

Review

# An Overview of Catalytic Carbonylative Double Cyclization Reactions

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**Abstract:** This short review is aimed at giving an overview of catalytic carbonylative double cyclization reactions, which are processes in which suitable organic substrates and carbon monoxide are sequentially activated by a promoting a catalyst to form two new cycles with the concomitant incorporation of carbon monoxide as a carbonyl function in the final product. Paradigmatic examples of this powerful synthetic methodology, which allows the one-step synthesis of complex molecular architectures from simple building blocks using the simplest and readily available C-1 unit (CO), are illustrated and discussed. The review is divided into five sections: (1) Introduction, (2) Functionalized Olefinic Substrates, (3) Functionalized Acetylenic Substrates, (4) Functionalized Halides, (5) Conclusions and Future Perspectives.

**Keywords:** carbonylation; cyclization; double cyclization; fused heterocycles; heterocyclization; heterocycles; homogeneous catalysis; metal-catalyzed reactions; palladium; polycyclic heterocycles



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## 1. Introduction

The importance of carbon monoxide as a C-1 unit in organic synthesis can hardly be overemphasized [1]. It is a readily available feedstock that can be easily obtained by steam reforming of light hydrocarbons (including natural gas), partial oxidation of petroleum hydrocarbons, or gasification of coal to give syngas (CO and H<sub>2</sub>) [2]. It can be installed into an organic substrate, usually under catalytic conditions, leading to the direct formation of high value-added carbonylated compounds with 100% atom economy (carbonylation reactions) [1]. It should also be noted that recent progress in the chemical utilization of carbon dioxide has led to the implementation of efficient methods for reducing CO<sub>2</sub> to CO [3]. Therefore, carbonylation reactions may also represent a very important indirect method for the conversion of carbon dioxide (the main waste currently produced by human activities, and principal responsible for the greenhouse effect [4]) into useful chemicals and materials.

Since their discovery at the beginning of the 19th century, carbonylation reactions have acquired steadily increasing importance both at the industrial and academic level. A huge number of examples of these important processes have been reported in the scientific as well as the patent literature [1]. In particular, the development of more efficient and selective catalytic systems associated with the use of suitably functionalized starting materials has opened the way to achieving sophisticated synthetic processes, with the formation of complex carbonylated molecular architectures that have potential applications in many fields of science (including drug discovery and material science) in one step. Among these processes, carbonylative double cyclization represents a particularly important methodology as it makes possible the construction of two new cycles in one synthetic procedure

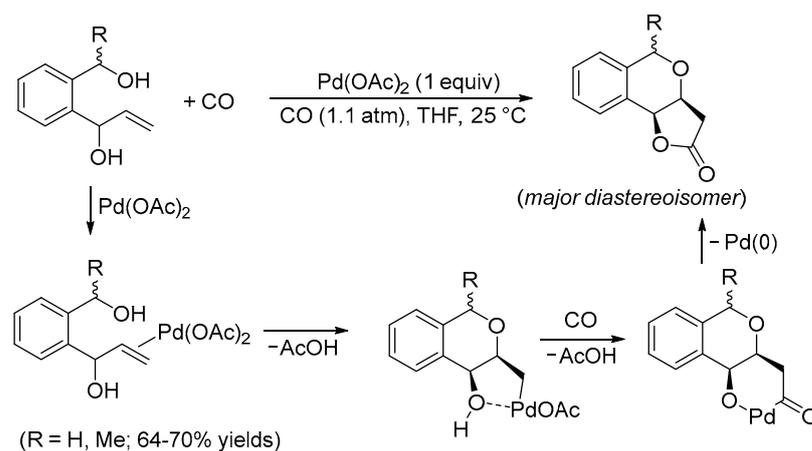
with formation of carbonylated polycyclic structures starting from readily available and suitably functionalized substrates.

The present short review is aimed at offering a description of paradigmatic synthetic methodologies based on catalytic carbonylative double cyclization reactions.

## 2. Functionalized Olefinic Substrates

It is well-known that palladium(II)-based catalysts activate unsaturated carbon–carbon bonds towards the attack of a variety of nucleophilic groups (mainly oxygen- or nitrogen-based). The intramolecular version of this reactivity is of particular importance as it allows the construction of heterocyclic derivatives in a straightforward manner and under mild reaction conditions (Pd(II)-catalyzed heterocyclization reactions) [5]. On the other hand, it is also very well known that Pd(II) catalysts promote many important kinds of carbonylation processes, particularly under oxidative conditions, including cyclization processes in which carbon monoxide is inserted as a carbonyl function inside the newly formed ring (cyclocarbonylation reactions) [6]. It is therefore not surprising that several important methods have been developed in which a single Pd(II)-based catalytic system promotes, in one synthetic step, the sequential heterocyclization–cyclocarbonylation of suitably functionalized olefinic substrates that carry two nucleophilic moieties placed in appropriate positions to undergo double cyclization.

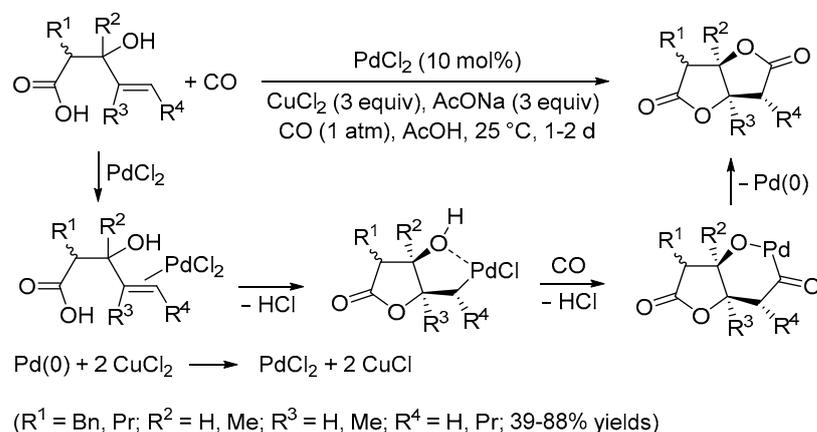
Pioneering studies on this kind of reactivity were conducted by the Semmelhack and Yoshida research groups during the 1980s. In 1984, Semmelhack et al. reported the Pd(II)-promoted stereoselective carbonylative double cyclization of 1-(2-(hydroxymethyl)phenyl)prop-2-en-1-ols to give 3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromen-2-ones with a *cis* junction between the newly formed rings using a stoichiometric amount of Pd(OAc)<sub>2</sub> [7]. The process started with the intramolecular 6-*exo-trig* nucleophilic attack of the benzylic hydroxyl group to the double bond, activated by coordination to the Pd(II) center. This led to the formation of a *cis*-type alkylpalladium intermediate stabilized by chelation of the second hydroxyl group. The final bicyclic product was then formed through CO migratory insertion followed by intramolecular nucleophilic displacement by the hydroxyl, possibly via the formation of a palladacycle followed by reductive elimination (Scheme 1).



**Scheme 1.** Synthesis of 3,3a,5,9b-tetrahydro-2H-furo[3,2-c]isochromen-2-ones from 1-(2-(hydroxymethyl)phenyl)prop-2-en-1-ols [7].

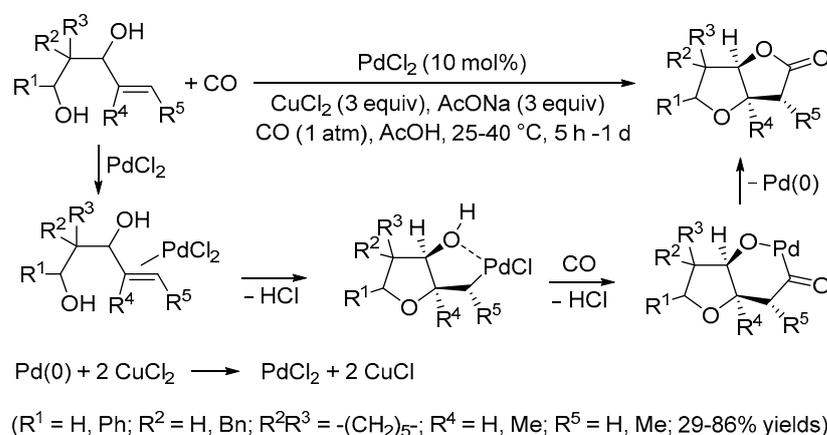
Interestingly, when an oxidant for Pd(0) such as CuCl<sub>2</sub> was employed to make the process catalytic, the reaction led to the formation of (*E*)-(2-(3-chloroprop-1-en-1-yl)phenyl)methanol from allylic chlorination (74% yield) [7]. Later on, however, suitable conditions were elaborated by the Yoshida group for performing the carbonylative double cyclization of 3-hydroxy-4-pentenoic acids to stereoselectively give tetrahydrofuro[3,2-*b*]furan-2,5-diones with a *cis* junction between the rings under Pd(II) catalysis (10 mol% PdCl<sub>2</sub> in the presence of 3 equiv of CuCl<sub>2</sub> and 3 equiv of AcONa, in glacial acetic acid as the

solvent, at room temperature and under 1 atm of CO) (Scheme 2) [8]. The process took place through 5-*exo-trig* cyclization by the intramolecular nucleophilic attack of the carboxylic group to the double bond coordinated to the metal center, stabilized by hydroxyl chelation, to give a *cis*-type alkylpalladium complex followed by CO insertion and intramolecular nucleophilic displacement, possibly via the formation of a palladacycle followed by reductive elimination (Scheme 2) [8].



