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 catalyst to afford the formation of two new cycles with concomitant incorporation of carbon monoxide as a carbonyl function into 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;

1. Introduction

The importance of the use of carbon monoxide as a C-1 unit in organic synthesis can hardly be overemphasized [1]. Carbon monoxide is a readily available feedstock, which 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_2) [2] and can be installed into an organic substrate, usually under catalytic conditions, with the direct formation of high value added carbonylated compounds with 100% atom economy (carbonylation reactions) [1]. It should also be considered that recent progress in the chemical utilization of carbon dioxide has led to the implementation of efficient methods for the reduction of CO_2 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 a steadily increasing importance both at industrial and academic level, and nowadays a huge number of examples of these important processes has been reported in the scientific as well as 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 the achievement of sophisticated synthetic processes, with formation of complex carbonylated molecular architectures, with potential applications in many fields of science (including drug discovery and material science) in one step. Among processes like these, carbonylative double cyclization processes represent a particularly important methodology, as they allows obtaining the construction of

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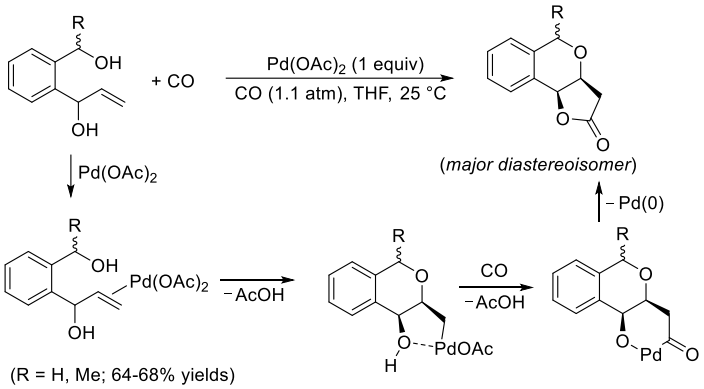
two new cycles in one synthetic procedure with formation of carbonylated polycyclic structures starting from readily available and suitably functionalized substrates.

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-know that palladium(II)-based catalysts are able to activate unsaturated carbon-carbon bonds towards the nucleophilic 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 are able to 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 is able to promote, in one synthetic step, the sequential heterocyclization – cyclocarbonylation of suitably functionalized olefinic substrates, bearing two nucleophilic moieties placed in appropriate positions for undergoing the double cyclization process.

Pioneering studies on this kind of reactivity were conducted by the Semmelhack and Yoshida research groups during the 1980ties. Thus, in 1984 Semmelhack and coworkers 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-2*H*-furo[3,2-*c*]isochromen-2-ones with a *cis* junction between the newly formed rings using a stoichiometric amount of $Pd(OAc)_2$ [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, with 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, through the formation of a palladacycle followed by reductive elimination) (Scheme 1).



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

Interestingly, when a classical reoxidant for Pd(0) such as $CuCl_2$ 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%

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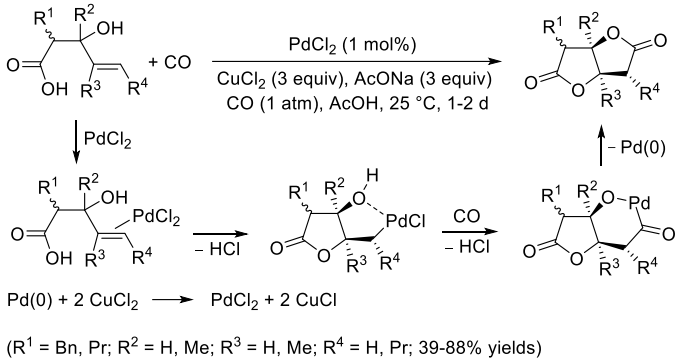
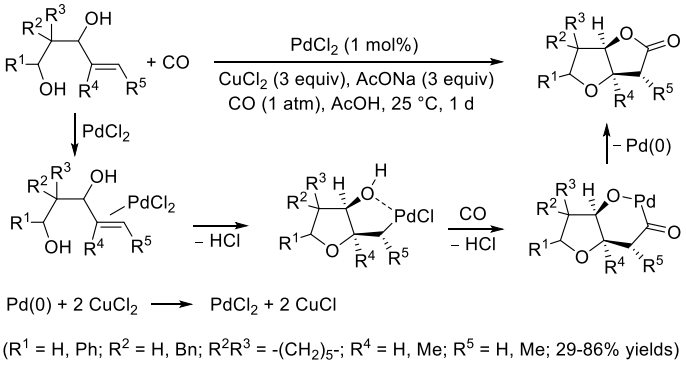
$PdCl_2$ in the presence of 3 equiv of $CuCl_2$ and 3 equiv of AcONa, in glacial acetic acid as the solvent, at room temperature and under 1 atm of CO] (Scheme 2) [8]. The process took place through 5-*exo*-*trig* cyclization (by intramolecular nucleophilic attack of the carboxylic group to the double bond coordinated to the metal center, stabilized by chelation of the hydroxyl) 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-en-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 the construction of this important core by 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.

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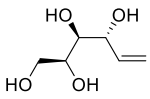
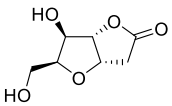
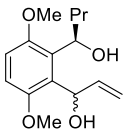
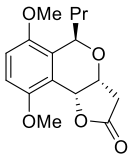
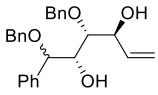
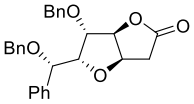
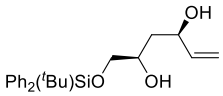
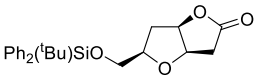
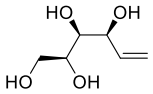
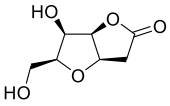
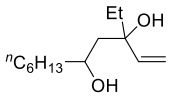
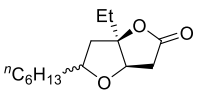
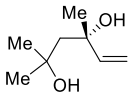
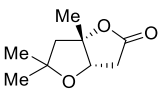
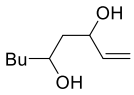
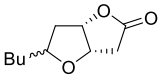
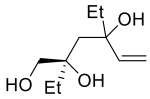
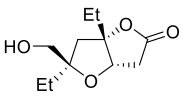
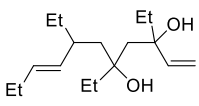
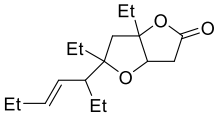
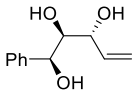
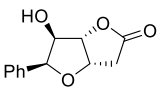
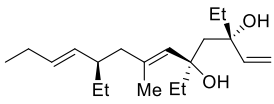
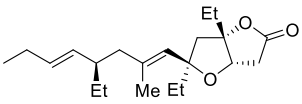
Table 1. Representative examples of the Pd(II)-promoted carbonylative double cyclization of enediol derivatives in the synthesis of natural and bioactive products.

Entry	Conditions	Substrate	Product	Yield (%)	Ref.
1	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 41 h			63	[10]
2	$PdCl_2(MeCN)_2$, (10 mol%), $CuCl_2$ (2.4 equiv), CO (1 atm), THF, 25 °C, 24 h			65	[11]
3	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 8 h			85	[12]
4	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (4 equiv), CO (1 atm), AcOH, 25 °C, 24 h			93	[13]
5	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 33 h			38	[14]
6	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 15 h			>80	[15]
7	$Pd(OAc)_2$ (1.5 equiv), CO (1.1 atm), THF, 23 °C, 4 h			87	[16]
8	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 15 h			81	[17]
9	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C			63	[18]
10	$PdCl_2$, CuCl, AcONa, CO, AcOH			33	[19]
11	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 10 h			85	[20]
12	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 23 °C, 24 h			75	[21]

