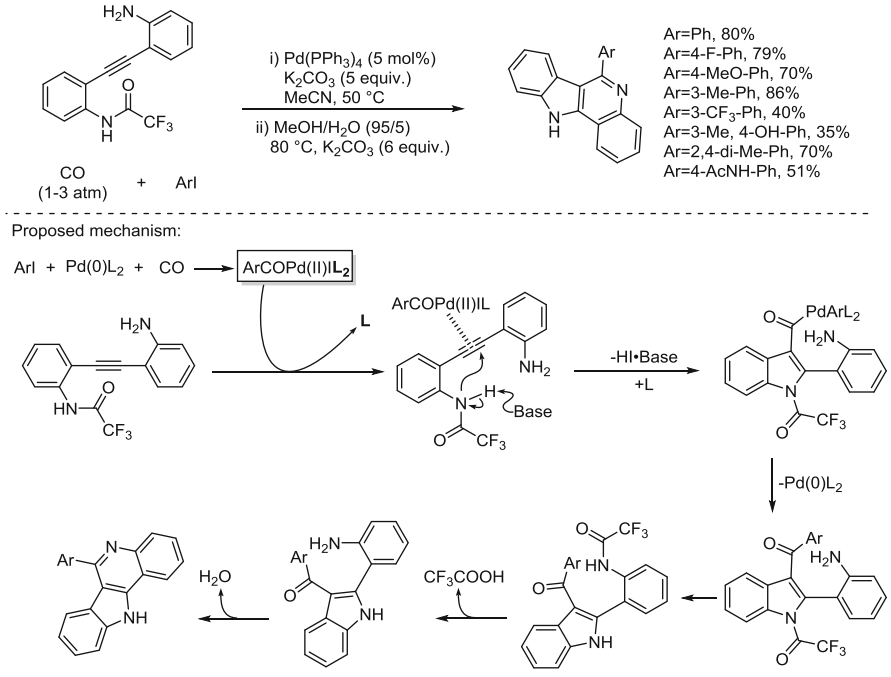
carbonylation. In 2014, Wu, Beller and their coworkers reported a synthesis of quinazolinones by carbonylation/nucleophilic aromatic substitution sequence [63]. Started from 2-bromofluorobenzene and 2-aminopyridines, they obtained both linear and angular fused quinazolinones using $Pd(OAc)_2$/*n*-$BuPAd_2$ as the catalytic system (Scheme 32). In this regio-switchable procedure toward two isomers, the basicity difference between Et_3N ($pK_a = 10.8$) and DBU ($pK_a = 12$) played a key role. In 2015, Xu and Alper updated Torii's procedure (Scheme 33) reaction by using $Pd(OAc)_2$ and DIBPP as the catalytic system [64]. Under their optimized conditions, nine examples of pyrido[2,1-*b*]quinazolin-11-ones and six examples of dipyrido[1,2-*a*:2,3:*b*]pyrimidin-5-ones were synthesized through Pd/DIBPP-catalyzed dearomatizing carbonylation. It was notable that the starting materials could be prepared from Pd-catalyzed amination of the 1,2-dibromides without isolation.

In 1999, Cacchi et al. described a one-pot process synthesis of 6-aryl-11*H*-indolo[3,2-*c*]quinolines through a straightforward palladium-catalyzed carbonylative cyclization of *o*-(*o*′-aminophenylethynyl)trifluoroacetanilide with aryl iodides [65]. In this procedure, 2-(2-aminophenyl)-3-aroyl-1*H*-indol was formed as the primary product, which underwent intramolecular condensation to form the six-membered ring system (Scheme 34).

The above strategy was also employed in the carbonylative synthesis of 3-substituted 4-aroylisoquinolines by Dai and Larock [66]. In the presence of

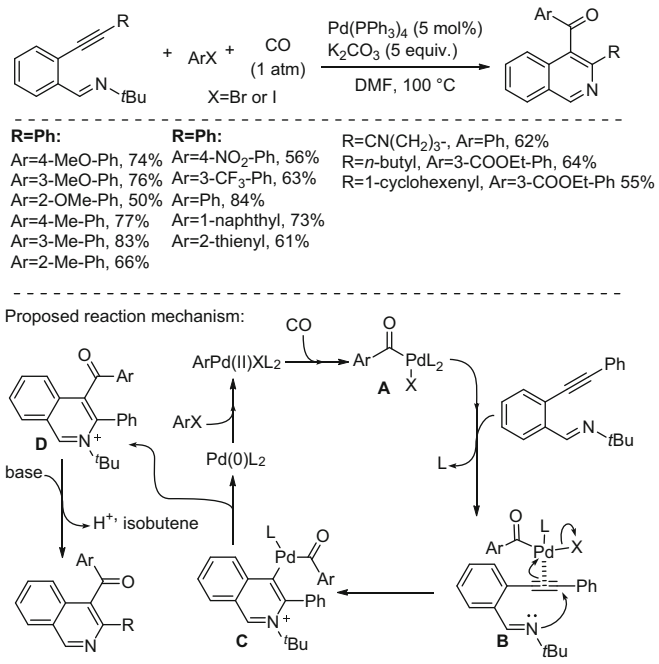


Scheme 33 Pd-catalyzed dearomatizing carbonylation to form quinazolin-11-ones and pyrimidin-5-ones



Scheme 34 One-pot process synthesis of 6-aryl-11*H*-indolo[3,2-*c*]quinolones

5 mol% of $Pd(PPh_3)_4$ as the catalyst and 5 equiv. of K_2CO_3 as the base, 2-(1-alkynyl)benzaldimines were cyclized to the desired products in moderate to good yields (Scheme 35). In the first step of the reaction, aroylpalladium complexes (**A**) were formed from aryl bromides or iodides by sequential oxidative addition and CO insertion. Then the aroylpalladium(II) species coordinate to the alkynes, and subsequent nucleophilic attack from the imine nitrogen produced the intermediate **C**. Primary product **D** was then released from **C** by reductive elimination and

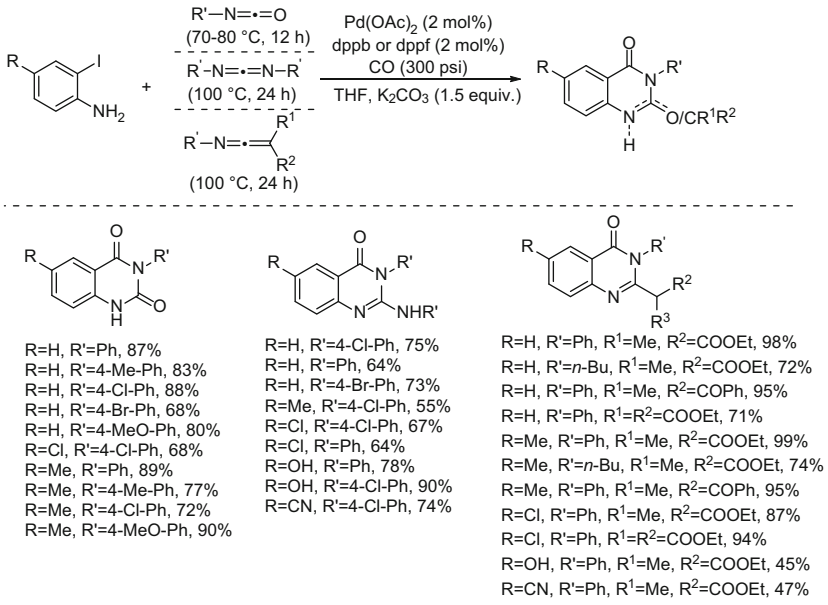


Scheme 35 Pd-catalyzed carbonylative cyclization of 2-(1-alkynyl)benzaldimines to form 3-substituted 4-aroylisoquinolines

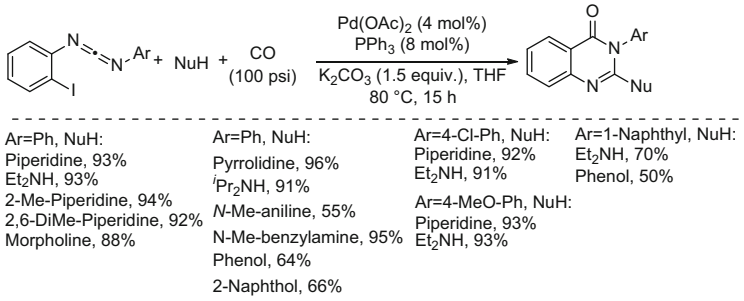
further deprotection of the tertiary butyl group in the presence of base to give the final products.

In 2000, Larksarp and Alper disclosed a catalyst system comprising $Pd(OAc)_2$-dppf for the cyclocarbonylation of *o*-iodoanilines with heterocumulenes at 70–100°C for 12–24 h to give the corresponding 4(3*H*)-quinazolinone derivatives in good to excellent yields (Scheme 36) [67, 68]. Heterocumulenes such as isocyanates, carbodiimides, and ketenimines could be used in their procedures to prepare different substituted products.

Based on these earlier works of their own group, Zeng and Alper later reported a highly practical and efficient method for the synthesis of 2-heteroquinazolin-4(*3H*)-ones through palladium-catalyzed tandem reaction [69] in good to excellent yields (Scheme 37). Using the same catalytic system, the authors developed a domino process for the synthesis of quinazolino[3,2-*a*]quinazolinones (Scheme 38) [70]. The starting carbodiimides were efficiently prepared by metathesis reactions of the corresponding isocyanates with *N*-(*o*-iodoaryl)triphenyliminophosphoranes. It was noteworthy that five new bonds and two fused heterocycles were formed in a single step. Less bulky alkyl amines led very good yields and steric hindrance in the amines decreased the yields. When *N*,*N*′-dimethylethylenediamine was used as the amine, the desired product with a nine-membered ring structure was not observed.



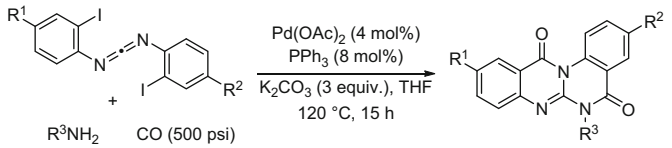
Scheme 36 Cyclocarbonylation of *o*-iodoanilines with various heterocumulenes



Scheme 37 Pd-catalyzed tandem reaction to synthesize 2-heteroquinazolin-4(3*H*)-ones

In 2008, Zheng and Alper developed a palladium-catalyzed cyclocarbonylation of 2-iodoanilines with imidoyl chlorides under 500 psi of CO [71]. The reaction was believed to proceed via in situ formation of an amidine, followed by oxidative addition, CO insertion, and intramolecular cyclization to give the substituted quinazolin-4(3*H*)-ones in 63–91% yields (Scheme 39).

In 2013, Wu, Beller, and their coworkers developed a novel palladium-catalyzed four-component carbonylative coupling system for the selective construction of 4(3*H*)-quinazolinones in a one-pot fashion [72]. Starting from 2-bromoanilines, trimethyl orthoformate, and amines under 10 bar of CO, the desired products were isolated in good yields catalyzed by 2 mol% of $Pd(OAc)_2$ and *n*-$BuPAd_2$.

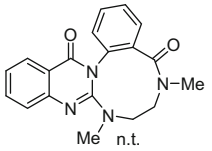


R¹=R²=H:
R³=*n*-Hexyl, 81%
R³=^{i}Pr, 83%
R³=Cy, 85%
R³=^{t}Bu, 38%
R³=Bn, 85%
R³=4-MeO-Bn, 89%
R³=4-Me-Bn, 87%
R³=4-F-Bn, 85%
R³=Ph, 41%
R³=Allyl, 80%

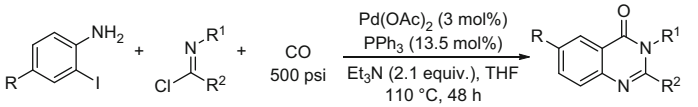
R¹=R²=Me:
R³=*n*-Hexyl, 75%
R³=^{i}Pr, 77%

R¹=R²=Cl:
R³=*n*-Hexyl, 87%
R³=^{i}Pr, 86%

R¹=Me, R²=H, R³=^{i}Pr
R¹=H, R²=Me, R³=^{i}Pr
} 85% (ratio: 3/2)



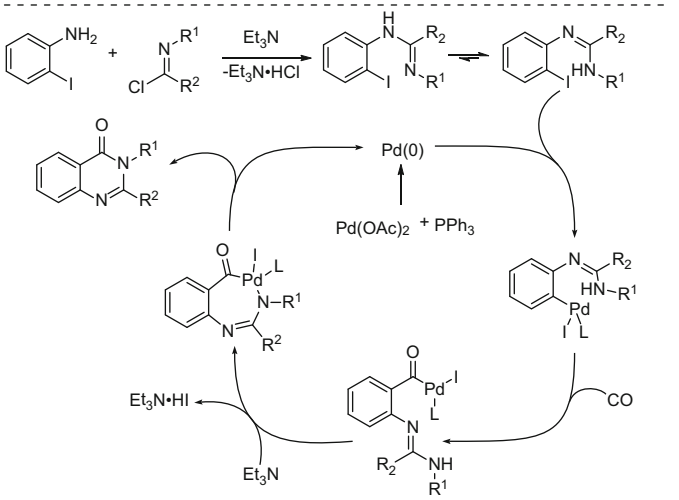
Scheme 38 Pd-catalyzed tandem reaction to synthesize quinazolino[3,2-*a*]quinazolinones



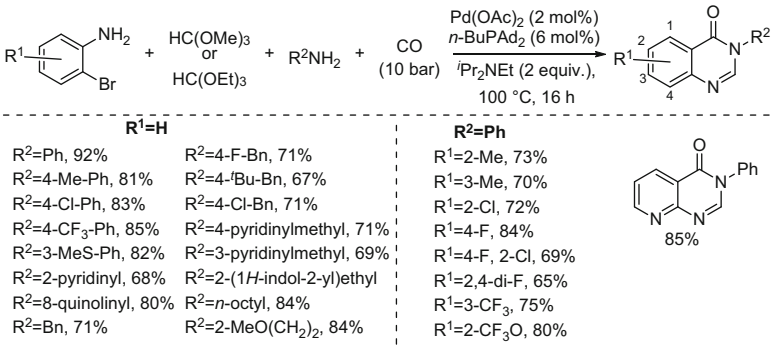
R=H:
R¹=Ph, R²=Ph, 74%
R¹=4-MeO-Ph, R²=Ph, 80%
R¹=4-Me-Ph, R²=Ph, 76%
R¹=Ph, R²=4-Me-Ph, 70%
R¹=R²=4-Me-Ph, 91%
R¹=4-Cl-Ph, R²=Ph, 67%

R=H:
R¹=Ph, R²=4-Cl-Ph, 65%
R¹=R²=4-Cl-Ph, 63%
R¹=^{i}Pr, R²=Ph, 82%
R¹=*n*-Bu, R²=Ph, 81%
R¹=Ph, R²=^{t}Bu, 90%
R¹=Ph, R²=2-furyl, 87%

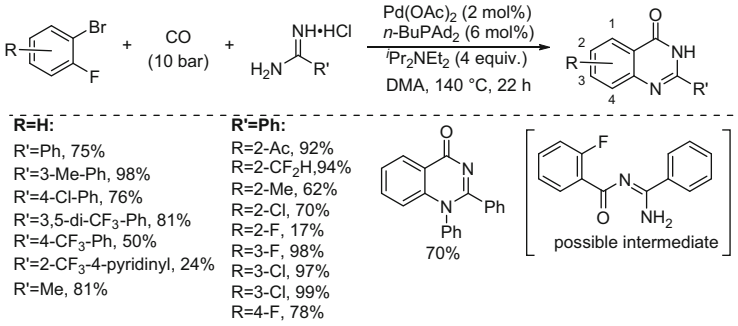
R=Me, R¹=R²=4-Me-Ph, 66%
R=Cl, R¹=R²=4-Me-Ph, 74%
R=CN, R¹=R²=4-Me-Ph, 67%



Scheme 39 Pd-catalyzed cyclocarbonylation of 2-iodoanilines with imidoyl chlorides



Scheme 40 Pd-catalyzed four-component carbonylative coupling to form 4(3*H*)-quinazolinones

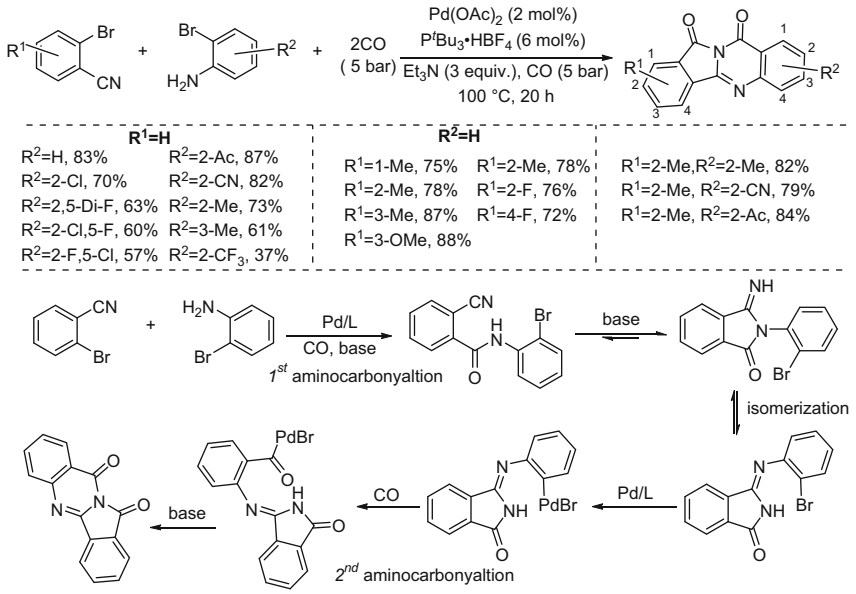


Scheme 41 Pd-catalyzed quinazolinones synthesis from 1-bromo-2-fluorobenzenes and amidines

Notably, the process tolerated the presence of various reactive functional groups and was very selective for quinazolinones (Scheme 40).

Later on, Wu's group reported the synthesis of quinazolinones from 1-bromo-2-fluorobenzenes and amidines with 2 mol% of $Pd(OAc)_2$ and 6 mol% *n*-$BuPAd_2$ as the catalyst (Scheme 41) [39]. The reaction was believed to initialize from the aminocarbonylation to form the *N*-(amino(phenyl)methylene)-2-fluorobenzamide intermediate. The nucleophilic substitution and rearrangement led to the final products. As an evidence, 1,2-diphenylquinazolin-4(1*H*)-one was obtained in 70% yield when *N*-phenylbenzimidazole hydrochloride was used as the amidine.

In the same year, Wu, Beller, and their coworkers reported a domino synthesis of quinazolinediones through a double carbonylation process. Starting from commercially available 2-bromobenzonitriles and 2-bromoanilines series, 20 examples of isoindolo[1,2-*b*]quinazoline-10,12-dione structures were synthesized in the presence of $Pd(OAc)_2$ and $P^tBu_3{\cdot}HBF_4$ as the catalyst (Scheme 42). After determination of the final product by X-ray crystalline structure and the validation of 2-phenyl-3-iminoisoindolin-1-one as the isomerization intermediate, the authors proposed a two-sequential aminocarbonylation reaction pathway in Scheme 42.

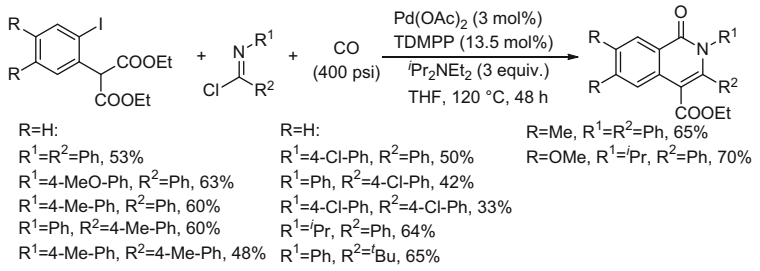


Scheme 42 Synthesis of isoindolo[1,2-*b*]quinazoline-10,12-diones through double carbonylation

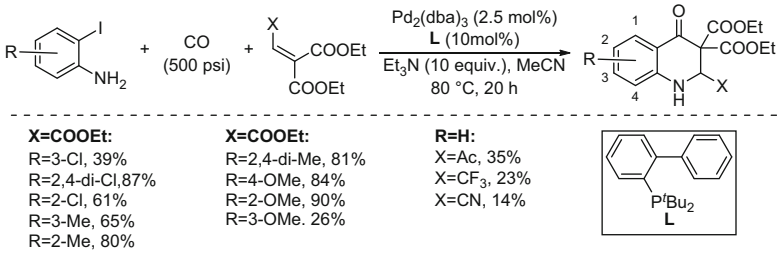
In Zeng and Alper 2008 [73] (Scheme 43), a wide variety of substituted isoquinolin-1(2*H*)-ones was synthesized in reasonable to good yields by the palladium-catalyzed cyclization of diethyl(2-iodoaryl)malonates with imidoyl chlorides and carbon monoxide in tetrahydrofuran. A palladium-catalyzed carbonylation–decarboxylation process may be involved in the one-step synthesis of the isoquinolin-1(2*H*)-ones. Later on, Okuro and Alper reported a palladium-catalyzed intermolecular cyclocarbonylation of 2-iodoanilines with diethyl ethoxycarbonyl-butendienoate [74]. By the similar procedure involving Michael addition and subsequent carbonylation, 2,3,3-triethoxycarbonyl-2,3-dihydro-4(1*H*)-quinolinone derivatives were obtained in moderate to good yields (Scheme 44).

In 2008, Broggini's group [75] reported a carbonylative synthesis of 4-[(methoxycarbonyl) methyl]-3,4-dihydroisoquinolin-1-ones from *N*-allylamides of 2-iodobenzoic acids under high pressure of CO (Scheme 45). The reaction stared with the oxidative addition of aryl iodides with in situ generated Pd(0). The following intramolecular carbopalladation gave (σ-alkyl)Pd complexes, which underwent CO insertion and nucleophilic attack by MeOH to form the final products.

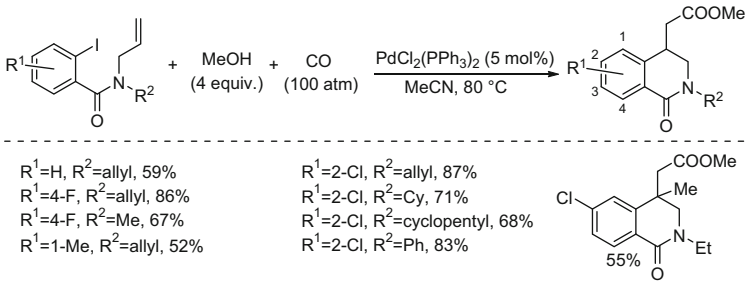
In 2001, Kang and Kim reported a reaction between γ-allenic sulfonamides and aryl iodides in the presence of $Pd(PPh_3)_4$ (5 mol%) to form 3-aroyl-2- or 3-pyrrolines [76]. When started from δ-allenic sulfonamides, this procedure afforded two examples of piperidine-substituted enones in moderate yields (Scheme 46).



Scheme 43 Pd-catalyzed carbonylative cyclization of diethyl(2-iodoaryl)malonates with imidoyl chlorides

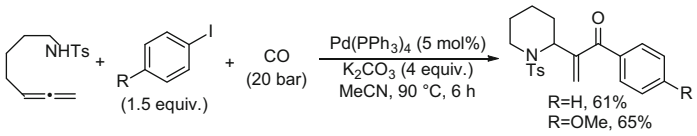


Scheme 44 Pd-catalyzed carbonylative synthesis of 2,3,3-triethoxycarbonyl-2,3-dihydro-4(1*H*)-quinolinone

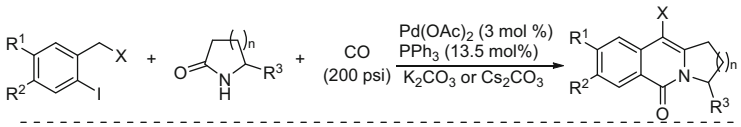


Scheme 45 Pd-catalyzed coupling between *N*-allylamides of 2-iodobenzoic acids

In 2008, Alper's group developed an efficient and simple synthesis of biologically fused ring isoquinolines by utilizing a palladium-catalyzed carboxamidation reaction and aldol condensation reaction cascade protocol (Scheme 47) [77]. The first step of the reaction was the oxidative addition of the aryl iodides with Pd(0) to give aryl-palladium species, and then CO insertion formed aroylpalladium complex which was then attacked by the amide nitrogen to give the imide intermediate. Finally, the intramolecular condensation led to the final product.



Scheme 46 $Pd(PPh_3)_4$-catalyzed carbonylative coupling between γ-allenic sulfonamides and aryl iodides



X=COOEt

R^1=R^2=R^3=H, n=1, 95%
R^1=R^2=H, R^3=COOEt, n=1, 92%
R^1=R^2=R^3=H, n=2, 75%
R^1=R^2=R^3=H, n=3, 65%
R^1=R^2=OMe, R^3=H, n=1, 90%
R^1=R^2=OMe, R^3=COOEt, n=1, 85%
R^1=R^2=OMe, R^3=H, n=2, 60%
R^1=R^2=-OCH_2O-, R^3=H, n=1, 95%
R^1=R^2=-OCH_2O-, R^3=COOEt, n=1, 90%

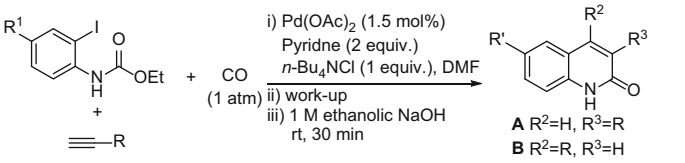
X=CN

R^1=R^2=R^3=H, n=1, 95%
R^1=R^2=R^3=H, n=2, 85%
R^1=R^2=H, R^3=COOEt, n=1, 93%
R^1=R^2=OMe, R^3=H, n=1, 65%
R^1=R^2=-OCH_2O-, R^3=H, n=1, 63%
R^1=R^2=-OCH_2O-, R^3=COOEt, n=1, 80%

X=SO_2Ph

R^1=R^2=R^3=H, n=1, 90%
R^1=R^2=H, R^3=COOEt, n=1, 85%

Scheme 47 Pd-catalyzed carbonylative synthesis of fused ring isoquinolines



R^1=H

R=*n*-Bu, 55% (A/B=70/30)
R=Cy, 50% (A/B=82/18)
R=Ph, 42% (A)
R=TMS, 38% (A)
R=$(CH_2)_4$OH, 25% (A/B=80/20)
R=$(CH_2)_3$CN, 47% (A/B=81/19)

R^1=H

R=$(CH_2)_3$COOMe, 41% (A/B=81/19)
R=Ph, 42% (A)
R=TMS, 38% (A)

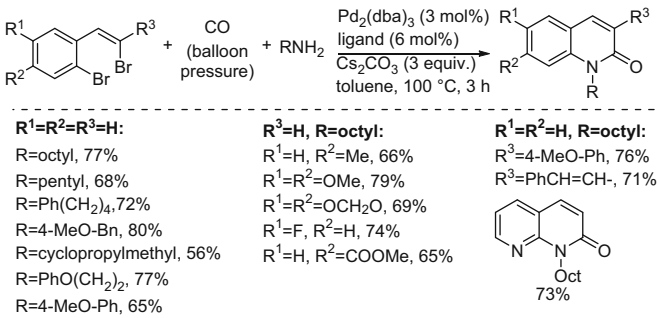
R^1=OMe

R=*n*-Bu, 53% (A/B=69/31)

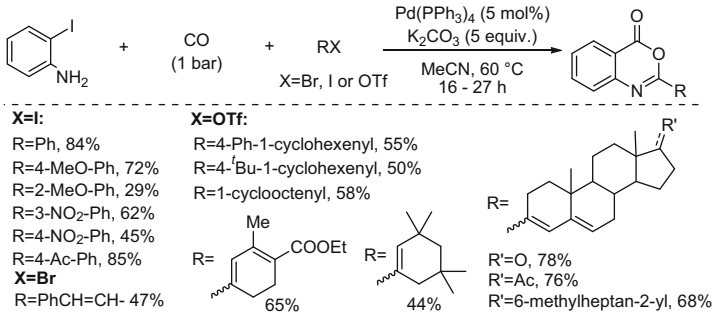
For internal alkynes: R^2=R^3=*n*-Pr, 71%, R^2=R^3=Ph, 22%

Scheme 48 Pd-catalyzed synthesis of 3,4-disubstituted 2-quinolones from alkynes and *N*-substituted *o*-iodoanilines

Larock's group developed a palladium-catalyzed synthesis of 3,4-disubstituted 2-quinolones through the annulation of alkynes and *N*-substituted *o*-iodoanilines under 1 atm of CO [78, 79]. The best results were obtained using alkoxycarbonyl, *p*-tolylsulfonyl, and trifluoroacetyl substituents. The nitrogen protection groups were lost during the course of the reaction resulting in the formation of *N*-unsubstituted 2-quinolones in moderate to good yields (Scheme 48).



Scheme 49 Pd-catalyzed intermolecular cascade sequences to the 2-quinolones

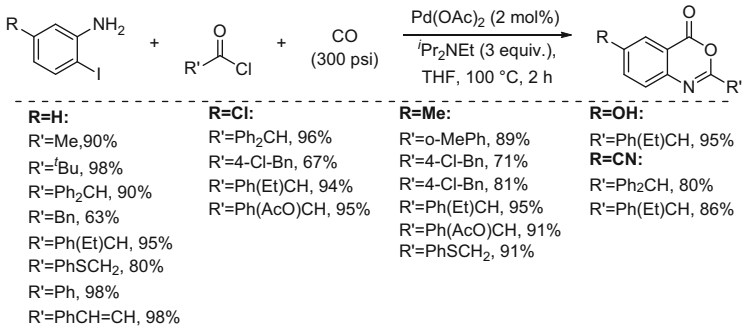


Scheme 50 Pd-catalyzed carbonylative synthesis of 4*H*-3,1-benzoxazin-4-ones from 2-iodoanilines and aryl halides and triflates

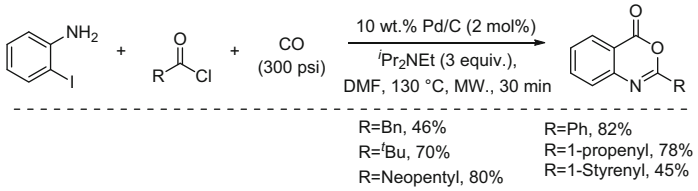
In Tadd and Willis (2009) [80], palladium-catalyzed intermolecular aminocarbonylation/intramolecular amidation cascade sequences can be used to convert a range of 2-(2-haloalkenyl)aryl halide substrates efficiently and selectively to the corresponding 2-quinolones. Delaying the introduction of the CO atmosphere allows amination/carbonylation sequence and the preparation of an isoquinoline (Scheme 49).

In 1996, Cacchi, Marinelli et al. reported a palladium-catalyzed reaction of *o*-iodoaniline with unsaturated halides or triflates [81]. In the presence of K_2CO_3 and catalytic amounts of $Pd(PPh_3)_4$ under an atmosphere of carbon monoxide, 2-aryl- and 2-vinyl-4*H*-3,1-benzoxazin-4-ones were obtained in good to high yields (Scheme 50). It was noteworthy that when R was androsta-3,5-dienes, the corresponding products were also obtained in 68–78% yields.