**Scheme 2.** Synthesis of tetrahydrofuro[3,2-*b*]furan-2,5-diones from 3-hydroxy-4-pentenoic acids [8].

The same research group then published the carbonylative double cyclization of 4-ene-1,3-diols under similar reaction conditions to obtain tetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones (Scheme 3) [9].



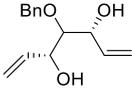
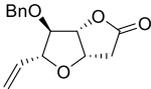
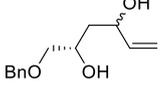
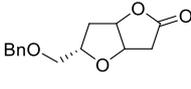
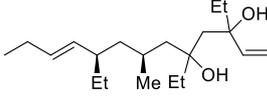
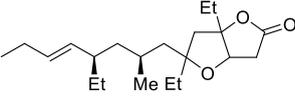
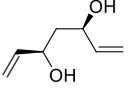
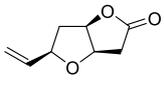
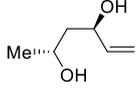
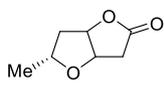
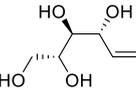
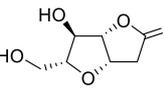
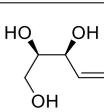
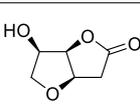
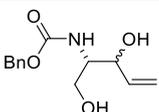
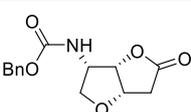
**Scheme 3.** Synthesis of tetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones from 4-ene-1,3-diols [9].

Considering that the bicyclic tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one substructure is largely found in natural and biologically active molecules, the methods disclosed by Semmelhack and Yoshida for constructing this important core by the carbonylative double cyclization of enediol derivatives have been largely employed as the key step in the semi- or total synthesis of natural products and bioactive compounds. Representative examples are shown in Table 1.

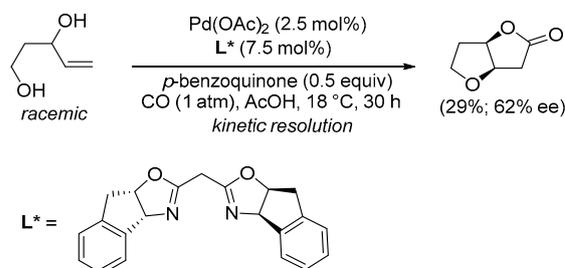
**Table 1.** Representative examples of the Pd(II)-promoted carbonylative double cyclization of enediol derivatives in the synthesis of natural and bioactive products.

Entry	Conditions	Substrate	Product	Yield (%)	Refs.
1	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 41 h			63	[10]
2	PdCl <sub>2</sub> (MeCN) <sub>2</sub> , (10 mol%), CuCl <sub>2</sub> (2.4 equiv), CO (1 atm), THF, 25 °C, 24 h			65	[11]
3	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 8 h			85	[12]
4	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (4 equiv), CO (1 atm), AcOH, 25 °C, 24 h			93	[13]
5	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 33 h			38	[14]
6	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 15 h			>80	[15]
7	Pd(OAc) <sub>2</sub> (1.5 equiv), CO (1.1 atm), THF, 23 °C, 4 h			87	[16]
8	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 15 h			81	[17]
9	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C			63	[18]
10	PdCl <sub>2</sub> , CuCl, AcONa, CO, AcOH			33	[19]
11	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 10 h			85	[20]
12	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 23 °C, 24 h			75	[21]
13	Pd(OAc) <sub>2</sub> (1.5 equiv), N-methylmorpholine (3 equiv), CO, THF, 25 °C, 15 h			58	[22]

Table 1. Cont.

Entry	Conditions	Substrate	Product	Yield (%)	Refs.
14	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 20 h			65	[23]
15	Pd(OAc) <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 15 h			63, 70	[24,25]
16	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 24 h			33	[26]
17	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 24 h			87	[27]
18	PdCl <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 12 h			61	[28]
19	PdCl <sub>2</sub> (MeCN) <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (5 equiv), AcOLi (5 equiv), [Fe(CO) <sub>5</sub> ] (0.5 equiv), AcOH, 60 °C, 1 h			47	[29]
20	PdCl <sub>2</sub> (MeCN) <sub>2</sub> (10 mol%), Cu(OAc) <sub>2</sub> (4 equiv), LiCl (4 equiv), [Fe(CO) <sub>5</sub> ] (0.25 equiv), AcOH, 60 °C, 15 min			67	[30]
21	PdCl <sub>2</sub> (MeCN) <sub>2</sub> (10 mol%), CuCl <sub>2</sub> (4 equiv), AcOLi (4 equiv), [Fe(CO) <sub>5</sub> ] (0.3 equiv), AcOH, 60 °C, 30 min			75	[31]

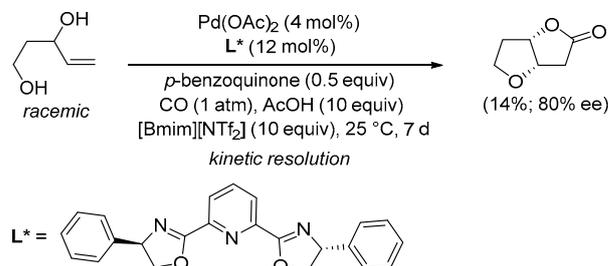
Interestingly, using the appropriate enantiopure ligand, a kinetic resolution of ( $\pm$ )-pent-4-ene-1,3-diols was possible with the formation of the corresponding bicyclic lactone in noracemic form. This was exemplified by the Pd(OAc)<sub>2</sub>-catalyzed carbonylation of ( $\pm$ )-pent-4-ene-1,3-diol performed in the presence of an enantiopure bis(oxazoline) ligand and *p*-benzoquinone as an external oxidant to give (3*aR*,6*aR*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one in 29% yield and 62% ee (Scheme 4) [32].



**Scheme 4.** Kinetic resolution of ( $\pm$ )-pent-4-ene-1,3-diol in [bmim][NTf<sub>2</sub>] leading to enantioenriched (3*aS*,6*aS*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one [33].

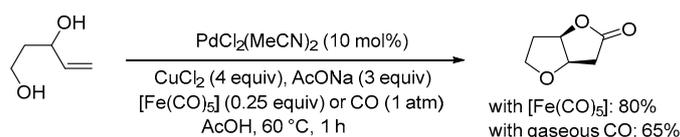
More recently, the kinetic resolution of ( $\pm$ )-pent-4-ene-1,3-diols to give nonracemic tetrahydrofuro[3,2-*b*]furan-2(3*H*)-ones [2-(*S,S*) up to 80% ee, 2-(*R,R*) up to 57% ee] has been realized under similar conditions [4 mol% of Pd(OAc)<sub>2</sub>, 12 mol% of 2,6-bis[(4*R*)-4-

phenyl-2-oxazoliny]pyridine as enantiopure ligand, 0.5 equiv of *p*-benzoquinone, and 10 equiv AcOH] using an ionic liquid as the solvent (such as 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, [Bmim][NTf<sub>2</sub>], 10 equiv), as shown in Scheme 5 [33].



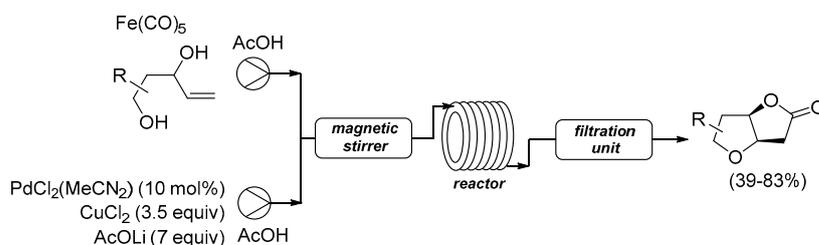
**Scheme 5.** Carbonylative double cyclization of pent-4-ene-1,3-diol using [Fe(CO)<sub>5</sub>] as in situ CO source [34].

Interestingly, the Gracza group reported that the use of iron pentacarbonyl as an in situ liquid CO source may lead to improved results (significantly shorter reaction times, in particular) in the Pd(II)-catalyzed carbonylative double cyclization of enediols with a terminal double bond, as shown in Scheme 6 [29,34,35].



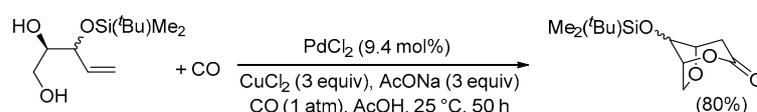
**Scheme 6.** Carbonylative double cyclization of 4-ene-1,3-diols using [Fe(CO)<sub>5</sub>] as in situ CO source under flow conditions [36].

The same research group recently reported their reaction under flow conditions using a continuous microflow system, as shown in Scheme 7 [31,36].



**Scheme 7.** Kinetic resolution of (±)-pent-4-ene-1,3-diol leading to enantioenriched (3*a**R*,6*a**R*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one [32].

The carbonylative double cyclization process of enediols has also been reported to occur with 4-ene-1,2-diol derivatives. In this case, after the initial 5-*exo-trig* *O*-cyclization, in the cyclocarbonylation it is the free hydroxyl at C-2 that acts as internal nucleophile, with the formation of a 6-membered ring. This is illustrated by the formation of 8-((*tert*-butyldimethylsilyloxy)-2,6-dioxabicyclo[3.2.1]octan-3-one from 3-((*tert*-butyldimethylsilyloxy)pent-4-ene-1,2-diol, as shown in Scheme 8 [37].