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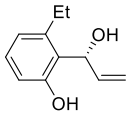
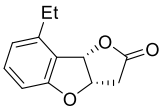
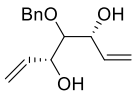
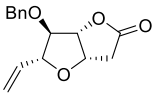
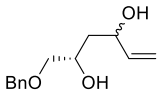
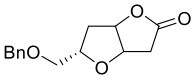
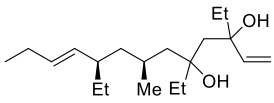
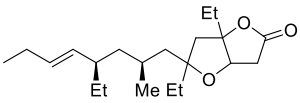
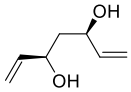
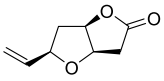
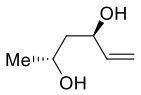
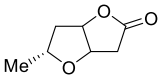
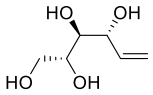
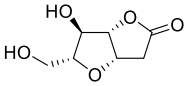
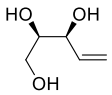
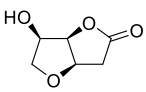
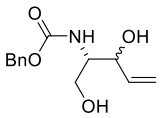
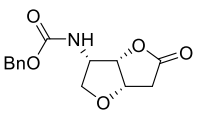
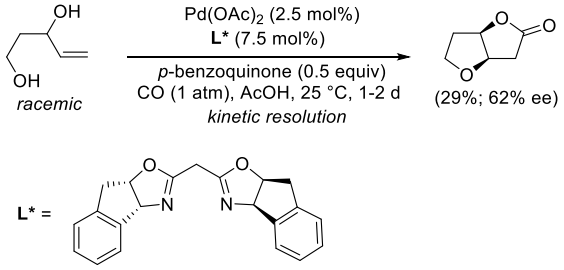
13	$Pd(OAc)_2$ (1.5 equiv), *N*-methylmorpholine (3 equiv), CO, THF			58	[22]
14	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 20 h			65	[23]
15	$Pd(OAc)_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (39 equiv), CO (1 atm), AcOH, 25 °C, 15 h			63, 70	[24, 25]
16	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 24 h			33	[26]
17	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 24 h			87	[27]
18	$PdCl_2$ (10 mol%), $CuCl_2$ (3 equiv), AcONa (3 equiv), CO (1 atm), AcOH, 25 °C, 12 h			61	[28]
19	$PdCl_2(MeCN)_2$ (10 mol%), $CuCl_2$ (5 equiv), AcOLi (5 equiv), $[Fe(CO)_5]$ (0.5 equiv), AcOH, 60 °C, 1 h			47	[29]
20	$PdCl_2(MeCN)_2$ (10 mol%), $Cu(OAc)_2$ (4 equiv), LiCl (4 equiv), $[Fe(CO)_5]$ (0.25 equiv), AcOH, 60 °C, 15 min			67	[30]
21	$PdCl_2(MeCN)_2$ (10 mol%), $CuCl_2$ (4 equiv), AcOLi (4 equiv), $[Fe(CO)_5]$ (0.3 equiv), AcOH, 60 °C, 30 min			75	[31]

Interestingly, using the appropriate enantiopure ligand, kinetic resolution of (±)-pent-4-ene-1,3-diols is possible, with formation of the corresponding bicyclic lactone in noracemic form. This is exemplified by the $Pd(OAc)_2$-catalyzed carbonylation of (±)-pent-4-ene-1,3-diol performed in the presence of an enantiopure bis(oxazoline) ligand and *p*-benzoquinone as external oxidant, to give (3a*R*,6a*R*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one in 29% yield and 62% ee (Scheme 4) [32].



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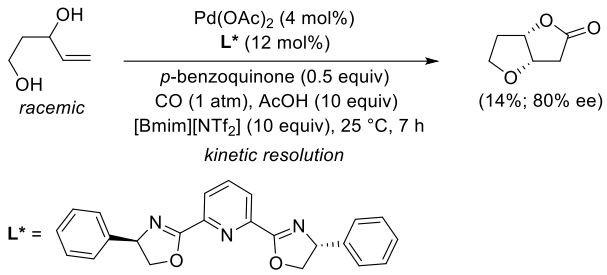
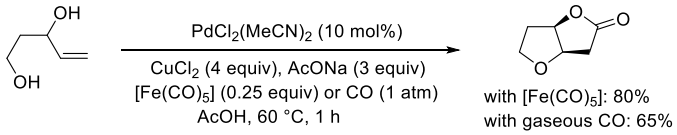
Scheme 4. Kinetic resolution of (±)-pent-4-ene-1,3-diol leading to enantioenriched (3a*R*,6a*R*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one [32].

More recently, the kinetic resolution of (±)-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 $Pd(OAc)_2$, 12 mol% of 2,6-bis[(4*R*)-4-phenyl-2-oxazolinyl]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_2], 10 equiv), as exemplified in Scheme 5 [33].



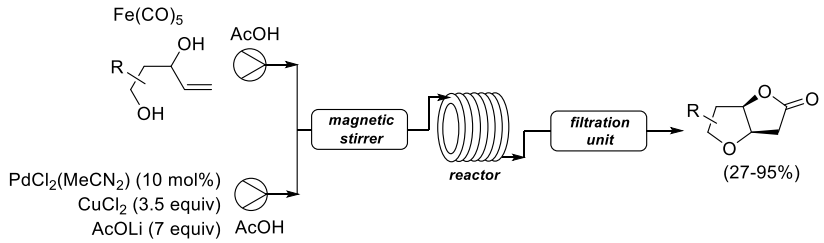
Scheme 5. Kinetic resolution of (±)-pent-4-ene-1,3-diol in [bmim][NTf_2] leading to enantioenriched (3a*S*,6a*S*)-tetrahydrofuro[3,2-*b*]furan-2(3*H*)-one [33].

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



Scheme 6. Carbonylative double cyclization of pent-4-ene-1,3-diol using $[Fe(CO)_5]$ as in situ CO source [34].

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. Carbonylative double cyclization of 4-ene-1,3-diols using $[Fe(CO)_5]$ as in situ CO source under flow conditions [36].

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 nuclophile, with formation of a 6-membered ring. This is exemplified by the formation of 8-((*tert*-butyldimethylsilyl)oxy)-2,6-dioxabicyclo[3.2.1]octan-3-one from 3-((*tert*-butyldimethylsilyl)oxy)pent-4-ene-1,2-diol, as shown in Scheme 8 [37].

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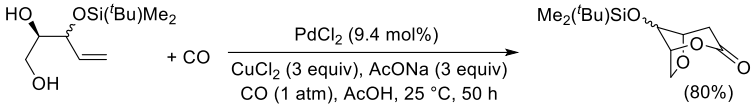
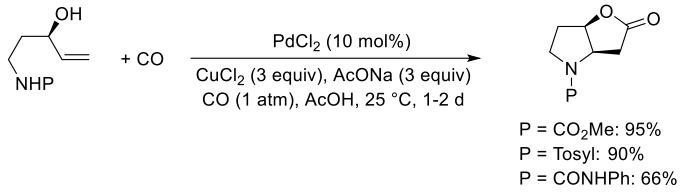


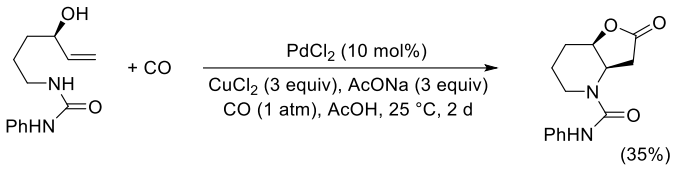
Scheme 8. 5-*exo-trig* *O*-cyclization followed by cyclocarbonylation with 6-membered ring closure [37].

The nucleophilic group undergoing the initial heterocyclization process can also be nitrogen-based. Thus, as early as 1985, the Tamaru and Yoshida group disclosed the Pd(II)-catalyzed carbonylative double cyclization of the *N*-protected 5-aminopent-1-en-3-ols to yield *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 carbamoyl group (P = CONHMe) turned out as the most suitable, as exemplified in Scheme 9 [39].



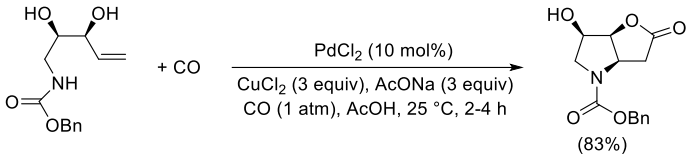
Scheme 9. Formation of 6-hydroxyhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one derivatives from *N*-protected 5-aminopent-1-en-3-ols [39].