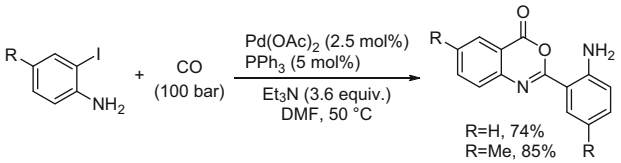
In 1999, Larksarp and Alper [82] reported a one-pot carbonylative regioselective synthesis of 2-substituted-4*H*-3,1-benzoxazin-4-ones from *o*-iodoanilines and acid chlorides (Scheme 51). In the presence of $Pd(OAc)_2$ and diisopropylethylamine, the desired products were obtained in good to excellent yields. The reaction was believed to proceed via in situ amide formation from an *o*-iodoaniline and an acid chloride, followed by oxidative addition to Pd(0), CO insertion, and intramolecular



Scheme 51 Pd-catalyzed carbonylative coupling with *o*-iodoanilines and acid chlorides



Scheme 52 Pd/C-catalyzed carbonylative synthesis of 4*H*-3,1-benzoxazin-4-ones

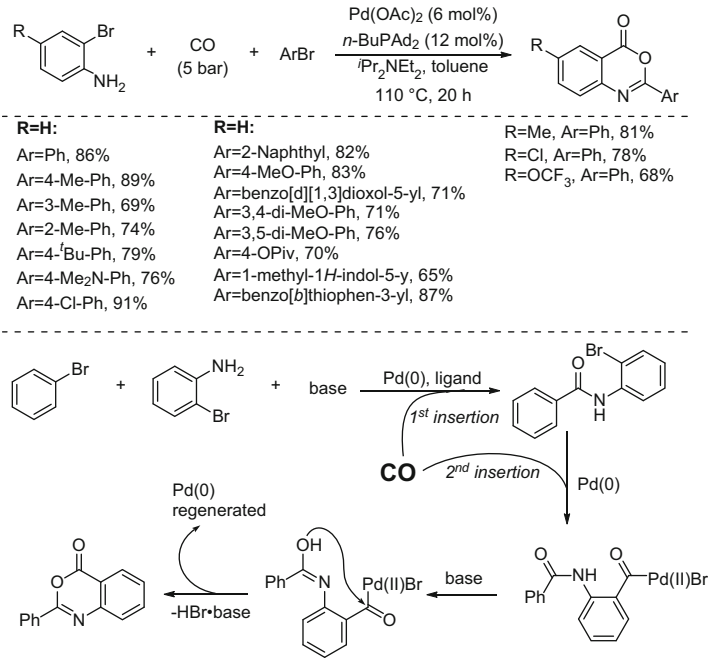


Scheme 53 Pd-catalyzed double carbon monoxide insertion of 2-iodoanilines

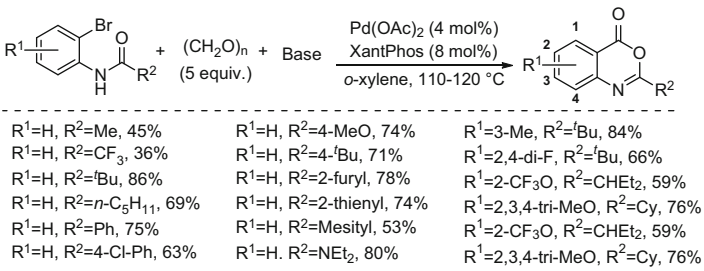
cyclization to form the 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives. In 2010, Salvadori et al. [83] realized the same reaction using Pd/C as the heterogeneous catalyst under microwave dielectric heating conditions (Scheme 52).

Ács et al. transformed 2-iodoanilines to the corresponding 2-aryl-benzo[*d*][1,3] oxazin-4-one derivatives via double carbon monoxide insertion (Scheme 53) [84]. This reaction required a high CO pressure (100 bar).

In 2011, Wu et al. described an alternative synthesis of 2-arylbenzoxazinones from commercially available 2-bromoanilines and aryl bromides (Scheme 54) [85]. The first step was the chemoselective aminocarbonylation of the aryl bromides to form the *N*-aroyl-2-bromoaniline intermediate. The second CO insertion into the aryl-palladium bond furnished the final product. In 2014, Li and Wu reported a palladium-catalyzed carbonylative synthesis of benzoxazinones from *N*-(*ortho*-bromoaryl)amides using paraformaldehyde as the carbonyl source [86]. Under this CO-free conditions, various substituted benzoxazinones were obtained in



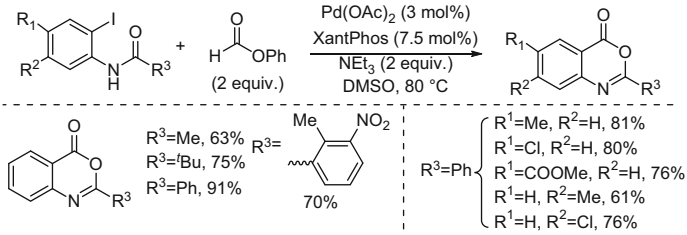
Scheme 54 Pd-catalyzed synthesis of 2-arylbenzoxazinones from 2-bromoanilines and ArBr



Scheme 55 Pd-catalyzed carbonylative synthesis of benzoxazinones using paraformaldehyde as CO source

good yields under optimized conditions (Scheme 55). Using ^{13}C-labeled paraformaldehyde, 4-^{13}C-labeled benzoxazinone derivative was obtained, which has many important applications in pharmaceutical and biological topics.

In 2015, Konishi et al. reported a synthesis of 4*H*-3,1-benzoxazin-4-one derivatives from *N*-(*ortho*-iodoaryl)amides by using phenyl formate as the CO source (Scheme 56) [87]. Under basic conditions, phenyl formate decomposed to phenol and carbon monoxide. The authors proposed that the reaction proceeded through the phenoxycarbonylation of the aryl iodide intermediates and basic condensation of the intermediates led to the desired products in moderate to good yield.



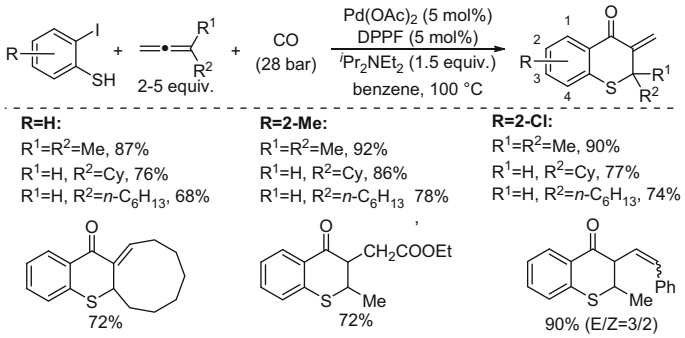
Scheme 56 Carbonylative synthesis of 4*H*-3,1-benzoxazin-4-ones using phenyl formate as CO source

6 Other Six-Membered Heterocycles

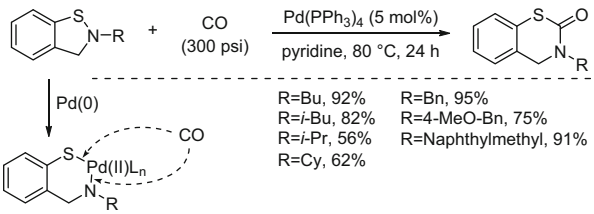
Palladium-catalyzed carbonylation of C–X bonds has also found some application in some other six-membered heterocycle synthesis. In 1999, Xiao and Alper reported a regioselective heteroannulation of 2-iodothiophenols with allene CO pressure in the presence of palladium catalyst to form various thiochroman-4-one derivatives (Scheme 57) [88]. In 2008, the same group reported a novel synthesis of another type of sulfur-containing heterocycles, 3-substituted-3,4-dihydro-2*H*-1,3-benzothiazin-2-ones, by palladium-catalyzed carbonylation reaction of 2-substituted-2,3-dihydro-1,2-benzisothiazoles in pyridine (Scheme 58) [89]. The authors suggested that the reaction is initialized with the oxidation of S–N bonds with Pd(0) and then CO insertion into the S–Pd bonds or N–Pd bonds to form the product-releasing intermediates. Finally, the reductive elimination gave the products.

In 2001, Brown et al. gave an example of carbonylative synthesis of chromane derivative from 1-iodo-2-((3-methylbut-3-en-1-yl)oxy)benzene in the presence of two equivalents of silane (Scheme 59) [90].

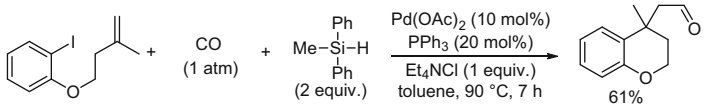
In 2012, Ryu's group gave several examples of the synthesis of functionalized δ-lactam and δ-lactones through Pd/light-accelerated atom-transfer carbonylation reactions (Scheme 60) [91]. These three-component coupling reactions involved a hybrid organometallic-radical pathway and showed the potential of the utilization of alkyl halides in carbonylative heterocycle synthesis.



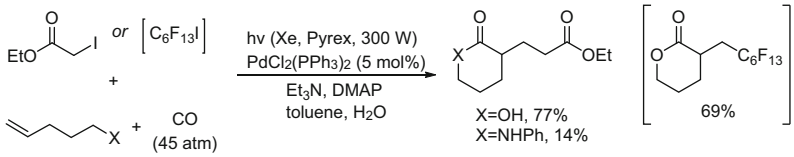
Scheme 57 Pd-catalyzed carbonylative synthesis of thiochroman-4-one derivatives



Scheme 58 Pd-catalyzed carbonylation reaction of 2-substituted-2,3-dihydro-1,2-benzisothiazoles



Scheme 59 Reductive carbonylation to form 2-(4-methylchromen-4-yl)acetaldehyde



Scheme 60 Pd/light-accelerated atom-transfer carbonylation reactions to form lactams and lactones

7 Summary

Palladium-catalyzed synthesis of heterocycles from carbon–halide bonds in the presence of CO has been applied in many types of six-membered heterocyclic compounds. The combination of amino- or alkoxycarbonylation with various intramolecular condensations, nucleophilic substitutions, or further carbonylation reactions was effective for the construction of various carbonyl-derived six-membered rings and fused ring system. We believe that the combination of carbonylation with other types of intramolecular reaction would be a useful tool for the synthesis of more advanced heterocyclic compounds.

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Pd-Catalyzed Carbonylative Synthesis of Other-Membered Heterocycles from Aryl Halides

Dennis U. Nielsen, Zhong Lian, Anders T. Lindhardt, and Troels Skrydstrup

Abstract In this chapter, representative examples from the literature are illustrated for the construction of heterocycles from palladium-catalyzed carbonylation reactions of aryl halides. Remarkably, the catalytic systems are highly efficient in many cases for generating not only medium-sized ring systems but also even larger structures such as 24-membered heterocycles. This includes not only a variety of pharmaceutically relevant molecules, such as the benzodiazepines, but also peptidic structures. Finally, the methodology is adaptable to carbon isotope labeling starting from ^{13}C- to ^{14}C-isotopically labeled carbon monoxide.

Keywords Carbonylation • Catalysis • Heterocycles • Large rings • Palladium

Contents

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1 Introduction

In the previous chapter(s), we have seen the application of carbonylation chemistry for the assembly of a wide variety of small and structurally diverse heterocycles from aryl halides, many of these possessing structures of pharmaceutical and agrochemical interest. Remarkably, this transition metal-catalyzed methodology with carbon monoxide can also be exploited for the efficient construction of even larger carbonyl-containing ring systems from seven-membered heterocycles, such as the benzodiazepines to macrocyclic peptide structures up to sizes of 24, and importantly in synthetically useful yields. This attests once again to the effectiveness of the catalytic system for promoting these ring closing palladium-catalyzed alkoxy- and aminocarbonylations. Although the number of examples in the literature dealing with the exploitation of this reaction for accessing large macrocycles is few, we believe from a retrosynthetic perspective, and when possible, such a bond disconnection approach relying on a Pd-catalyzed carbonylation should be seriously considered for preparing such larger carbonyl-containing ring systems. We hope this small review on this topic will inspire others to consider such an approach and thereby widening the scope of this useful and catalytic transformation.

2 Seven-Membered Heterocycles

Most attention has by far been devoted to the development of protocols for accessing five- or six-membered heterocycles by palladium-catalyzed carbonylative reactions as was earlier described in the previous chapters of this book. However, seven-membered rings have also been synthesized using this methodology. One of the most important classes of these larger heterocyclic rings are the benzodiazepines, which were discovered by Leo Sternbach at Hoffman La-Roche. Some of the more well-known names and structures are depicted in Fig. 1. Xanax and valium are renowned for their anti-anxiety effects, whereas rohypnol is better known as the “date rape drug.” For this particular reason, it is imperative that there are suitable techniques and standards to be able to detect the presence of this particular benzodiazepine.

This section will present methods for accessing seven-membered rings by utilizing carbon monoxide and Pd catalysis, of which the group of Howard Alper at the University of Ottawa has been active in this field. A recent example of one of these transformations can be seen in Scheme 1 for the synthesis of 11 benzoazepinones [1]. The starting material was synthesized applying a Baylis–Hillman reaction followed by acetylation of the alcohol group. The reaction is suggested to go through a Tsuji-Trost hydroamination mechanism generating in situ an allylic amine, which subsequently acts as the nucleophile in the ensuing aminocarbonylation. A brief optimization revealed the bidentate ligand, dppb, to be the optimal ligand for this transformation. Employing the inorganic base,

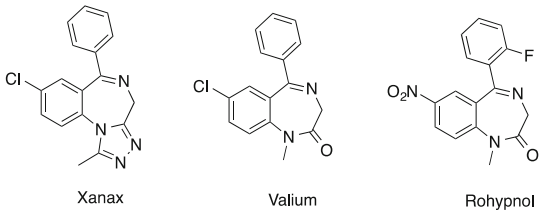
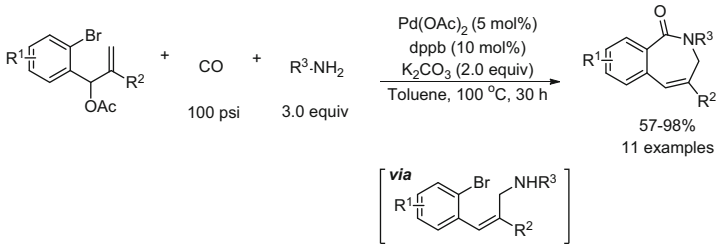
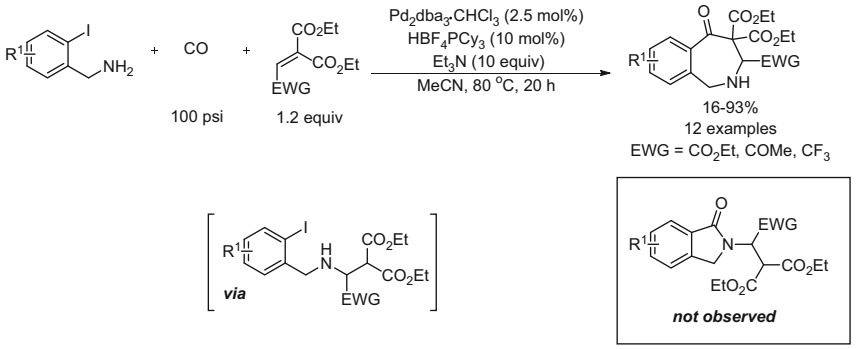


Fig. 1 Known benzodiazepine-based drugs



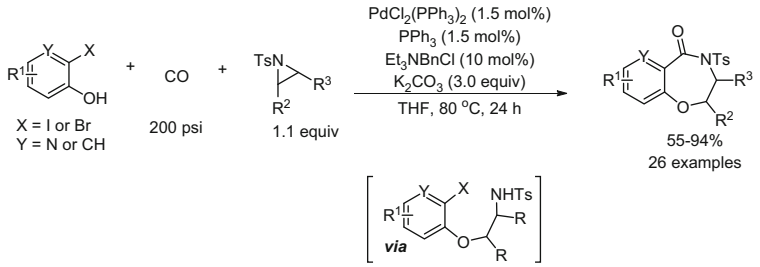
Scheme 1 Pd-catalyzed carbonylative approach to 2,3-dihydro-1H-benzo[*c*]azepin-1-ones



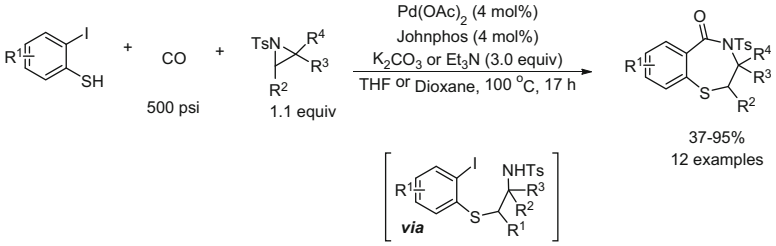
Scheme 2 Access to 1,2,3,4-tetrahydro-5*H*-benzo[*c*]azepin-5-ones

K_2CO_3, resulted in an approximately 50% higher isolated yield compared to that of DBU. Furthermore, decreasing the CO pressure from 400 to 100 psi had a beneficial effect.

A different class of benzoazepinones was published by the Alper group shortly after, the synthesis of which is illustrated in Scheme 2 [2]. The desired heterocycles were obtained through a Michael addition of 2-iodobenzyl amines to electron-deficient olefins, which then readily undergo an intramolecular carbonylative cyclization. Trialkylphosphines were shown to be superior for this reaction, with HBF_4PCy_3 being slightly more efficient than the bulkier $HBF_4P(t\text{Bu})_3$ ligand. Decreasing the amount of Et_3N retarded the reaction, whereas decreasing the CO pressure from 500 to 100 psi improved the isolated yield of the desired heterocycle.



Scheme 3 Synthesis of 1,4-benzo- and pyrido-oxazepinones



Scheme 4 Pd-catalyzed carbonytive approach to 1,4-benzothiazepin-5-ones

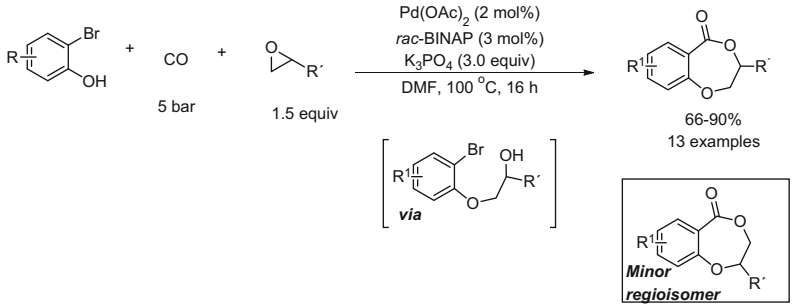
Notably, the competing aminocarbonylation forming the corresponding lactam was never observed during the optimization (Scheme 2).

In 2010, the Alper group reported on an innovative domino ring-opening/lactamization reaction affording 3,4-dihydrobenzo[*f*][1,4]oxazepin-5(2*H*)-ones (Scheme 3) [3]. This compound class was accessed by ring-opening of a strained tosylated aziridine and followed by an intramolecular aminocarbonylation. This methodology could be applied to a range of 2-halophenols and 2-halopyridinols. Utilizing Cs_2CO_3 instead of K_2CO_3 or $Pd(OAc)_2$ instead of $PdCl_2(PPh_3)_2$ gave similar results. The isolated yield of the desired heterocycle could be significantly increased by adding triethylbenzylammonium chloride as a phase-transfer catalyst. Employing a modified catalytic system allowed the extension of this reaction to include 2-iodothiophenols to access 1,4-benzothiazepin-5-ones as shown in Scheme 4 [4]. Notably, this catalytic system required Johnphos as the ligand instead of PPh_3 as was the case for the previously described system. Other bidentate ligands such as Xantphos, dppf, and *rac*-BINAP only provided the 1,4-benzothiazepin-5-ones in low to moderate yields. Increasing the ratio of Pd:ligand from 1:1 to 1:2 retarded the CO insertion. Furthermore, the use of a phase-transfer catalyst was omitted in this system.

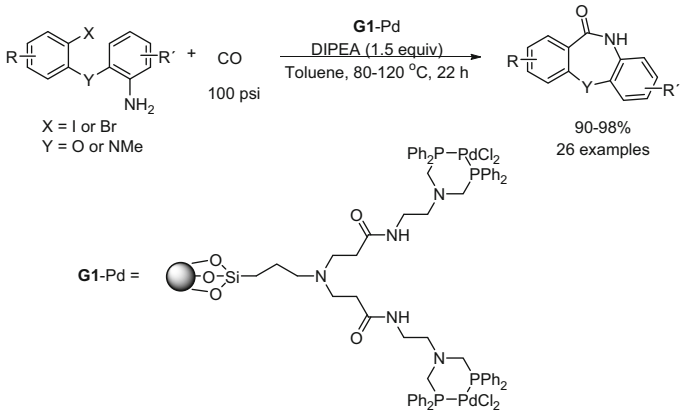
A conceptually similar strategy was recently published by the groups of Beller and Wu at the Leibniz Institute for Catalysis in Rostock, where epoxides were explored instead of tosylated aziridines, which enabled access to 2,3-dihydrobenzodioxepinones [5]. Initial bidentate ligand screening in acetonitrile employing K_2CO_3 as the base revealed *rac*-BINAP as the best choice providing a

modest yield of 27% and a 4:1 regioselectivity. Monodentate ligands such as cataCXium A and PPh_3 were ineffective for this transformation. The yield and regioselectivity could be increased to 90% and 9:1, respectively, by using DMF as the solvent and K_3PO_4 as the base. Interestingly, the regioselectivity could be reversed by conducting the reaction in water and adding catalytic amounts of $ZnBr_2$ as a Lewis acid (50% GC-yield, 15:85 regioselectivity). This reaction was applied to a range of substituted epoxides, and high yields and regioselectivities were observed for this ring-opening reaction at the less-hindered site (Scheme 5).

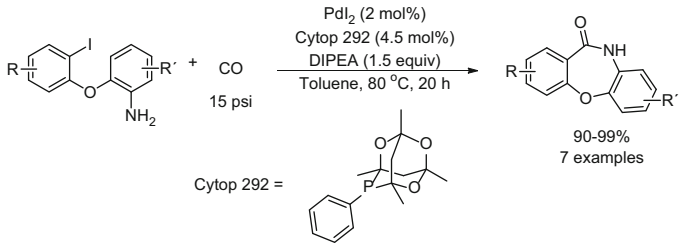
Interestingly, the Alper group has utilized a heterogenous dendrimeric palladium catalyst for the formation of dibenzo-oxazepinones and dibenzodiazepinones (Scheme 6) [6]. This protocol enabled the formation of the desired heterocycles in excellent yields. Furthermore, the catalyst could be recycled up to eight times by simple air filtration. An efficient homogenous methodology for obtaining the same compound class was enabled by utilizing the air-stable ligand Cytop 292 under an atmospheric pressure of carbon monoxide as illustrated in Scheme 7 [7]. Other



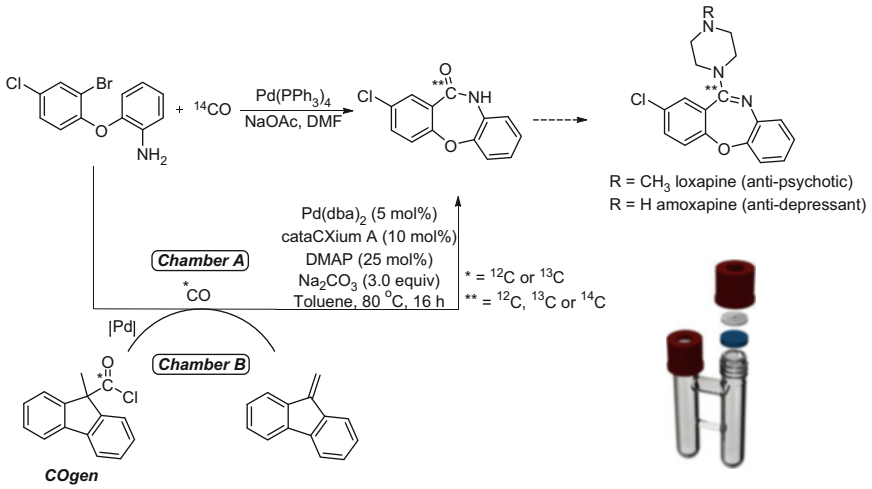
Scheme 5 Employing epoxides on the route to 2,3-dihydrobenzodioxepinones



Scheme 6 Employment of a heterogenous Pd-dendrimer as a catalyst for forming seven-membered rings



Scheme 7 Efficient synthesis of dibenzo-oxazepinones using Cytop 292 as the ligand

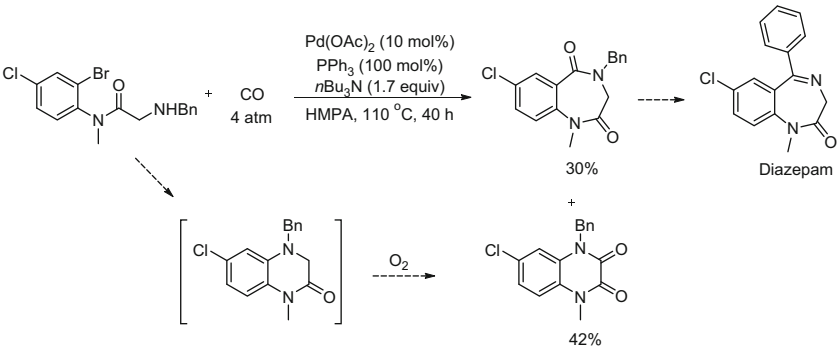


Scheme 8 Isotope labeling of loxapine and amoxapine. The two-chamber reactor (COware) is illustrated as well

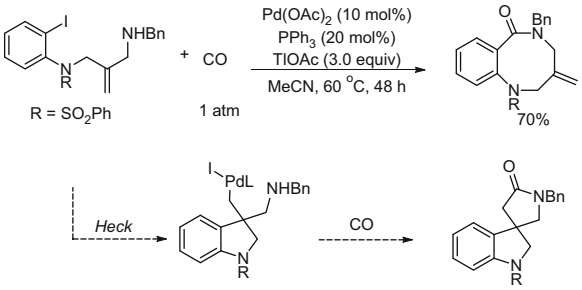
ligands such as PPh_3 and dppb proved inferior compared to Cytop 292. The choice of the PdI_2 salt proved critical since other Pd(II) sources such as $Pd(PCy_3)_2Cl_2$ only provided trace amounts of the desired compound. Finally, the CO pressure could be lowered from 100 to 15 psi without affecting the isolated yield of the product.

As depicted in Scheme 8, AztraZeneca has developed a similar route, which enables for the ^{14}C-isotope labeling of bioactive molecules containing this structural motif [8]. This type of carbon isotope labeling is an invaluable tool in studying the drug metabolism. The ^{14}C-isotope labeled carbon monoxide was produced from the ^{14}C-labeled sodium formatate. A similar strategy for synthesizing the ^{12}C- and ^{13}C-labeled loxapine intermediary product was published by the Skrydstrup group in 2011 [9]. This approach was based on ex situ formation of CO from a solid acid chloride (COgen) in a sealed two-chamber reactor (COgen). This is illustrated in Scheme 8.

Diazepam, also sold under the trade name Valium, and being undoubtedly one of the most well-known benzodiazepine-based drugs, can also be synthesized by a palladium-catalyzed carbonylation, albeit in a low yield (Scheme 9) [10]. This is



Scheme 9 Synthesis of diazepam via Pd-catalyzed carbonylative cyclization

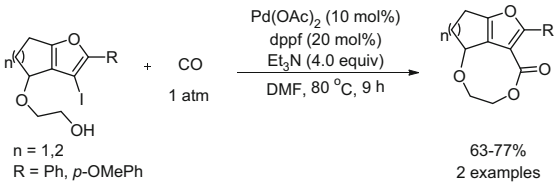


Scheme 10 Palladium-catalyzed carbonylative formation of an eight-membered heterocyclic ring

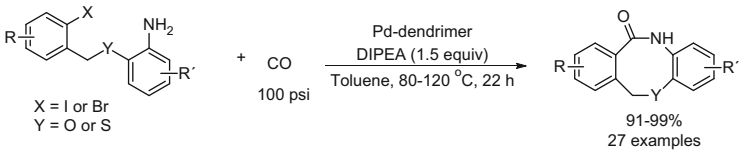
due to a competing nucleophilic aromatic substitution which takes place with or without palladium. This intermediate is rapidly oxidized in atmospheric air to the corresponding ketoamide, which was the main product in this reaction. The undesired amination could be somewhat suppressed by increasing the CO pressure from 1 to 4 atm. Higher CO pressure was not attempted. Furthermore, the same group has applied a similar strategy in the total synthesis of other benzodiazepine-based drugs [11].

3 Larger Heterocycles

Besides the formation of the seven-membered ring structures, there are also sporadic reports on the formation of eight and even larger heterocyclic ring systems through similar synthetic strategies. In 1993, Grigg et al. reported the palladium-catalyzed carbonylative synthesis of an eight-membered lactam (Scheme 10) [12]. In this protocol, the formation of a spirocyclic compound formed through an intramolecular Heck reaction followed by a carbonylative lactamization competed



Scheme 11 Synthesis of eight-membered lactones



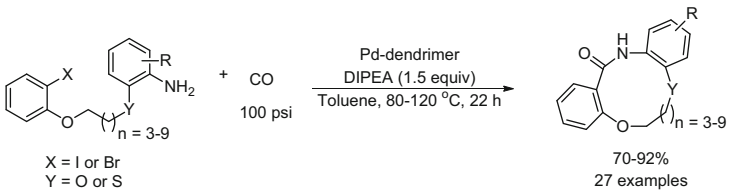
Scheme 12 Access to eight-membered lactams using a heterogenous Pd-dendrimer

with the cyclization to give the eight-membered lactam. Increasing the amount of thallium(I) acetate played a key role in avoiding the formation of the undesired spirocycle by suppressing the initial Heck reaction. This effect was studied earlier by the same group [13].

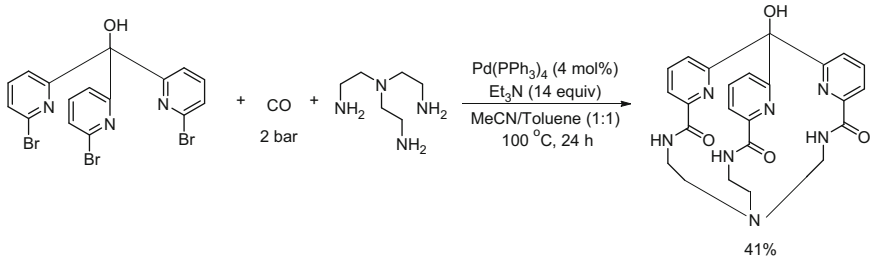
Besides employing aminocarbonylations to construct eight-membered heterocycles, the palladium-catalyzed alkoxycarbonylation is another useful synthetic transformation. In 2010, Richard Larock from Iowa State University reported an efficient method for the palladium-catalyzed intramolecular cyclocarbonylation of hydroxyl-substituted 3-iodofurans under one atmosphere of pressure of carbon monoxide to obtain tricyclic lactones containing a furan moiety (Scheme 11) [14]. In the presence of an external nucleophile, the intermolecular carbonylation reaction was favored, especially when employing electron-rich monodentate phosphine ligands. Interestingly, the cyclocarbonylation occurred almost exclusively by omitting the phosphine ligand. For the intramolecular reaction, the presence of dppf reduced the reaction time from 72 to 9 h. However, only two examples of this methodology were presented in this work.

The Alper group provided a more thorough study utilizing the same Pd-dendrimer strategy as was illustrated in the previous section (see Scheme 6) [6]. Employing this strategy enabled the formation of a variety of eight-membered lactams in high yields under a CO pressure of 100 psi (Scheme 12).

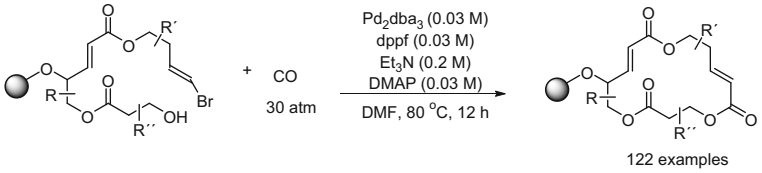
Furthermore, this methodology could be extended to even larger macrocycles as illustrated in Scheme 13 [15]. In this way, the Alper group was able to prepare a number of oxygen-, nitrogen-, or sulfur-containing macrocycles. The heterogeneous dendrimeric catalyst displayed high activity and a series of macrocycles spanning from 12- to 18-membered rings were generated under their conditions in good yields. Meanwhile, this catalytic system could once again be recovered by simple filtration with only a slight loss of activity.



Scheme 13 Formation of macrocycles via palladium-catalyzed aminocarbonylations



Scheme 14 Synthesis of cryptand employing aminocarbonylations



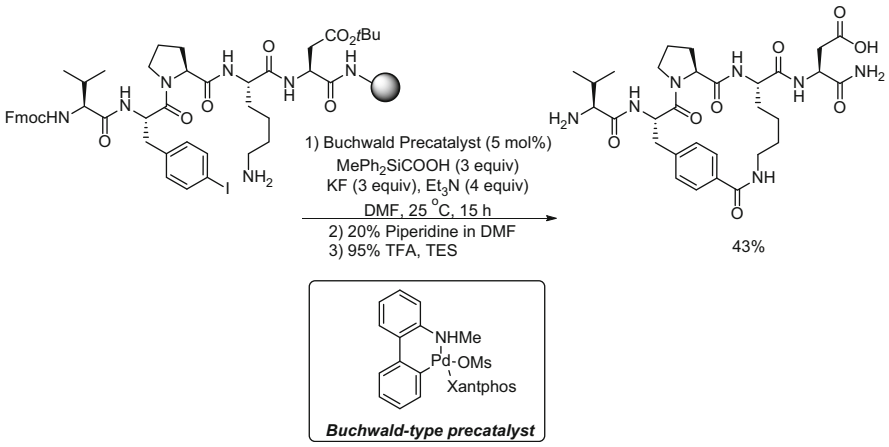
Scheme 15 Solid-phase synthesis of a macrosphelide library

The synthesis of a similar sized macrocycle (cryptand) in a 41% yield was reported by Knight et al., which was enabled by three consecutive aminocarbonylation reactions (average yield for each carbonylation reaction, 74%) using tris-aminoethylamine and tris(2-pyridyl)methanol as illustrated in Scheme 14 [16].