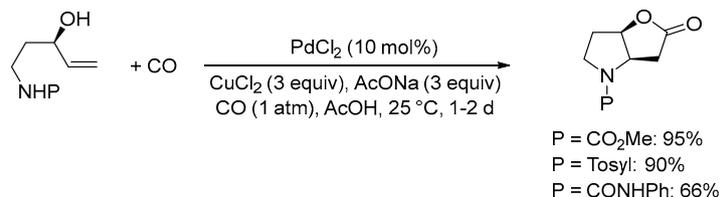


**Scheme 8.** 5-*exo-trig* *O*-cyclization followed by cyclocarbonylation with 6-membered ring closure [37].

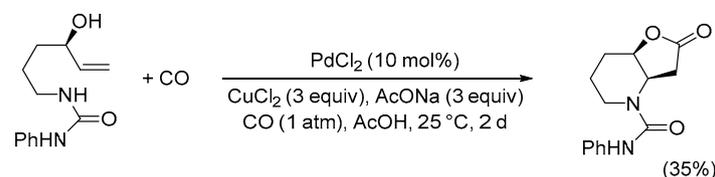
The nucleophilic group undergoing initial heterocyclization can also be nitrogen-based. Thus, as early as 1985 the Tamaru and Yoshida group found that the Pd(II)-catalyzed

carbonylative double cyclization of the *N*-protected 5-aminopent-1-en-3-ols yielded *N*-protected 6-hydroxyhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-ones, using the same conditions employed for 4-penten-1,3-diols [38]. Among the protective groups tested, the  $-\text{CO}_2\text{Me}$  group turned out as the most suitable, as exemplified in Scheme 9 [39].

As predicted, owing to the higher degrees of freedom of the alkyl chain, *N*-protected 6-aminohex-1-en-3-ols were significantly less reactive, and relatively good results were usually observed with  $\text{P} = \text{CONHPh}$ , as shown in Scheme 10 [39].

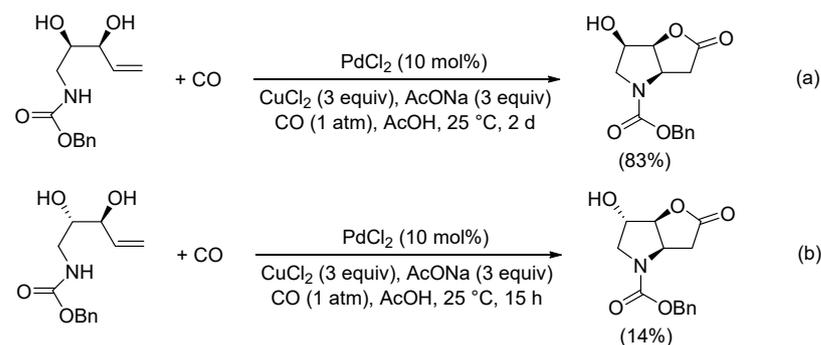


**Scheme 9.** Formation of 6-hydroxyhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one derivatives from *N*-protected 5-aminopent-1-en-3-ols [39].



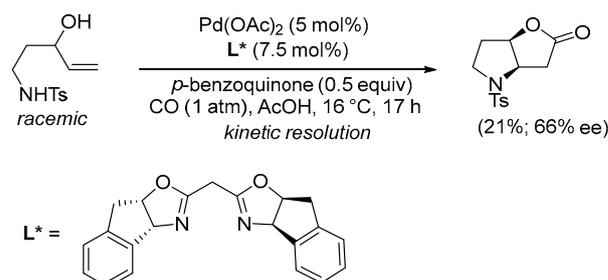
**Scheme 10.** Synthesis of 2-oxo-*N*-phenylhexahydrofuro[3,2-*b*]pyridine-4(2*H*)-carboxamide from 1-(4-hydroxyhex-5-en-1-yl)-3-phenylurea [39].

Later on, Jäger et al. reported the carbonylation of benzyl ((2*R*,3*S*)-2,3-dihydroxypent-4-en-1-yl)carbamate (Scheme 11a) as a key step in the synthesis of novel 1,4-iminoglycitol derivatives as potential glycosidase inhibitors [40]. On the other hand, the  $\text{PdCl}_2$ -catalyzed carbonylation of benzyl ((2*S*,3*S*)-2,3-dihydroxypent-4-en-1-yl)carbamate gave benzyl (3*aR*,6*S*,6*aS*)-6-hydroxy-2-oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxylate in a 14% yield (Scheme 11b) [41].



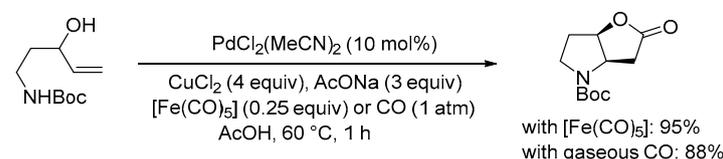
**Scheme 11.** Synthesis of (a) benzyl (3*aR*,6*R*,6*aS*)-6-hydroxy-2-oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxylate (a precursor for the formation of glycosidase inhibitor derivatives) [40] and (b) benzyl (3*aR*,6*S*,6*aS*)-6-hydroxy-2-oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxylate [41].

Kinetic resolution of *N*-protected 5-aminopent-1-en-3-ols in the  $\text{Pd}(\text{II})$ -catalyzed carbonylative double cyclization has been reported by Gracza et al. Thus, using enantiopure bisoxazoline ligands, nonracemic hexahydro-2*H*-furo[3,2-*b*]pyrrol-2-ones could be obtained as in Scheme 12 [42].



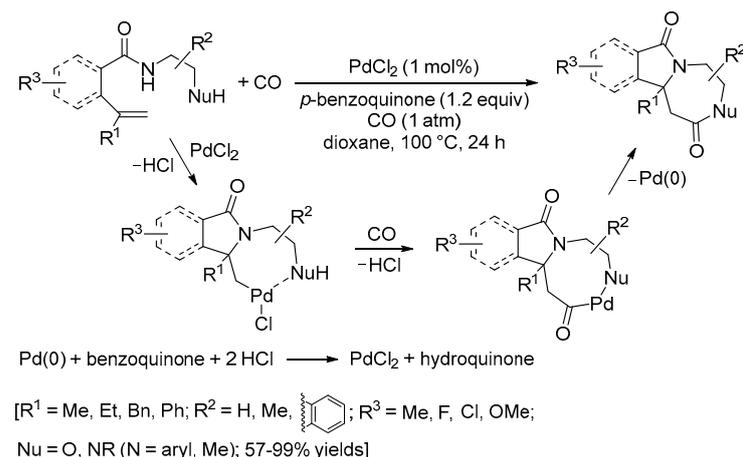
**Scheme 12.** Kinetic resolution of ( $\pm$ )-*N*-(3-hydroxypent-4-en-1-yl)-4-methylbenzenesulfonamide leading to enantioenriched (3*R*,6*aR*)-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one [42].

The gaseous CO-free conditions elaborated by the Gracza group for the carbonylation of 4-ene-1,3-diols, involving the use of liquid  $[\text{Fe}(\text{CO})_5]$  as an in situ CO source (Scheme 6), have also been successfully employed by the same research team in the Pd(II)-catalyzed carbonylative double cyclization of *N*-protected 5-aminopent-1-en-3-ols, as in Scheme 13 [34].



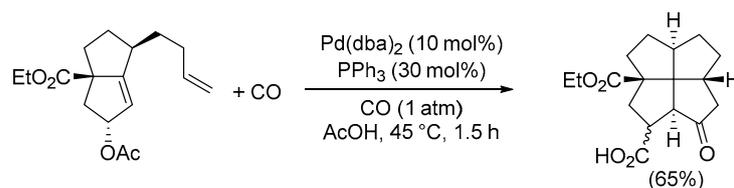
**Scheme 13.** Carbonylative double cyclization of *tert*-butyl (3-hydroxypent-4-en-1-yl)carbamate using  $[\text{Fe}(\text{CO})_5]$  as in situ CO source [34].

An interesting carbonylative double cyclization process has recently been developed by the Li group [43]. It involved the reaction of *N*-(2-aminoethyl)pent-4-enamide or *N*-(2-hydroxyethyl)pent-4-enamide derivatives with CO (1 atm) in the presence of  $\text{PdCl}_2$  as a catalyst (1 mol%) and *p*-benzoquinone as an oxidant (1.2 equiv) (Scheme 14). As shown in Scheme 14, the initial 5-*exo-trig* *N*-cyclization was followed by CO insertion and intramolecular nucleophilic displacement via the formation of an 8-membered ring palladacycle followed by reduction elimination [43].



**Scheme 14.** Carbonylative double cyclization of *N*-(2-aminoethyl)pent-4-enamide and *N*-(2-hydroxyethyl)pent-4-enamide derivatives [43].

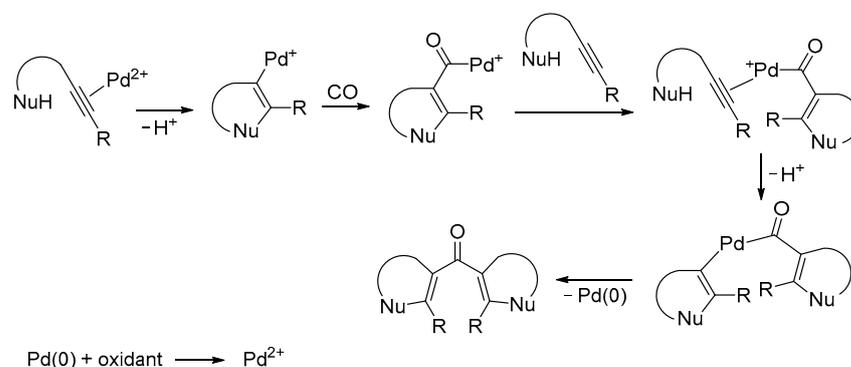
A general approach leading to carbonylative double cyclization is the intramolecular Pauson–Khand reaction starting from suitable diene or enyne substrates. Since several excellent reviews have been published on this reaction [44–46], even in the most recent literature [47–49], this process will not be treated here; however, a particularly striking example in Scheme 15 gives the reader an idea of the powerfulness of this synthetic method for constructing complex carbonylated polycyclic compounds [50].