As predictable 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 P = CONHPh, as exemplified in Scheme 10 [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 and coworkers reported the carbonylation of benzyl ((2*R*,3*S*)-2,3-dihydroxypent-4-en-1-yl)carbamate (Scheme 11) as a key step in the synthesis of novel 1,4-iminoglycitol derivatives as potential glycosidase inhibitors [40].



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

On the other hand, $PdCl_2$-catalyzed carbonylation of benzyl ((2*S*,3*S*)-2,3-dihydroxypent-4-en-1-yl)carbamate afforded benzyl (3a*R*,6*S*,6a*S*)-6-hydroxy-2-oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxylate in 23% yield (Scheme 12) [41].

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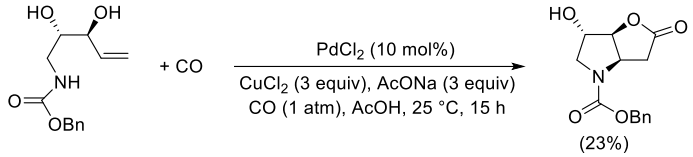
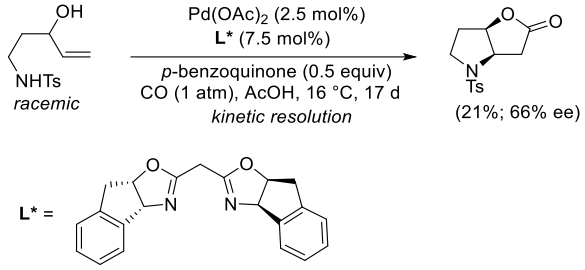


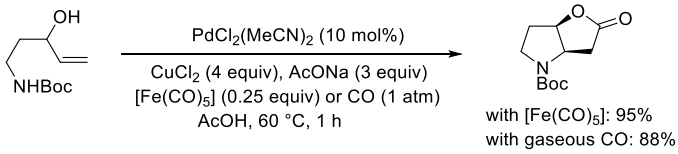
Scheme 12. Synthesis of benzyl (3a*R*,6*S*,6a*S*)-6-hydroxy-2-oxohexahydro-4*H*-furo[3,2-*b*]pyrrole-4-carboxylate from ((2*S*,3*S*)-2,3-dihydroxypent-4-en-1-yl)carbamate [41].

Kinetic resolution of *N*-protected 5-aminopent-1-en-3-ols in the Pd(II)-catalyzed carbonylative double cyclization has been reported by Gracza and coworkers. Thus, using enantiopure bisoxazoline ligands, nonracemic hexahydro-2*H*-furo[3,2-*b*]pyrrol-2-ones could be obtained, as exemplified in Scheme 13 [42].



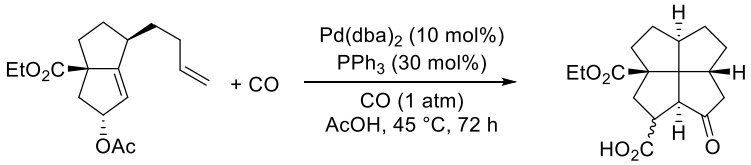
Scheme 13. Kinetic resolution of (±)-*N*-(3-hydroxypent-4-en-1-yl)-4-methylbenzenesulfonamide leading to enantioenriched (3a*R*,6a*R*)-4-tosylhexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one [42].

The gaseous CO-free conditions elaborated group of Gracza for the carbonylation of 4-ene-1,3-diols, involving the use of liquid [Fe(CO)$_5$] as in situ CO source (Scheme 6), have also been successfully employed by the same research team in the Pd(II)-catalyzed carboylative double cyclization of *N*-protected 5-aminopent-1-en-3-ols, as exemplified in Scheme 14 [34].



Scheme 14. Carbonylative double cyclization of *tert*-butyl (3-hydroxypent-4-en-1-yl)carbamate using [Fe(CO)$_5$] as *in situ* CO source [34].

A general approach leading to carbonylative double cyclization is the intramolecular Pauson-Khand reaction starting from suitable enyne substrates. Since several excellent reviews have been published on this reaction [43-45], even in the most recent literature [46-48], this process will not be treated here; however, a particularly striking example is shown in Scheme 15, to give the reader an idea of the powerfulness of this synthetic method for the construction of complex carbonylated polycyclic compounds [49].



Scheme 15. Synthesis of 2a-(ethoxycarbonyl)-8-oxododecahydropentaleno[1,6-*cd*]pentalene-1-carboxylic acid from ethyl 5-acetoxy-1-(but-3-en-1-yl)-2,3,4,5-tetrahydropentalene-3a(1*H*)-carboxylate by Pauson-Khand–type intramolecular reaction [49].

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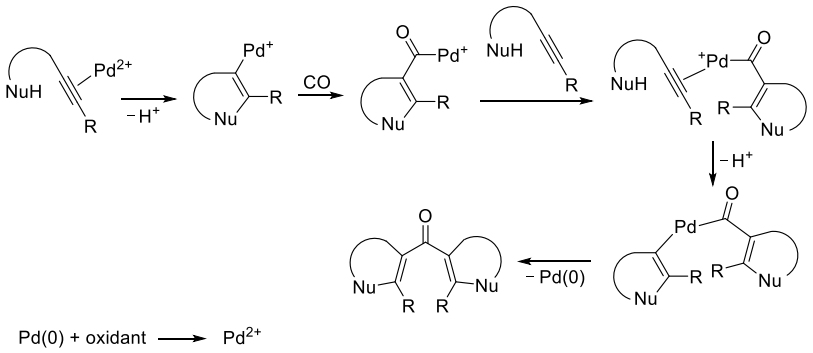
3. Functionalized Acetylenic Substrates

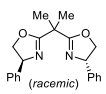
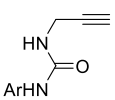
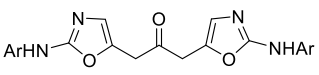
Starting from suitably functionalized acetylenic substrates, bearing a nucleophilic group in appropriate position, Kato and coworkers have reported an interesting Pd(II)-catalyzed carbonylative double cyclization process without CO incorporation into the rings, which leads to di(hetero)cyclic ketones [50]. According to Scheme 16, the process, which has been called by the authors "cyclization-carbonylation-cyclization coupling reaction" or "CCC reaction", starts with the electrophilic activation of the triple bond by a Pd(II) species, followed by intramolecular nucleophilic attack to the activated triple bond, with 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 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 catalytically active Pd(II) by the use of an external oxidant, usually benzoquinone. The system $CuCl_2/O_2$ has also been occasionally used [51], although it should be noted that in this case the $CO–O_2$ mixture employed fell within the explosion limits for a $CO–O_2$ mixture (the $CO-O_2$ mixtures are potentially explosive over a large range of composition: the flammability range for CO in O_2 is 16.7-93.5 % at room temperature and it becomes even larger at higher temperatures [52]).



Scheme 16. The "cyclization-carbonylation-cyclization coupling" concept leading to di(hetero)cyclic ketones [50].

This method has been successfully employed by the group of Kato for the synthesis of a variety of di(heterocyclic)ketones; representative examples are shown in Table 2, entries 1-8. Entry 9 of Table 2 shows a recent extention of the concept to allenic substrates (2-methyl-1-phenyl-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 (%)	Ref.
1	$Pd(tfa)_2$ (5 mol%),  (10 mol%), *p*-benzoquinone (2 equiv), CO (1 atm), MeOH, 0 °C, 5-12 h	 (Ar = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4)		90-92	[50]