In 2003, Takahashi and co-workers described a combinatorial synthesis of macrosphelide analogues (16-membered ring structures) exploiting palladium-catalyzed carbonylations on a polymer support (Scheme 15) [17]. This strategy provided a high-speed and efficient synthesis of 122 macrosphelide analogues.

The same group extended this concept to include 24-membered macrocycles in a later study [18]. Furthermore, the Takahashi group has studied 21-membered cyclic peptide model systems, where the cyclization was enabled through an aminocarbonylation (Scheme 16) [19]. The catalytic system applied in this study is carried out under milder conditions compared to the previous study (Scheme 15) which is due to the fact that both the electrophile and the nucleophile in this case are more reactive. Furthermore, Et_3N and DMAP were replaced by molecular sieves to avoid removal of

Scheme 16 Synthesis of a peptide macrocyclic model system



Scheme 17 Solid-phase macrolactamization

the Boc-protecting groups. Heating the reaction above 50°C also resulted in cleavage of the Boc-groups. Lowering the CO pressure to 5 atm resulted in lower conversion and increasing the CO pressure to 20 atm did not have any effect. A palladium-screening revealed $Pd(P(tBu)_3)_2$ to be the most efficient Pd(0) source.

Very recently, the groups of Skrydstrup and Sandström reported a methodology for Pd-catalyzed aminocarbonylation of peptides using solid-phase chemistry (A. Skogh et al., unpublished results). This was enabled by utilizing a Xantphos-ligated Buchwald-type pre-catalyst, which has been shown to be very effective for aminocarbonylation of aryl bromides at low temperatures [20]. Furthermore, the CO was produced in situ by reacting methyldiphenylsilacarboxylic acid in the presence of potassium fluoride. A side-chain macrolactamization was carried out between a lysine fragment and an iodinated phenylalanine residue to produce an 18-membered ring in 43% (Scheme 17).

4 Conclusion and Future Perspectives

Although the number of applications of the palladium-catalyzed carbonylation still remains limited compared to five- and six-membered ring formations, it is nonetheless remarkable that such cyclizations can be highly efficient even for the construction of large ring systems. This suggests that the catalytic systems are particularly robust considering the slow kinetics that must arise from the ring closure in systems generating up to 24-membered macrocycles. The high yields obtained even for such ring structures imply that even larger macrocycles can be attained applying this transition metal-catalyzed methodology. Finally, palladium-catalyzed carbonylations also have the advantage over other cyclization processes in which this two-bond formation methodology allows for the introduction of carbon isotopes such as ^{13}C- and ^{14}C carbon, thereby allowing for a range of useful applications of the synthesized ring structures. Undoubtedly, the future is very bright for applying these carbonylative cyclization reactions.

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Synthesis of Heterocycles via Radical Carbonylation

Ilhyong Ryu and Takahide Fukuyama

Abstract Alkyl, aryl, and alkenyl radicals react with CO to form the corresponding acyl radicals, which serve as key intermediates for the synthesis of a wide variety of carbonyl compounds. This chapter focuses on the applications of radical carbonylation for the synthesis of heterocyclic compounds. Radical carbonylation process is reliable for alkyl substrates, since alkyl radicals are sufficiently stable to isomerization unlike rather instable alkyl Pd species. Acyl radicals, key intermediates in the radical carbonylation, have both nucleophilic and electrophilic characters, depending on the attacking reagents and the electrophilic nature is particularly useful to achieve synthesis of nitrogen-containing heterocycles by the reactions with imines, amines, azides, and amidines.

Keywords Acyl radical · Atom transfer carbonylation · Intramolecular homolytic substitution · Radical cyclization · α-Ketenyl radical

Contents

Carbon monoxide is a potentially abundant feedstock, which is produced from naphtha and coal as the resources in industry, and has an important role in C1 chemistry. A wide variety of transition metal-catalyzed carbonylation reactions have been developed to date [1–3], and some of which have already found industrial applications. Spending a long period of hibernation, radical carbonylations had

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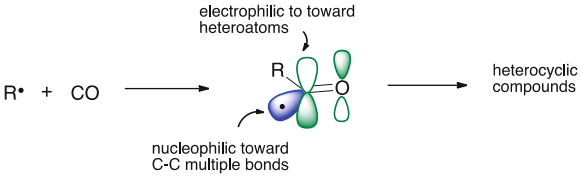
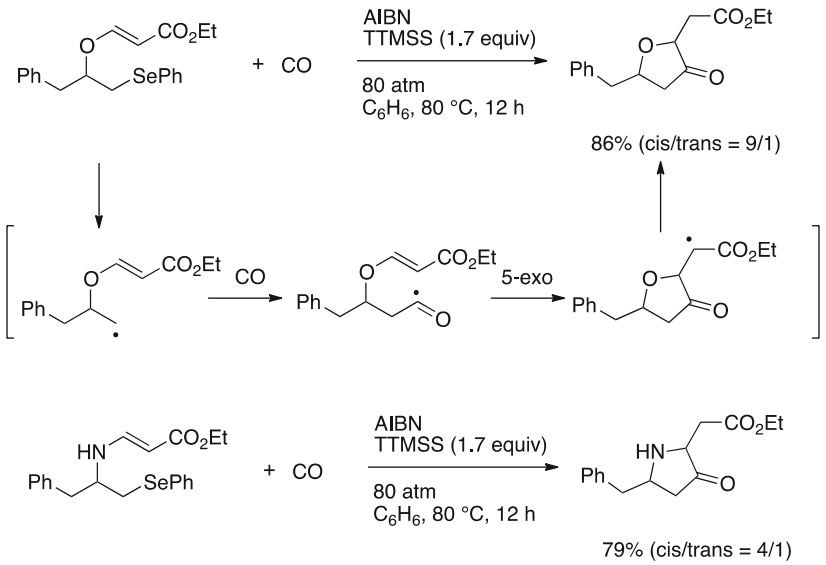
restarted in the 1990s, having the opportunity of the discovery of the first efficient radical carbonylation leading to aldehydes [4]. Nowadays radical carbonylation chemistry has been recognized as a promising repertoire in carbonylation chemistry. (For reviews on radical carbonylations, see [5–9]). One important issue in radical carbonylation distinguished from transition metal-catalyzed carbonylation is what the process is reliable for *alkyl* substrates, since the resulting alkyl radical species do not isomerize unlike the case of somewhat labile metal alkyl species. Key species arising from carbonylation of radicals are acyl radicals. Acyl radicals have nucleophilic nature toward carbon–carbon multiple bonds and also exhibit electrophilic nature toward heteroatoms such as nitrogen and oxygen (Scheme 1). The nucleophilic nature is considered to be due to the interaction between acyl radical SOMO and olefin LUMO and the electrophilic nature to be the interaction between LUMO of acyl radical carbonyl and lone pair of heteroatoms. In designing the synthesis of heterocycles by acyl radical cyclization, these double-face characters can be a direction to be considered. This chapter focuses on the synthesis of heterocyclic compounds, in which radical carbonylation serves as the basis.

Acyl radical cyclization onto C–C multiple bonds provides cyclic ketones [10]. If the alkenyl tether has a heteroatom, the corresponding heterocyclic compounds can be obtained. 5-Exo acyl radical cyclizations can be applied to the formation of five-membered ring heterocycles by way of radical carbonylation. Engman and coworkers reported synthesis of 2,5-disubstituted tetrahydrofuran-3-ones by radical carbonylation and the 5-exo subsequent cyclization of the resultant acyl radicals (Scheme 2) [11, 12]. The reaction of vinyloxy ethyl selenides with CO in the presence of AIBN (2,2′-azobisisobutyronitrile) as a radical initiator and TTMSS (tris(trimethylsilyl)silane) as a radical mediator gives tetrahydrofuran-3-ones in good yields. Tributylgermanium hydride can also be employed as a radical mediator. The same strategy is applicable to the synthesis of pyrrolidin-3-ones starting from vinylated aminoalkyl phenyl selenides [12]

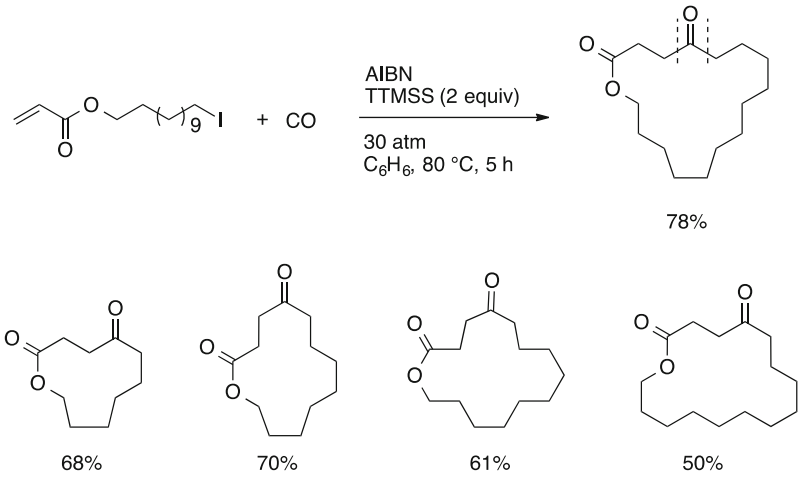
Three-component coupling reaction comprised of alkyl iodides, carbon monoxide, and acrylic acid esters under radical conditions provides a useful means for the synthesis of 4-keto esters [13, 14], and the scheme is applied to synthesis of macrocyclic keto esters [15, 16]. The reaction of ω-iodoalkyl acrylates with CO in the presence of AIBN as a radical initiator and TTMSS as a radical mediator gives 10–17-membered keto lactones in good yields (Scheme 3). Highly diluted conditions are employed to encourage carbonylative macrocyclization over premature quenching of the alkyl radicals by TTMSS. Later on Kishimoto and Ikariya



Scheme 1 Structure and natures of acyl radicals



Scheme 2 Synthesis of tetrahydrofran-3-ones and pyrolidin-3-ones via acyl radical cyclization onto a C=C bond



Scheme 3 Synthesis of macrocyclic keto esters via acyl radical cyclization onto a C=C bond

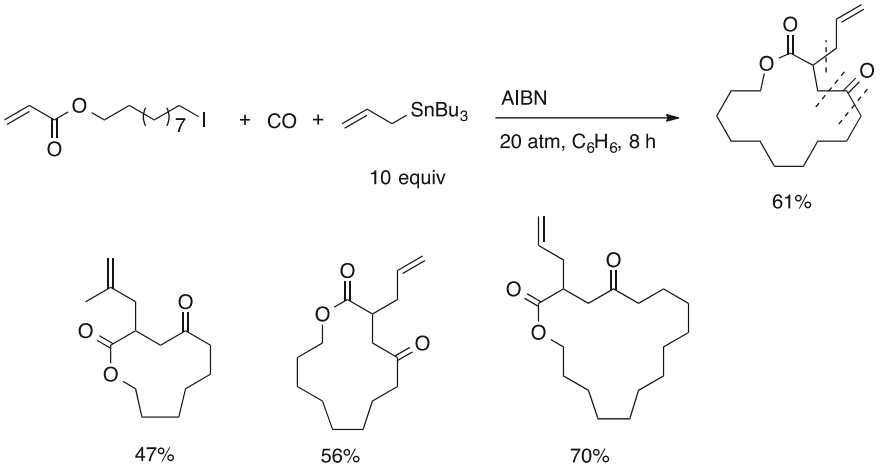
reported the TTMSS-mediated macrocyclic keto ester synthesis in supercritical carbon dioxide worked quite well. [17]

Allyltributyltin acts as an excellent unimolecular chain transfer reagent, which serves as a radical acceptor and at the same time a source of tributyltin radical [18]. The combination of the reagent with radical carbonylation is particularly useful to obtain allyl-functionalized products [19, 20]. The reaction of

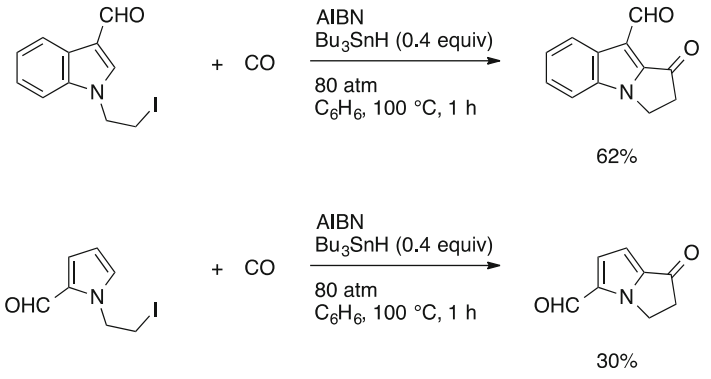
ω-iodoalkyl acrylates with CO mediated by allyltributyltin or methallyltributyltin affords allyl-substituted macrocyclic keto esters in good yields (Scheme 4) [16].

Miranda and coworkers applied tin hydride-mediated radical carbonylation/cyclization sequence [10] to the synthesis of cyclopentanones fused by nitrogen heterocycles, such as indole and pyrrole (Scheme 5) [21]. In the reaction of *N*-iodoethyl indole with CO in the presence of Bu_3SnH as a radical mediator, acyl radical undergoes intramolecular addition to C-2 position of the indole ring to give the envisaged tricyclic compound via aromatization by an in situ oxidation process.

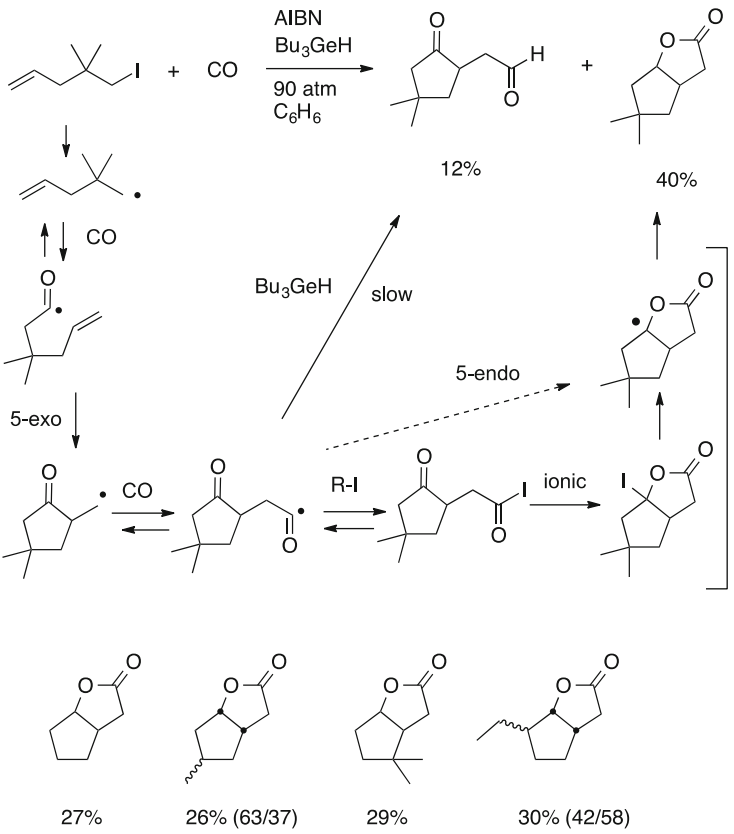
In the study aiming at cyclizative double carbonylation of 4-pentenyl iodides [22], unusual bicyclic lactone ring formation is observed when slow radical



Scheme 4 Synthesis of allyl-functionalized macrocyclic keto esters via acyl radical cyclization onto a C=C bond



Scheme 5 Synthesis of indole- and pyrrole-fused cyclopentanones via acyl radical cyclization onto a C=C Bond

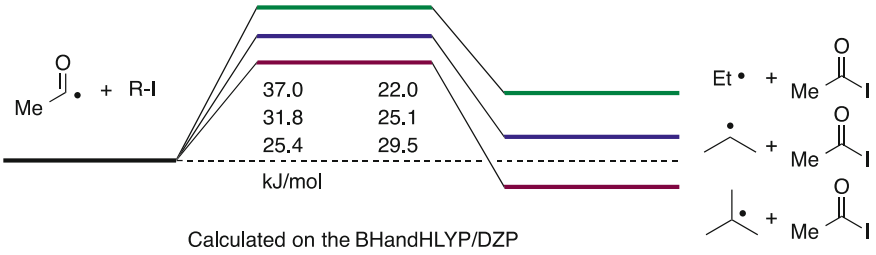


Scheme 6 Bicyclic lactone ring formation via Bu_3GeH-mediated cyclizative double carbonylation of 4-pentenyl iodides

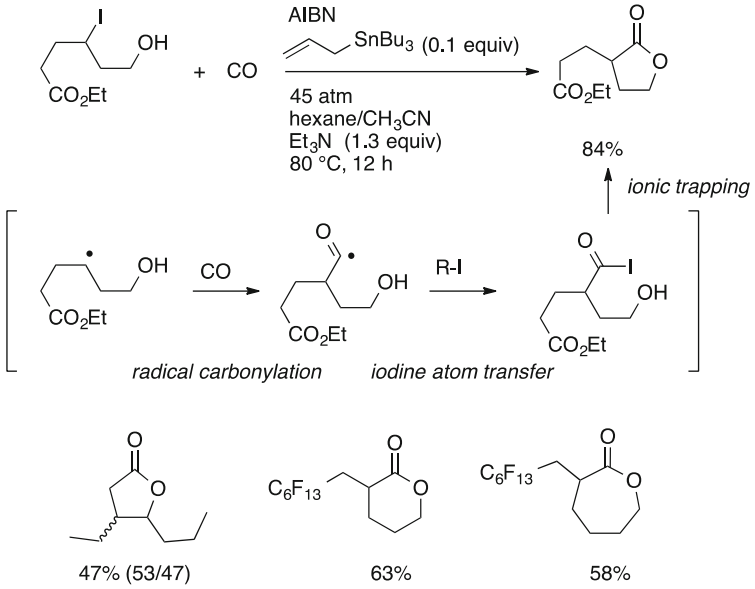
mediator such as Bu_3GeH is employed (Scheme 6), whereas the use of tin hydride only gives the expected double Carbonylation products, 4-keto aldehydes. The lactone ring formation is not because of 5-endo radical cyclization of acyl radical onto carbonyl oxygen but because of iodine atom transfer reaction to give acyl iodide, which is allowed by slow hydrogen transfer from Bu_3GeH. Spontaneous ionic cyclization of the resulting acyl iodide then takes place, and ultimately the cyclized lactone iodide is reduced by Bu_3GeH/AIBN.

Iodine atom transfer to acyl radicals is not necessarily a smooth process except for the case which gives stable alkyl radicals such as *tert*-butyl radical (Scheme 7) [23]. However, even sluggish iodine atom transfer to acyl radicals, the subsequent ionic capture of the resulting acyl iodides by electrophiles, can shift the equilibrium to forward, which makes atom transfer carbonylation possible to carry out even for primary and secondary alkyl iodides [24, 25].

Indeed, coupled with an appropriate radical initiation process (photo-irradiation or thermal initiation with AIBN/TTMSS or allyltin), alkyl iodides undergo atom



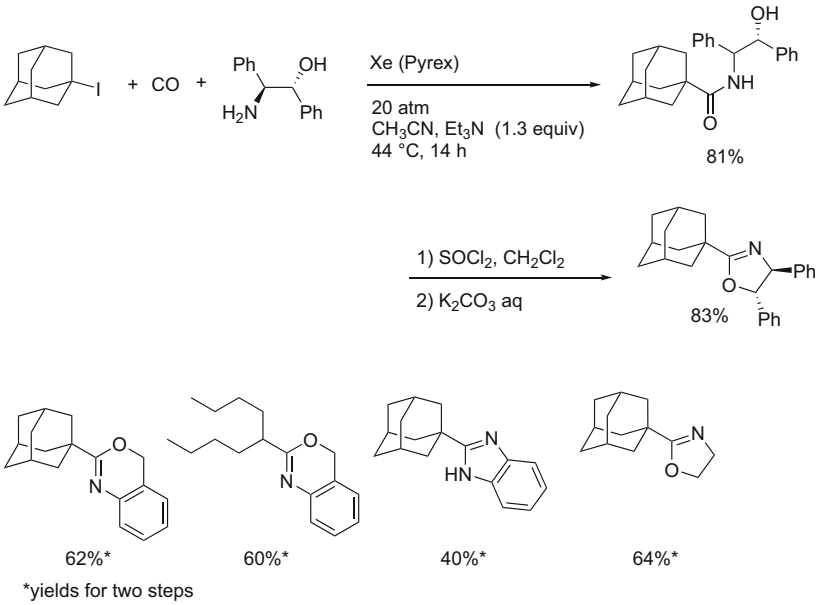
Scheme 7 Energy diagram on iodine atom transfer from iodoalkanes to acyl radicals



Scheme 8 Lactone synthesis via iodine atom transfer carbonylation of iodoalcohols

transfer carbonylation in the presence of alcohols and a base to give good yields of carboxylic acid esters [24, 25]. This reaction can be successfully applied to the synthesis of lactones [26]. The reaction of ω-hydroxyalkyl iodides with CO in the presence of a catalytic amount of AIBN and allyltributyltin and Et_3N takes place smoothly to give five- to seven-membered ring lactones in moderate to good yields (Scheme 8).

Atom transfer carbonylation of alkyl iodides with diamines and ω-hydroxylamines leads to the formation of functionalized amides that could easily cyclize to afford nitrogen-containing heterocycles via the subsequent dehydrative cyclization reaction (Scheme 9). According to the two-step process, nitrogen-containing heterocycles, such as benzoxazines, benzimidazoles, and oxazolines, are prepared in good yields [27].

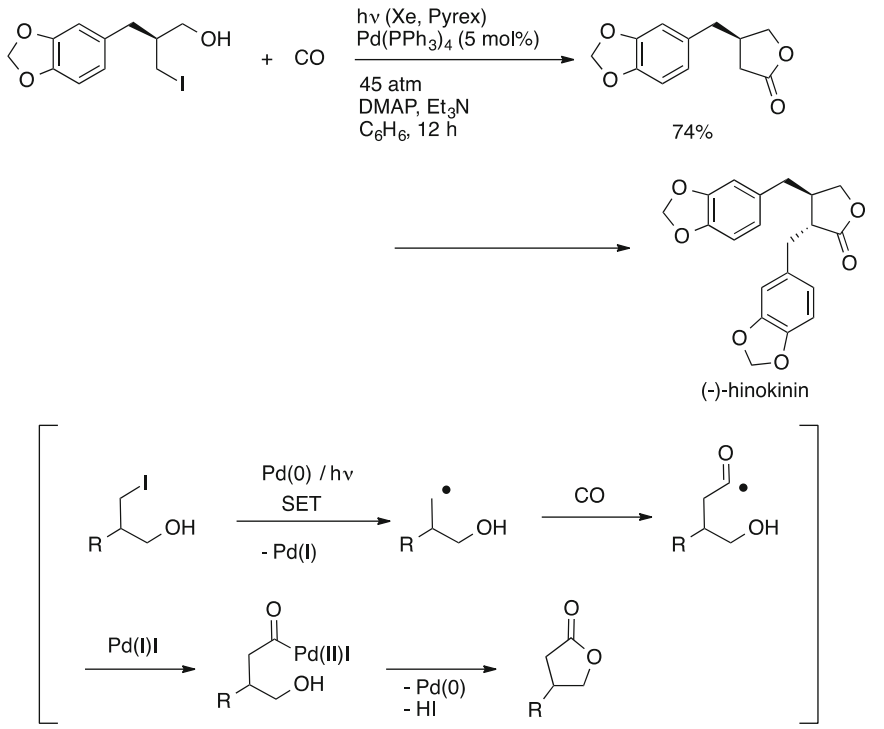


Scheme 9 Synthesis of heterocyclic compounds via atom transfer carbonylation/dehydrative cyclization sequence

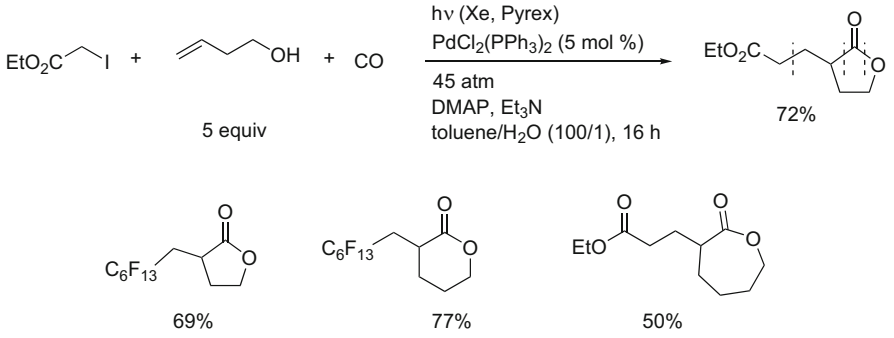
The addition of a catalytic amount of palladium complex turned out to accelerate the atom transfer carbonylation under irradiation conditions (for a review, see [28]). Since atom transfer carbonylation of primary alkyl iodides is quite sluggish, the employment of Pd/light system is especially useful. The Pd/light-induced atom transfer reaction is applied to lactone synthesis [29]. For example, the synthesis of a precursor of (−)-hinokinin is achieved based on the species hybrid concept (Scheme 10). Under photo-irradiation, single-electron transfer from Pd(0) to alkyl iodides takes place to lead to alkyl radical and Pd(I)I species, the latter of which is regarded as persistent radical. The alkyl radical adds to CO to form an acyl radical, which couples with PdI radical to give acylpalladium species, and the intramolecular alcoholysis gives the desired lactone and regenerates Pd(0) species.

The Pd/light-induced atom transfer reaction is successfully applied to three-component type lactone synthesis comprising RI, alkenyl alcohols, and CO. For example, the reaction α-iodo ethyl acetate with 3-butenol and CO proceeds well to give α-substituted lactone in a 72% yield (Scheme 11) [30, 31]. Similar reaction using perfluorohexyl iodide also works well. A series of five- to seven-membered lactones are obtained according to this procedure.

C–H functionalization is among the most important topics in organic synthesis. Unique synthesis of six-membered lactones is attained based on direct carbonylation at δ-C–H bonds of saturated alcohols, in which Barton-type 1,5-radical translocation reaction from O to δ-C operates (Scheme 12) [32, 33]. Thus, using a combination of

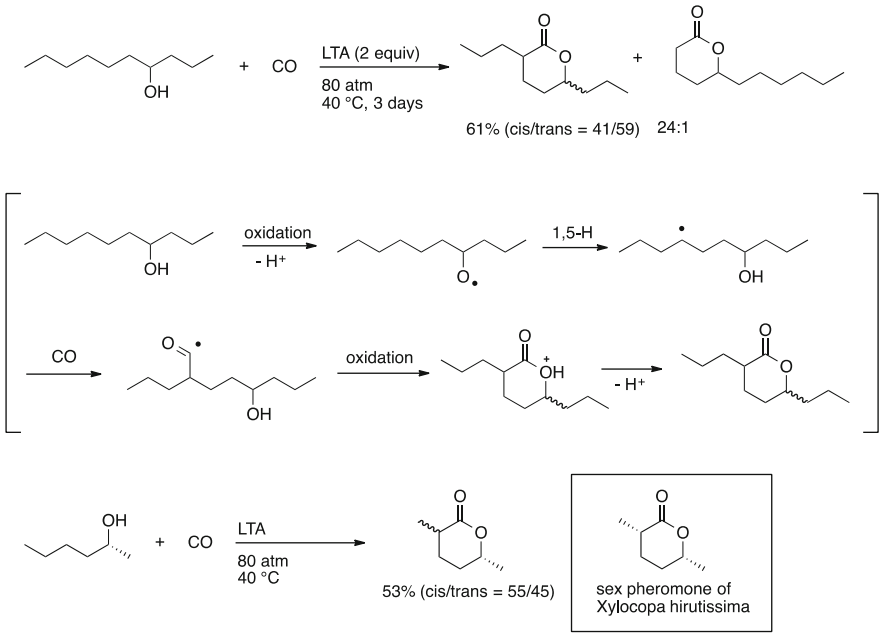


Scheme 10 Formal synthesis of (−)-hinokinin via Pd/light induced atom transfer carbonylation



Scheme 11 Three-component lactone synthesis via Pd/light induced atom transfer carbonylation

lead tetraacetate (LTA) as one-electron oxidant and CO, one-electron oxidation of saturated alcohols takes place to generate oxygen-centered radicals, which undergo 1,5-H transfer to create δ-alkyl radicals. Radical carbonylation followed by the oxidation and the deprotonative cyclization affords δ-lactones in good yields. In the



Scheme 12 δ-Lactone synthesis via oxidative C–H carbonylation of saturated alcohols

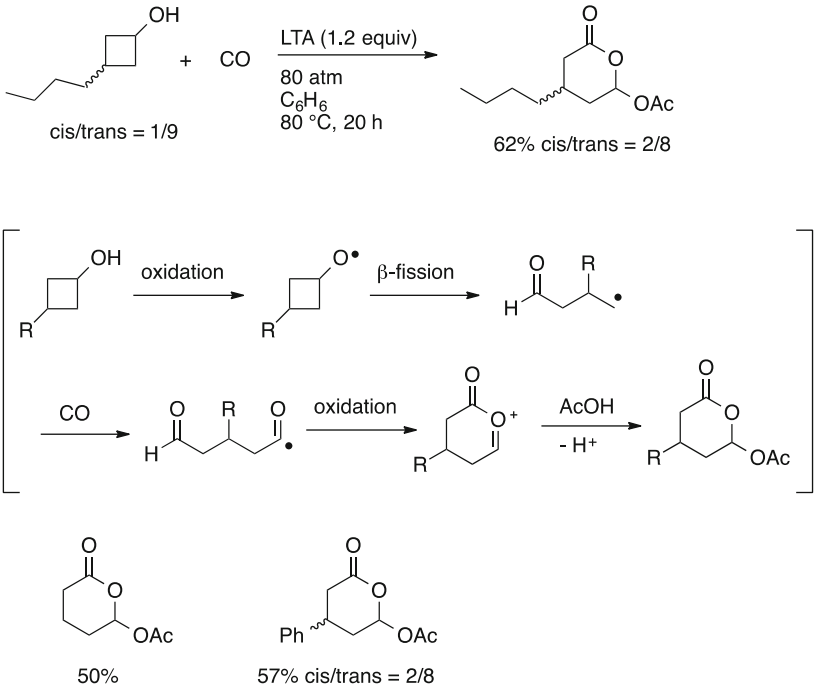
first example given in Scheme 12, high regioselectivity in favor of methylene group is observed, and this is a reflection of the weaker bond strength of methylene C–H compared to methyl C–H (95 vs. 98 kcal/mol). The oxidative C–H carbonylation is successfully applied to the one-step synthesis of carpenter bee sex pheromone starting from chiral 2-hexanol.

It is also possible to prepare six-membered ring lactones using carbonylative oxidative ring cleavage of cyclobutanols (Scheme 13) [34].

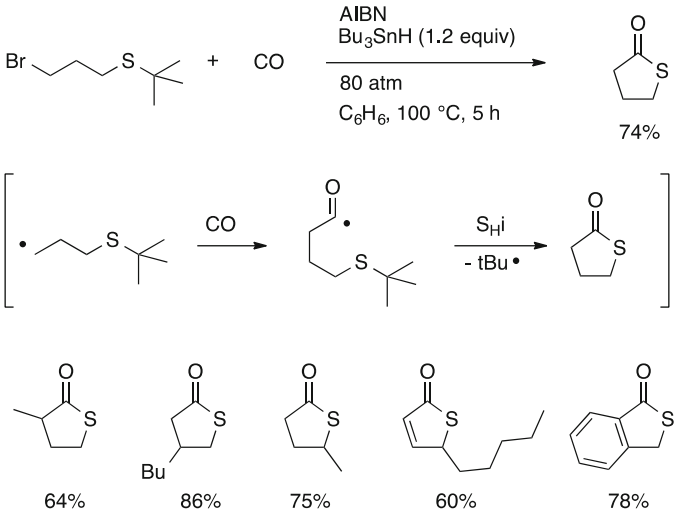
Radical substitution at heteroatoms is successfully combined with radical carbonylation. Thiolactones can be obtained by intramolecular homolytic substitution of acyl radical at sulfur [35]. For example, the reaction of *tert*-butyl bromopropyl thioether with CO in the presence of tributyltin hydride gives γ-thiolactone in a 74% yield (Scheme 14). α,β-Unsaturated thiolactone and benzothiolactone are also obtained from the corresponding vinyl iodide and aryl iodide, respectively.