**Scheme 15.** Synthesis of 2a-(ethoxycarbonyl)-8-oxododecahydro-pentaleno[1,6-*cd*]pentalene-1-carboxylic acid from ethyl 5-acetoxy-1-(but-3-en-1-yl)-2,3,4,5-tetrahydropentalene-3a(1H)-carboxylate by Pauson–Khand-type intramolecular reaction [50].

### 3. Functionalized Acetylenic Substrates

Starting from suitably functionalized acetylenic substrates bearing a nucleophilic group in the appropriate position, Kato et al. reported an interesting Pd(II)-catalyzed carbonylative double cyclization process without incorporating CO into the rings, which leads to di(hetero)cyclic ketones [51]. According to Scheme 16, the process, which the authors call the “cyclization–carbonylation–cyclization coupling reaction” or “CCC reaction”, starts with the electrophilic activation of the triple bond by a Pd(II) species followed by an intramolecular nucleophilic attack on the activated triple bond with the formation of the first ring. (Only the *endo* cyclization mode is shown in Scheme 16 for simplicity.) The ensuing cyclic vinylpalladium intermediate then undergoes carbon monoxide insertion followed by the coordination of another molecule of the acetylenic substrate. This opens the way to a second cyclization, which is followed by reductive elimination to give the final product and Pd(0). The latter is reoxidized to give catalytically active Pd(II) by the use of an external oxidant, usually *p*-benzoquinone. The system CuCl<sub>2</sub>/O<sub>2</sub> has also been used occasionally [52] although it should be noted that in this case the CO–O<sub>2</sub> mixture fell within the explosion limits. In fact, these mixtures are potentially explosive over a large range of composition: the flammability range for CO in O<sub>2</sub> is 16.7–93.5% at room temperature and becomes even larger at higher temperatures [53].



**Scheme 16.** The “cyclization–carbonylation–cyclization coupling” concept leading to di(hetero)cyclic ketones [51].

This method has been successfully employed by the Kato group to synthesize a variety of di(heterocyclic)ketones; representative examples are shown in Table 2, entries 1–8. Entry 9 shows a recent extension of the concept to allenic substrates (2-methyl-1-phenyl-1,2,3-dien-1-ones, in particular) for the synthesis of bis(3-furanyl)methanones.

**Table 2.** Examples of the “cyclization–carbonylation–cyclization coupling” concept leading to di(hetero)cyclic ketones.

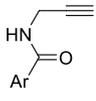
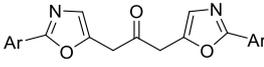
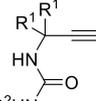
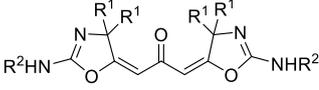
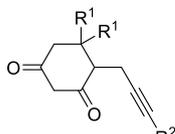
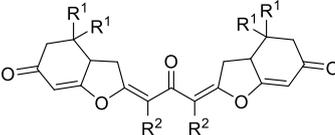
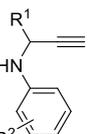
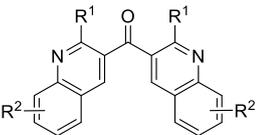
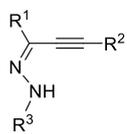
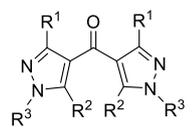
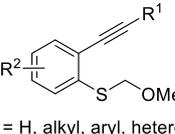
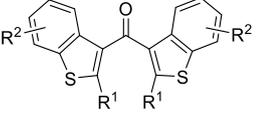
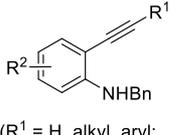
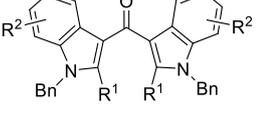
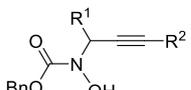
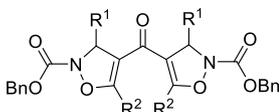
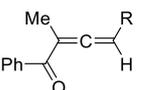
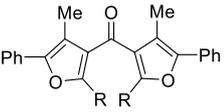
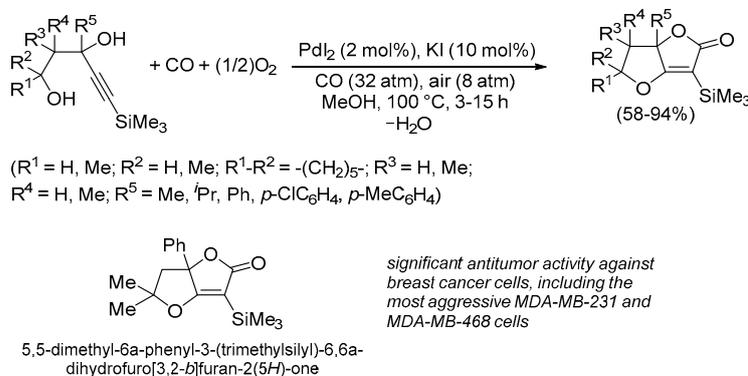
Entry	Conditions	Substrate	Product	Yields (%)	Refs.
1	 Pd(tfa) <sub>2</sub> (5 mol%), (10 mol%), <i>p</i> -benzoquinone (2 equiv), CO (1 atm), MeOH, 0 °C, 5–12 h	 (Ar = Ph, 4-MeOC <sub>6</sub> H <sub>4</sub> , 4-ClC <sub>6</sub> H <sub>4</sub> , 4-BrC <sub>6</sub> H <sub>4</sub> )		90–92	[51]
2	 Pd(L)(tfa) <sub>2</sub> (5 mol%), L =  <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), MeOH, 7 to 25 °C, 18–48 h	 (R <sup>1</sup> = alkyl; R <sup>2</sup> = alkyl, benzyl, aryl)		24–89	[54]
3	 Pd(tfa) <sub>2</sub> (5–10 mol%), (7.5–12 mol%), <i>p</i> -benzoquinone (2 equiv), CO (1 atm), MeOH, –30 to 0 °C, 2–53 h	 (R <sup>1</sup> = H, Me; R <sup>2</sup> = H, alkyl, aryl)		71–99	[55]
4	 Pd(tfa) <sub>2</sub> (5 mol%), (7.5 mol%), <i>p</i> -benzoquinone (2 equiv), CO (1 atm), MeOH, 25 °C, 1–63 h	 (R <sup>1</sup> = H, Me; R <sup>2</sup> = H, alkyl, vinyl, SiEt <sub>3</sub> )		10–89	[56]
5	 Pd(L)(tfa) <sub>2</sub> (5 mol%), L =  <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), MeOH, –5 to 25 °C, 1–46 h	 (R <sup>1</sup> = H, alkyl; R <sup>2</sup> = alkyl, aryl, SiMe <sub>3</sub> ; R <sup>3</sup> = aryl, tosyl)		70–94	[57]
6	 Pd(L)(tfa) <sub>2</sub> (5 mol%), L =  <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), MeOH, –30 to 25 °C, 24–144 h	 (R <sup>1</sup> = H, alkyl, aryl, heteroaryl; R <sup>2</sup> = H, Me, Cl, OMe)		75–100	[52,58]
7	 Pd(L)(tfa) <sub>2</sub> (5 mol%), L =  <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), <i>i</i> PrOH, –5 to 15 °C, 47–72 h	 (R <sup>1</sup> = H, alkyl, aryl; R <sup>2</sup> = H, Br, Me, OMe)		73–92	[59]

Table 2. Cont.

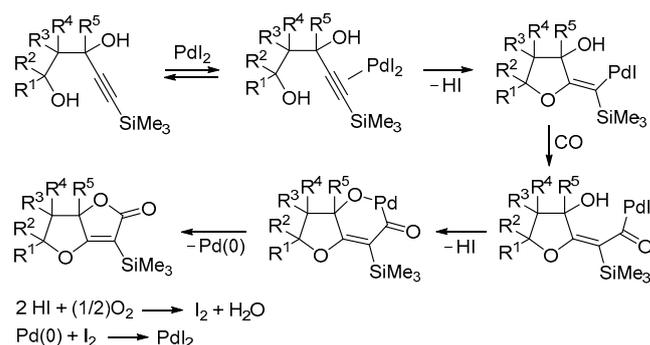
Entry	Conditions	Substrate	Product	Yields (%)	Refs.
8	Pd(L)(tfa) <sub>2</sub> (5 mol%),  L = <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), MeOH, −20 to 0 °C, 24–76 h	 (R <sup>1</sup> = aryl, alkyl; R <sup>2</sup> = alkyl)		70–94	[60]
9	Pd(L)(tfa) <sub>2</sub> (5 mol%),  L = <i>p</i> -benzoquinone (1.5 equiv), CO (1 atm), MeOH, −5 to 25 °C, 24–55 h	 (R = alkyl, aryl)		12–86	[61]

The Pd(II)-catalyzed carbonylative cyclization of functionalized acetylenic derivatives with CO incorporation into the cycle was disclosed by our research group a few years ago [62–65] using the PdI<sub>2</sub>/KI catalytic system, which we had already successfully used to promote a plethora of carbonylation reactions [66–70]. Thus, starting from readily available 4-yne-1,3-diols under oxidative conditions (using oxygen from the air as a benign oxidative agent), novel dihydrofurofuranone derivatives with antitumor activity were synthesized (Scheme 17). In particular, 5,5-dimethyl-6a-phenyl-3-(trimethylsilyl)-6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)-one showed a significant antiproliferative activity in vitro on human breast cancer cell lines, including the most aggressive triple-negative breast cancer cells (MDA-MB-231 and MDAMB-468) while being practically non-toxic to normal cells (human mammary epithelia cells, MCF-10A, as well as murine fibroblasts 3T3-L1) [62–64].