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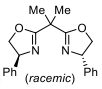
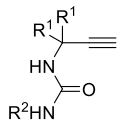
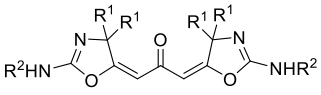
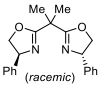
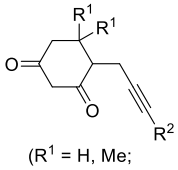
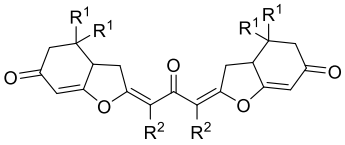
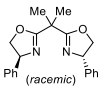
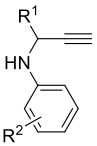
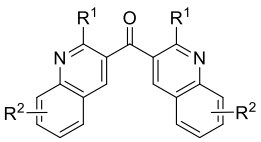
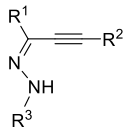
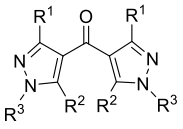
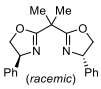
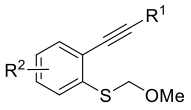
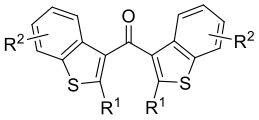
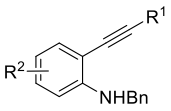
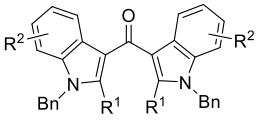
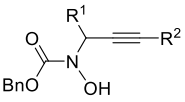
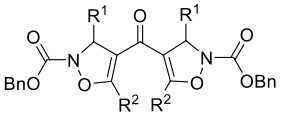
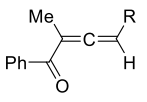
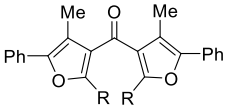
2	Pd(**L**)(tfa)$_2$ (5 mol%), **L** =  *p*-benzoquinone (1.5 equiv), CO (1 atm), MeOH, 7 °C to 25 °C, 18-48 h	 (R^1 = alkyl; R^2 = alkyl, benzyl, aryl)		24-89	[53]
3	Pd(tfa)$_2$ (5-10 mol%),  (7.5-12 mol%), *p*-benzoquinone (2 equiv), CO (1 atm), MeOH, –30 to 0 °C, 2-53 h	 (R^1 = H, Me; R^2 = H, alkyl, aryl)		71-99	[54]
4	Pd(tfa)$_2$ (5 mol%),  (7.5 mol%), *p*-benzoquinone (2 equiv), CO (1 atm), MeOH, 25 °C, 1-63 h	 (R^1 = H, Me; R^2 = H, alkyl, vinyl, $SiEt_3$)		10-89	[55]
5	Pd(**L**)(tfa)$_2$ (5 mol%), **L** =  *p*-benzoquinone (1.5 equiv), CO (1 atm), MeOH, –5 °C to 25 °C, 1-46 h	 (R^1 = H, alkyl; R^2 = alkyl, aryl, $SiMe_3$; R^3 = aryl, tosyl)		70-94	[56]
6	Pd(tfa)$_2$ (5 mol%),  (7.5 mol%), *p*-benzoquinone (1.5 equiv), CO (1 atm), MeOH, –30 °C to 25 °C, 24-144 h	 (R^1 = H, alkyl, aryl, heteroaryl; R^2 = H, Me, Cl, OMe)		75-100	[51, 57]
7	Pd(**L**)(tfa)$_2$ (5 mol%), **L** =  *p*-benzoquinone (1.5 equiv), CO (1 atm), ^{i}PrOH, –5 °C to 15 °C, 47-72 h	 (R^1 = H, alkyl, aryl; R^2 = H, Br, Me, OMe)		73-92	[58]
8	Pd(**L**)(tfa)$_2$ (5 mol%), **L** =  *p*-benzoquinone (1.5 equiv), CO (1 atm), MeOH, –20 °C to 0 °C, 24-76 h	 (R^1 = aryl, alkyl; R^2 = alkyl)		70-94	[59]
9	Pd(**L**)(tfa)$_2$ (5 mol%), **L** =  *p*-benzoquinone (1.5 equiv), CO (1 atm), MeOH, 0 °C to 25 °C, 24-55 h	 (R = alkyl, aryl)		12-86	[60]

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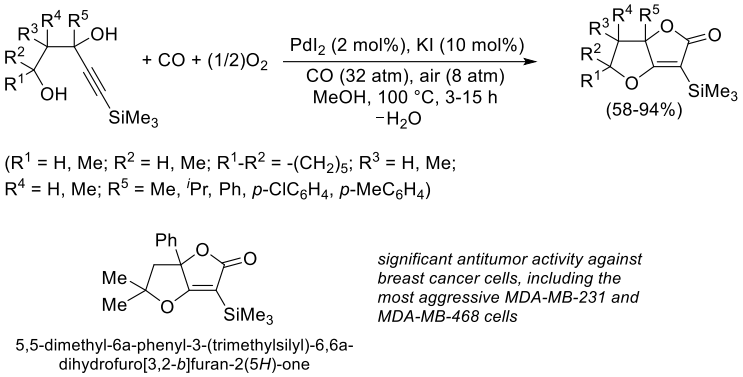
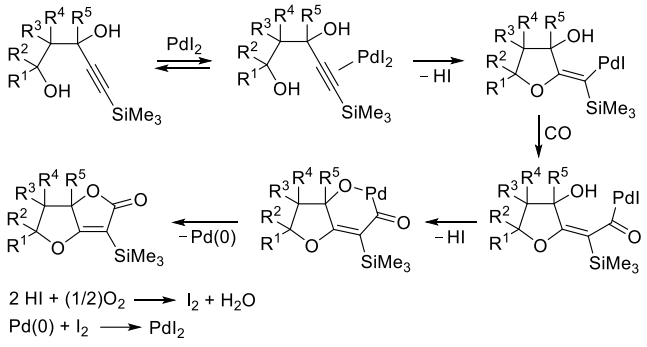
The Pd(II)-catalyzed carbonylative cyclization of functionalized acetylenic derivatives with CO incorporation into the cycle was disclosed by our research group a few years ago [61-64] using the PdI_2/KI catalytic system already successfully employed by us for promoting a plethora of carbonylation reactions [65-69]. Thus, starting from readily available 4-yne-1,3-diols under oxidative conditions (using oxygen from air as benign oxidative agent), novel dihydrofurofuranone derivatives with antitumor activity have been 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 on normal cells (human mammary epithelia cells, MCF-10A, as well as murine fibroblasts 3T3-L1) [61-63].



Scheme 17. Synthesis of 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)ones by PdI_2/KI-catalyzed carbonylative double cyclization of 4-yne-1,3-diols [61-63].

Mechanistically, the process involves an initial 5-*exo-dig* heterocyclization [by 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 takes place (probably, through the formation of a palladacycle followed by reductive elimination), to give the product and Pd(0). The latter is then reoxidized to PdI_2 according to the mechanism we demonstrated several years ago in the PdI_2/KI-catalyzed oxidative dialkoxycarbonylation of alkynes [70], which involves oxidation of 2 mol of HI (formed during the process) by oxygen to give I_2, followed by oxidative addition of I_2 to Pd(0) (Scheme 18; anionic iodide ligands are omitted for clarity) [63].



Scheme 18. Proposed mechanism for the by PdI_2/KI-catalyzed carbonylative double cyclization of 4-yne-1,3-diols leading to 6,6a-dihydrofuro[3,2-*b*]furan-2(5*H*)ones [63].

The method has then been extended to the use of 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 $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) as unconventional solvent (Scheme 19) [71]. The catalyst-solvent system could be conveniently recycled several times without appreciable