The reaction of 3-[(trimethylstannyl)diphenylsilyl]propyl bromide with CO in the presence of TTMSS gives silacyclopentanone via intramolecular homolytic substitution of acyl radical at Si (Scheme 15) [36]. In this reaction, unusual 1,4-Sn shift from Si to C takes place and lowers the yield of silacyclopentanone.

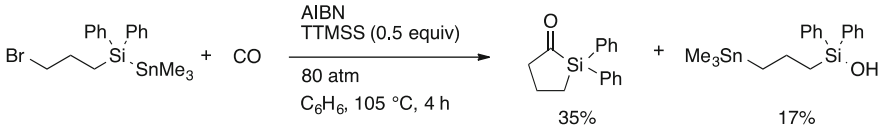
Combination of radical carbonylation with the subsequent cyclization onto N–C double bonds gives a promising tool for the synthesis of a variety of lactams. When the reaction of bromopropylimines under pressurized CO in the presence of tributyltin hydride is carried out, five-membered lactams are obtained in good yields



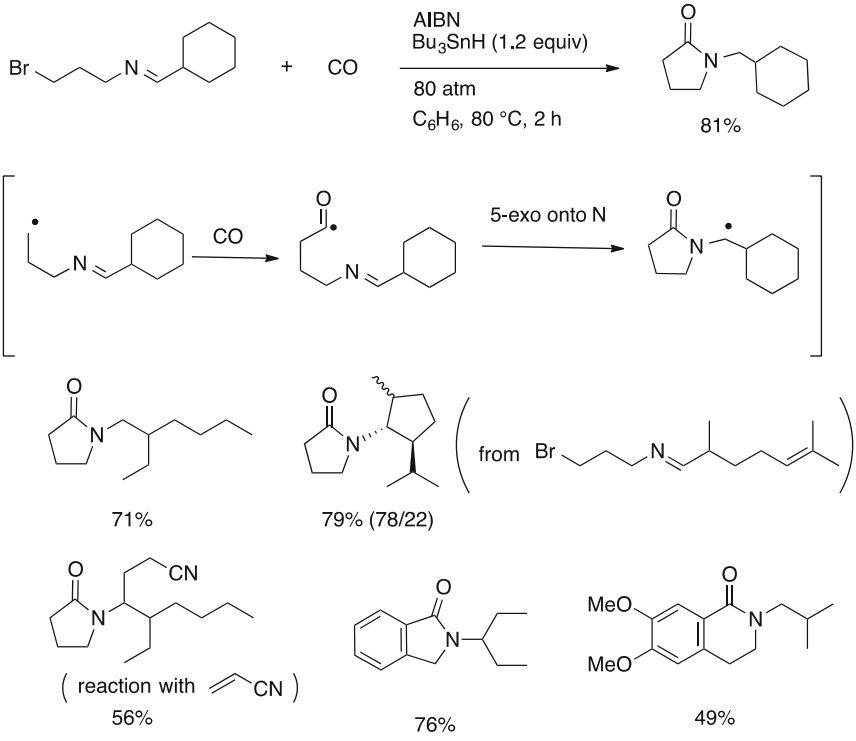
Scheme 13 δ-Lactone synthesis via carbonylative oxidative ring cleavage of cyclobutanols



Scheme 14 Synthesis of thiolactones via intramolecular homolytic substitution of acyl radical at sulfur



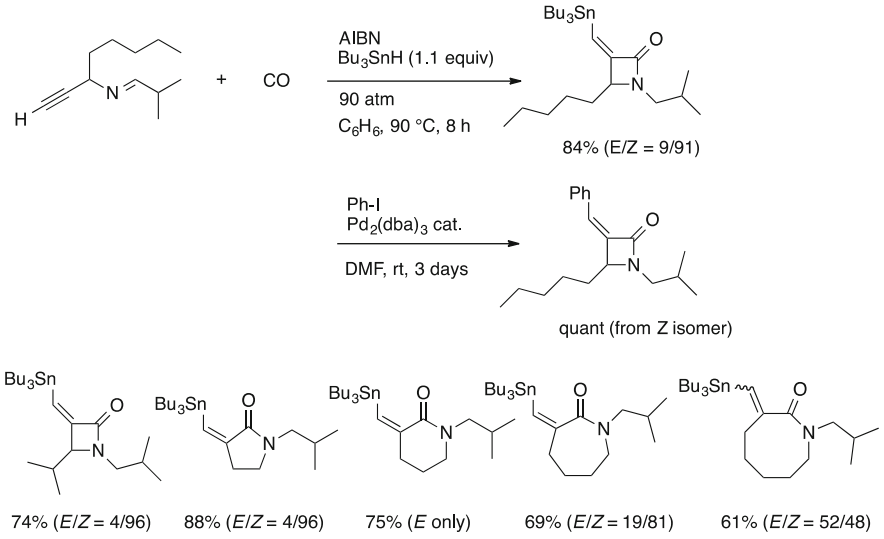
Scheme 15 Synthesis of a silacyclopentanone via intramolecular homolytic substitution of acyl radical at silicon



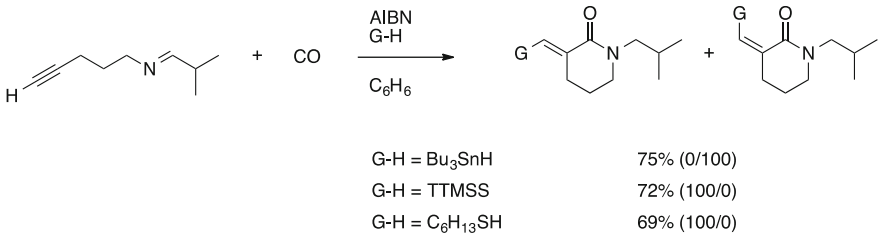
Scheme 16 Lactam synthesis via acyl radical cyclization of onto imine nitrogen

(Scheme 16) [37]. Cyclization of acyl radical takes place exclusively at imine nitrogen. The perfect selectivity for the 5-exo cyclization of acyl radical onto imine nitrogen is rationalized by dual orbital effect between nitrogen lone pair and acyl radical π* and acyl radical SOMO and imine π*, which is suggested by DFT calculation [38–41]. Benzolactams are also obtained from the corresponding aryl bromides.

Stannylcarbonylation of aza-enynes using Bu_3SnH/CO in the presence of AIBN gives α-stannylmethylene lactams in good yields (Scheme 17) [42]. The obtained stannylmethylene lactam is subjected to Pd-catalyzed Stille coupling reaction with iodobenzene to give phenylmethylene lactam. The scope of the reaction is wide,



Scheme 17 Lactam synthesis via stannylcarbonylation of aza-enynes



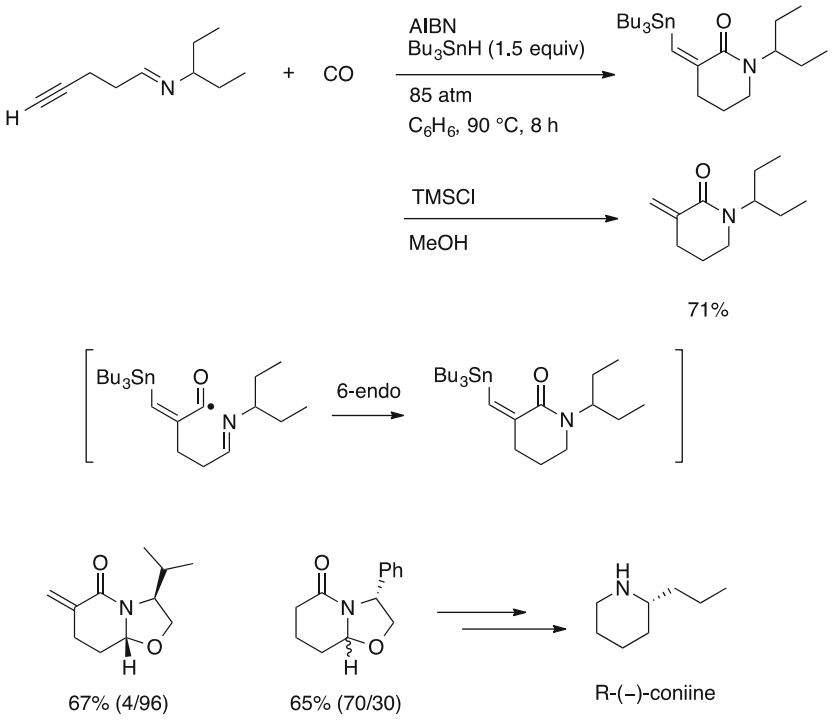
Scheme 18 Comparison of Bu_3SnH, TTMSS, and hexanethiol-mediated stannylcarbonylation of an aza-enyne

covering four- to eight-membered lactams. The subsequent treatment of the products with TMSCl/MeOH gives destannylated α-methylene lactams quantitatively.

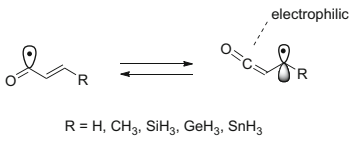
TTMSS and 1-hexanethiol can be used for the similar lactam synthesis by carbonylation of aza-enynes [43]. Interestingly, using these radical mediators, *E*-stereoselectivity is generally observed, while the reaction using tributyltin hydride exhibits *Z*-stereoselectivity (Scheme 18). DFT calculations suggest that coordination of carbonyl oxygen to tributylstannyl group renders the *Z*-form structure more stable.

Dual orbital effect between nitrogen and acyl radical allows for δ-lactam synthesis by selective 6-endo cyclization in preference to 5-exo cyclization onto N–C double bonds (Scheme 19) [40, 44]. N-Philic 6-endo cyclization is also attained for chiral oxazoline. The reaction is applicable to formal synthesis of (R)-(−)-coniine.

Vinyl radical carbonylation gives α,β-unsaturated acyl radicals as the first intermediate. Theoretical work suggests that α,β-unsaturated acyl radicals exist in



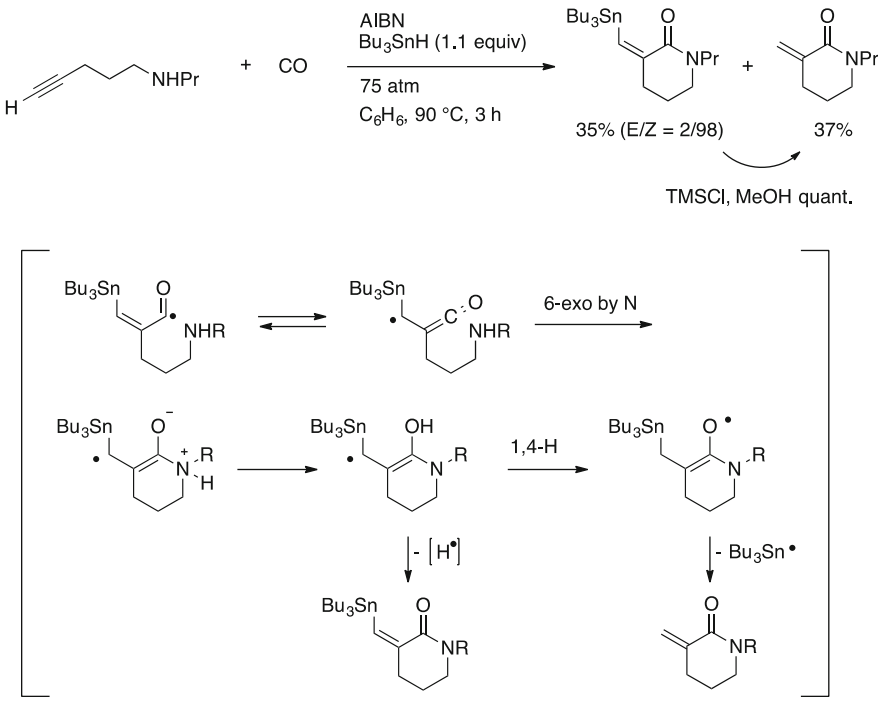
Scheme 19 Lactam synthesis via 6-endo acyl radical cyclization onto an N=C bond



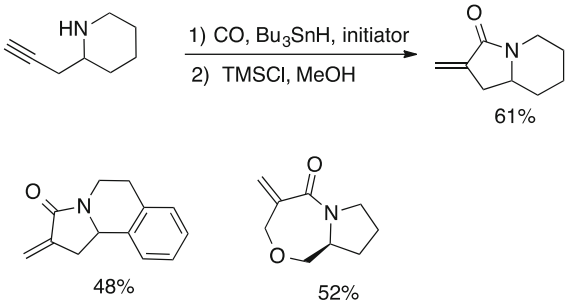
Scheme 20 Equilibrium between α,β-unsaturated acyl radicals and α-ketenyl radicals

an equilibrium with α-ketenyl radicals (Scheme 20) [45, 46]. We hypothesized that the carbonyl of α-ketenyl radicals can be electrophilic enough to react with a hydroxyl or amino group, and this serves as a resource of developing a useful method to give heterocycles.

Carbonylation of ω-alkynylamines in the presence of tributyltin hydride gives a mixture of α-stannylmethylene lactams and α-methylene lactams (Scheme 21) [47, 48]. Since the α-stannylmethylene group can be converted to α-methylene group by simple acid treatment (TMSCl/MeOH), the two-step procedure (stannylcarbonylation plus protodestannylation) provides a useful method for the synthesis of α-methylene lactams. Five- to eight-membered lactams can be synthesized by this method. In this reaction, nucleophilic addition of an amine moiety to the ketene carbonyl of α-ketenyl radical followed by proton transfer gives



Scheme 21 Synthesis of α-methylene lactams via carbonylation of ω-alkynylamines

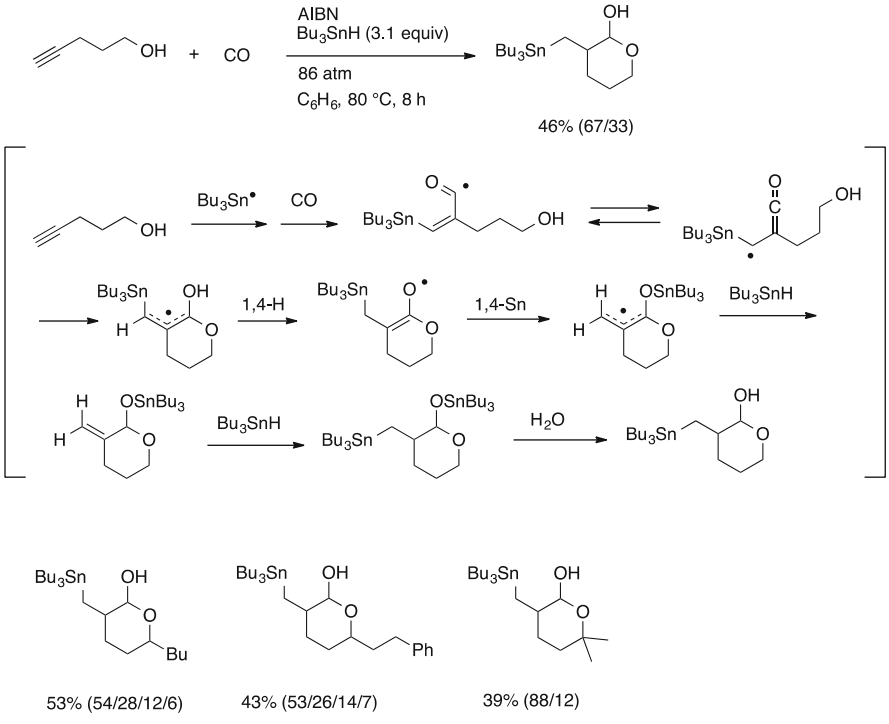


Scheme 22 Synthesis of bicyclic and tricyclic α-methylene lactams by two-step procedure

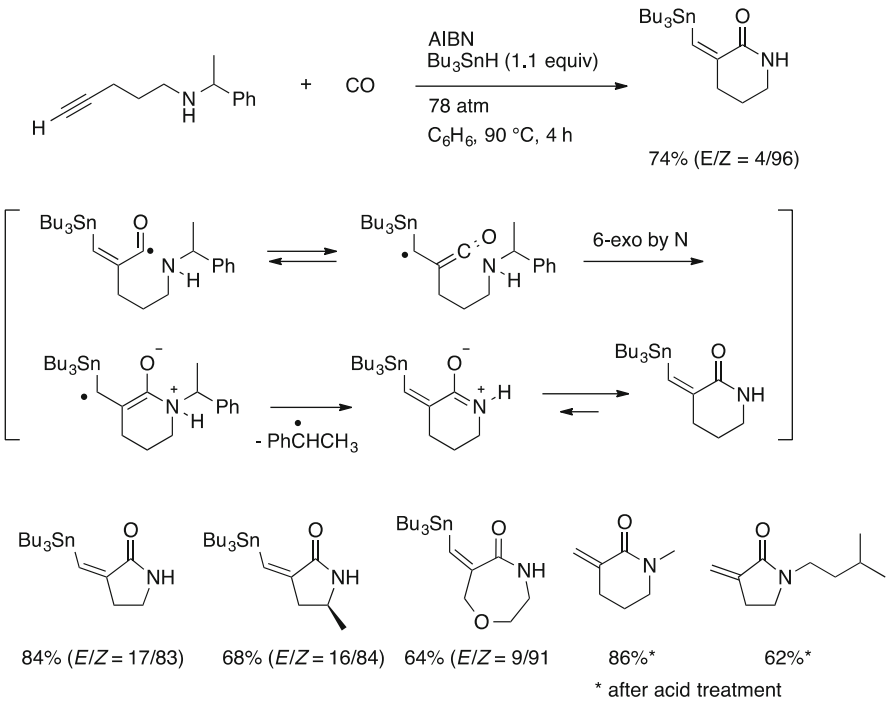
1-hydroxyallyl radical. The subsequent 1,4-H shifts leads to oxoallyl radical, which then liberates tributyltin radical to give α-methylene lactam. The DFT calculations suggest that 1,4-H shift of five- to eight-membered model lactams is highly exothermic (−71.2 to −105.7 kJ/mol) [48]. On the other hand, α-stannylmethylene lactams may be formed via oxidation from 1-hydroxyallyl radical and/or oxoallyl radical. Bicyclic and tricyclic α-methylene lactams are obtained from the corresponding alkynyl-substituted cyclic amines (Scheme 22).

Stannylcarbonylation of ω-alkynyl alcohols using tributyltin hydride and AIBN under CO pressures gives stannyl-substituted lactols (Scheme 23) [49]. The reaction pathway leading to the lactols is puzzling but a possible mechanism is illustrated in Scheme 23. Addition of tributyltin radical to alkyne terminus followed by CO trapping generates α,β-unsaturated acyl radical, which is in an equilibrium with α-ketenyl radical. Intramolecular trapping of the α-ketenyl radical by an internal hydroxy group then takes place to lead to a hydroxyallyl radical, which undergoes consecutive 1,4-hydrogen and 1,4-Sn shift to give a stannyloxy allyl radical. Hydrogen abstraction from tributyltin hydride followed by hydrostannylation gives bisstanylated lactol as a precursor for stannyl lactol.

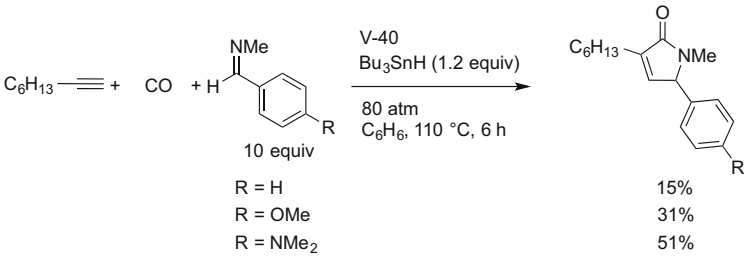
The high nitrogen philicity of acyl radicals can lead to the synthesis of lactams via intramolecular homolytic substitution reaction (S_Hi) of acyl radicals at nitrogen atom, in which phenethyl or *tert*-butyl substituent works as a radical leaving group. For example, stannylcarbonylation of an alkynyl phenethylamine followed by the elimination of a phenethyl radical takes place to give δ-lactam in good yield (Scheme 24) [48, 50]. Unlike the case of thiolactones, the S_Hi-type reaction probably proceeds in two-step mechanism comprising (i) nucleophilic trapping of the α-ketenyl radical by amine to give zwitter ionic radical intermediate, and (ii) β-fission to leave α-phenethyl radical out. DFT calculation supports this indirect S_Hi mechanism [48].



Scheme 23 Synthesis of lactols via stannylcarbonylation of ω-alkynyl alcohols



Scheme 24 Lactam synthesis via S_Hi-type reaction of acyl radical at nitrogen



Scheme 25 Synthesis of α,β-unsaturated lactams via radical-mediated [2+2+1] cycloaddition of 1-octyne, imines, and CO

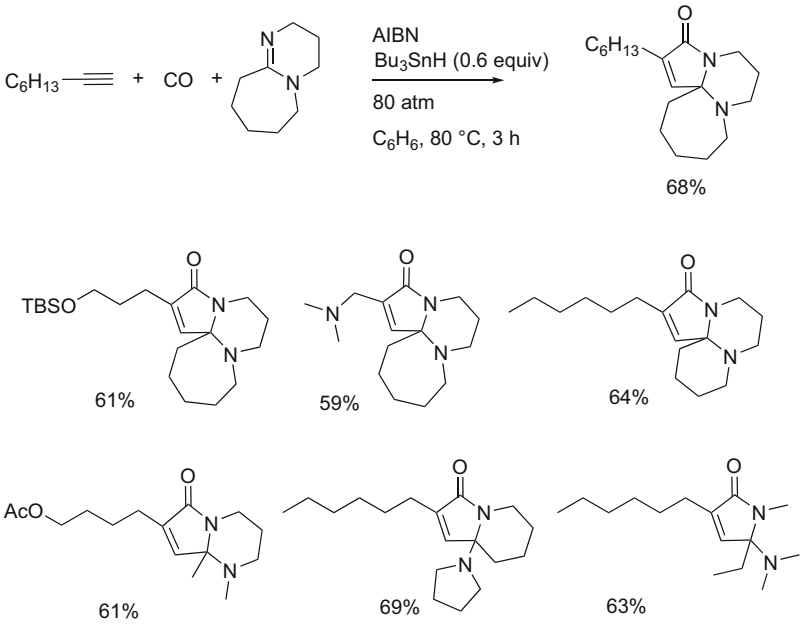
Three-component reaction of terminal alkynes, CO, and aromatic imines is achieved to give α,β-unsaturated lactams via rather unique [2 + 2 + 1] type cycloaddition reaction (Scheme 25) [51]. The reaction efficiency is affected by a substituent at *para*-position of the phenyl ring. Thus, aromatic imine having electron-donating dimethylamino substituent gives higher yield of the cycloaddition product. Interestingly, the annulation method represents a formal aza-Pauson–Khand reaction.

The [2 + 2 + 1] cycloaddition reaction of terminal alkynes, CO, and amidines, which has nitrogen atom directly at a C = N bond, proceeds smoothly to give α,β-unsaturated lactams in good yields [51]. For example, reaction of 1-octyne with CO and DBU gave tricyclic lactam in 68% yield. A variety of alkynes and amidines can be used in the radical-mediated [2 + 2 + 1] cycloaddition reaction (Scheme 26).

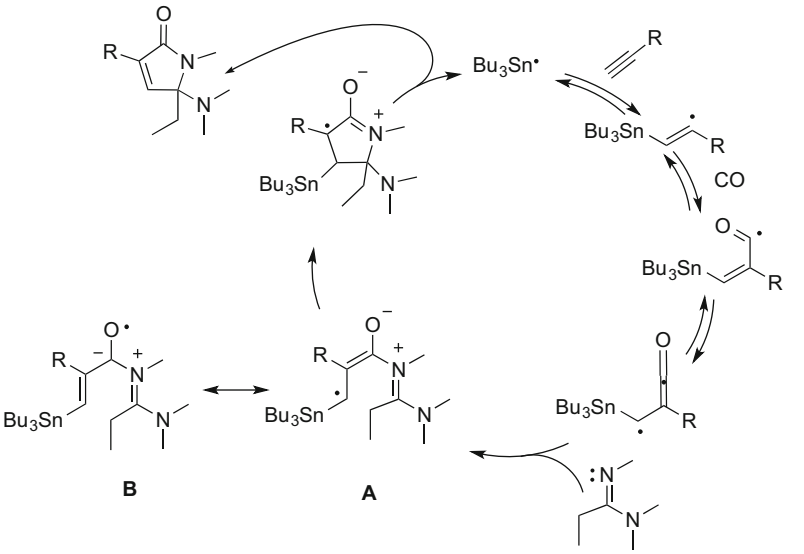
A possible mechanism for the [2 + 2 + 1] cycloaddition reaction is shown in Scheme 27. Intermolecular trapping of the α-ketenyl radical by amidine affords a highly conjugated, highly stabilized zwitter ionic radical intermediate **A**, which can be drawn in several canonical forms including **B**. Electrocyclization followed by β-fission leads to the formation of α,β-unsaturated lactam and regenerates the tributyltin radical.

4,4-Spirocyclic γ-lactams containing a quaternary carbon center can be synthesized by sequential aryl radical cyclization, radical carbonylation, and cyclization of acyl radical onto an azide group [52]. An example for the synthesis of 4,4-spirocyclic oxindole γ-lactam is shown in Scheme 28.

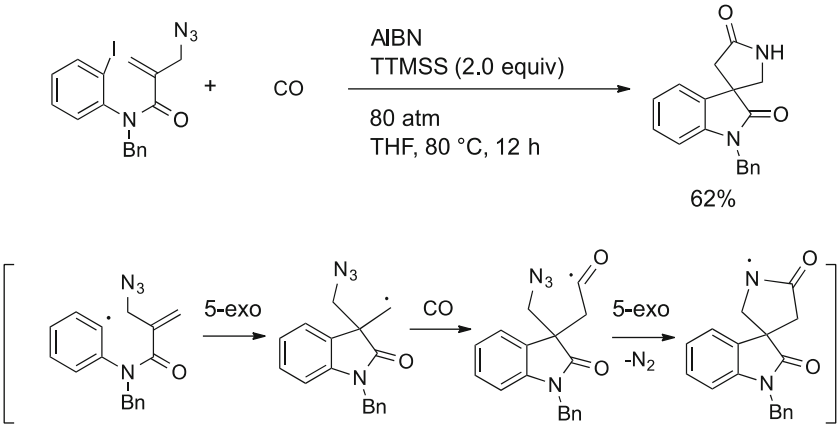
As we see in many examples illustrated in this chapter, radical carbonylation provides useful method for the synthesis of a variety of heterocyclic compounds, in which acyl radicals serve as the key species. Acyl radical cyclization onto C–C double bonds can have a heterocyclic variation when the cyclic chain has a heteroatom. Atom transfer carbonylation gives acyl iodides as the key



Scheme 26 Synthesis of α,β-unsaturated lactams via radical-mediated [2+2+1] cycloaddition of alkynes, amidines, and CO



Scheme 27 A possible mechanism for radical-mediated [2+2+1] cycloaddition reaction



Scheme 28 Synthesis of a 4,4-spirocyclic γ-lactam by cascade cyclization

intermediates, and therefore the reaction can be combined well with the subsequent ionic cyclization with an internal hydroxyl and amino group, which furnish lactones and lactams, respectively. In case of the slow iodine atom transfer reaction, Pd/light system is useful for the acceleration. Acyl radicals cyclize onto N–C double bonds selectively in N-philic manner. The carbonylative cyclization has a wide scope covering 4- to 8-exo cyclization for which dual orbital effect of acyl radicals and N–C double bonds account for the easiness. Nitrogen-philic cyclization is extended to include selective 6-endo cyclization onto C–N double bond. Carbonylation and the

subsequent intramolecular homolytic substitution of acyl radical at sulfur, silicon, and even nitrogen take place to give the corresponding thiolactone, silacyclopentanone, and lactams. Especially amino-functionalized alkynes are useful substrates for the synthesis of nitrogen-containing heterocycles, in which the alkyne portion can be converted to α-ketenyl radicals, serving as a target of nucleophilic attack of amines and amidines. Since the radical carbonylation chemistry is continuously growing, further exciting methods for the synthesis of heterocyclic compounds will be developed in the coming years.

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Synthesis of Functionalized Heterocycles via Oxidative Carbonylation

Qi Xing and Fuwei Li

Abstract With the assistance of a proper oxidant, carbonylation of two nucleophiles can take place directly in carbonylation conditions, which is defined as oxidative carbonylation. This process starts with the reaction of nucleophiles with the metal catalyst in oxidation state ($M^{(n+2)}$), followed by insertion of CO and subsequent reductive elimination, providing the carbonylated products and the metal catalyst in reduction state ($M^{(n)}$). The oxidant could reoxidize $M^{(n)}$ to $M^{(n+2)}$ to promote the catalytic cycle. Oxidative carbonylation avoids the difficult oxidative addition of R–X to metal catalyst, so this kind of carbonylation could proceed in mild conditions. What's more is that oxidative carbonylation doesn't need prefunctionalization of substrates. So, it's no wonder that considerable attention has been drawn to construct important carbonylated compounds through oxidative carbonylation. Particularly, much progress in synthesis of carbonylated heterocycles via oxidative carbonylation has been achieved in the past decades. Here, we summarized the main achievements in this area from 1982 to the beginning of 2015.

Keywords Catalytic • Heterocycles • Oxidative carbonylation • Synthesis

Contents

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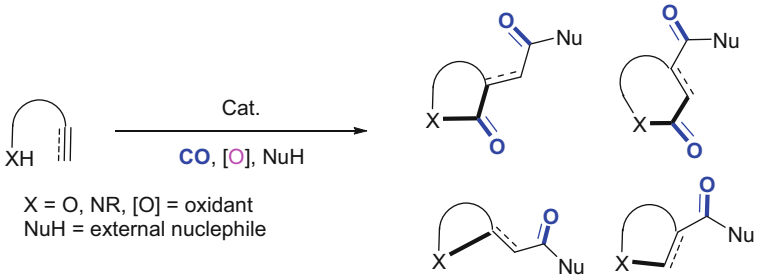
Carbonylated heterocycles as an important class of compounds can be found in many biologically active natural products. Therefore, many efforts have been devoted to developing improved methods for synthesis of these compounds (for selected reviews on synthesis of heterocycles, see [1–14]). CO as the simplest C-1 unit has been widely used to construct carbonylated compounds (for selected examples, see [15–26]). Heck and co-workers pioneered the carbonylation of organic halides with CO in 1963 [27]. In this work, the oxidative addition of organohalides to Pd(0) takes place firstly followed by coordination and insertion of CO, and finally reductive elimination occurs giving the carbonylated product. However, the π acidity of CO renders the CO-coordinated low-valence metal electron deficient, which makes oxidative addition of organohalides to Pd(0) difficult [28]. As a result, harsh conditions are often required for this kind of carbonylation. In addition, prefunctionalized substrates as electrophiles are needed for this reaction, which traduced the green chemistry principles. With the assistance of a proper oxidant, carbonylation of two nucleophiles can take place directly in carbonylation conditions, which is defined as oxidative carbonylation [29, 30]. This process starts with the reaction of nucleophiles with the metal catalyst in oxidation state ($M^{(n+2)}$), followed by insertion of CO and subsequent reductive elimination, providing the carbonylated products and the metal catalyst in reduction state ($M^{(n)}$). The oxidant could reoxidize $M^{(n)}$ to $M^{(n+2)}$ to promote the catalytic cycle. Oxidative carbonylation avoids the difficult oxidative addition of R–X to metal catalyst, so this kind of carbonylation could proceed in mild conditions. What's more is that oxidative carbonylation doesn't need prefunctionalization of substrates. So, it's no wonder that considerable attention has been drawn to construct important carbonylated compounds through oxidative carbonylation [18, 24, 26]. Particularly, much progress in synthesis of carbonylated heterocycles via oxidative carbonylation has been achieved in the past decades [13, 14]. Here, we summarized the main achievements in this area from 1982 to the beginning of 2015.