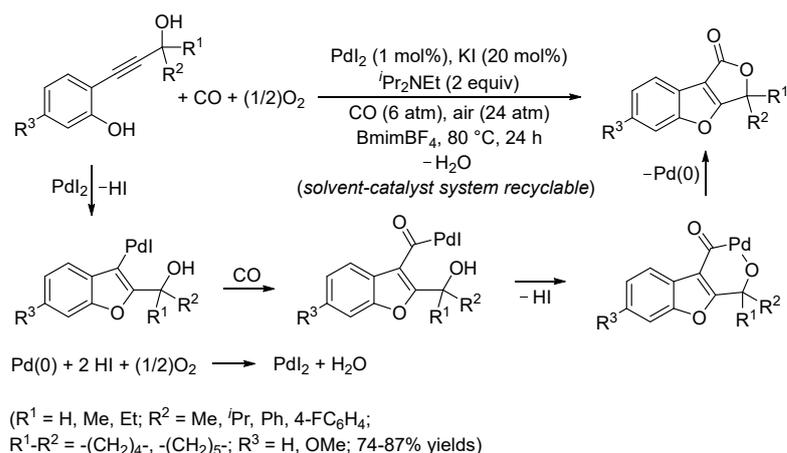
**Scheme 17.** Synthesis of 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)ones by PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of 4-yne-1,3-diols [62–64].

Mechanistically, the process involved an initial 5-*exo-dig* heterocyclization by an intramolecular nucleophilic attack of the terminal hydroxyl group to the triple bond coordinated to Pd(II) followed by carbon monoxide insertion. Intramolecular nucleophilic displacement then took place, probably by forming a palladacycle followed by a reductive elimination, to give the product and Pd(0). The latter was then reoxidized to PdI<sub>2</sub> according to the mechanism we demonstrated several years ago in the PdI<sub>2</sub>/KI-catalyzed oxidative dialkoxycarbonylation of alkynes [71], which involves oxidation of 2 mol of HI (formed during the process) to give I<sub>2</sub> followed by the oxidative addition of I<sub>2</sub> to Pd(0) (Scheme 18; anionic iodide ligands are omitted for clarity) [64].



**Scheme 18.** Proposed mechanism for the PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of 4-yne-1,3-diols leading to 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)ones [64].

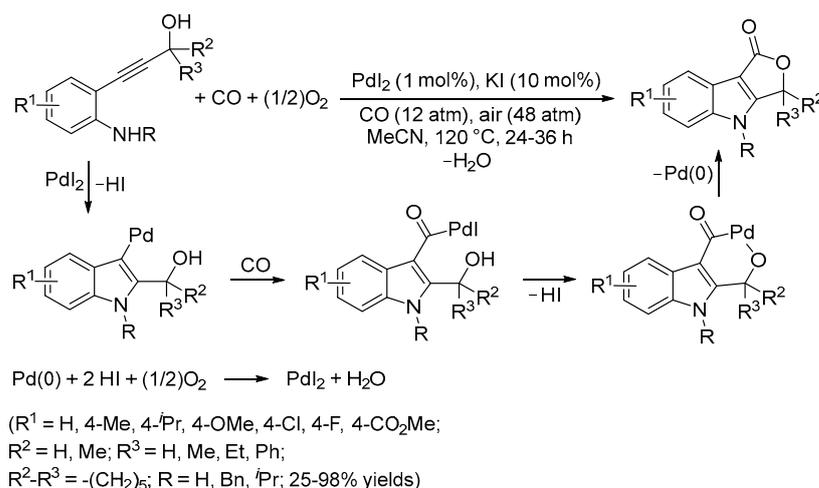
The method was then extended to using 2-(3-hydroxy-1-yn-1-yl)phenols as substrates to give furo[3,4-*b*]benzofuran-1(3*H*)ones in the ionic liquid BmimBF<sub>4</sub> (1-butyl-3-methylimidazolium tetrafluoroborate) as an unconventional solvent (Scheme 19) [72]. The catalyst–solvent system could be conveniently recycled several times without appreciable loss of activity. Interestingly, this process turned out to be unselective when carried out in a classical solvent (such as DME or MeCN), in forming mixtures of the desired furobenzofuranone derivative and the simple benzofuran product from non-carbonylative heterocyclization.



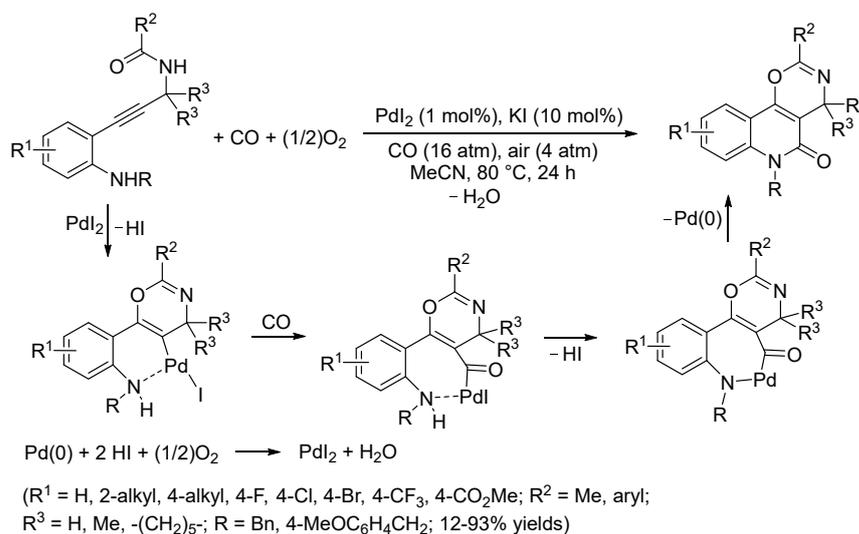
**Scheme 19.** Synthesis of furo[3,4-*b*]benzofuran-1(3*H*)ones by PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of 2-(3-hydroxy-1-yn-1-yl)phenols in ionic liquid BmimBF<sub>4</sub> [72].

In a similar way, starting from 2-(hydroxyprop-1-ynyl)anilines as the substrates, 3,4-dihydrofuro[3,4-*b*]indol-1-ones were synthesized in one step with yields up to 98% from an initial 5-*endo-dig* *N*-heterocyclization followed by cyclocarbonylation (Scheme 20) [65].

Interestingly, the use of the analogue substrates having a secondary propargylaminic moiety rather than the propargylalcoholic group [2-(3-(alkylamino)prop-1-yn-1-yl)anilines] led to a complex reaction mixture when allowed to react under conditions similar to those shown in Scheme 20. However, a selective and novel double cyclization process was observed with the *N*-acyl derivatives, i.e., in the case of *N*-(3-(2-aminophenyl)prop-2-yn-1-yl)acetamides, with formation of 4,6-dihydro-5*H*-[1,3]oxazino[5,6-*c*]quinolin-5-ones. (Scheme 21) [73]. In this case, the reaction began with an intramolecular nucleophilic attack by the amide carbonyl oxygen on the coordinated triple bond leading to 6-*endo-dig* ring closure and the formation of a vinylpalladium intermediate stabilized by coordination of the aniline amino group. Carbon monoxide insertion followed by intramolecular nucleophilic displacement, possibly through the formation of a palladacycle, then delivers the product (Scheme 21) [73].

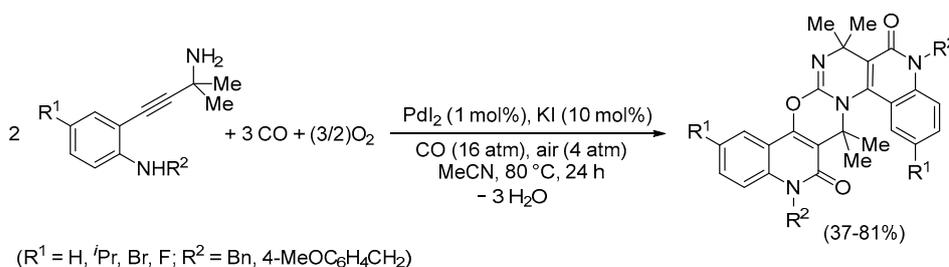


**Scheme 20.** Synthesis of 3,4-dihydrofuro[3,4-*b*]indol-1-ones by PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of 2-(hydroxyprop-1-ynyl)anilines [65].