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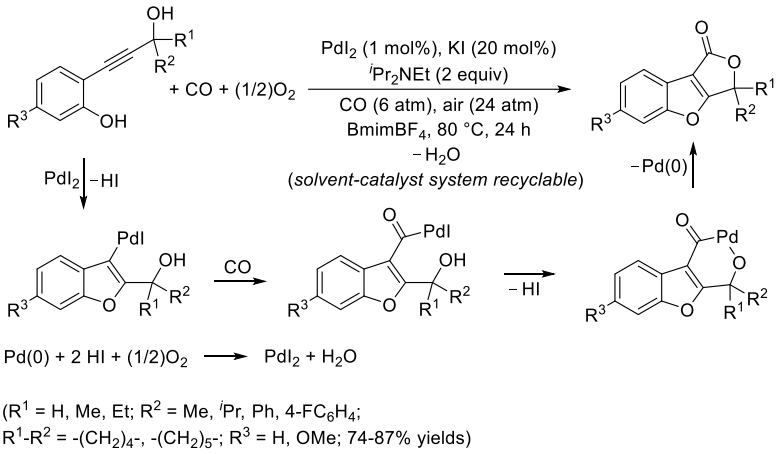
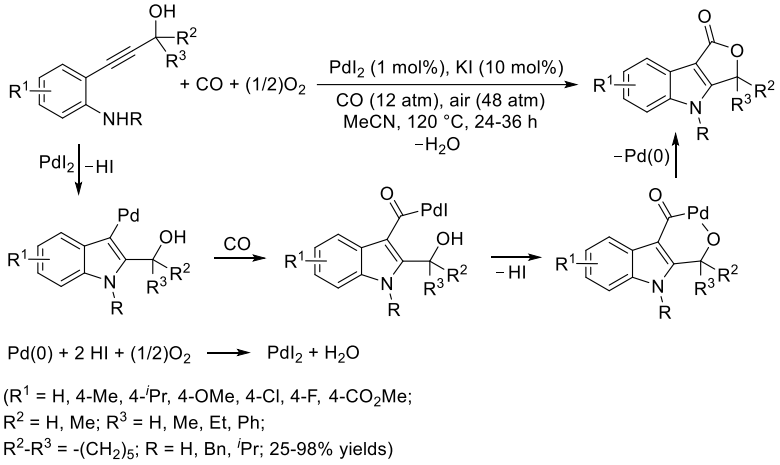
loss of activity. Interestingly, this process turned out to be unselective when carried out in a classical solvent (such as DME or MeCN), with formation of mixtures of the desired furobenzofuranone derivative and the simple benzofuran product deriving from non-carbonylative heterocyclization.



Scheme 19. Synthesis of furo[3,4-*b*]benzofuran-1(3*H*)ones by PdI_2/KI-catalyzed carbonylative double cyclization of 2-(3-hydroxy-1-yn-1-yl)phenols in ionic liquid $BmimBF_4$ [71].

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) [64].



Scheme 20. Synthesis of 3,4-dihydrofuro[3,4-*b*]indol-1-ones by PdI_2/KI-catalyzed carbonylative double cyclization of 2-(hydroxyprop-1-ynyl)anilines [64].

Interestingly, the use of the analogues substrates bearing a secondary propargylaminic moiety rather than the propargylacoholic group [that are, 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) [72]. In this case, the reaction begins with the intramolecular nucleophilic attack by the amide carbonyl oxygen to the coordinated triple bond, with 6-*endo-dig* ring closure and 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) [72].

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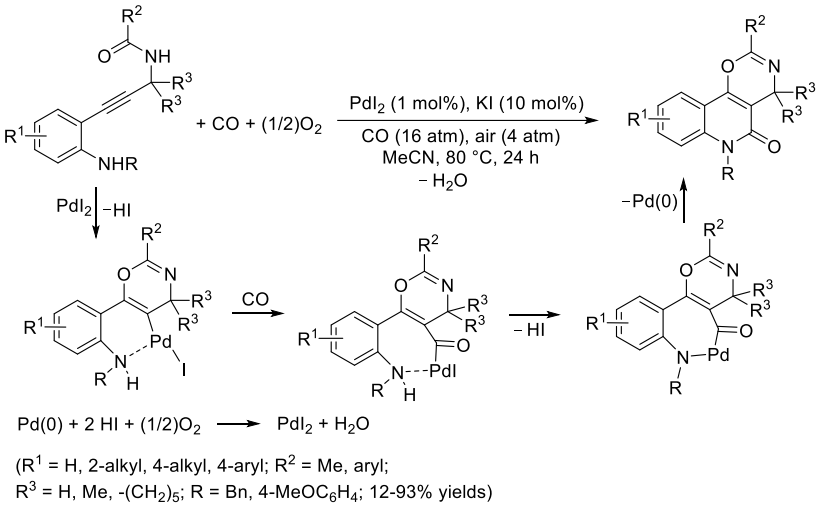
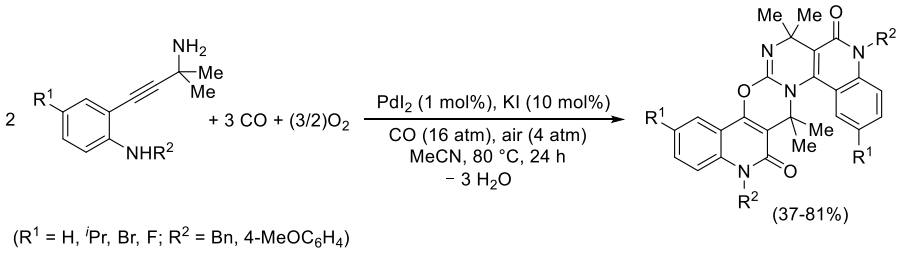


Scheme 21. Synthesis of 4,6-dihydro-5*H*-[1,3]oxazino[5,6-*c*]quinolin-5-ones by PdI_2/KI-catalyzed carbonylative double cyclization of *N*-(3-(2-aminophenyl)prop-2-yn-1-yl)acetamides [72].

A striking carbonylative tetracyclization process was observed in the case of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines, bearing a primary propargylaminic moiety, which led to 7,7,16,16-tetramethyl-5*H*,14H-benzopyrido[3'',4'':5',6']pyrimido[2',1':2,3][1,3]oxazino[5,6-*c*]quinoline-6,15-diones in one step (Scheme 22) [72].



Scheme 22. Synthesis of 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 by PdI_2/KI-catalyzed carbonylative tetracyclization of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines [72].

In fact, these substrates firstly underwent PdI_2-catalyzed oxidative carbonylation of the primary amino group to give the corresponding urea [73, 74], which then reacted through *O*-6-*endo*-*dig* cyclization from the ureidic carbonyl group followed by two cyclocarbonylations in sequence to yield the final product (Scheme 23) [72].

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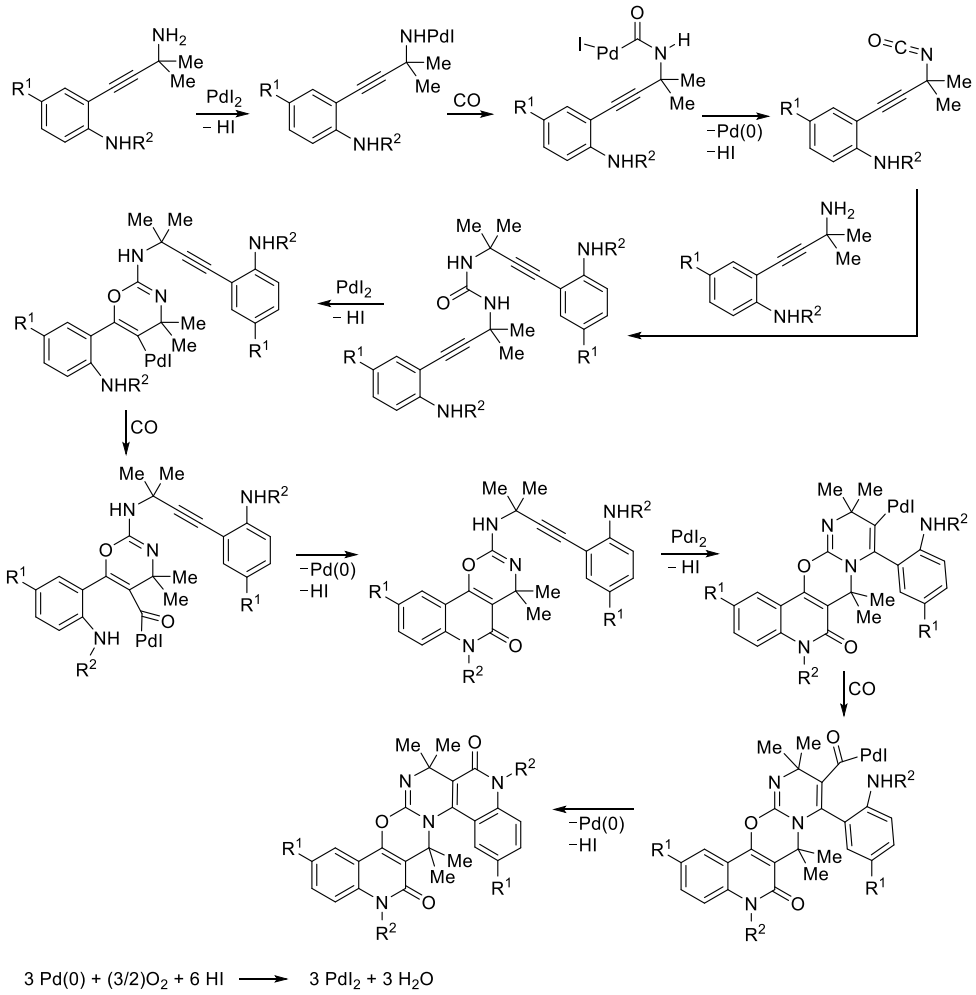

Scheme 23. Plausible mechanism for the PdI_2/KI-catalyzed carbonylative tetracyclization of 2-(3-amino-3-methylbut-1-yn-1-yl)anilines to give 7,7,16,16-tetramethyl-5*H*,14*H*-benzopyrido[3'',4'':5',6']pyrimido[2',1':2,3][1,3]oxazino[5,6-*c*]quinoline-6,15-diones [72].