1 Synthesis of Heterocycles via Oxidative Carbonylation of Alkyne or Alkene Derivatives Incorporated with a Nucleophile (OH or NHR)

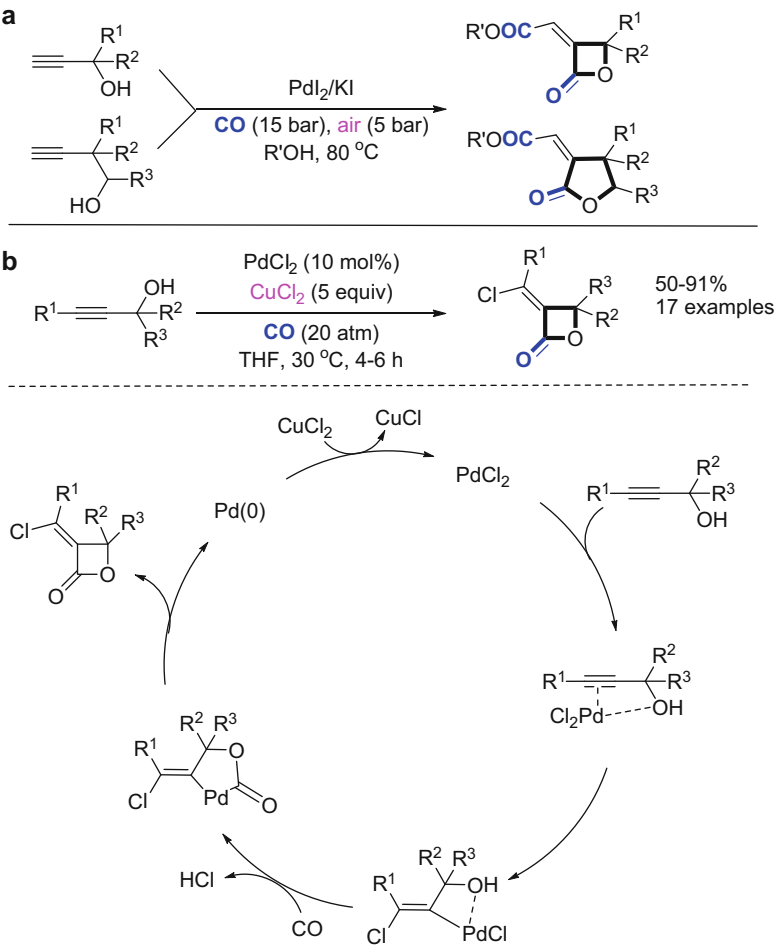
Cyclization of unsaturated substrates incorporated with a proper nucleophile is an efficient route to synthesize various carbonylated heterocycles (Scheme 1). Many advances in application of this methodology for synthesis of oxygen- or nitrogen-containing carbonylated heterocycles have been reported by different groups all around the world. Generally, this method provides endo-carbonyl or exo-carbonyl compounds as the main products depending on the type of substrates and reaction conditions. Meanwhile, different sizes and types of heterocycles are generated depending on the chain length of substrates and reaction regioselectivity.

1.1 Synthesis of Four-Membered Heterocycles via Oxidative Carbonylation of Alkyne or Alkene Derivatives Incorporated with a Nucleophile

Lactones are important skeletons in some biologically active natural products. Oxidative cyclocarbonylation of alkynols represents a powerful methodology for the synthesis of lactones. As early as 1994, Gabriele and co-workers reported a PdI_2-/KI-catalyzed oxidative carbonylation of tertiary α-hydroxyalkynes to give β-lactones stereoselectively with air as the oxidant [31]. Later, they extended this method to but-3-yn-1-ols to synthesize five-membered lactones (Scheme 2a) [32]. In 2003, Ma and co-workers developed a palladium-catalyzed cyclocarbonylation of 2-alkynols with $CuCl_2$ for the synthesis of (*Z*)-α-chloroalkylidene-β-lactones (Scheme 2b) [33]. Good regio- and stereoselectivities were obtained, and the optically active (*Z*)-α-chloroalkylidene-β-lactones could be obtained in high ee values using optically active propargylic alcohols.



Scheme 1 Oxidative carbonylation of unsaturated substrates incorporated with a nucleophile to carbonylated heterocycles

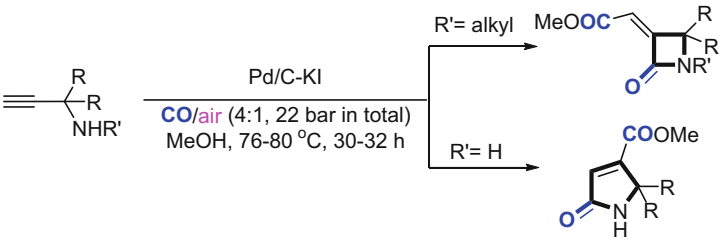


Scheme 2 Synthesis of four-membered lactones via oxidative carbonylation of alkynols

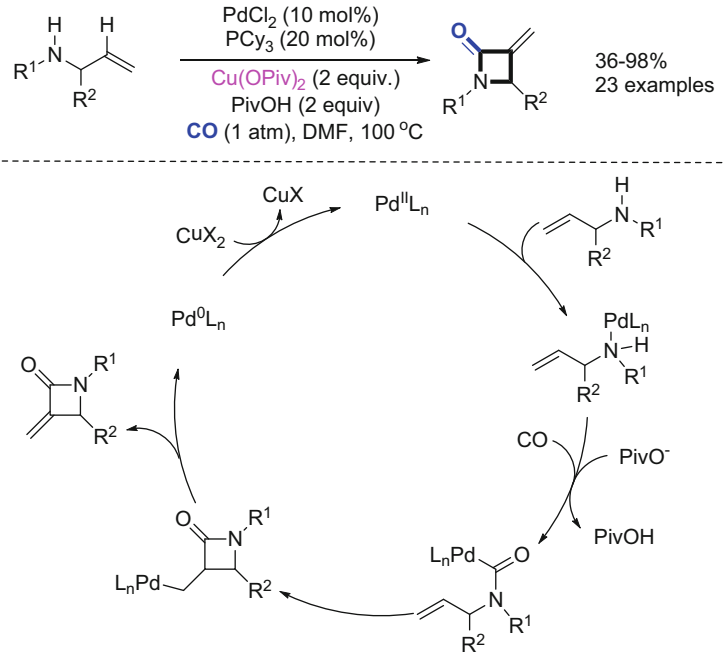
Later, the same group further studied this reaction: the scope of the reaction, mechanism, and the subsequent coupling reactions [34].

Similarly, oxidative cyclocarbonylation of alkynylamines provides lactams as the products. In 1995, Bonardi and co-workers reported a palladium-catalyzed oxidative carbonylation of 1-substituted prop-2-ynylamines [35]. This oxidative carbonylation method gave different products with different *N*-substituents. Using *N*-alkyl-substituted prop-2-ynylamines resulted in the formation of β-lactams, while γ-lactams were obtained with *N*-unsubstituted prop-2-ynylamines (Scheme 3).

Recently, the group of Lei developed an efficient method for the synthesis of α-methylene-β-lactams via palladium-catalyzed oxidative carbonylation of *N*-allylamines with $Cu(OPiv)_2$. A four-membered-ring transition state is supported by DFT calculations (Scheme 4) [36].



Scheme 3 Synthesis of lactams via oxidative carbonylation of prop-2-ynylamines

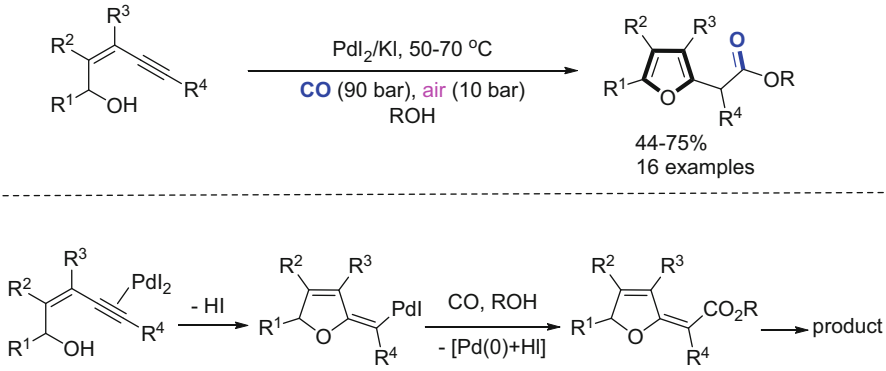


Scheme 4 Synthesis of four-membered lactams via oxidative carbonylation of *N*-allylamines

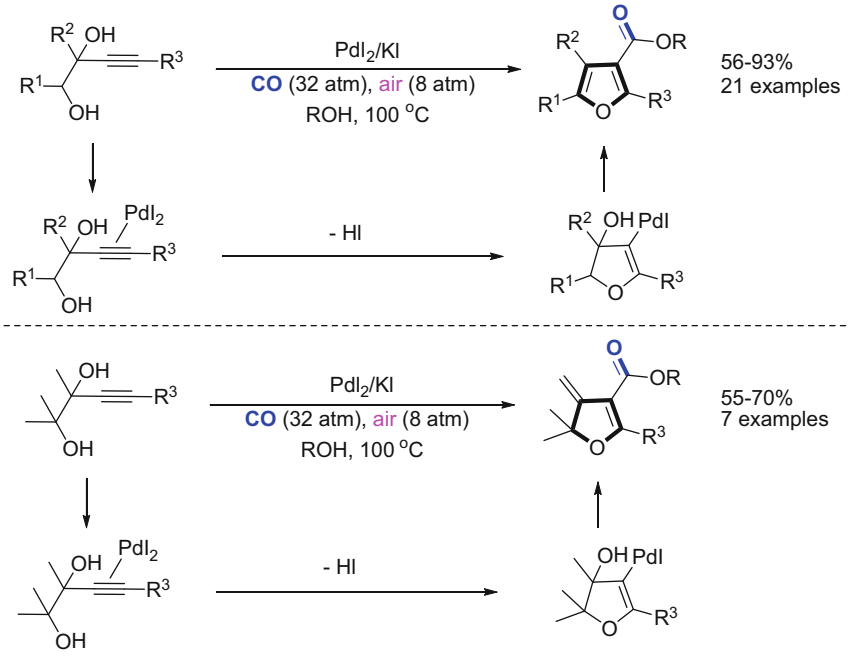
1.2 Synthesis of Five-Membered Heterocycles via Oxidative Carbonylation of Alkyne or Alkene Derivatives Incorporated with a Nucleophile

1.2.1 Synthesis of Five-Membered Oxygen-Containing Heterocycles via Oxidative Carbonylation of Alkyne or Alkene Derivatives Incorporated with a Nucleophile

Gabriele and co-workers reported the novel synthesis of furanacetic derivatives via oxidative carbonylation of acyclic (*Z*)-2-en-4-yn-1-ols [37, 38]. The cyclization–alkoxycarbonylation process occurs in an alcoholic media at 50–70°C and under



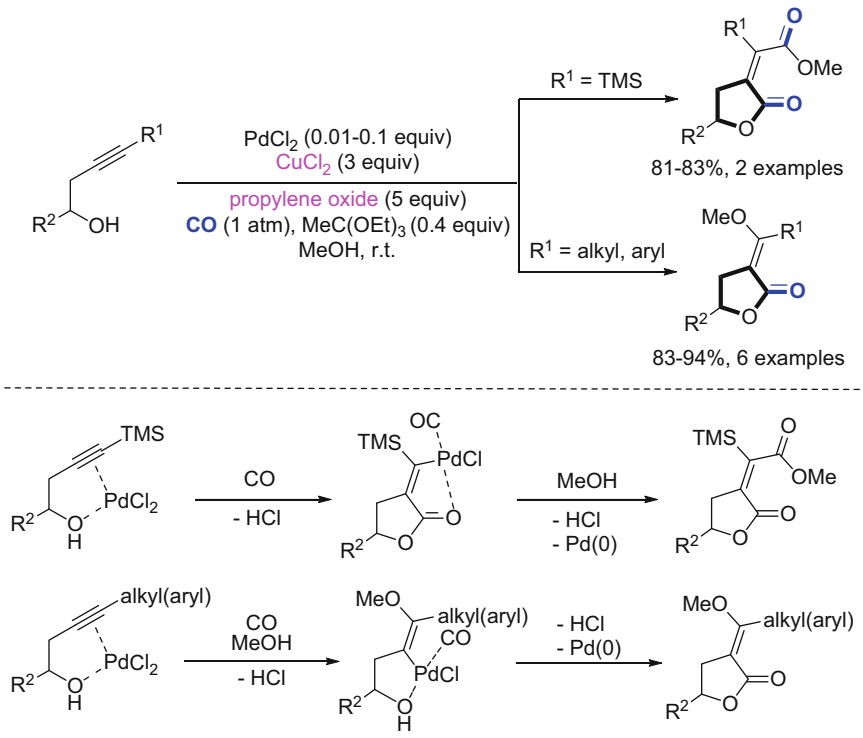
Scheme 5 Synthesis of furanacetic derivatives via oxidative carbonylation



Scheme 6 Synthesis of furanacetic derivatives via oxidative carbonylation

100 atm pressure of a 9:1 mixture of carbon monoxide and air with the catalysis of PdI_2/KI. With isolation of the nonaromatic precursors of the final product, a reaction mechanism was proposed accordingly (Scheme 5).

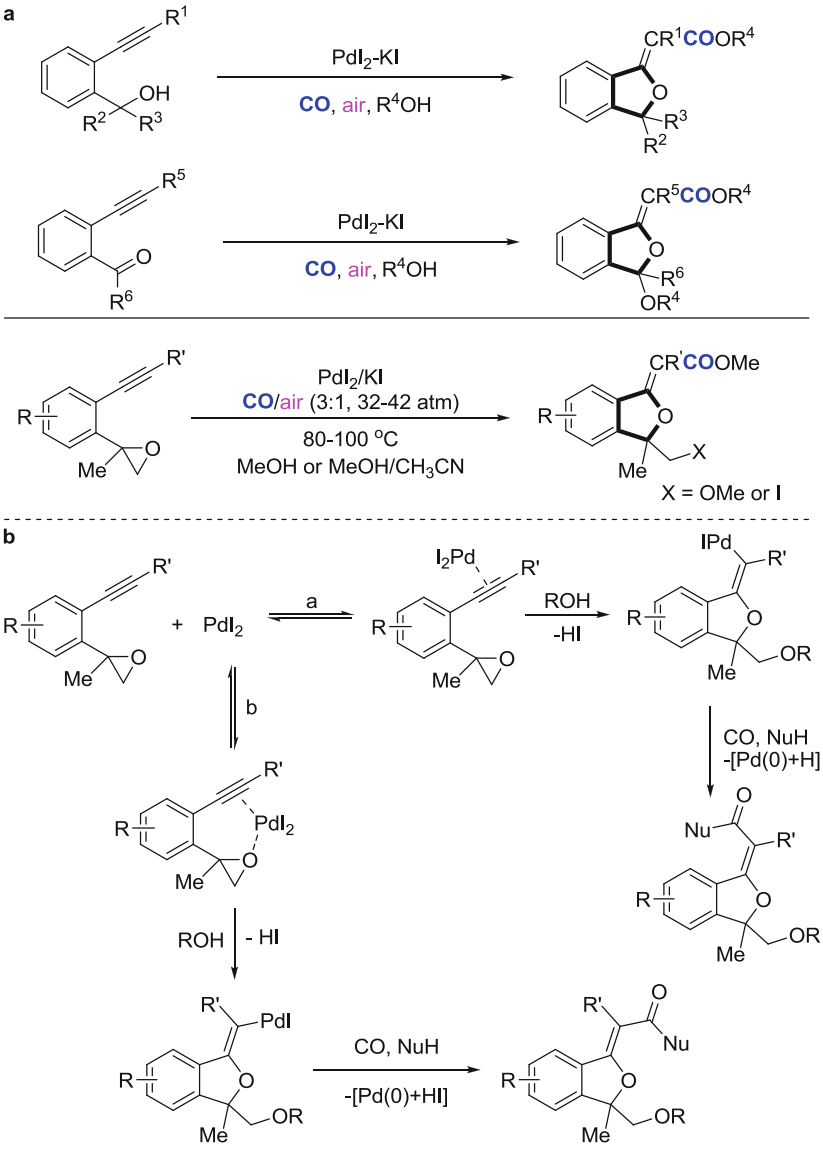
Similarly, as reported later by the same group, 3-yne-1,2-diols could be transformed into furan-3-carboxylic esters through a sequential 5-endo-dig heterocyclization–alkoxycarbonylation–dehydration process using air as the external oxidant. Under similar conditions, 4-methylene-4,5-dihydrofuran-3-carboxylates were obtained from 2-methyl-3-yne-1,2-diols (Scheme 6) [39, 40].



Scheme 7 Synthesis of oxygen-containing heterocycles via methoxycarbonylation of alkynoles

In 1991, Tamaru reported the palladium-catalyzed carbonylation of 3-butyne-1-ols. In this process, different substituents on acetylenic termini led to different courses of reaction. When the substituent is trimethylsilyl group, *cis* dicarbonylation proceeds selectively, while, with alkyl or aryl substituents, *trans* alkoxycarbonylation takes place selectively (Scheme 7). Recently, the group of Kato further developed methoxycarbonylation of terminal alkynes with bisoxazolines as the box ligands. In addition, they succeeded in applying this methodology to the synthesis of β-methoxyacrylate natural products [41, 42].

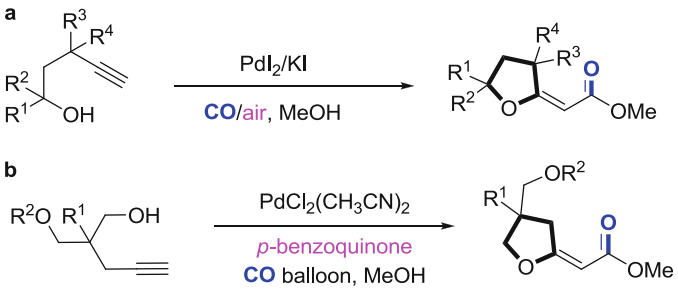
Palladium-catalyzed oxidative carbonylation of 2-alkynylbenzyl alcohols, 2-alkynylbenzaldehydes, and 2-alkynylphenyl ketones to 1-(alkoxycarbonyl)methylene-1,3-dihydroisobenzofurans and 4-(alkoxycarbonyl)benzo[*c*]pyrans was described by Costa and Gabriele et al. in 2004 (Scheme 8a) [43]. The reaction occurs through intramolecular attack by the nucleophilic oxygen atom (either already present in the starting material or generated in situ by ROH attack on the carbonyl group) on the triple bond coordinated to Pd(II) and subsequent alkoxycarbonylation. The presence of substituents in the position α to the alcoholic or ketonic hydroxy group leads to the selective formation of five-membered ethereal rings. In contrast, six-membered rings are preferentially formed in the absence of at least one of these substituents. Alternatively, different substituted alkynyloxiranes could also be converted into



Scheme 8 Synthesis of isobenzofurans via palladium-catalyzed oxidative carbonylation of 2-alkynylbenzyl alcohols, 2-alkynylphenyl ketones, and alkynyloxiranes

functionalized 1,3-dihydroisobenzofurans and tetrahydrofuran derivatives in fair to good yields by a cascade reaction, consisting of a sequential nucleophilic ring opening–heterocyclization–oxidative carbonylation process (Scheme 8b) [44].

As reported by Gabriele and co-workers, palladium-catalyzed oxidative cyclization–alkoxycarbonylation of 4-yn-1-ols under 100 atm of 9:1 mixture of



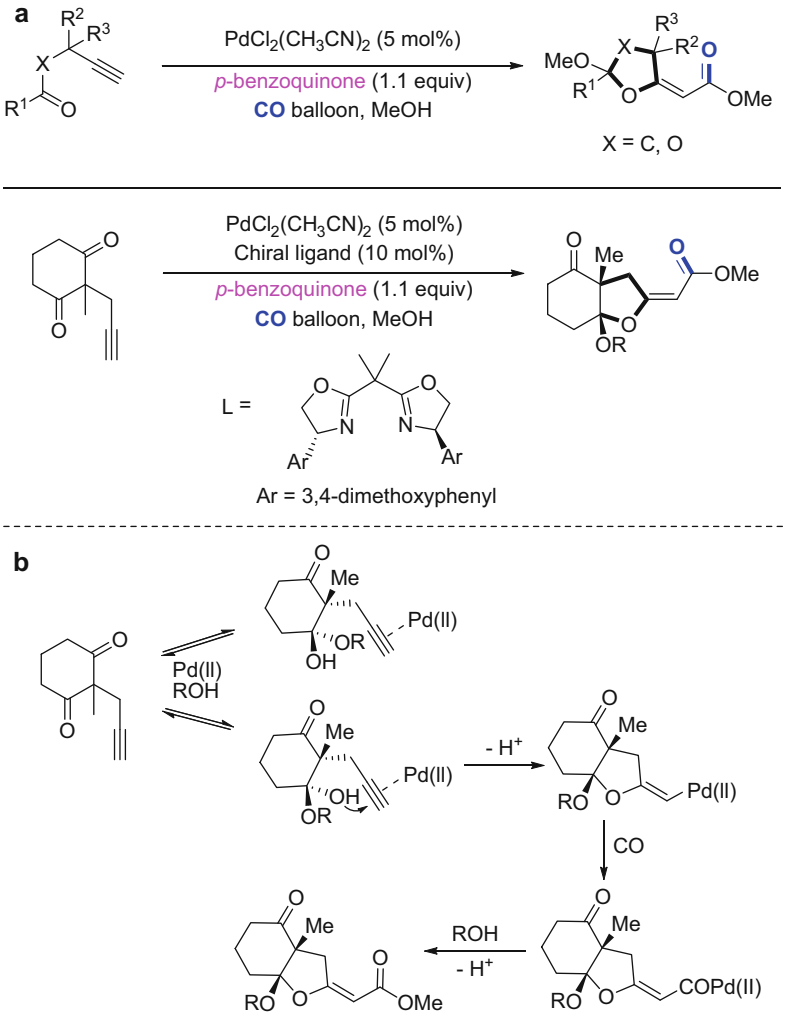
Scheme 9 Synthesis of tetrahydrofurans via oxidative carbonylation of 4-yn-1-ols

carbon monoxide and air could provide 2*E*-[(methoxycarbonyl)methylene]tetrahydrofurans in good yields (Scheme 9a). Meanwhile, the cycloisomerization–hydromethoxylation as a competing reaction could be easily prevented by increasing the KI excess [45]. Later, by using *p*-benzoquinone, Akita, Kato, and co-workers improved this method to be applicable to broader substrates with avoidance of KI and high pressure (Scheme 9b) [46]. Following this, they succeeded in performing the reaction in an asymmetric manner by applying chiral bisoxazolines as ligands [47, 48].

Besides alkynyl alcohols, alkynyl ketones could also underwent oxidative cyclocarbonylation to give carbonated heterocycles. Akita and Kato et al. developed palladium-catalyzed oxidative cyclization–carbonylation of 4-yn-1-ones affording cyclic ketals in moderate to good yields (Scheme 10a). The cyclic ketals can be easily converted into 2-cyclopentenones, which are useful intermediates of natural products [49]. Later, the same group extended this method to the cyclocarbonylation of propargylic acetates [50], propargylic esters [51], and 2-propargyl-1,3-dione [52, 53]. Furthermore, using chiral bisoxazoline ligands, they realized the asymmetric cyclization–carbonylation of 2-alkyl-2-propargylcyclohexane-1,3-diones successfully. Bicyclic-β-alkoxyacrylates were obtained in 51–74 % yields with 72–82 % enantiomeric excesses (Scheme 10b). This methodology was applied by Mukai and co-workers in the total synthesis of naturally occurring diacetylenic spiroacetal enol ethers [54]. A related mechanistic study including experiments and DFT studies was also done by Carfagna and co-workers [55].

In 2009, palladium-catalyzed carbonylation of 1,2-allenyl ketones was developed by the same group under a CO atmosphere with *p*-benzoquinone as the oxidant. Difuranylketones were obtained in moderate to good yields (Scheme 11) [56].

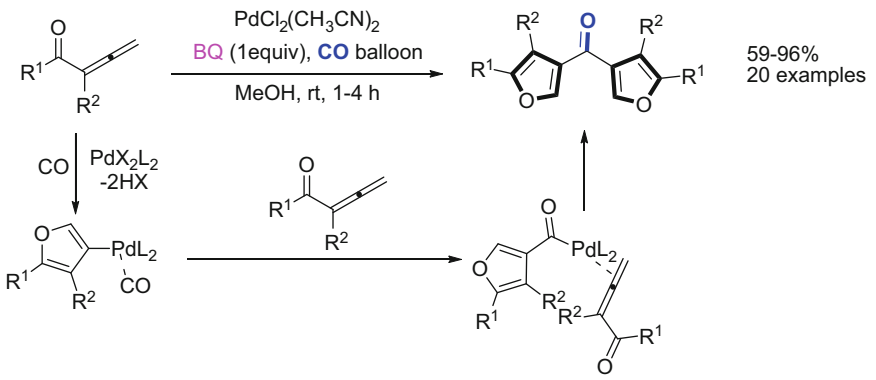
The group of Ma applied the $PdCl_2$-catalyzed chlorocyclocarbonylation of 2,3-allenols to the synthesis of 3-chloromethyl-2(5H)-furanones in mild conditions (Scheme 12). Optically active 3-chloromethyl-2(5H)-furanones could be obtained from readily available optically active 2,3-allenols. In addition, six-membered



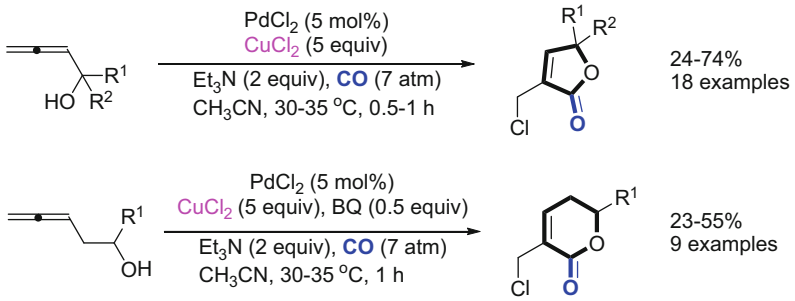
Scheme 10 Synthesis of five-membered oxygen-containing heterocycles via oxidative carbonylation of alkynones or propargylic acetates

3-chloromethyl-5,6-dihydropyran-2-ones could be prepared from 3,4-allenols in similar conditions [57].

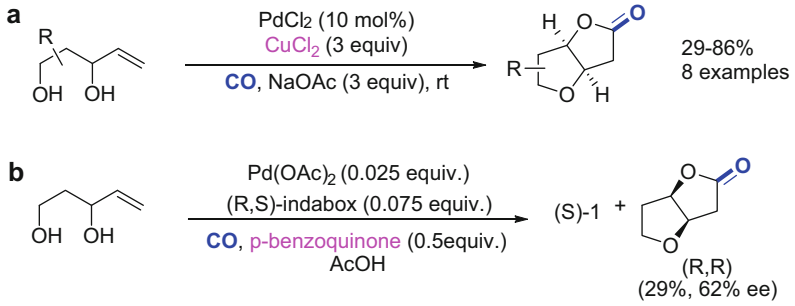
Yoshida and co-workers selectively prepared *cis* 3-hydroxytetrahydrofuran acetic acid lactones by an intramolecular palladium-catalyzed oxycarbonylation of 4-penten-1,3-diols under 1 atm of CO with $CuCl_2$ as the oxidant (Scheme 13a) [58]. The group of Gracza developed the asymmetric intramolecular oxycarbonylation of pent-4-ene-1,3-diols using chiral palladium(II) complexes. In the presence of $Pd(OAc)_2$-{(R,S)-indabox}, *p*-benzoquinone in acetic acid under an atmosphere of CO, the desired products were obtained in an enantiomerical manner



Scheme 11 Synthesis of difuranylketones via palladium-catalyzed carbonylative dimerization of allenyl ketones



Scheme 12 Synthesis of oxygen-containing heterocycles via oxidative carbonylation of allenols

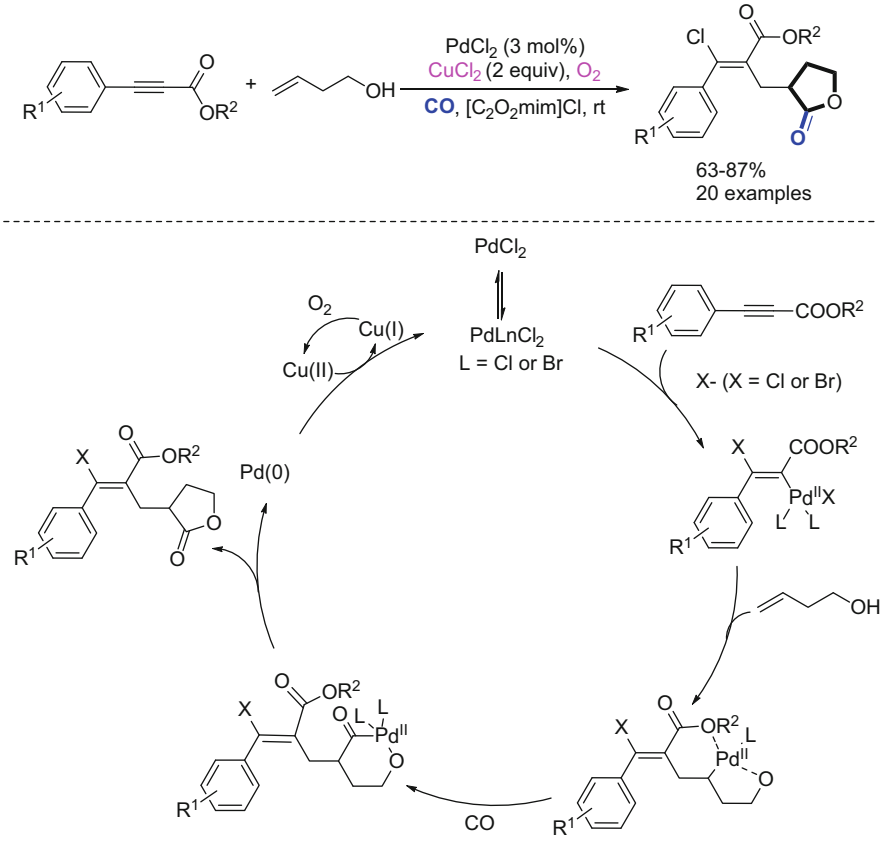


Scheme 13 Synthesis of cyclic lactones via oxycarbonylation of unsaturated diols

in low yields (Scheme 13b) [59]. Later, they extended the substrates to 4-benzyloxyhepta-1,6-diene-3,5-diols providing bicyclic lactones in good yields and with excellent threo-diastereoselectivity. However, the level of asymmetric induction is rather poor [60]. These methodologies were applied to the synthesis of

natural products such as kumausyne, crisamicin A, deoxynojirimycin, and so on [61–65].

When intramolecular cyclocarbonylation was properly combined with an intermolecular cascade reaction, higher-value products could be obtained. For example, Jiang and Yang et al. reported a novel palladium-catalyzed cascade annulation in liquids to construct functionalized γ-lactones from alkynotes and homoallyl alcohol. This process included the carbonylation of the C(sp^3)–palladium bond. Ethyl, allyl, and phenyl alkynoates and substituted phenylpropiolic acid were allowed to react under the optimal conditions with good to excellent yields. In addition, both electron-withdrawing and electron-donating substituents on the aromatic ring were well tolerated. A possible reaction mechanism was proposed based on the experiment results and previous literature (Scheme 14) [66].