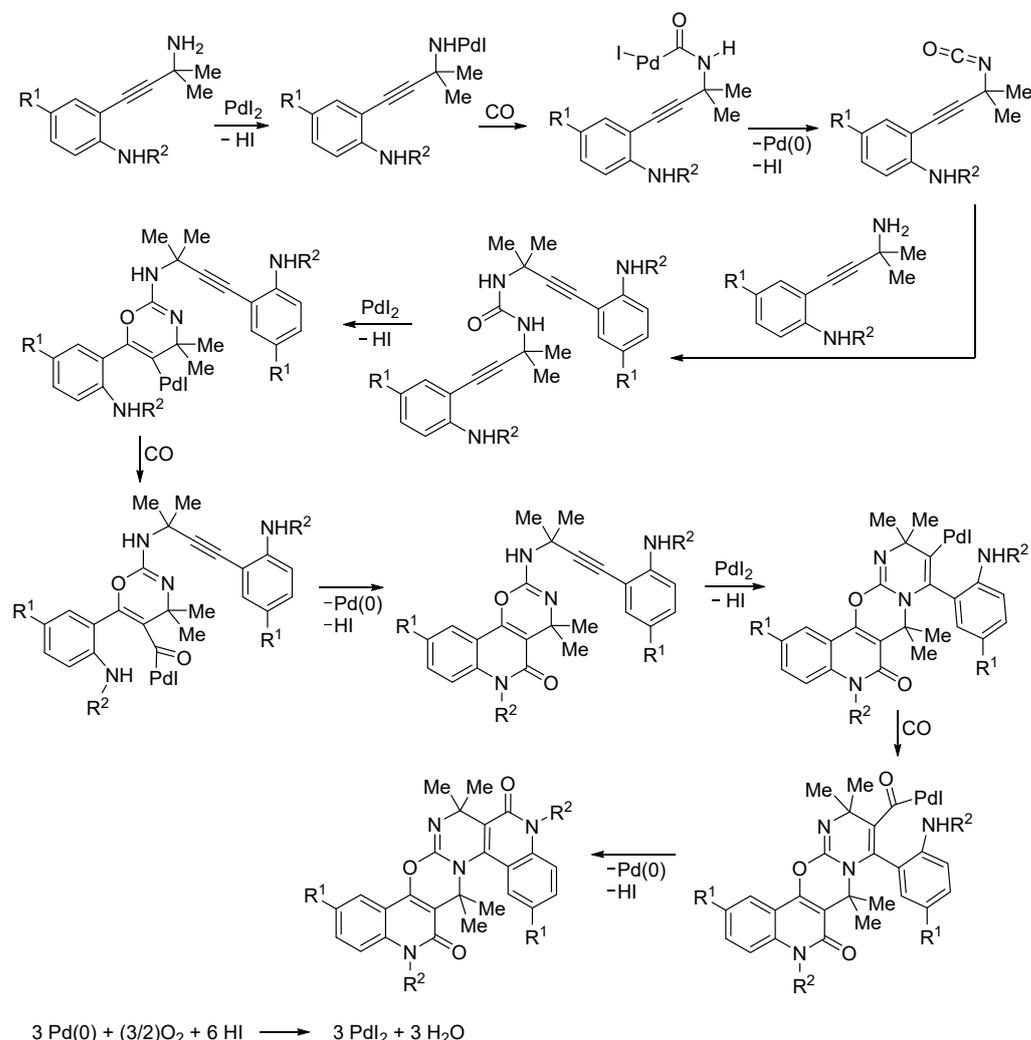
**Scheme 21.** Synthesis of 4,6-dihydro-5*H*-[1,3]oxazino[5,6-*c*]quinolin-5-ones by PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of *N*-(3-(2-aminophenyl)prop-2-yn-1-yl)acetamides [73].

A striking carbonylative tetracyclization process was observed in the case of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines having a primary propargylaminic moiety, which led to 7,7,16,16-tetramethyl-5*H*,14*H*-benzopyrido[3''*A*'':5',6']pyrimido[2',1':2,3][1,3]oxazino[5,6-*c*]quinoline-6,15-diones in one step (Scheme 22) [73].



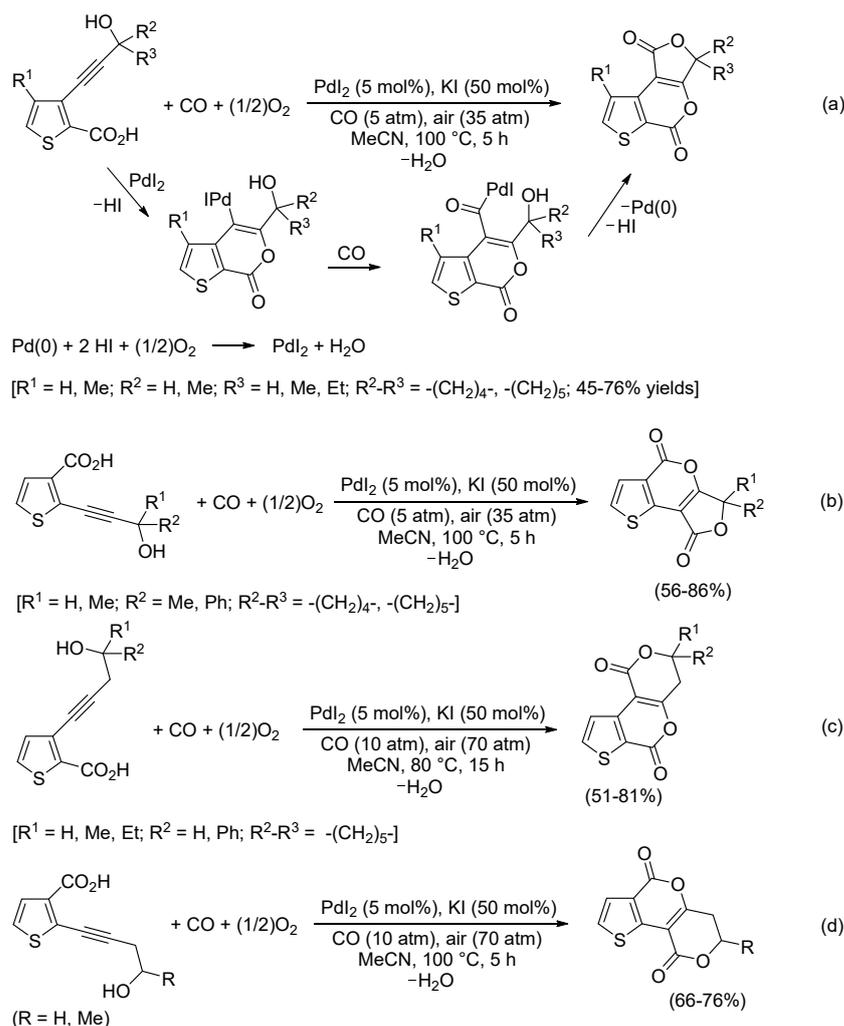
**Scheme 22.** Synthesis of 7,7,16,16-tetramethyl-5*H*,14*H*-benzopyrido[3''*A*'':5',6']pyrimido[2',1':2,3][1,3]-oxazino[5,6-*c*]quinoline-6,15-diones by PdI<sub>2</sub>/KI-catalyzed carbonylative tetracyclization of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines [73].

In fact, these substrates first underwent PdI<sub>2</sub>-catalyzed oxidative carbonylation of the primary amino group to give the corresponding urea [74,75], which then reacted through *O*-6-*endo-dig* cyclization from the ureidic carbonyl group followed by two successive cyclo-carbonylations to yield the final product (Scheme 23) [73].



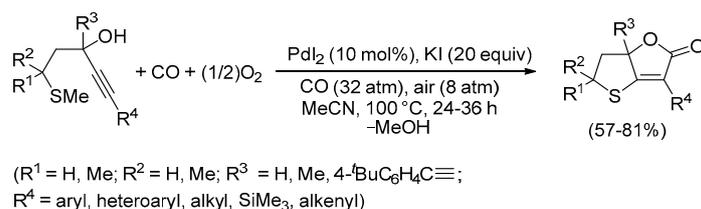
**Scheme 23.** Plausible mechanism for the PdI<sub>2</sub>/KI-catalyzed carbonylative tetracyclization of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines to give 7,7,16,16-tetramethyl-5*H*,14*H*-benzopyrido[3'',4'':5',6']-pyrimido[2',1':2,3][1,3]oxazino[5,6-*c*]quinoline-6,15-diones [73].

More recently, we studied the reactivity of thiophenecarboxylic acids having an  $\omega$ -hydroxyalkynyl substituent in vicinal position under PdI<sub>2</sub>/KI-catalyzed oxidative carbonylation conditions and found that also these substrates underwent carbonylative double cyclization to give previously unknown 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-dione (Scheme 24a), 4*H*-furo[3,4-*b*]thieno[2,3-*d*]pyran-4,8(6*H*)-dione (Scheme 24b), 3,4-dihydro-1*H*,6*H*-pyrano[4,3-*b*]thieno[3,2-*d*]pyran-1,6-dione (Scheme 24c), and 6,7-dihydro-4*H*,9*H*-pyrano[4,3-*b*]thieno[2,3-*d*]pyran-4,9-dione (Scheme 24d) derivatives [76]. The process begins with 6-*endo-dig* cyclization from the carboxylic group followed by cyclocarbonylation, as exemplified in Scheme 24a to synthesize 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-diones from 3-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylic acids [76].



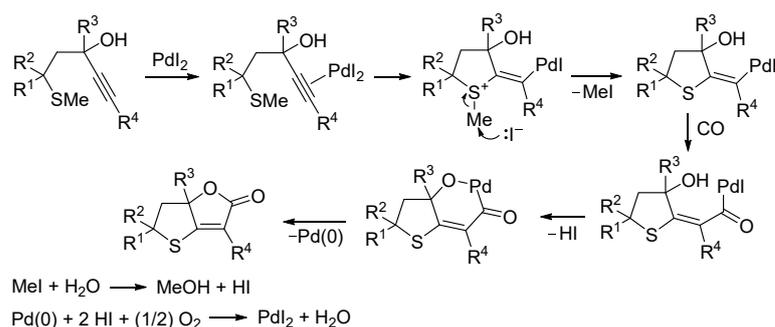
**Scheme 24.** Synthesis of (a) 1H-furo[3,4-b]thieno[3,2-d]pyran-1,5(3H)-diones, (b) 4H-furo[3,4-b]thienopyran-4,8(6H)-diones, (c) 3,4-dihydro-1H,6H-pyrano[4,3-b]thieno[3,2-d]pyran-1,6-diones, and (d) 6,7-dihydro-4H,9H-pyrano[4,3-b]thieno[2,3-d]pyran-4,9-diones by  $\text{PdI}_2$ /KI-catalyzed carbonylative double cyclization of thiophenecarboxylic acids bearing an  $\omega$ -hydroxyalkynyl substituent in vicinal position [76].