More recently, we have studied the reactivity of thiophenecarboxylic acids bearing an ω-hydroxyalkynyl substituent in vicinal position under PdI_2/KI-catalyzed oxidative carbonylation consitions, and found that also these substrates are able to undergo carbonylative double cyclization to give previously unknown 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-dione, 4*H*-furo[3,4-*b*]thieno[2,3-*d*]pyran-4,8(6*H*)-dione, 3,4-dihydro-1*H*,6*H*-pyrano[4,3-*b*]thieno[3,2-*d*]pyran-1,6-dione, and 6,7-dihydro-4*H*,9*H*-pyrano[4,3-*b*]thieno[2,3-*d*]pyran-4,9-dione derivatives (Scheme 24) [75].

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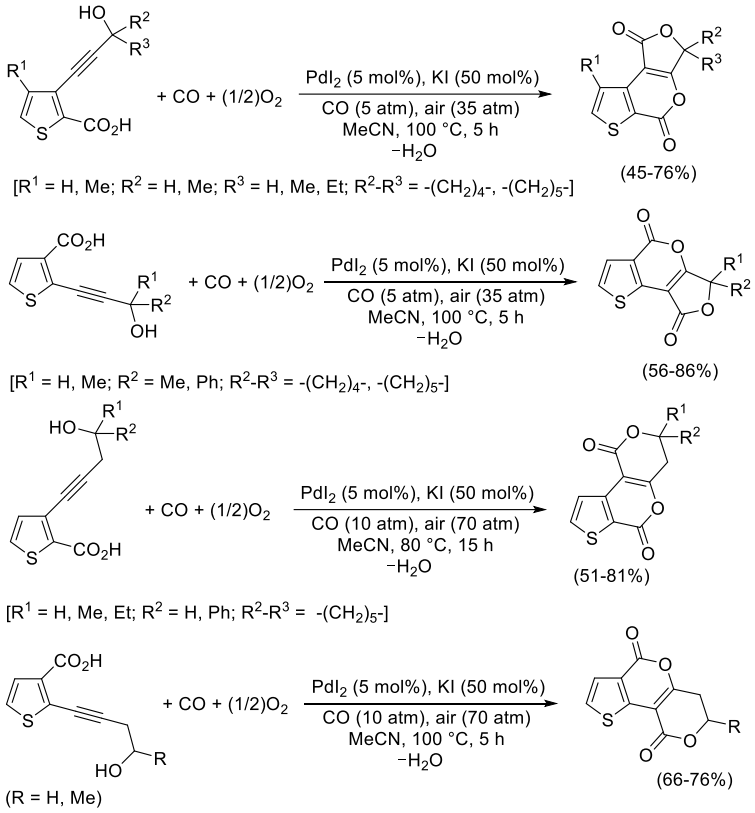
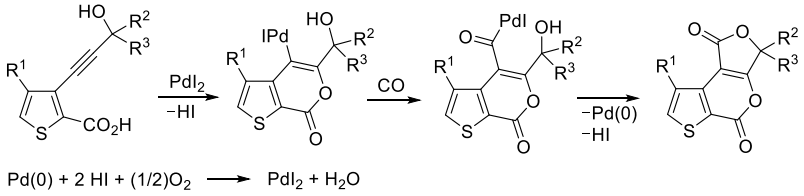


Scheme 24. Synthesis of 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-diones, 4*H*-furo[3,4-*b*]thieno[2,3-*d*]pyran-4,8(6*H*)-diones, 3,4-dihydro-1*H*,6*H*-pyrano[4,3-*b*]thieno[3,2-*d*]pyran-1,6-diones, and 6,7-dihydro-4*H*,9*H*-pyrano[4,3-*b*]thieno[2,3-*d*]pyran-4,9-diones by PdI_2/KI-catalyzed carbonylative double cyclization of thiophenecarboxylic acids bearing an ω-hydroxyalkynyl substituent in vicinal position [75].

The process begins with 6-*endo*-*dig* cyclization from the carboxylic group followed by cyclocarbonylation, as exemplified in Scheme 25 for the synthesis of 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 [75].



Scheme 25. Proposed mechanism for the PdI_2/KI-catalyzed carbonylative double cyclization of 3-(3-hydroxyprop-1-yn-1-yl)thiophene-2-carboxylic acids to give 1*H*-furo[3,4-*b*]thieno[3,2-*d*]pyran-1,5(3*H*)-diones [75].

We have also found that even sulfurated acetylenic substrates, under appropriate conditions, can undergo PdI_2/KI-catalyzed carbonylative double cyclization. However, considering the instability of the free thiol group under the oxidative conditions employed [76, 77], it is necessary in this case to protect the sulfur atom with a methyl group, which can be easily removed, after cyclization, under the reaction conditions thanks to the presence of the excess of iodide anions. Accordingly, starting from 5-(methylthio)-1-yn-3-ols, we have been able to synthesize 6,6a-dihydrothieno[3,2-*b*]furan-2(5*H*)-ones as a new class of *S*,*O*-bicyclic heterocycles, as shown in Scheme 26 [78].

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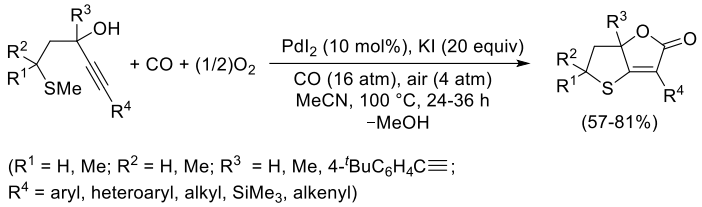
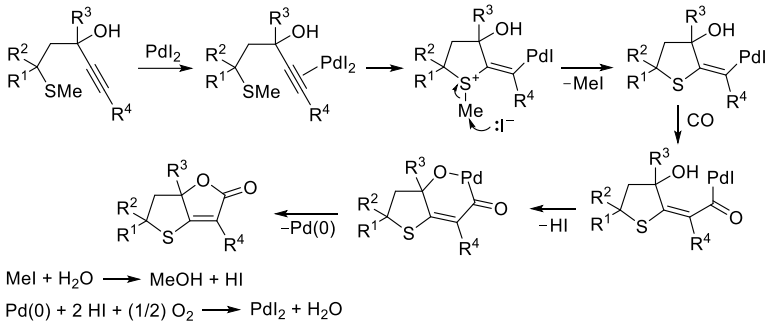


Scheme 26. Synthesis of 6,6a-dihydrothieno[3,2-*b*]furan-2(5*H*)-ones by PdI_2/KI-catalyzed carbonylative double cyclization of 5-(methylthio)-1-yn-3-ols [78].

Mechanistically, the process begins with 5-*exo*-*dig* *S*-cyclization by intramolecular nucleophilic attack of the sulfur of the thiomethyl group to the triple bond coordinated to PdI_2. This is followed by demethylation of the ensuing sulfonium cation by the iodide anion, with formation of the corresponding vinylpalladium intermediate and methyl iodide. The latter readily reacts with water [initially present as 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 intermediates undergoes carbon monoxide insertion followed by nucleophilic displacement to give tha final product together with Pd(0) and a second mol of HI. Lastly, Pd(0) is, as usual, oxidized back to PdI_2 by its reaction with 2 mol of HI and 0.5 mol of O_2 (Scheme 27) [78].