Scheme 14 Synthesis of γ-lactones via palladium-catalyzed cascade carbonylative annulation

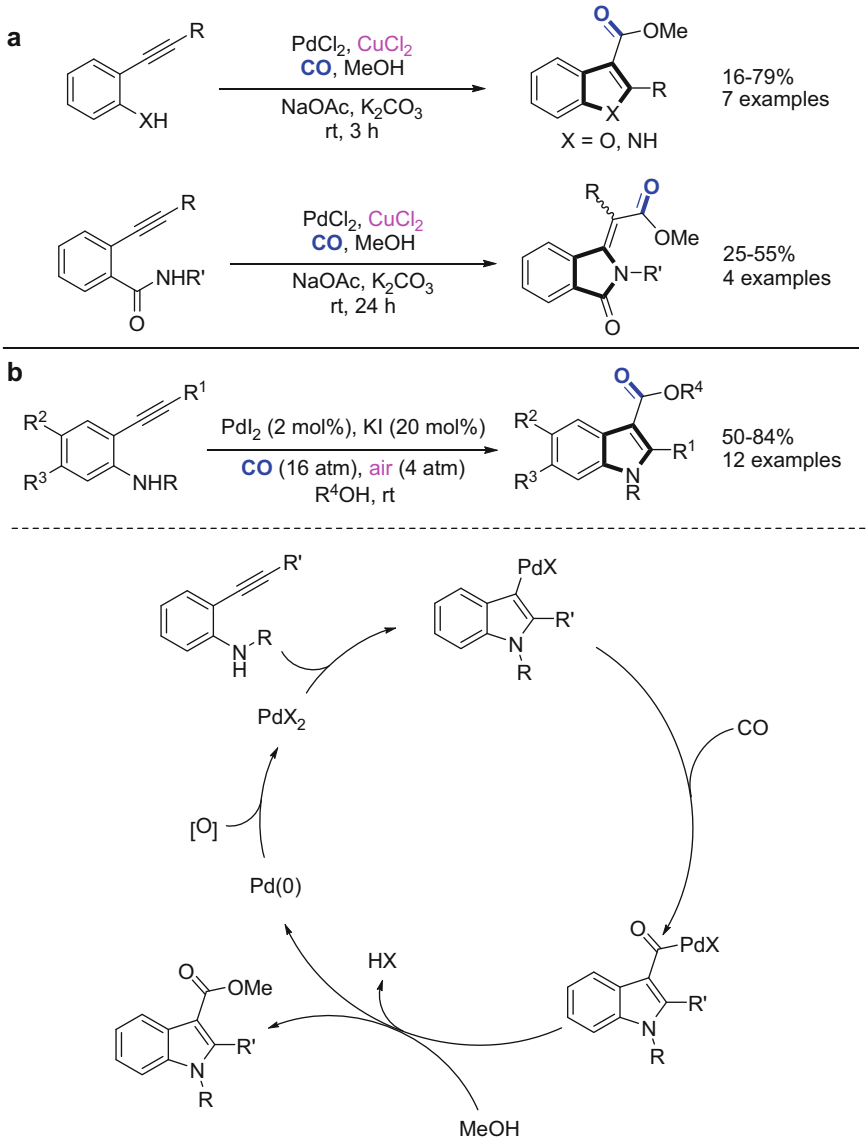
1.2.2 Synthesis of Five-Membered Nitrogen-Containing Heterocycles via Oxidative Carbonylation of Alkyne and Alkene Derivatives Incorporated with a Nucleophile

Comparing with other types of heterocycles, nitrogen-containing heterocycles represent privileged structures and show a variety of biological activities. Oxidative carbonylation of alkynylaniline derivatives represents an efficient approach to this kind of heterocycles. In 1994, Sakamoto and co-workers reported the sequential cyclization/carbonylation of 2-alkynylanilines and alkynylphenol in the presence of catalytic amount of palladium dichloride and copper dichloride. The corresponding indole-3-carboxylates and benzofuran-3-carboxylates were obtained in moderate yields. The reaction of 2-alkynylbenzamides gave 3-alkylidenisoindole derivatives (Scheme 15a) [67]. In 2012, Gabriele and co-workers applied the PdI_2/KI system to the oxidative carbonylation of 2-alkynylaniline derivatives with oxygen as the only oxidizing agent. A variety of 2-alkynylanilines bearing an internal triple bond and a second aryl amino group could be conveniently converted into *N*-substituted indole-3-carboxylic esters in fair to high yields. With the assistance of $HC(OR)_3$, the *N*-unsubstituted indole-3-carboxylic esters were obtained by the oxidative carbonylation of primary 2-alkynylanilines and subsequent acidic treatment (Scheme 15b) [68]. The reaction pathway started with the generation of the indolylpalladium complex from the reaction of ethynylanilines and palladium dichloride. Subsequently, the insertion of carbon monoxide into carbon–palladium bond gave the indolylacylpalladium species, which reacted with methanol to give the final products.

Recently, Mancuso and Gabriele et al. found that PdI_2-catalyzed oxidative carbonylation of 2-alkynylbenzamides underwent different reaction pathways depending on the nature of the external nucleophile and reaction conditions (Scheme 16). In the presence of a secondary amine as external nucleophile, 2-ethynylbenzamides are selectively converted into 3-[(dialkylcarbamoyl)methylene]isoindolin-1-ones through the intermediate formation of the corresponding 2-ynamide derivatives followed by intramolecular nucleophilic attack by the nitrogen of the benzamide moiety on the conjugated triple bond. On the other hand, in the presence of an alcohol R′OH as the external nucleophile and $HC(OR')_3$ as a dehydrating agent, 2-alkylnylbenzamides bearing a terminal or an internal triple bond underwent oxidative carbonylation to give 3-[(alkoxycarbonyl)methylene]-isobenzofuran-1(3H)imines selectively. This process started with the 5-exo-dig intramolecular nucleophilic attack of the oxygen of the benzamide moiety on the triple bond coordinated to the metal center followed by alkoxycarbonylation [69].

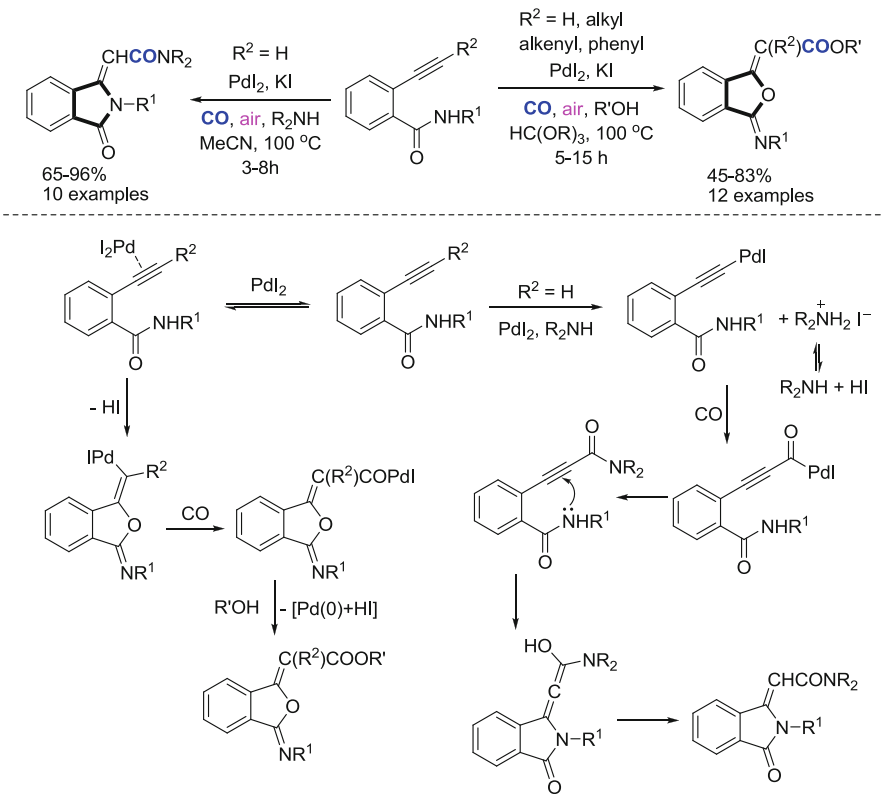
As reported by Gabriele and co-workers, 2-alkynylaniline imines could be converted into carbonylated indoles based on a multicomponent cascade reaction, involving ROH nucleophilic attack to the imine moiety, followed by a palladium-catalyzed heterocyclization/alkoxycarbonylation process. A number of indoles were obtained in good yields (Scheme 17) [70].

They also developed the direct synthesis of pyrrole-2-acetic esters by palladium-catalyzed oxidative carbonylation of (*Z*)-(2-en-4-ynyl)amines. They found that carbon dioxide effectively promotes this reaction by reversibly binding to the amino



Scheme 15 Palladium-catalyzed oxidative carbonylation for the synthesis of indoles and benzofurans

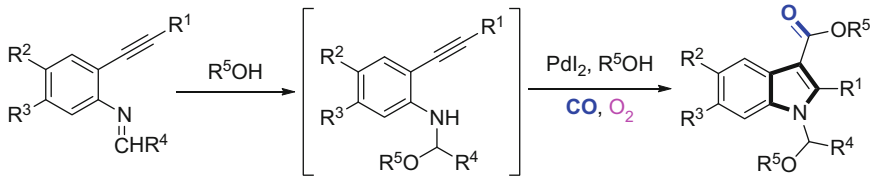
group, thus "freeing" the HI necessary for the reoxidation of Pd(0) (Scheme 18a) [71]. In 2012, PdI_2-catalyzed oxidative heterocyclization/alkoxycarbonylation of *N*-Boc-1-amino-3-yn-2-ols to functionalized pyrroles was developed by Gabriele. Reactions were carried out in alcoholic solvents at 80–100°C and under 20 atm (at 25°C) of a 4:1 mixture of CO–air, in the presence of Pd_2–KI catalytic system. By a basic



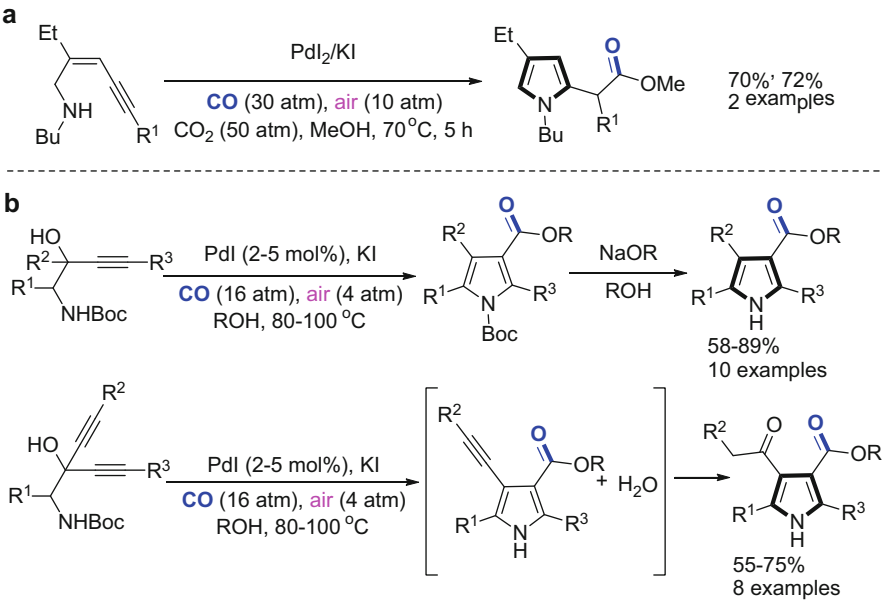
Scheme 16 Control synthesis of isoindolin-1-ones and isobenzofuran-1(3H)imines via oxidative carbonylation of 2-alkynylbenzamides

treatment, deprotected pyrrole-3-carboxylic esters were obtained in moderate to good yields. When the reaction was carried out on *N*-Boc-2-alkynyl-1-amino-3-yn-2-ols, bearing an additional alkynyl substituent α to the hydroxyl group, *N*-deprotection occurred spontaneously under the reaction conditions, together with regioselective water addition to the triple bond of the alkynyl substituent, providing polysubstituted and multifunctionalized pyrrole derivatives (Scheme 18b) [72].

In 2007, Tang and co-workers developed a palladium-catalyzed carbonylative annulation of 2-(1-alkynyl)benzenamines for the preparation of 3-(halo(substituted) methylene)-indolin-2-ones (Scheme 19). In the presence of PdX_2 and CuX_2, a variety of 2-(1-alkynyl)anilines underwent the carbonylative annulation reaction with CO smoothly to afford the target product in moderate to good yields. The reaction is proposed to start with the coordination of $PdCl_2$ with the triple bond and nitrogen, followed by *cis*- and *trans*-halopalladation to generate the corresponding vinylpalladium species. Afterward, the coordination and insertion of CO with the vinylpalladium species and subsequent reductive elimination provided the desired



Scheme 17 Synthesis of indoles via the multicomponent cascade reaction terminated by carbonylation

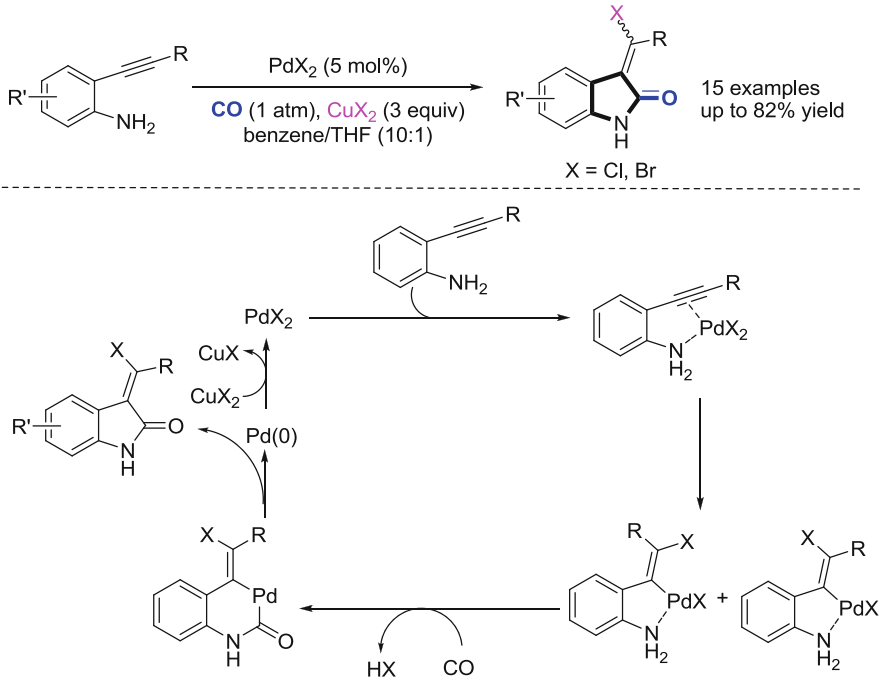


Scheme 18 Synthesis of carbonylated pyrroles via oxidative carbonylation

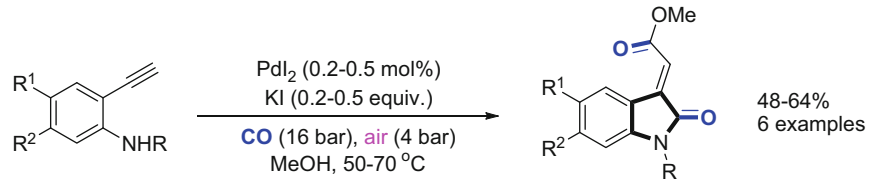
products and a Pd(0) species. Finally, the active Pd(II) species could be regenerated by the oxidative reaction of Pd(0) with CuX_2 [73].

Using methanol as the solvent, the 2-ethynylanilines underwent oxidative carbonylation to give (*E*)-3-(methoxycarbonyl)methylene-1,3-dihydroindol-2-ones in the presence of catalytic amount of PdI_2 in conjunction with KI. This reaction was completely stereoselective with no formation of (*Z*)-3-(methoxycarbonyl)methylene-1,3-dihydroindol-2-ones being observed (Scheme 20) [74].

In 2005, Costa and co-workers reported a cascade carboxylation–alkoxycarbonylation of *N*-alkyl-substituted dialkylpropynylamines in the presence of carbon dioxide and carbon monoxide. In this process, carbon dioxide and carbon monoxide were caused to react in sequence, providing oxazolidinone derivatives as the final products. In the absence of alkyl groups α to the triple bonds, the introduction of



Scheme 19 Synthesis of indolin-2-ones via oxidative carbonylation of 2-(1-alkynyl) benzenamines

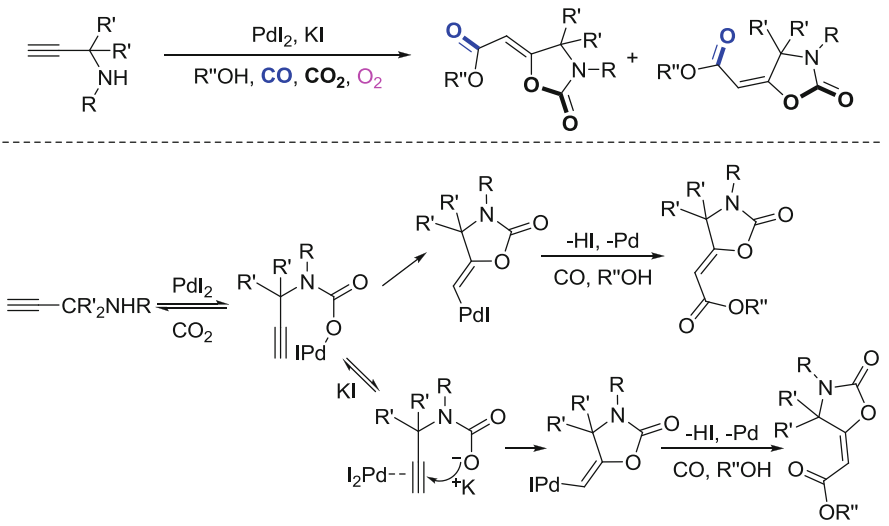


Scheme 20 Synthesis of indol-2-one derivatives via oxidative carbonylation of 2-ethynylanilines

carbon dioxide only and not that of carbon monoxide was observed under the similar conditions (Scheme 21) [75].

Notably, in the presence of water, α,α-disubstituted 2-ynylamines underwent sequential oxidative aminocarbonylation–cyclocarbonylation with the catalysis of PdI_2/KI, providing 2-oxazolidinone derivatives in good to excellent yields. In the case of α-monosubstituted propargylamine, the initially formed oxazolidinone derivatives underwent shift of the double bond into the cycle with formation of a 3H-oxazol-2-one derivative in good yields (Scheme 22) [76].

The group of Costa applied PdI_2-/KI-catalyzed oxidative carbonylation to prop-2-ynylamides under a mixture of CO and air for the synthesis of 5-(alkoxycarbonyl) methylene-3-oxazolines (Scheme 23) [77]. Under similar reaction conditions,

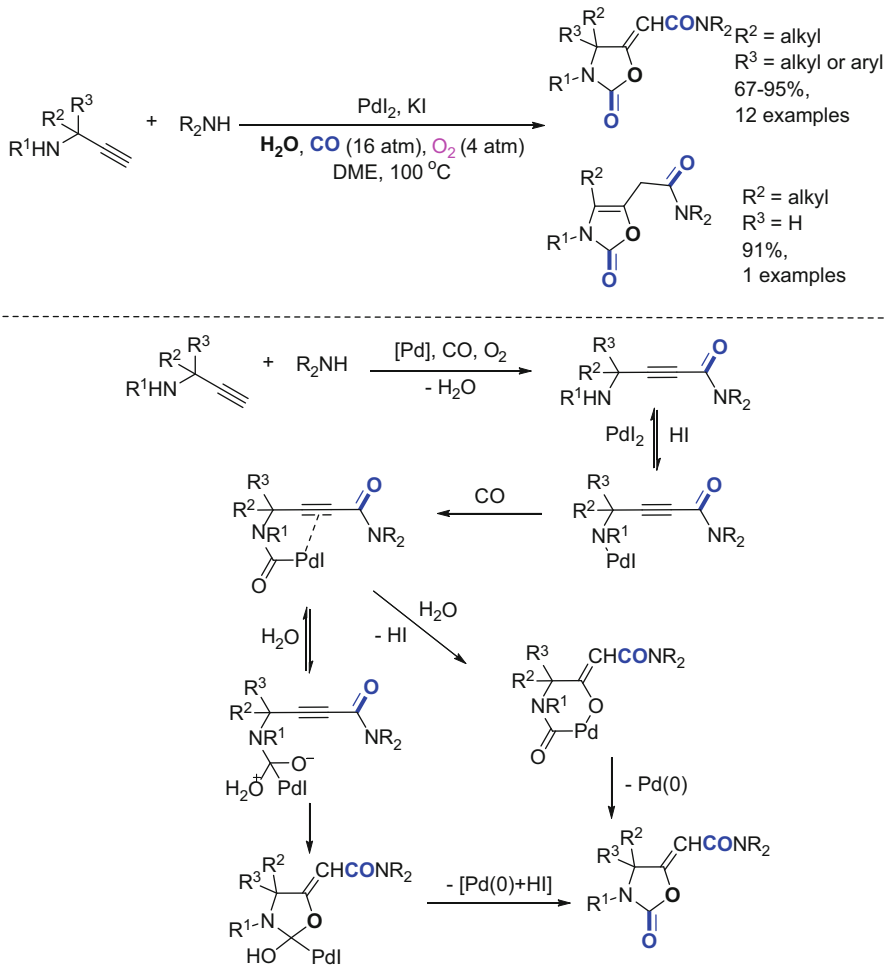


Scheme 21 Oxidative carbonylation of propargyl amines with carbon dioxide and carbon monoxide

4-yn-1-ones containing different substituents, prop-2-ynyl α-ketoesters, and prop-2-ynyl α-ketoamides underwent heterocyclization–alkoxycarbonylation to give tetrahydrofuran, dioxolane, and oxazoline, dihydropyridinone, and tetrahydropyridinedione derivatives in satisfactory yields [78].

By applying proper ligands and reaction conditions, these intramolecular cyclization/carbonylation reactions could be expanded to a cyclization/carbonylation/cyclization process, which would be a synthetically valuable method for direct preparation of ketones bearing two heterocycles. In 2011, Kato and co-workers developed a cyclization–carbonylation–cyclization (CCC-coupling reaction) coupling reaction of propargyl acetates and amides for the synthesis of ketones with two heterocyclic groups (Scheme 24a). The box ligands played an important role for this reaction by enhancing the electrophilicity of palladium(II) and thus promote coordination of the second triple bond in the second part of the tandem reaction [79]. In 2014, the same group applied this methodology to the CCC-coupling reaction of 2-alkynylanilines providing bis(1-benzyl-1H-indol-3-yl)methanones in good yields (Scheme 24b) [80].

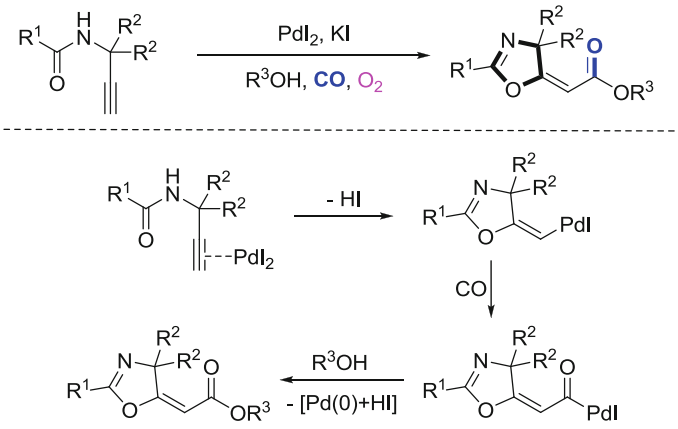
Intramolecular oxidative aminocarbonylation of alkenyl amine derivatives is also an efficient method for constructing complex heterocyclic products. In the presence of palladium and copper salts, *N*-tosylhomoallylamines furnished 3-methyl-2-pyrrolidones at 1 atm of CO and at room temperature (Scheme 25a) [81]. In 2003, Sasai and co-workers realized this reaction in an enantioselective manner using chiral spiro bis(isoxazoline) ligands (Scheme 25b) [82]. In 2009, the group of Lambert successfully prepared α-pyrrolidinyl ketones from *N*-tosylpentenamine and electron-rich aromatic nucleophiles via a tandem aminochlorocarbonylation/Friedel–Crafts acylation reaction (Scheme 25c). In the presence of Pd



Scheme 22 Synthesis of 2-oxazolidinones via water-promoted oxidative carbonylation of 2-ynylamines

(II) and indium(III) triflate, α-pyrrolidinyl ketones were obtained in moderate to good yields with $CuCl_2$ as oxidant and chlorine source [83]. This methodology was applied to the total synthesis of (±)-ferruginine, (±)-anatoxin-a, and 1,4-iminoglycitols [84–86].

In 2002, Bates and Sa-Ei reported the palladium(II)-catalyzed cyclocarbonylation of *O*-homoallylhydroxylamines in the presence of a base, methanol, and carbon monoxide with copper(II) as oxidant, providing isoxazolidines as the product (Scheme 26). An electron-withdrawing group on the hydroxylamine nitrogen was essential, and the products were obtained exclusively as *cis* isomers when carbamate groups were used [87].

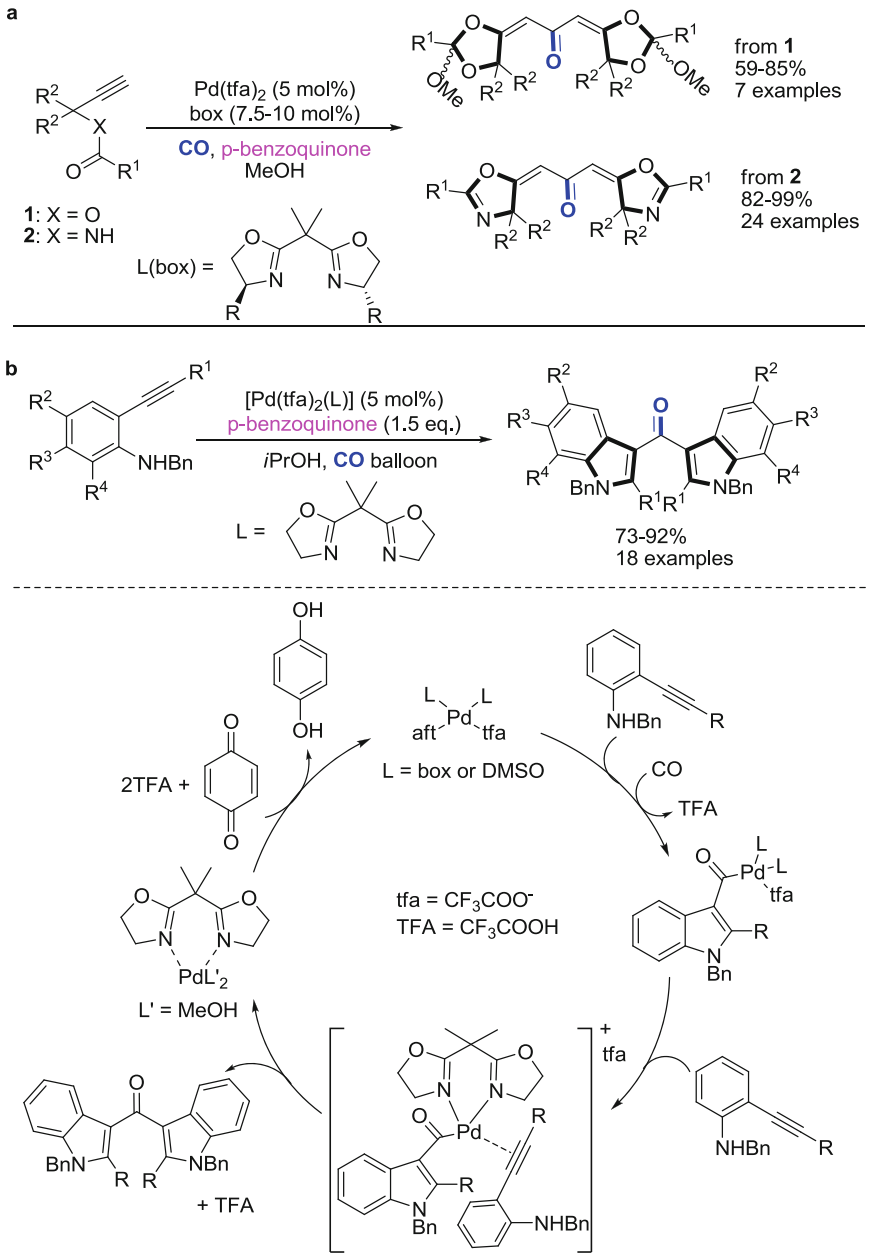


Scheme 23 Synthesis of oxazolines via oxidative carbonylation of prop-2-ynylamides

1.3 Synthesis of Six-Membered Heterocycles via Oxidative Carbonylation of Alkyne or Alkene Derivatives Incorporated with a Nucleophile

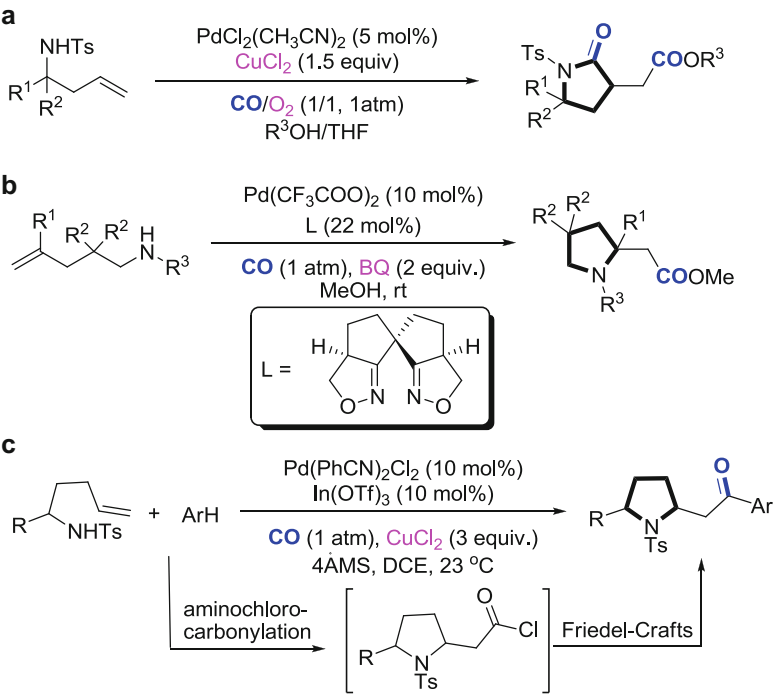
With proper substrates and reaction regioselectivity, six-membered heterocycles could be generated selectively. The groups of Gabriele and Costa made impressive studies in this respect. With the catalysis of palladium, 2-prop-2-ynyloxyphenols underwent a tandem oxidative aminocarbonylation–cyclization to provide 2,3-dihydrobenzo[1,4]dioxine derivatives (Scheme 27). Reactions were carried out in the presence of catalytic amounts of PdI_2 in conjunction with an excess of KI in DMA under 20 atm of a 4:1 mixture of CO/air. Under similar conditions, the reaction of 2-prop-2-ynyloxyanilines provides 3,4-dihydro-2H-benzo[1,4]oxazine as the product. For this reaction, the Z isomers were formed preferentially [88].

A palladium-catalyzed cyclization–alkoxycarbonylation of 2-ethynylaniline derivatives to 4-*H*-3,1-benzoxazines, quinazoline-2-ones, and quinoline-4-ones was developed in 2004 [89]. In 2008, the group of Gabriele synthesized quinoline-3-carboxylic esters from 1-(2-aminoaryl)-2-yn-1-ols through palladium-catalyzed 6-endo-dig cyclization followed by dehydration and oxidative methoxycarbonylation under 80 atm of CO/O_2 (4:1) mixture. In addition, indole-2-acetic esters could also be obtained via 5-exo-dig cyclization and subsequent dehydrating methoxycarbonylation [90]. In 2011, they prepared isoquinoline-4-carboxylic esters and isochromene-4-carboxylic esters by palladium-catalyzed oxidative carbonylation of (2-alkynylbenzylidene)amine derivatives. Isoquinoline derivatives were obtained from (2-alkynylbenzylidene)(*tert*-butyl)amines through *N*-cyclization in the presence of dehydration agent, while isochromenes were obtained from *N*-(2-alkynylbenzylidene)-*N*′-phenylhydrazines through *O*-cyclization ensuing from water attack on the imino group (Scheme 28) [91].

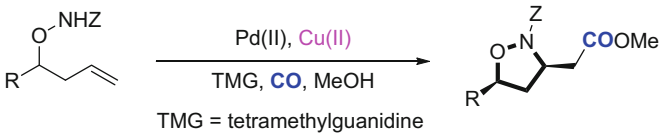


Scheme 24 Synthesis of ketones bearing two heterocycles through CCC-coupling reaction

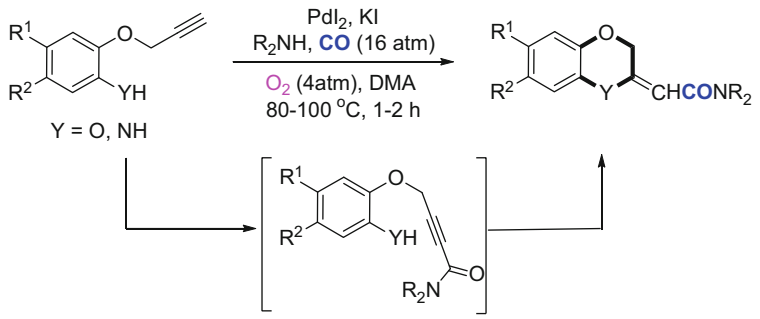
In 2008, Szolcsányi and co-workers applied Pd(II)-catalyzed aminocyclization/cyclocarbonylation of 2-(undec-1-en-6-ylamino)ethanol to the racemic synthesis of bicyclic piperidine alkaloids calvine and epicalvine (Scheme 29) [92].