We also found that even sulfurated acetylenic substrates, under the right oxidative conditions, can undergo  $\text{PdI}_2$ /KI-catalyzed carbonylative double cyclization. However, considering the instability of the free thiol group to oxygen [77,78], it was necessary to protect the sulfur atom with an easily removable methyl group. This group, in fact, could be removed after cyclization because of the presence of excess iodide anions. Accordingly, starting from 5-(methylthio)-1-yn-3-ols, we were able to synthesize 6,6a-dihydrothieno[3,2-b]furan-2(5H)-ones as a new class of S,O-bicyclic heterocycles as shown in Scheme 25 [79].



**Scheme 25.** Synthesis of 6,6a-dihydrothieno[3,2-b]furan-2(5H)-ones by  $\text{PdI}_2$ /KI-catalyzed carbonylative double cyclization of 5-(methylthio)-1-yn-3-ols [79].

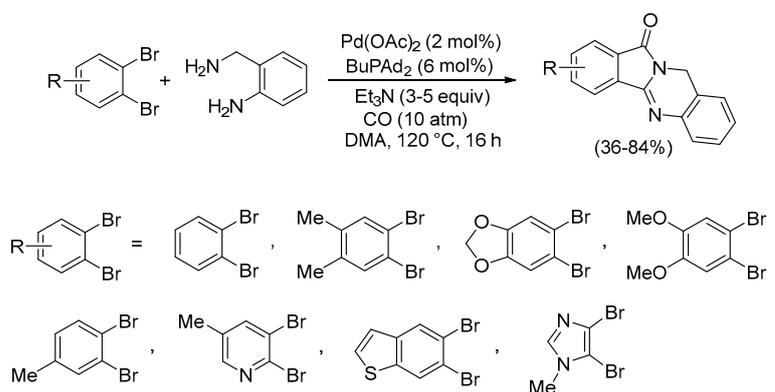
Mechanistically, the process began with 5-*exo-dig* S-cyclization by the intramolecular nucleophilic attack by the sulfur in the thiomethyl group on the triple bond coordinated to PdI<sub>2</sub>. This was followed by demethylation of the ensuing sulfonium cation by the iodide anion, with the formation of the corresponding vinylpalladium intermediate and methyl iodide. The latter readily reacted with water that was initially present as an impurity and then also formed in the final Pd(0) reoxidation step to give MeOH and one mol of HI. On the other hand, the vinylpalladium intermediate underwent carbon monoxide insertion followed by nucleophilic displacement to give the final product together with Pd(0) and a second mol of HI. Lastly, Pd(0) was, as usual, oxidized back to PdI<sub>2</sub> by reacting with 2 mol of HI and 0.5 mol of O<sub>2</sub> (Scheme 26) [79].



**Scheme 26.** Proposed mechanism for the PdI<sub>2</sub>/KI-catalyzed carbonylative double cyclization of 5-(methylthio)-1-yn-3-ols to give 6,6a-dihydrothieno[3,2-*b*]furan-2(5*H*)-ones [79].

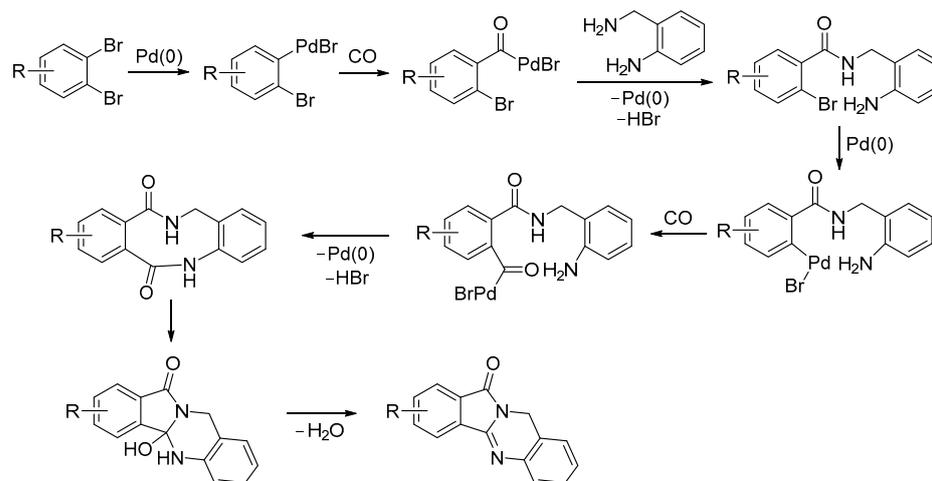
#### 4. Functionalized Halides

Under non-oxidative conditions, suitably functionalized halides may undergo Pd(0)-catalyzed double cyclization leading to high value-added polycyclic heterocyclic compounds. Thus, 1,2-dibromoarenes have been reported by Beller and Wu to undergo carbonylative double cyclization when allowed to react with 2-aminobenzyl amine using Pd(OAc)<sub>2</sub> in the presence of the catalyst precursor BuPAD<sub>2</sub> (Ad = 1-adamantyl) in the solvent *N,N*-dimethylacetamide (DMA) with Et<sub>3</sub>N as the base and under 10 atm of CO. In this manner, several isoindolo[1,2-*b*]quinazolin-12(10*H*)-one derivatives (analogues of the anticancer agent batracylin) were prepared in a 36–84% yield (Scheme 27) [80].



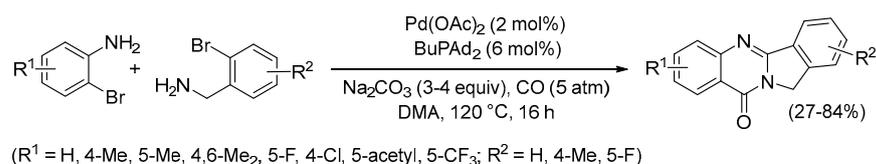
**Scheme 27.** Carbonylative double cyclization of 1,2-dibromoarenes with 2-aminobenzyl amine to yield isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones [80].

The process started with the oxidative addition of a C–Br bond to Pd(0) followed by CO insertion. Then the more nucleophilic benzylic amino group of the diamine caused nucleophilic displacement, which was followed by a further oxidative addition and CO insertion from the second C–Br bond, intramolecular nucleophilic displacement by the second amino group, and intramolecular condensation (Scheme 28) [80].



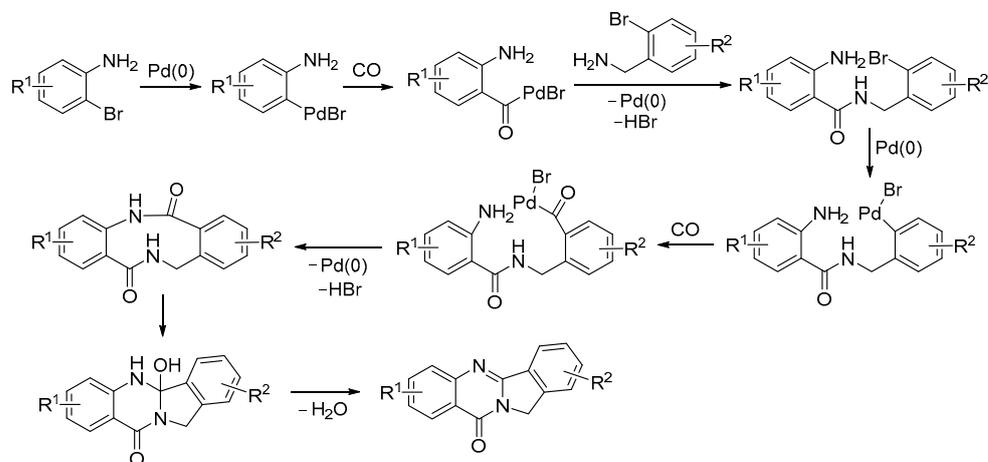
**Scheme 28.** Proposed mechanism for the carbonylative double cyclization of 1,2-dibromoarenes with 2-aminobenzyl amine leading to isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones [80].

In a similar way, and under similar conditions, isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones were synthesized by the Wu group starting from 2-bromoanilines and 2-bromobenzyl amines, as shown in Scheme 29 [81].



**Scheme 29.** Carbonylative double cyclization of 2-bromoanilines with 2-bromobenzyl amines to yield isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones [81].