Scheme 27. Proposed mechanism for the PdI_2/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 [78].

4. Functionalized Halides

Under non-oxidative conditions, suitably functionalized halides may undergo interesting Pd(0)-catalyzed double cyclization processes 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 $Pd(OAc)_2$ in the presence of $BuPAd_2$ (Ad = 1-adamantly) as the catalyst precursor, in *N*,*N*-dimethylacetamide (DMA) as the solvent, with Et_3N as 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) have been prepared in 36-84% yield (Scheme 28) [79].

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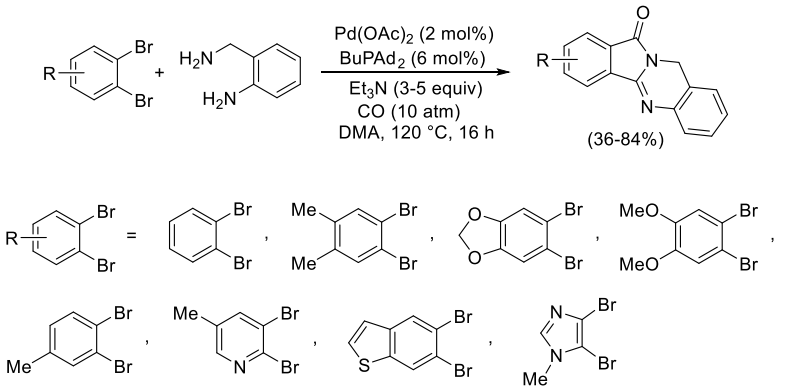
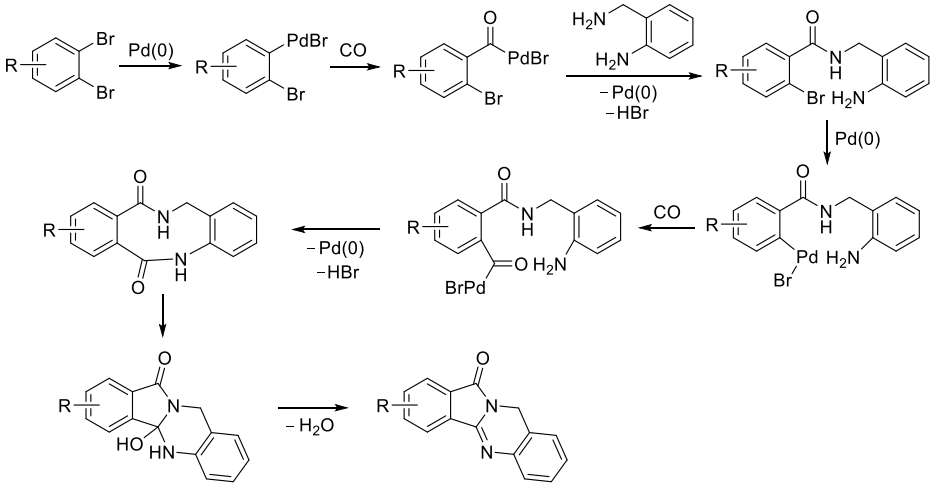


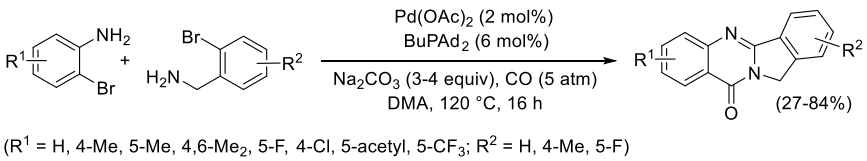
Scheme 28. Carbonylative double cyclization of 1,2-dibromoarenes with 2-aminobenzyl amine to yield isoindolo[1,2-*b*]quinazolin-12(10*H*)-ones [79].

Mechanistically, the process starts with the oxidative addition of a C–Br bond to Pd(0), followed by CO insertion. Then, nucleophilic displacement by the more nucleophilic benzylic amino group of the diamine takes place, followed by further oxidative addition and CO insertion from the second C–Br bond, intramolecular nucleophilic displacement by the second amino group, and intramolecular condensation (Scheme 29) [79].



Scheme 29. 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 [79].

In a similar way, and under similar conditions, isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones have been synthesized by the Wu's group starting from 2-bromoanilines and 2-bromobenzyl amines, as shown in Scheme 30 [80].



(R^1 = H, 4-Me, 5-Me, 4,6-Me_2, 5-F, 4-Cl, 5-acetyl, 5-CF_3; R^2 = H, 4-Me, 5-F)

Scheme 30. Carbonylative double cyclization of 2-bromoanilines with 2-bromobenzyl amines to yield isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones [80].

In this case, it is the 2-bromoaniline derivative that undergoes initial oxidative addition to Pd(0), followed by CO insertion (Scheme 31). This is followed by nucleophilic displacement by the 2-bromobenzyl amine, oxidative addition to Pd(0) of the second C–Br

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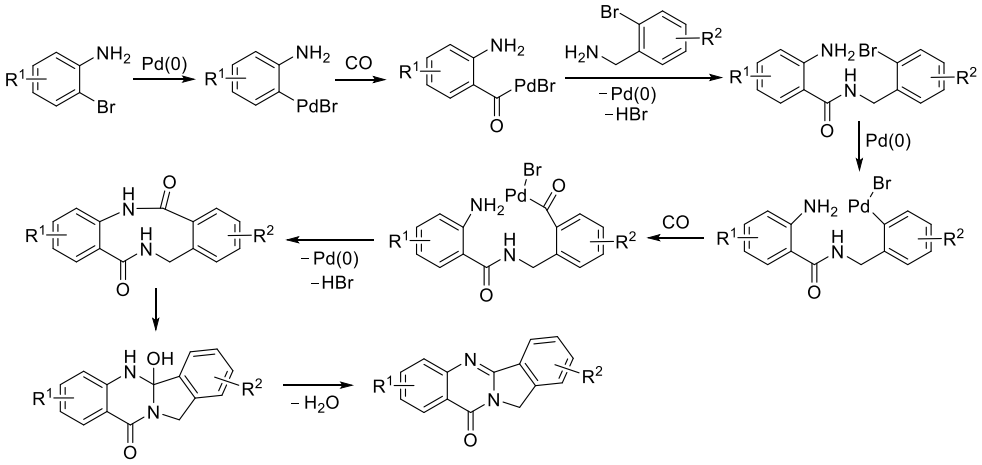
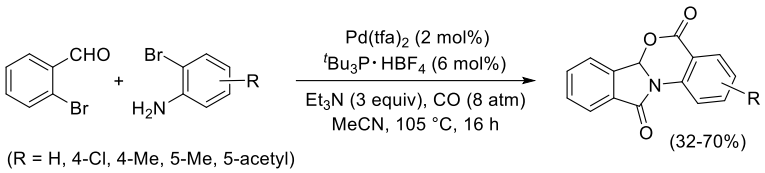
bond, CO, insertion, intramolecular nucleophilic displacement and intramolecular condensation (Scheme 31) [80].



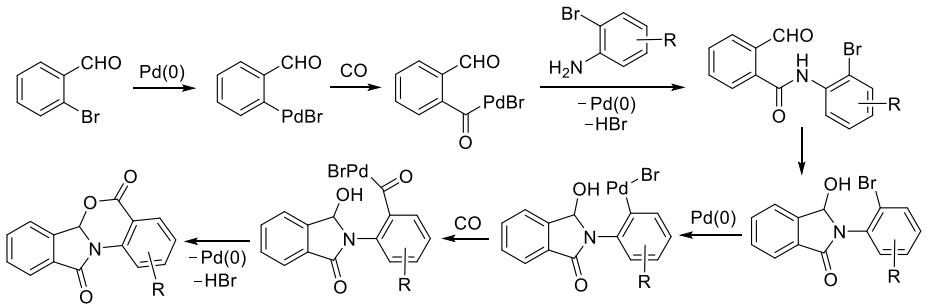
Scheme 31. Proposed mechanism for the carbonylative double cyclization of 2-bromoanilines with 2-bromobenzyl amines to yield isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones [80].

The group of Beller and Wu 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(6a*H*)-diones (Scheme 32) [81].



Scheme 32. 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(6a*H*)-diones [81].