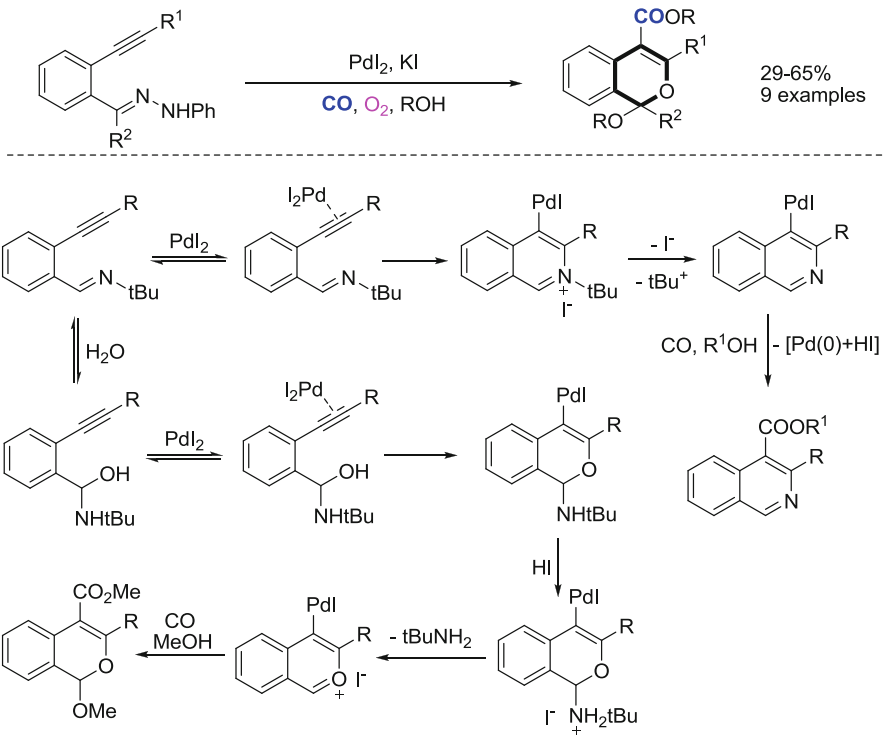
Scheme 25 Synthesis of pyrrolidine derivatives via oxidative carbonylation of alkenyl amine derivatives



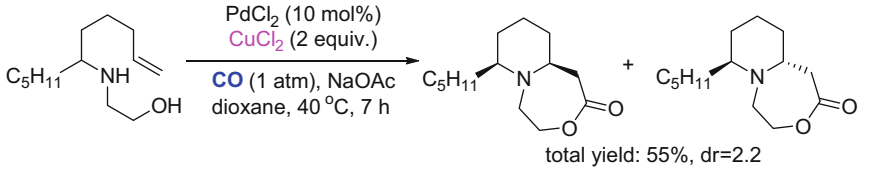
Scheme 26 Synthesis of isoxazolidines via carbonylation of *O*-homoallylhydroxylamines



Scheme 27 Synthesis of dioxine and oxazine derivatives via oxidative carbonylation

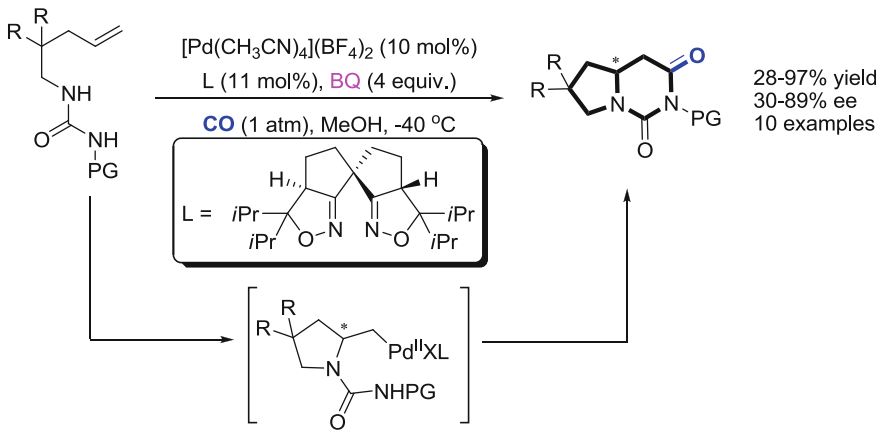


Scheme 28 Synthesis of isoquinolines and isochromenes via oxidative carbonylation of (2-alkynyl)benzylideneamine derivatives



Scheme 29 Racemic synthesis of calvine and epicalvine via carbonylation of 2-(undec-1-en-6-ylamino)ethanol

Sasai and co-workers realized an enantioselective synthesis of tetrahydropyrrolo [1,2-c]pyrimidine-1,3-diones via palladium-catalyzed intramolecular oxidative aminocarbonylation (Scheme 30). The use of a chiral spiro bis(isoxazoline) ligand (SPRIX) is essential to realize this reaction in an optically active form. Compared with other ligands, the low σ-donor ability of the isoxazoline coordination site and rigidity of the spiro skeleton make SPRIX the most suitable ligand for this reaction [93].



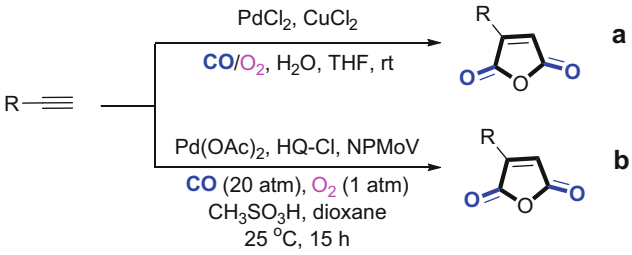
Scheme 30 Synthesis of cyclic β-amino acid derivatives via oxidative carbonylation of alkenyl ureas

2 Synthesis of Heterocycles via Oxidative Dicarbonylation of Alkynes

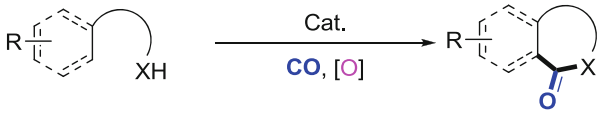
Under oxidative carbonylation conditions, maleic anhydrides can be formed from terminal alkynes via insertion of two CO molecules. In 1991, the group of Alper presented the $PdCl_2$-catalyzed dicarbonylation of terminal alkynes with formic acid and water, providing maleic anhydride derivatives as the major product (Scheme 31a) [94]. In 1999, Ishii and co-workers applied a triple catalytic system, Pd(II)/chlorohydroquinone/NPMoV, to the carbonylation of terminal alkynes (Scheme 31b). With dioxane as the solvent, maleic anhydrides were obtained as the major products [95]. What's more is that several methods have also been published from other groups with different oxidants [96–98].

3 Synthesis of Carbonylated Heterocycles via Oxidative Carbonylation with C–H Activation

Under proper oxidative conditions, carbonylation for synthesis of carbonylated heterocycles could be realized through C–H (sp^2 and sp^3) activation, in which case a heteroatom-containing group such as amine, amide, or hydroxyl group often acted both as directing group and nucleophile to participate in the reaction (Scheme 32). Generally, this method proceeded in an intramolecular way, and reports on the intermolecular multicomponent carbonylation with C–H activation are quite rare.



Scheme 31 Synthesis of maleic anhydrides via palladium-catalyzed oxidative carbonylation of alkynes

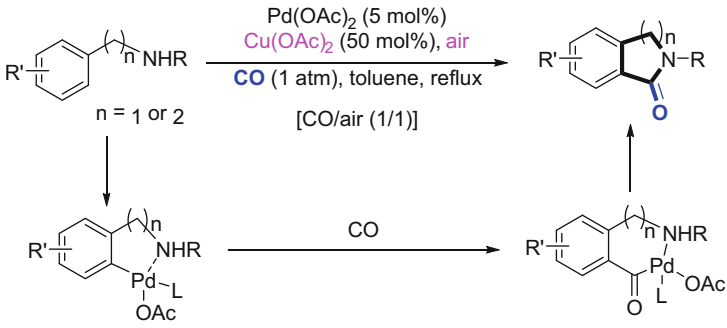


Scheme 32 Synthesis of carbonylated heterocycles via oxidative carbonylation with C–H activation

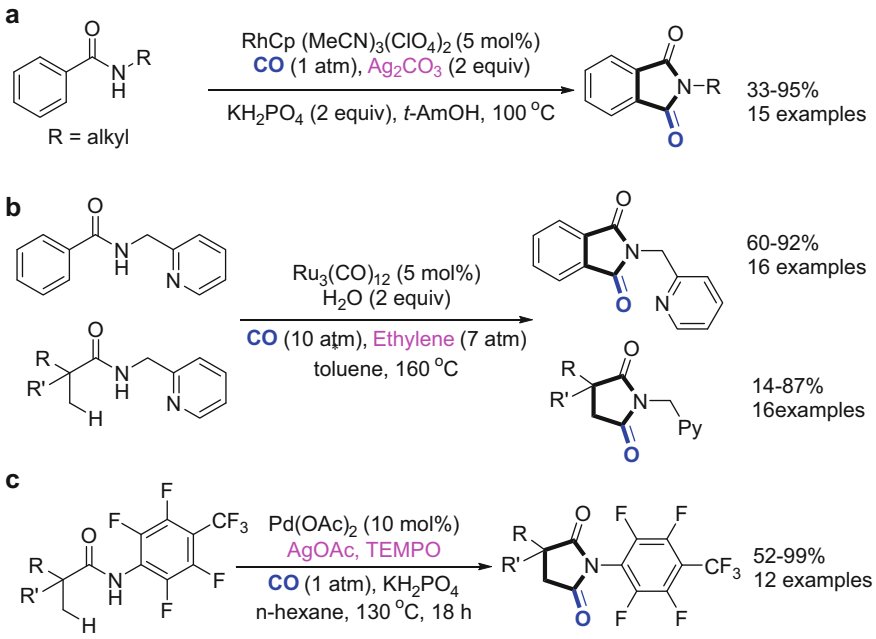
3.1 Synthesis of Five-Membered Heterocycles via Oxidative Carbonylation with C–H Activation

Orito and co-workers prepared a variety of five- or six-membered benzolactams by the direct aromatic carbonylation of secondary ω-phenylalkylamines using $Pd(OAc)_2$ and $Cu(OAc)_2$ in an atmosphere of CO gas containing air (Scheme 33) [99, 100]. In 2007, they applied this methodology to the synthesis of *N*-protected staurosporinones [101].

In 2011, Rovis and co-workers developed a rhodium(III)-catalyzed oxidative carbonylation of benzamides to form phthalimides with Ag_2CO_3 as the oxidant (Scheme 34a). C–H bonds of electron-rich aromatic amides showed better activity [102]. Chatani and co-workers found that utilizing a bidentate system, aromatic amides having a pyridin-2-ylmethylamine moiety could undergo cyclocarbonylation through C–H bond activation in the presence of catalytic amount of $Ru_3(CO)_{12}$ and CO (Scheme 34b). Phthalimides were obtained in moderate to good yields. In this process, ethylene acted as a H_2 acceptor [103, 104]. In 2011, they extended this methodology to the carbonylation of unactivated $C(sp^3)$–H bond of aliphatic amides with a regioselective preference for C–H bonds of methyl groups as opposed to methylene C–H bonds. In both cases, the presence of 2-pyridinylmethylamine moiety in the amide is crucial for the successful reaction. In 2010, Yu and co-workers reported palladium-catalyzed cyclocarbonylation of *N*-arylamides by $C(sp^3)$–H activation with AgOAc conjugated with a catalytic amount of TEMPO (Scheme 34c). The carbonylative C–H activation of arenes by using sulfonamide as a directing group was also reported by the same group [105, 106]. *N*-Methoxyamides also have the ability to facilitate C–H activation on



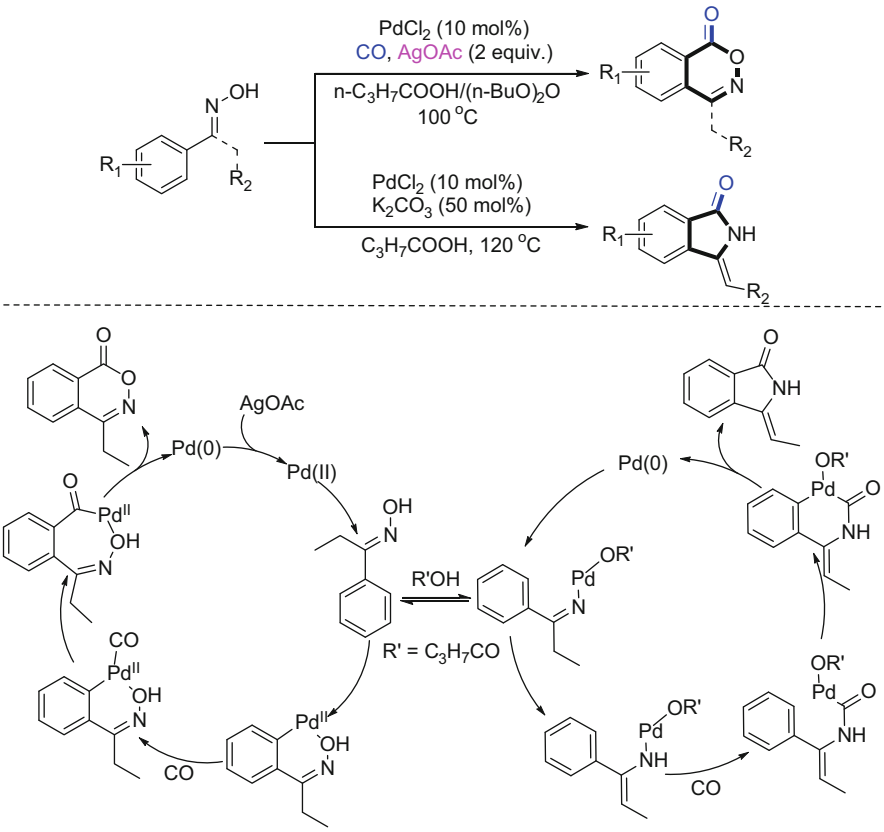
Scheme 33 Synthesis of benzolactams by direct carbonylation of ω-phenylalkylamines



Scheme 34 Synthesis of succinimide derivatives via carbonylative C–H activation of amides

sp^3 and sp^2 centers. In 2011, Booker-Milburn developed the carbonylative C–H activation of *N*-alkoxybenzamides in the presence of $Pd(OAc)_2$ and benzoquinone, providing substituted phthalimides in moderate to good yields [107].

Recently, the group of Jiang developed a selective palladium-catalyzed carbonylation of C(sp^2)–H bonds with aromatic oximes for the synthesis of benzo[d][1,2] oxazin-1-ones and 3-methyleneisoindolin-1-ones (Scheme 35). For the production of [d][1,2]oxazin-1-ones, the N–OH group of the oximes acted as a directing group,

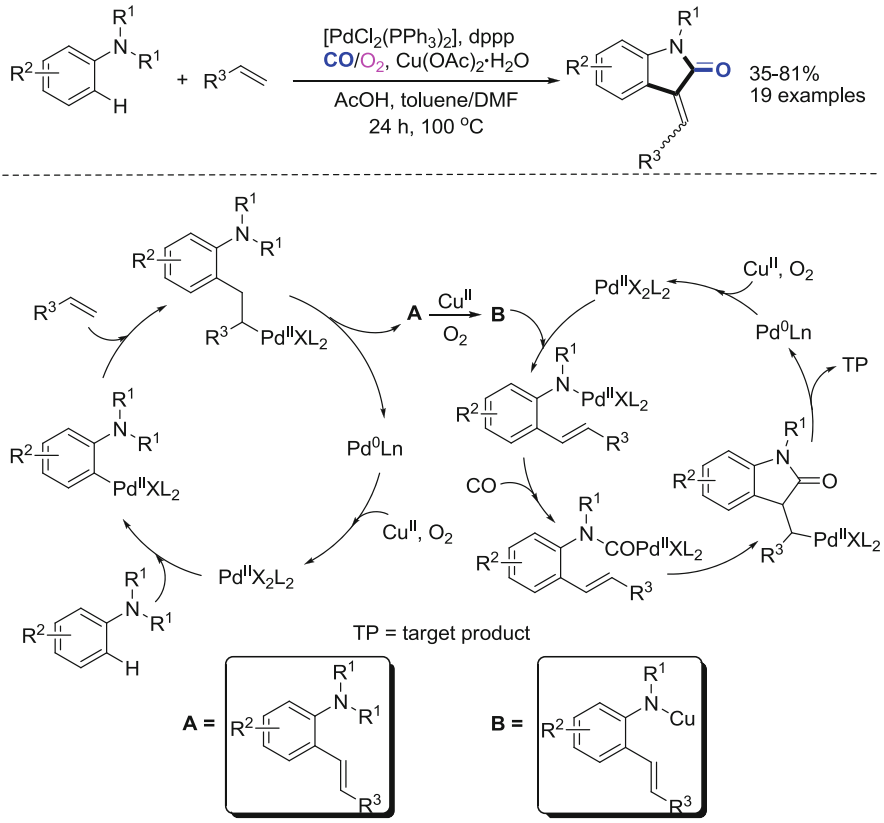


Scheme 35 Synthesis of different *N*-heterocycles via divergent carbonylation of aromatic oximes

while, in the presence of K_2CO_3, the N–OH group acted as an internal oxidant leading to the generation of 3-methyleneisoindolin-1-ones [108].

In 2013, Lei and co-workers successfully obtained 3-methyleneindolin-2-ones by palladium-/copper-catalyzed C–H alkenylation/*N*-dealkylative carbonylation of tertiary anilines in the presence of 1 atm of CO/O_2. Moderate to good yields were obtained (Scheme 36). Several experiments were carried out to explore the reaction mechanism. Based on the results, they proposed that the intermolecular selective *ortho*-alkenylation of *N*,*N*-dialkylanilines is the first and rate-determining step. In the presence of Cu(II) and O_2, the alkyl group leaves as aldehyde [109].

Recently, they further developed a palladium-catalyzed C–H double carbonylation of anilines to isatins in moderate to good yields (Scheme 37). The reaction proceeded under 1 atm of CO with $Cu(OPiv)_2$ as the oxidant. As they proposed, this process started with the activation of aryl N–H by the palladium complex, followed by insertion of CO to afford the carbamoyl intermediate. Subsequently, insertion of another CO and C–H activation occurred in succession generating a six-membered cyclic carbamoyl intermediate, which underwent reductive elimination to give the

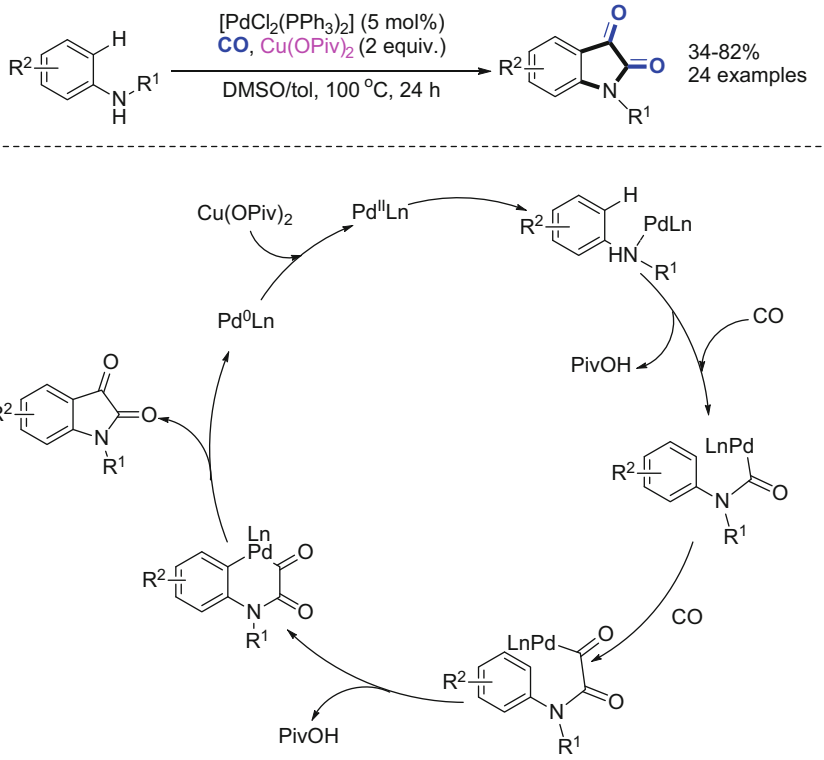


Scheme 36 Synthesis of indolin-2-ones via a cascade reaction of tertiary anilines with alkenes

product. Finally, the Pd^0 species is reoxidized to the Pd^{II} catalyst by Cu $(OPiv)_2$ [110].

3.2 *Synthesis of Six-Membered Heterocycles via Oxidative Carbonylation with C–H Bond Activation*

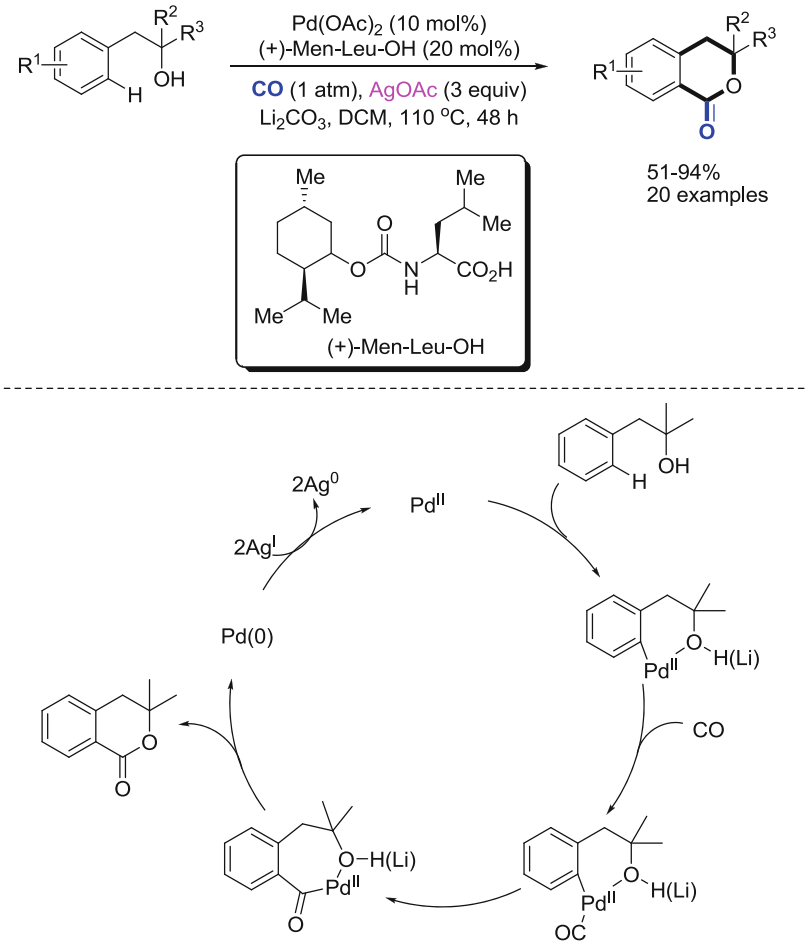
Hydroxyl group is also a good directing group for C–H activation; meanwhile, it could act as an intramolecular nucleophile to be incorporated into the final product. In 2011, Yu and co-workers realized the palladium-catalyzed C–H carbonylation of phenethyl alcohols using amino acid ligands to promote the reaction (Scheme 38). 1-Isochromanone derivatives were obtained in moderate to good yields. This transformation was used for the one-step synthesis of a histamine release inhibitor [111].



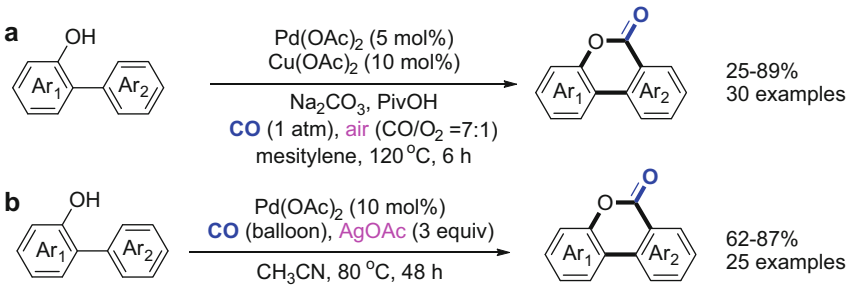
Scheme 37 Synthesis of isatins via oxidative double carbonylation of anilines

In 2013, the group of Shi developed palladium-catalyzed C–H bond activation/carbonylation of 2-arylphenol for the synthesis of dibenzopyranones (Scheme 39a). Various dibenzopyranones were prepared in the presence of $Pd(OAc)_2$ as a catalyst and $Cu(OAc)_2$ as a catalytic oxidant under an atmospheric pressure of CO and O_2. A series of deuterium labeling experiments were conducted. Based on the results, they proposed that the C–H activation step might go through a S_EAr mechanism, and the C–H activation might be involved in the rate-determining step [112]. Later, Chuang and co-workers realized the same reaction under acid–base-free and mild conditions with $Pd(OAc)_2$ as the catalyst and AgOAc as oxidant (39b). Benzopyrannone derivatives were obtained in good yields [113]. As displayed in both cases, substrates with electron-donating substituents showed better activity than the electron-withdrawing ones.

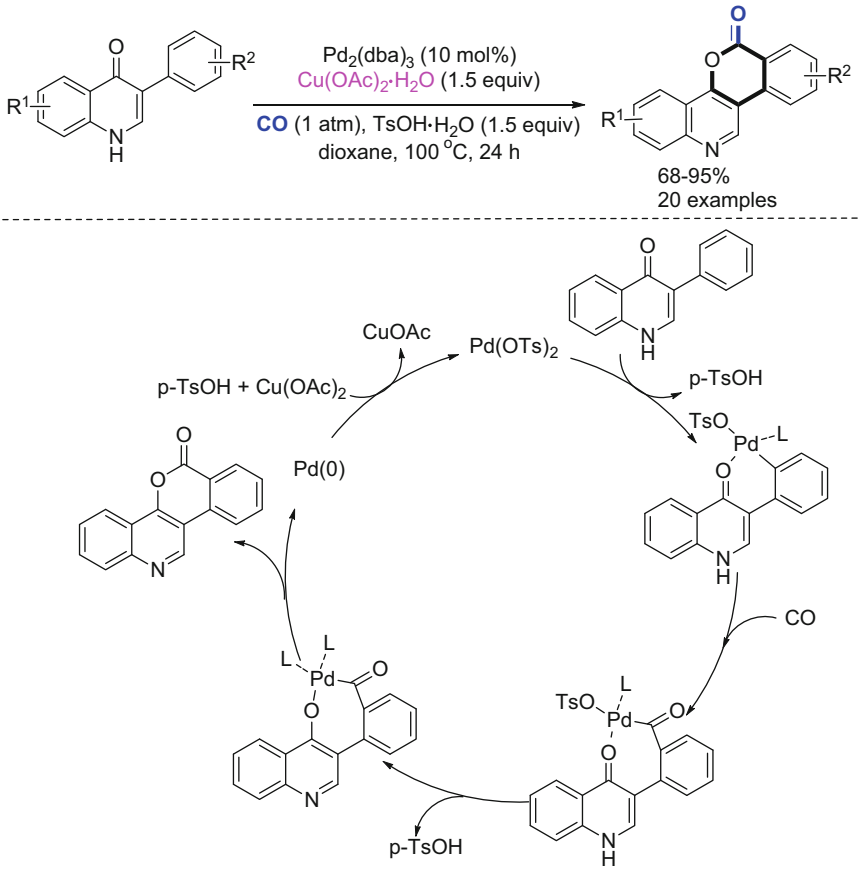
Recently, Jiang and co-workers reported a direct oxidative carbonylation of 3-phenylquinolin-4(1H)-one derivatives for the synthesis of polycyclic aromatic hydrocarbons (Scheme 40). This reaction proceeded under CO atmosphere with $Pd_2(dba)_3$ as the catalyst and $Cu(OAc)_2 \cdot H_2O$ as oxidant, providing polycyclic aromatic hydrocarbons in high to excellent yields. As they proposed, this oxidative carbonylation started with the reaction of $Pd_2(dba)_3$ with $Cu(OAc)_2$ and



Scheme 38 Synthesis of 1-isochromanones via oxidative carbonylation of phenethyl alcohols



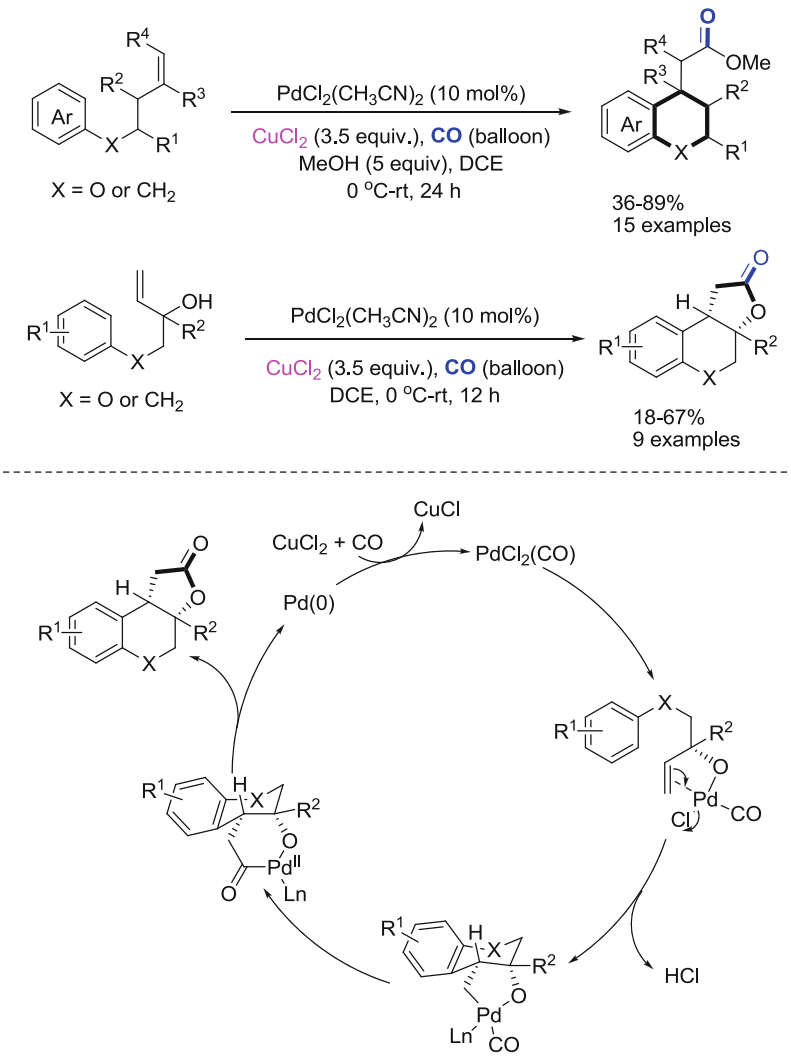
Scheme 39 Synthesis of benzopyranones via oxidative carbonylation of 2-arylphenols



Scheme 40 Synthesis of polycyclic aromatic hydrocarbons via oxidative carbonylation

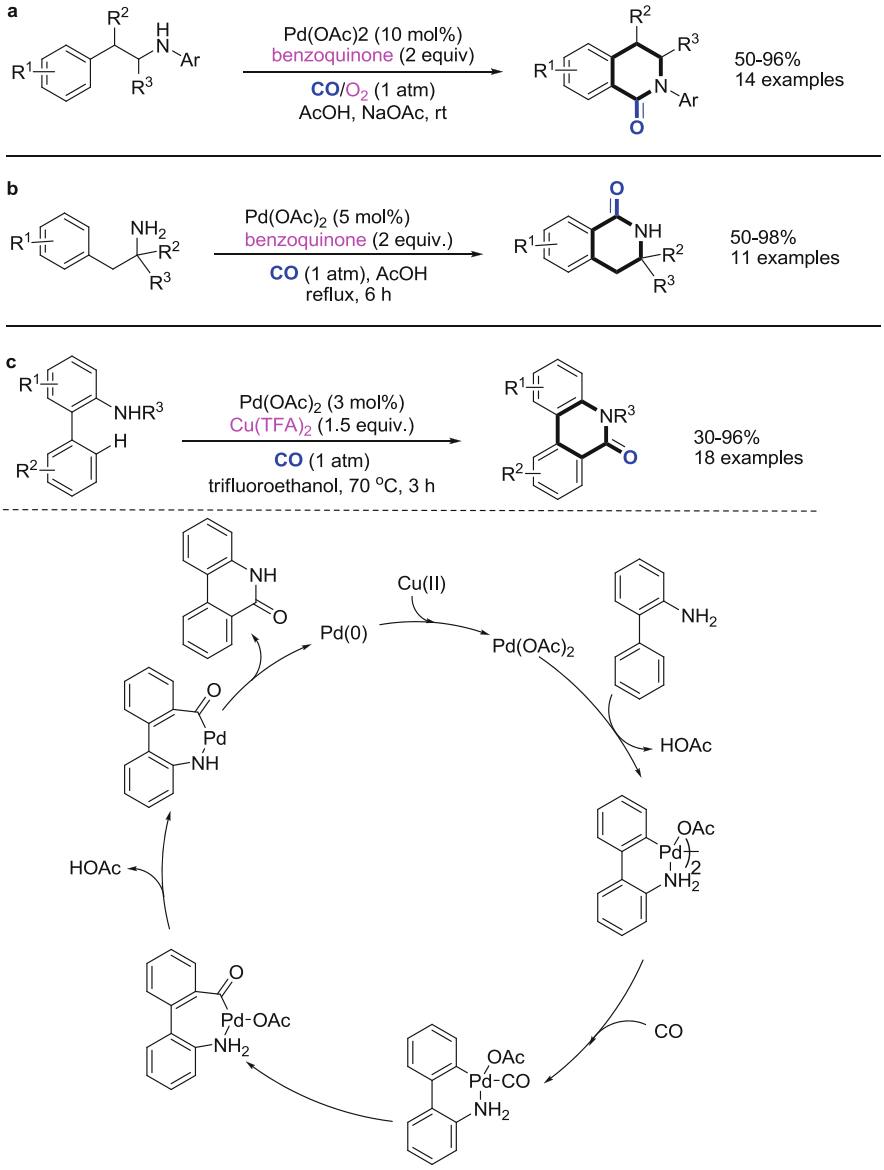
$TsOH \cdot H_2O$ to form $Pd(OTs)_2$. Subsequently, aryl C–H activation by $Pd(OTs)_2$ afforded the arylpalladium species, which further underwent CO insertion to form acylpalladium intermediate. Assisted by leaving *p*-TsOH, acylpalladium intermediate was transformed into the enolate intermediate followed by reductive elimination to give the final product [114].