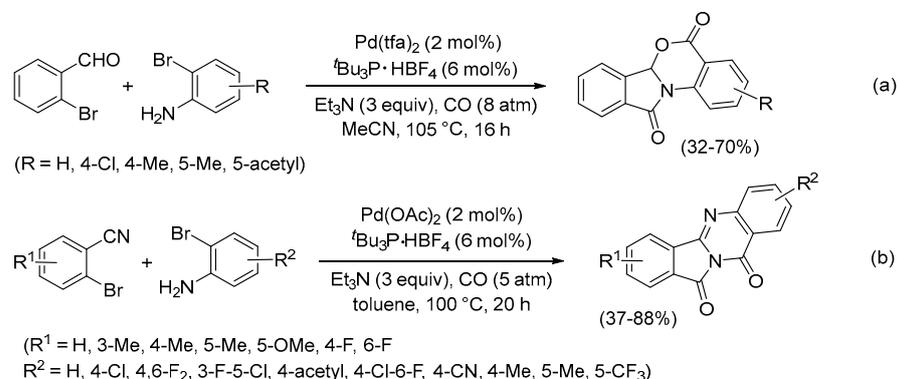
In this case, it was the 2-bromoaniline derivative that underwent initial oxidative addition to Pd(0), followed by CO insertion (Scheme 30). This was followed by nucleophilic displacement by the 2-bromobenzyl amine, the oxidative addition to Pd(0) of the second C-Br bond, CO insertion, intramolecular nucleophilic displacement, and intramolecular condensation (Scheme 30) [81].



**Scheme 30.** Proposed mechanism for the carbonylative double cyclization of 2-bromoanilines with 2-bromobenzyl amines to yield isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones [81].

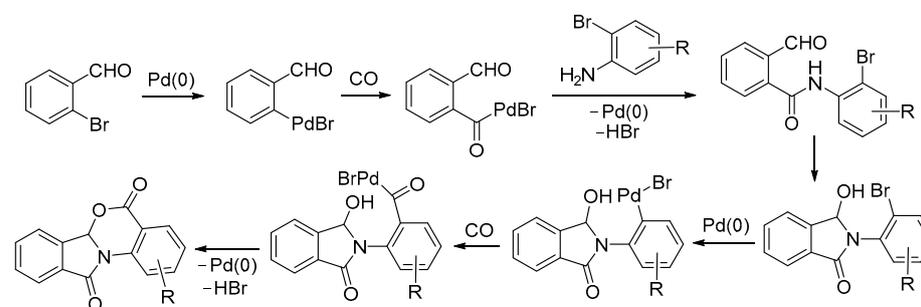
The Beller and Wu group also reported the Pd(0)-catalyzed reaction of 2-bromoanilines with 2-bromobenzaldehyde and CO, which resulted in a carbonylative double cyclization

leading to 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6*aH*)-diones (Scheme 31a) [82]. 2-Bromobenzonitriles also underwent carbonylative double cyclization when allowed to react with 2-bromoanilines to give isoindolo[1,2-*b*]quinazoline-10,12-diones (Scheme 31b) [83].



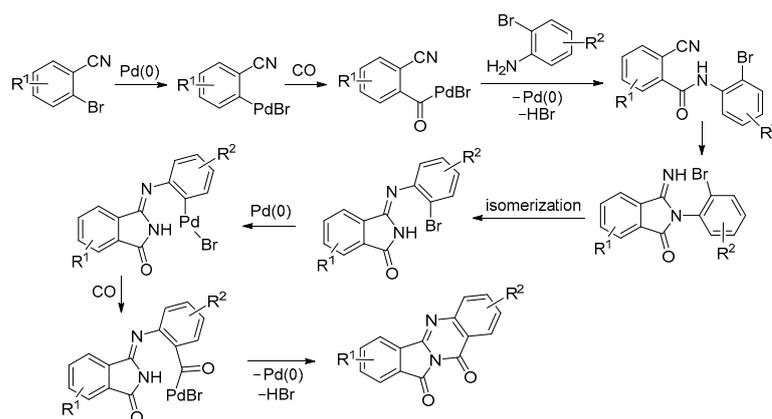
**Scheme 31.** Carbonylative double cyclization of 2-bromoanilines with (a) 2-bromobenzaldehyde to give 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6*aH*)-diones [82] or (b) 2-bromobenzonitriles to give isoindolo[1,2-*b*]quinazoline-10,12-diones [83].

As shown in Scheme 32, the process leading to 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6*aH*)-diones began with the oxidative addition of 2-bromobenzaldehyde to Pd(0), followed by CO insertion and nucleophilic displacement by the amino group of the 2-bromoaniline derivative. Then, there was an intramolecular nucleophilic attack of the nitrogen of the newly formed amido group on the formyl group, followed by the oxidative addition of the second C–Br group to Pd(0), CO insertion, and intramolecular nucleophilic displacement by the hydroxyl group. 2-Bromobenzoic acid could also be employed as a substrate in this reaction in place of 2-bromobenzaldehyde [82].



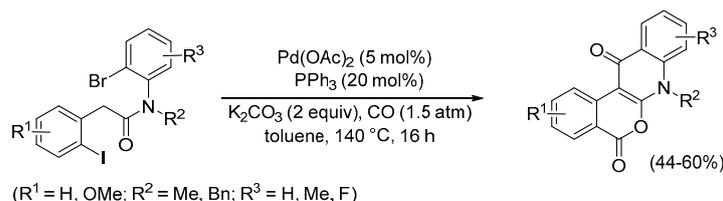
**Scheme 32.** Proposed mechanism for the carbonylative double cyclization of 2-bromoanilines with 2-bromobenzaldehyde to give 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6*aH*)-diones [82].

The first steps of the mechanistic pathway leading to isoindolo[1,2-*b*]quinazoline-10,12-diones are similar to those seen above for the reaction of 2-bromoanilines with 2-bromobenzaldehyde. Thus, the oxidative addition of the 2-bromobenzonitrile derivative was followed by CO insertion, nucleophilic displacement by the 2-bromoaniline, and an intramolecular nucleophilic attack by the nitrogen of the newly formed amide group on the cyano group, which formed the corresponding 2-(2-bromophenyl)-3-iminoisoindolin-1-one derivative (Scheme 33). Then, an unexpected isomerization of this intermediate took place, probably due to steric effects, to give a (*Z*)-3-((2-bromophenyl)imino)isoindolin-1-one intermediate. The oxidative addition of the C–Br bond of the latter to Pd(0) followed by CO insertion and intramolecular nucleophilic displacement delivered the final product (Scheme 33) [83].



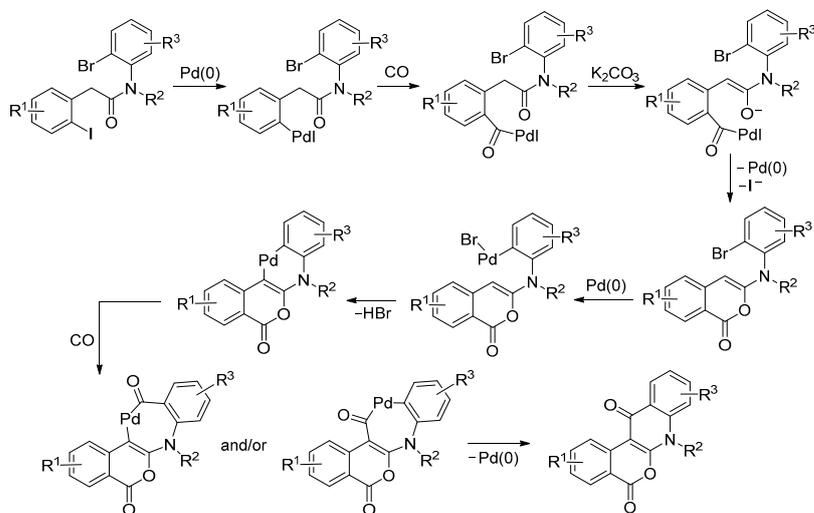
**Scheme 33.** Proposed mechanism for the carbonylative double cyclization of 2-bromoanilines with 2-bromobenzonitriles to give isoindolo[1,2-*b*]quinazoline-10,12-diones [83].

The carbonylative double cyclization of substrates having two aryl halide bonds and a suitable nucleophile, such as an enolate formed in situ under basic conditions, in an appropriate position was also reported, as shown by the synthesis of 5*H*-isochromeno[3,4-*b*]quinoline-5,12(7*H*)-diones starting from *N*-(2-bromophenyl)-2-(2-iodophenyl)acetamides (Scheme 34) [84].



**Scheme 34.** Carbonylative double cyclization of *N*-(2-bromophenyl)-2-(2-iodophenyl)acetamides to give 5*H*-isochromeno[3,4-*b*]quinoline-5,12(7*H*)-diones [84].

In this case, the more reactive C–I bond gave the initial oxidative addition to Pd(0), followed by CO insertion (Scheme 35). Then, intramolecular nucleophilic displacement by the enolate oxygen occurred, which led to the first cyclization. The oxidative addition of the C–Br bond to Pd(0), followed by  $Csp^2$ –H activation, CO insertion, and reductive elimination, eventually gave the final product [84].



**Scheme 35.** Proposed mechanism for the carbonylative double cyclization of *N*-(2-bromophenyl)-2-(2-iodophenyl)acetamides to give 5*H*-isochromeno[3,4-*b*]quinoline-5,12(7*H*)-diones [84].

## 5. Conclusions and Future Perspectives

Catalytic carbonylative double cyclization is a powerful technique for constructing two novel rings in sequential order with the simultaneous incorporation of carbon monoxide in the final product. Starting from simple building blocks, it allows the direct synthesis of high value-added, complex molecular architectures.

So far, several important examples have been reported in the literature, in particular starting from suitably functionalized olefinic, acetylenic, or halide substrates and under the catalysis of either Pd(II) or Pd(0) species. These reactions led to the formation of important polycyclic heterocyclic derivatives, which have shown important biological activity (including anticancer activity) or have been used as precursors to the synthesis of bioactive natural products.

Progress in catalysis is expected to give further impetus to this very attractive field of synthetic chemistry through the discovery of novel and more efficient one-step catalytic processes that produce polycyclic heterocycles with potential applications in fields such as material science and pharmaceutical chemistry.

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