As shown in Scheme 33, the process begins 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, intramolecular nucleophilic attack of the nitrogen of the newly formed amido group to the formyl group takes place, followed by a second 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 substrates in this reaction in place of 2-bromobenzaldehyde [81].



Scheme 33. 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(6a*H*)-diones [81].

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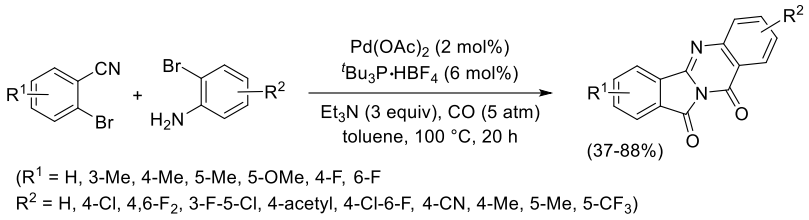
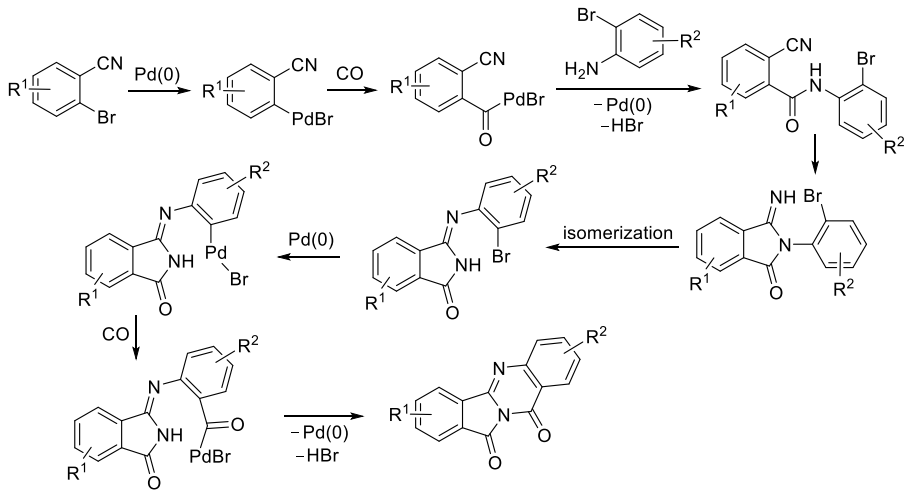
2-Bromobenzonitriles also underwent carbonylative double cyclization when allowed to react with 2-bromoanilines, to afford isoindolo[1,2-*b*]quinazoline-10,12-diones (Scheme 34) [82].



Scheme 34. Carbonylative double cyclization of 2-bromoanilines with 2-bromobenzonitriles to give isoindolo[1,2-*b*]quinazoline-10,12-diones [82].

The first steps of the mechanistic pathway are similar to those seen above for the reaction with 2-bromobenzaldehyde. Thus, oxidative addition of the 2-bromobenzonitrile derivative was followed by CO insertion, nucleophilic displacement by the 2-bromoaniline, and intramolecular nucleophilic attack of the nitrogen of the newly formed amido group to the cyano group, with formation of the corresponding 2-(2-bromophenyl)-3-iminoisoindolin-1-one derivative (Scheme 35). Then, an unexpected isomerization of this intermediate takes place, probably due to steric effects, to give a (*Z*)-3-((2-bromophenyl)imino)isoindolin-1-one intermediate. Oxidative addition of the C–Br bond of the latter to Pd(0), followed by CO insertion and intramolecular nucleophilic displacement deliver the final product (Scheme 35) [82].



Scheme 35. Proposed mechanism for the carbonylative double cyclization of 2-bromoanilines with 2-bromobenzonitriles to give isoindolo[1,2-*b*]quinazoline-10,12-diones [82].

The carbonylative double cyclization of substrates bearing two aryl halide bonds and a suitable nucleophile (such as an enolate, formed in situ under basic conditions) in appropriate position has also been 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 36) [83].

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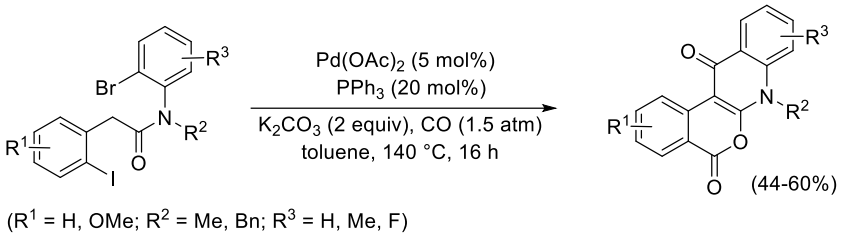
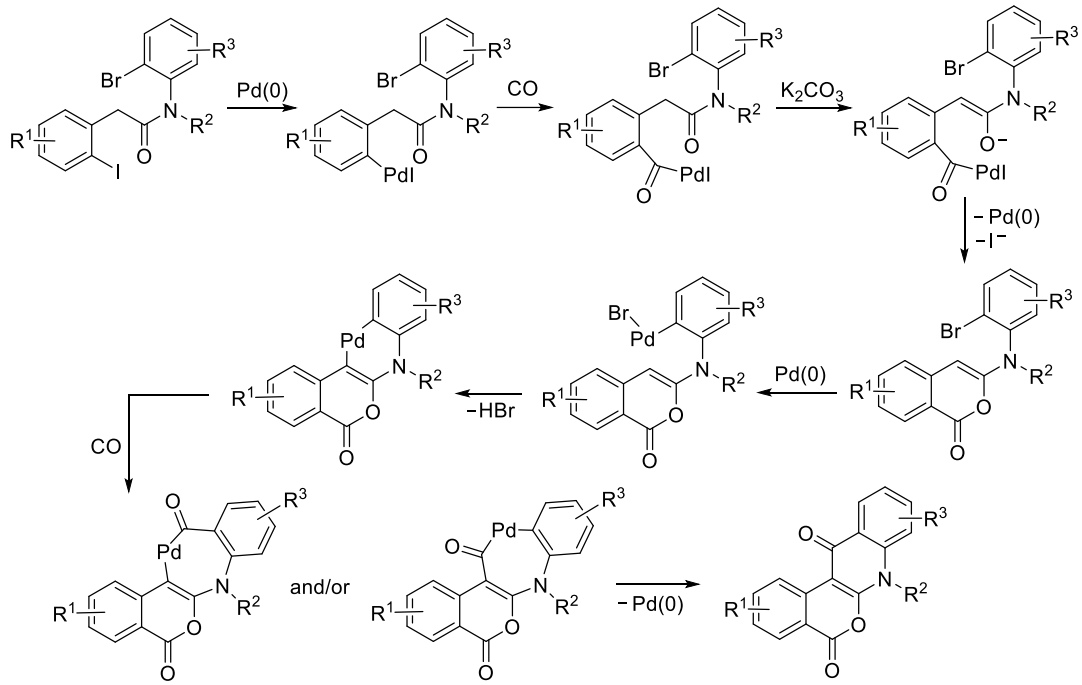


Scheme 36. Carbonylative double cyclization of *N*-(2-bromophenyl)-2-(2-iodophenyl)acetamides to give 5*H*-isochromeno[3,4-*b*]quinoline-5,12(7*H*)-diones [83].

In this case, the more reactive C–I bond gives the initial oxidative addition to Pd(0), followed by CO insertion (Scheme 37). Then, intramolecular nucleophilic displacement by the enolate oxygen takes place, which leads to the first cyclization. Oxidative addition of the C–Br bond to Pd(0), followed by C*sp*²–H activation, CO insertion, and reductive elimination eventually gives the final product [83].



Scheme 37. 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 [83].

4. Conclusions and Future Perspectives

Catalytic carbonylative double cyclization is a powerful methodology for the construction of two novel rings in sequential order with the simultaneous incorporation of carbon monoxide into the final product, which allows, starting from simple building blocks, the direct synthesis of high value added, complex molecular architectures.

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

In the next future, progress in catalysis is expected to give a further impulse to this very attractive field of synthetic chemistry, with the discovery of novel and more efficient

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catalytic processes able to afford in one step polycyclic heterocycles with potential applications in many fields of science (including material science and pharmaceutical chemistry).

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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