Palladium-catalyzed intramolecular carbonylative cyclization of aryl alkenes and aryl alkenols for the synthesis of structurally diverse chromanes was developed by Yang and Gong et al. (Scheme 41). This reaction proceeded under the balloon pressure of CO with $PdCl_2(CH_3CN)_2$ as the catalyst and $CuCl_2$ as the oxidant. As they proposed, the mechanism for the carbonylative cyclization of alkenols includes an intramolecular nucleopalladation/CO insertion/reductive elimination process. The palladium(0) that resulted from reductive elimination would be reoxidized to palladium(II) by $CuCl_2$ [115].



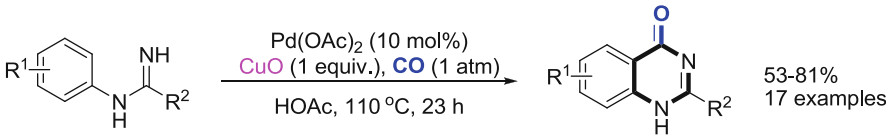
Scheme 41 Synthesis of chromanes via carbonylative cyclization of aryl alkenes/alkenols

By introduction of an aryl group onto the amine system, Gaunt and co-workers realized the C–H carbonylation of β-arylethylamine derivatives (Scheme 42a). The reaction proceeded in the presence of 10 mol% $Pd(OAc)_2$, 2 equivalents of benzoquinone, under 1 atm of CO and O_2, and with AcOH as solvent at room temperature. Dihydro-2-quinolone derivatives were obtained in moderate to good yields [116]. At almost the same time, Granell and co-workers reported the NH_2-directed carbocyclization of quaternary aromatic α-amino esters to six-membered benzolactams in the presence of catalytic amount of palladium with benzoquinone as the oxidant (Scheme 42b). The steric hindrance due to the R^2 and R^3 groups plays



Scheme 42 Synthesis of benzolactams via oxidative carbonylation with C–H activation

a crucial role in this process. Increasing the steric hindrance around the amino group prevents competitive acetylation. In addition, for the substrates used in this method, a strong bias to the six-membered lactams over five-membered ones was observed [117]. In 2013, the group of Zhang developed Pd(II)-catalyzed C–H carbonylation of biaryl-2-amine for the synthesis of phenanthridinones. The reaction proceeded in



Scheme 43 Synthesis of quinazolin-4(3H)-ones via carbocyclization of *N*-arylamidines

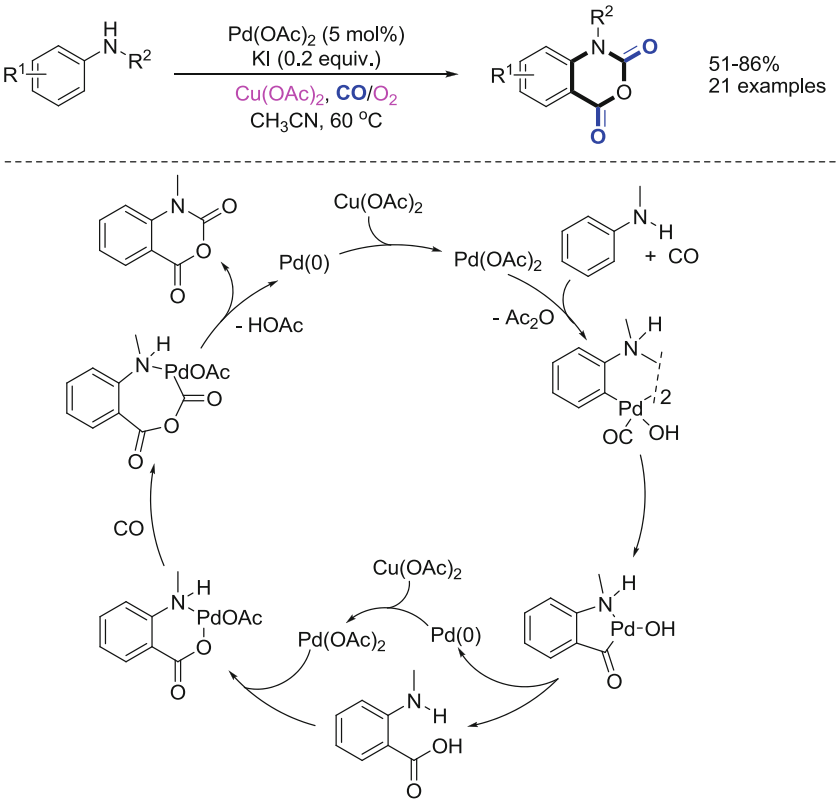
the presence of 3 mol% $Pd(OAc)_2$ and 1.5 equivalents of Cu(II) trifluoroacetate in trifluoroethanol. As they proposed, free-amine-assisted palladation of C–H bond occurs firstly to form the six-membered palladacycle intermediate, followed by CO coordination and insertion. Subsequently, a proton abstraction of the amino group may take place, and finally reductive elimination occurs to provide the desired products. The formed Pd(0) is reoxidized to Pd(II) by Cu(II) (Scheme 42c) [118].

Palladium catalysis has also been employed for the synthesis of quinazolin-4 (3H)-ones via intramolecular C–H carboamidation of *N*-arylamidines with CuO as the oxidant under atmospheric pressure of CO. Electron-rich substrates give better results than electron-deficient ones (Scheme 43) [119].

As reported by the group of Ren, isatoic anhydrides could be prepared efficiently through palladium-catalyzed regioselective C–H bond carbonylation of *N*-alkyl anilines (Scheme 44). A stoichiometric reaction of $Pd(OAc)_2$ with *N*-methylaniline under a CO atmosphere in the absence of $Cu(OAc)_2$ provided a palladium complex, which transformed into the isatoic anhydride in the presence of $Cu(OAc)_2$ and KI in CH_3CN under a CO atmosphere. Based on these results, a tentative mechanism including a dimeric palladium intermediate and *N*-methylanthranilic acid was proposed [120].

Quinolinones are another class of important six-membered nitrogen-containing heterocycles with numerous applications in drugs. Under oxidative conditions, the carbonylation of *N*-monosubstituted-2-vinylanilines provides 2(1*H*)-quinolinones, in which case the amino group was coupled directly with the terminal alkenyl group (Scheme 45). The optimal reaction conditions include 10 mol% $Pd(OAc)_2$, 50 mol% $Cu(OAc)_2$, solvent (CH_3CN), time (20 h), temperature (100°C), CO (2 bar), and air (0.7 bar). It was necessary for the aniline to be a secondary amine. As they proposed, the reaction started with the addition of the aniline nitrogen to the active Pd^{II} species to form a Pd–N bond followed by coordination and insertion of CO leading to a Pd–carbamoyl species. Then, insertion of the vinyl group into the Pd–CO bond could generate an alkylpalladium intermediate. Finally, β-hydride elimination occurred to provide the 2(1H)-quinolinone product. The resulted Pd^0 species is regenerated by Cu^{II} or O_2 to complete the catalytic cycle [121].

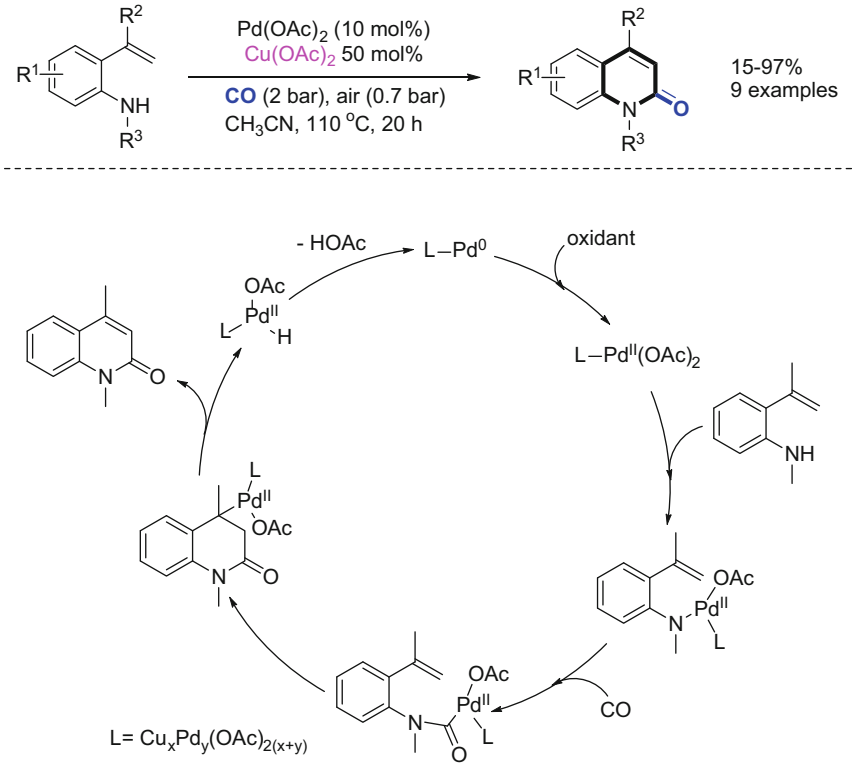
Recently, Wu and co-workers prepared 2-quinolinone derivatives in moderate to good yields by intermolecular carbonylative cyclization of *N*-aryl-pyridine-2-amines and internal alkynes with $Mo(CO)_6$ as a solid CO source. Various substituted 2-quinolinones were obtained from different kinds of internal alkynes and substituted *N*-arylpyridine-2-amines. As they proposed, the pyridine ring-assisted C–H activation took place firstly followed by the insertion of alkyne.



Scheme 44 Synthesis of isatoic anhydrides via oxidative carbonylation of *N*-alkyl anilines

Next, the coordination and insertion of CO and subsequent reductive elimination gave the desired product and Pd(0), which was reoxidized by BQ and/or AgOAc to active Pd^{II} (Scheme 46) [122].

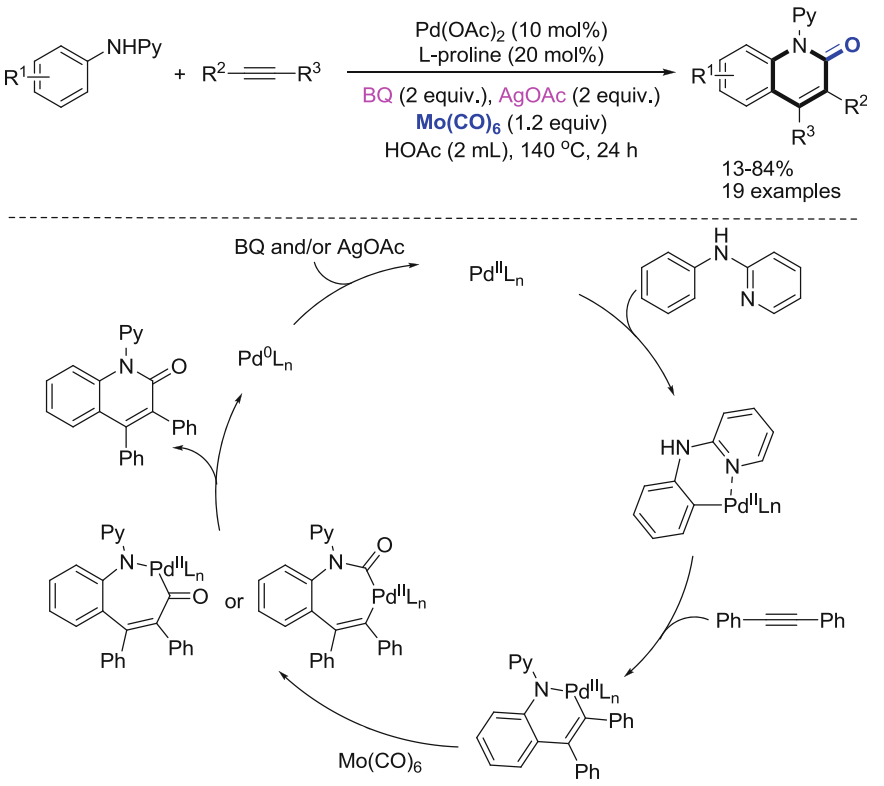
In 2009, Lloyd-Jones and Booker-Milburn et al. reported palladium-catalyzed C–H carbonylation of aryl urea derivatives with the urea moiety as directing group [123]. This reaction could proceed under 1 atm of carbon monoxide at room temperature, providing cyclic imidates in moderate to good yields. In their previous work, the *ortho*-palladate intermediate has been isolated from the reaction of the aryl urea with 1 equivalent of $[Pd(OTs)_2(CH_3CN)_2]$ in anhydrous THF. What's more is that conversion of the *ortho*-palladate into cyclic imidate by stoichiometric reaction with CO has been realized (Scheme 47a) [124]. In 2010, Yu and co-workers developed palladium-catalyzed carboxylation of *ortho*-C–H bond of anilides. As for benzanilides, the *ortho*-C–H bond of the aniline fragment was carboxylated selectively to give *N*-benzoylanthranilic acids, which underwent further cyclization by treating with Ac_2O to provide benzoxazinones in one pot (Scheme 47b) [125].



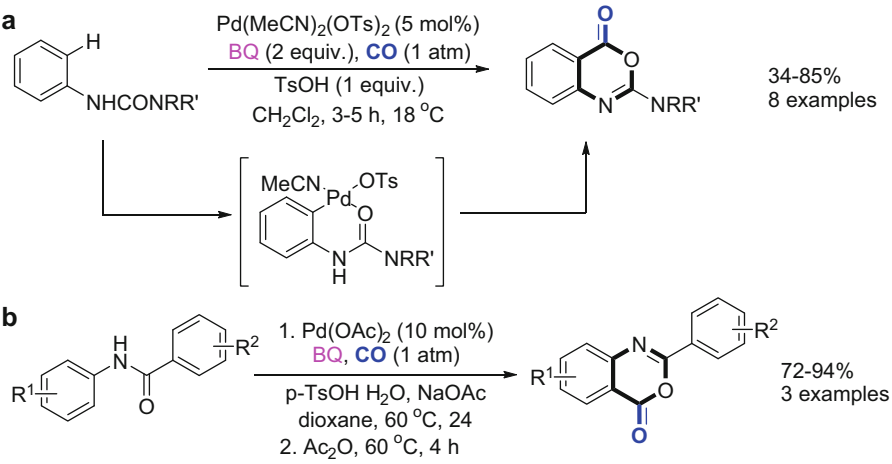
Scheme 45 Synthesis of 2(1H)-quinolinones via oxidative cyclocarbonylation of 2-vinylanilines

In 2013, the group of Guan developed a palladium-catalyzed alkenyl C–H bond carbonylation of enamides under balloon pressure of carbon monoxide with KI and Ac_2O as additives and $Cu(OAc)_2$ as oxidant (Scheme 48). A variety of substituted 1,3-oxazin-6-ones were obtained in good yields. Based on the reaction results employing a stoichiometric amount of $Pd(OAc)_2$, they proposed a reaction pathway, which started with the amide group-directed alkenyl C–H activation to form the vinylpalladium intermediate [126].

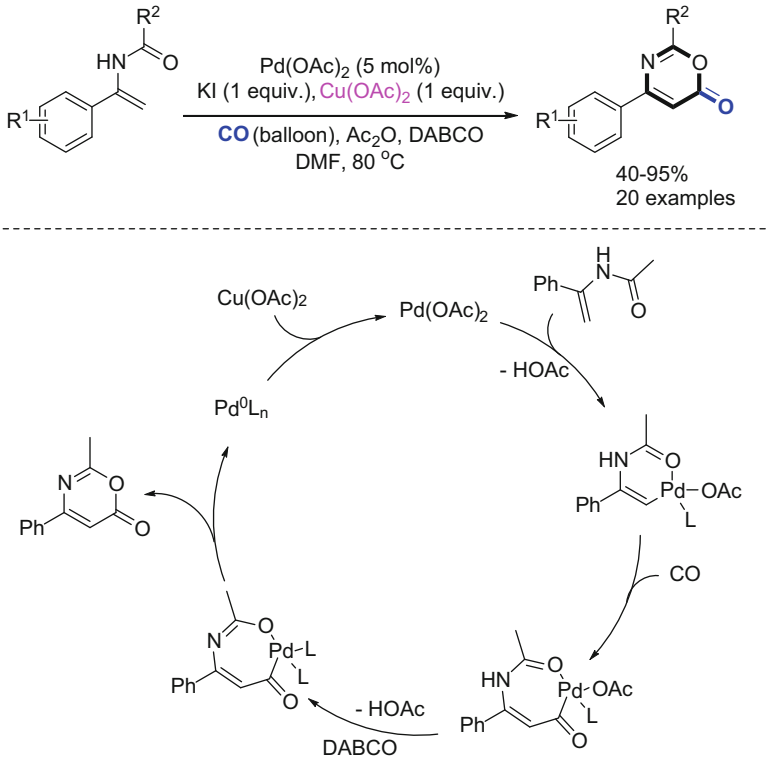
In 1998, Ryu and co-workers reported the δ-carbonylation of saturated alcohols to δ-lactones, in which lead tetraacetate (LTA) was used as a one-electron oxidant to generate the alkoxyl radicals (Scheme 49). Primary alcohols having primary δ-carbons, primary alcohols having secondary δ-carbons, secondary alcohols having primary δ-carbons, and secondary alcohols having secondary δ-carbons all underwent carbonylation to afford δ-lactones in moderate to good yields. The mechanism of this carbonylation involves (1) oxidation of a saturated alcohol by LTA to generate alkoxyl radicals, (2) conversion of this alkoxyl radical to a δ-hydroxyalkyl radical via a 1,5-hydrogen-transfer reaction, (3) generation of an acyl radical by CO trapping of the δ-hydroxyalkyl radical, and (4) oxidation and cyclization of the acyl radical to final δ-lactones [127].



Scheme 46 Synthesis of 2-quinolinone derivatives via oxidative carbonylation of *N*-aryl-pyridine-2-amines and internal alkynes



Scheme 47 Synthesis of benzoxazinones via C–H carbonylation of aniline derivatives

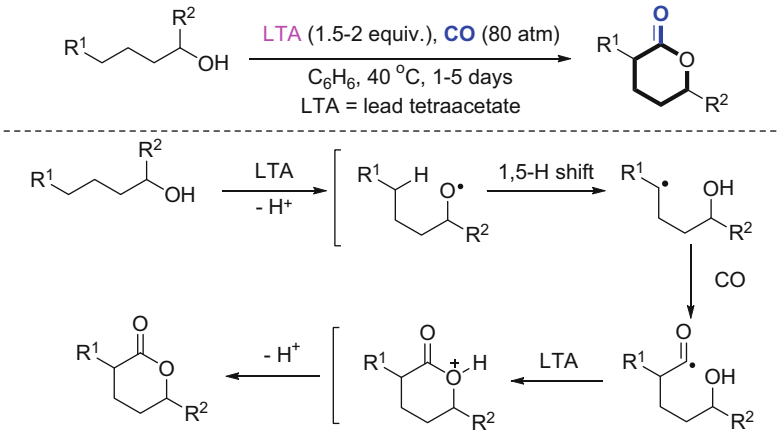


Scheme 48 Synthesis of 1,3-oxazin-6-ones via oxidative carbonylation of enamides

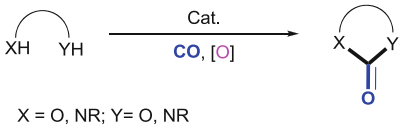
4 Synthesis of Carbonylated Heterocycles via Oxidative Carbonylation of Diamines, Amino Alcohols and Diols, and Related Compounds

As reported, oxidative carbonylation of amines or alcohols yields ureas or carbonate esters, respectively. Correspondingly, when applying this reaction to diamines, diols, or amino alcohols, cyclic ureas, cyclic carbonates, and oxazolidinones could be obtained as the products (Scheme 50). The only by-products are the reduced form of oxidant and protons, making this method an attracting approach to cyclic ureas, cyclic carbonates, and oxazolidinones, which are important classes of heterocycles with interesting biological activities.

Oxazolidinones are another important class of heterocycles showing interesting biological activities. An efficient method for the synthesis of this kind of compounds is the carbonylation of β-amino alcohols. In 1986, Tam reported palladium-catalyzed oxidative carbonylation of β-amino alcohols to oxazolidinones at 3 atm of CO with $CuCl_2$ as oxidant (Scheme 51a). Carbonylation of diols and aminodiols was also developed in similar conditions [128]. In 2000, Gabriele and co-workers

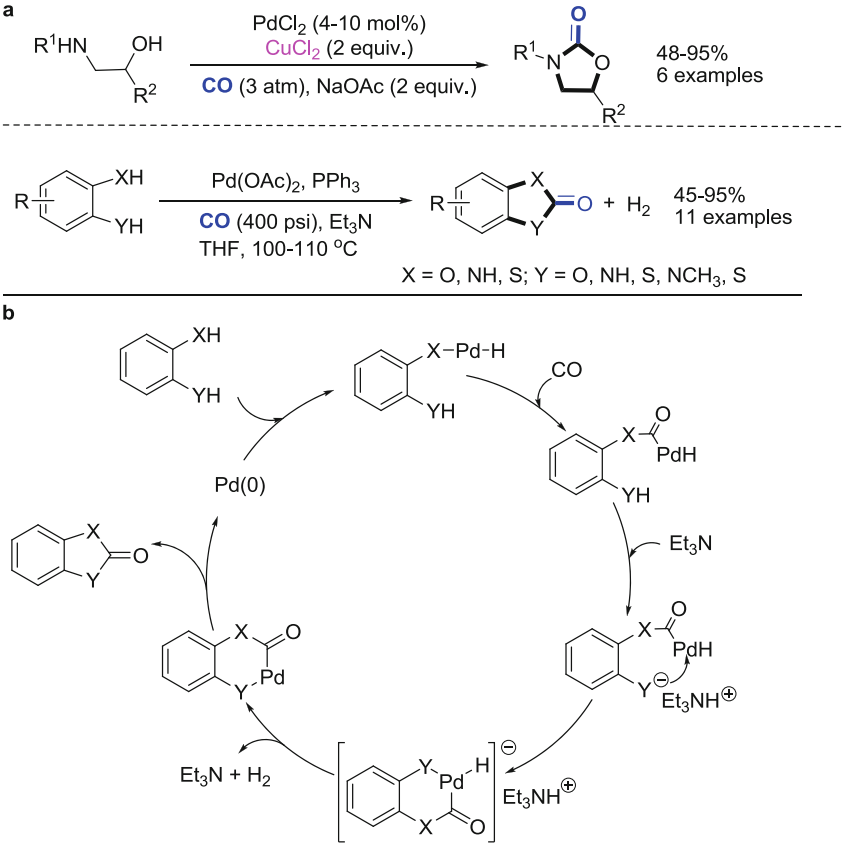


Scheme 49 Synthesis of δ-lactones via oxidative carbonylation of aliphatic alcohols



Scheme 50 Synthesis of carbonylated heterocycles via oxidative carbonylation of diamines, amino alcohols and diols

applied the PdI_2/KI catalyst system to the carbonylation of β-amino alcohols, generating 2-oxazolidinones in good yields. In this process, a large excess of both oxygen and iodide anions are essential. A KI/PdI_2 molar ratio of 200 with CO/O_2/air = 1/6/5 (60 atm total pressure) was used [129, 130]. In 2003, they improved this method to be carried out under relatively mild conditions (100°C and 20 atm of a 4:1 mixture of CO and air). The group of Xia made great progress in this methodology. They developed several efficient catalyst systems including $Pd(OAc)_2/I_2$ [131], $(NHC)Cu^I$ [132], salen–Co complex [133], (chitosan-*Schiff* base)cobalt (II) complex [134], and $Pd(OAc)_2$/[mmim]I [135] for this reaction providing 2-oxazolidinones in good yields. In addition, several recyclable catalyst systems were also developed by the same group, such as palladium on charcoal [136], Pd(Phen)Cl_2 stabilized by ionic liquid [137], and palladium on cross-linked polymer [138] for this reaction. Carbonylation of 2-amino-1-alkanols in an electrochemical way was developed by Feroci and Chiarotto using Pd(II) catalyst in combination with its anodic recycling at a graphite electrode. The reaction could be carried out at room temperature under atmospheric pressure of carbon monoxide [139]. In 2007, Lu and co-workers realized this reaction in a chiral way with the catalysis of selenium [140]. In 2011, Troisi and co-workers reported the synthesis of benzo-fused five-membered heterocycles via cyclocarbonylation of phenols, thiophenols, and anilines *ortho*-substituted by OH, SH, and NH groups in the presence of Et_3N,



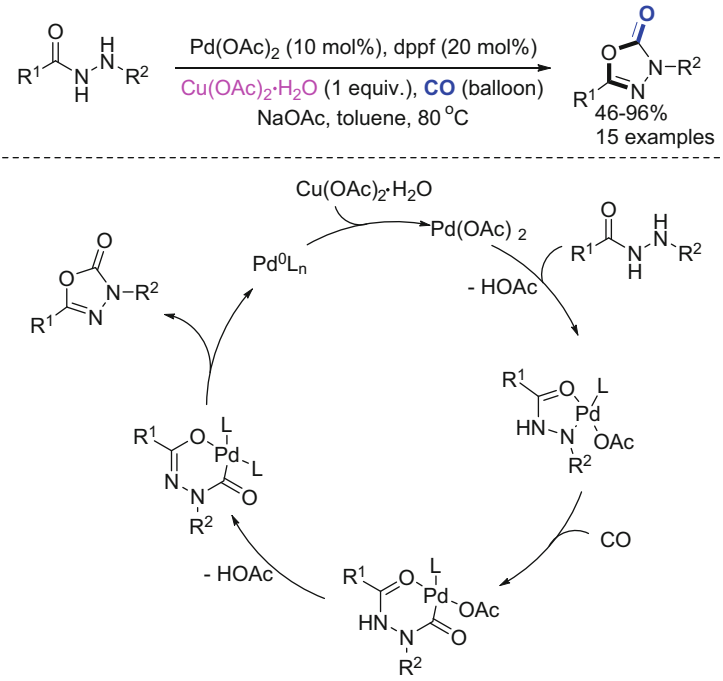
Scheme 51 Synthesis of oxazolidinone derivatives by oxidative cyclocarbonylation of β-amino alcohols

$Pd(OAc)_2$, and PPh_3 under CO pressure (Scheme 51b). For sulfonamides, o-hydroxybenzyl alcohol, and o-aminobenzyl alcohol, the corresponding six-membered heterocycles were obtained in moderate yields [141].

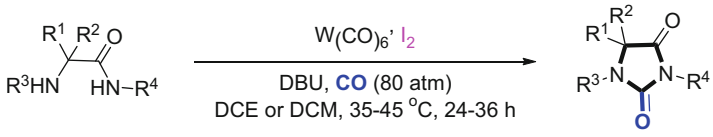
Very recently, Chen and co-workers developed a palladium-catalyzed oxidative cyclocarbonylation of hydrazides via the CO insertion between the amine group and the carbonyl group for the synthesis of 1,3,4-oxadiazol-2(3H)-ones (Scheme 52). In this process, the cyclocarbonylation took place between the amino group and carbonyl group under atmospheric pressure of CO [142].

The use of $W(CO)_6$ as the catalyst in the presence of I_2 as oxidant has been reported to promote the oxidative carbonylation of α-amino amides for the synthesis of hydantoins (Scheme 53) [143]. Later, the oxidative carbonylation of diamine diols to the cyclic urea core structure of the HIV protease inhibitor DMP 450 was also developed under similar conditions [144].

The oxidative carbonylation of diols allows for the synthesis of cyclic carbonates. Tam developed the stoichiometric oxidative carbonylation of 1,2-diols

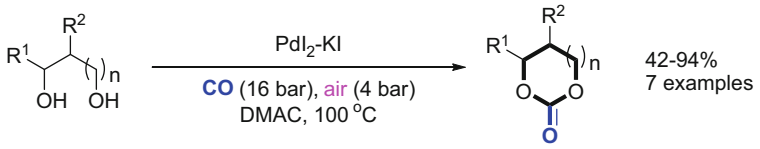


Scheme 52 Synthesis of 1,3,4-oxadiazol-2(3H)-ones via oxidative carbonylation of hydrazides

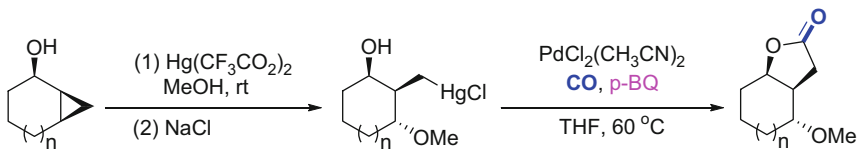


Scheme 53 Synthesis of hydantoins via oxidative carbonylation of α-amino amides

promoted by $PdCl_2$ in conjunction with 2 equivalents of AcONa to give [1,3] dioxolan-2-ones. He also reported a catalytic version of this reaction, but the substrate scope was limited, and the total catalytic turnover was low [128]. In 2009, Gabriele and co-workers applied their previously reported PdI_2–KI system to the oxidative carbonylation of 1,2- and 1,3-diols to produce five-membered and six-membered cyclic carbonates, respectively, with high catalytic efficiencies (Scheme 54) [145]. Later, the group of Li reported the synthesis of glycerol carbonate via the oxidative carbonylation of glycerol. $PdCl_2$(phen) was used as a catalyst with the aid of KI [146]. They evaluated the mechanism pathway based on PdI_2(phen) as the possible intermediate. A possible synergistic effect of I^- and 1,10-phenanthroline on the performance of the Pd complex was proposed. In 2011, Müller and co-workers adapted a bimetallic Wacker-type Pd/Mn redox catalyst



Scheme 54 Synthesis of cyclic carbonates via oxidative carbonylation of diols



Scheme 55 Synthesis of five-membered oxygen-containing heterocycles via oxidative carbonylation of organomercurials

system to the oxidative carbonylation of aliphatic polyols for the synthesis of cyclic carbonates [147].

Oxidative carbonylation of organomercurials offers another choice for the synthesis of carbonylated heterocycles. Kocovský and co-workers successfully synthesized *cis*- and *trans*-fused lactones via palladium-catalyzed oxidative carbonylation of organomercurials, which were obtained by the regioselective Hg (II)-mediated cleavage of cyclopropyl alcohols (Scheme 55) [148].

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