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Review

PdI_2-Based Catalysis for Carbonylation Reactions: A Personal Account

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Abstract: In this account, we review our efforts in the field of carbonylation reactions promoted by palladium iodide-based catalysts, which have proven to be particularly efficient in diverse kinds of carbonylation processes (oxidative carbonylations as well as additive and substitutive carbonylations). Particularly in the case of oxidative carbonylations, more emphasis has been given to the most recent results and applications.

Keywords: carbon monoxide; carbonylation; heterocycles; homogeneous catalysis; palladium; palladium iodide

1. Introduction

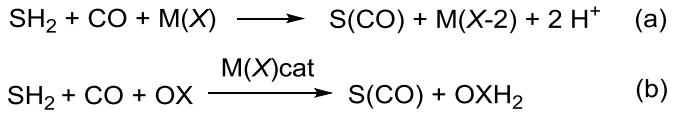
Metal-catalyzed carbonylation reactions are very important processes in industrial chemistry and organic synthesis, since they allow the direct incorporation of the simplest C-1 unit (carbon monoxide) into a substrate, with the direct formation of high value-added carbonylated compounds [1–30].

In this field, our research group has been active for many years. In particular, by employing palladium iodide-based catalysts, many carbonylation reactions have been developed, under oxidative as well as non-oxidative conditions. We have previously reviewed our efforts on oxidative carbonylations and carbonylative synthesis of heterocycles [23–30]. In this personal account, we will describe our achievements on PdI_2-catalyzed carbonylations leading to various carbonyl compounds under oxidative as well as non-oxidative conditions. Particularly in the case of oxidative carbonylations, more emphasis will be given to the most recent results and applications.

2. PdI_2-Catalyzed Oxidative Carbonylations

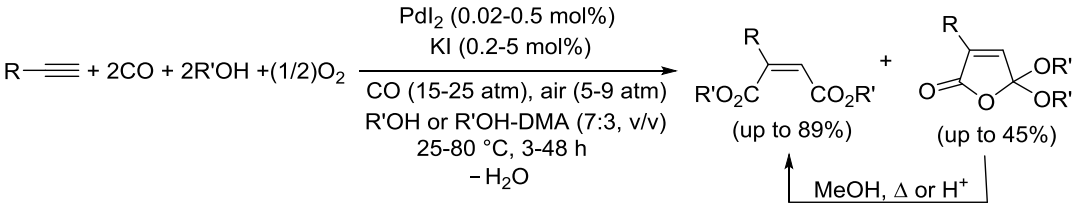
2.1. Background: PdI_2-Catalyzed Oxidative Dialkoxycarbonylation of Alkynes

According to the literature [26], in organic synthesis, oxidative carbonylation is a process in which carbon monoxide (CO) is inserted into (an) organic substrate(s) (SH_2) to yield a carbonylated product [S(CO)], under the promoting action of a metal species [M(*X*)], which is reduced to M(*X*-2) at the end of the process (Scheme 1a). A catalytic version of this reaction is achieved when operating in the presence of a suitable external oxidant (OX), able to reoxidize M(*X*-2) back to M(*X*), with the formation of OXH_2 (Scheme 1b) [26].

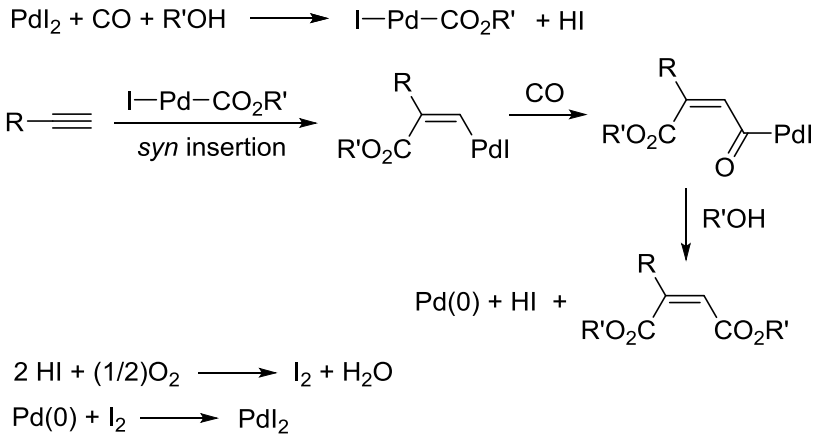


Scheme 1. (**a**) Oxidative carbonylation of organic substrate SH_2 promoted by the metal species M(*X*); (**b**) M(*X*)-catalyzed oxidative carbonylation of SH_2 in the presence of the external oxidant OX [26].

At the beginning of the nineties, we reported that a very simple palladium-based catalytic system, consisting of PdI_2 in conjunction with an excess of KI, was a very efficient catalyst for promoting the oxidative dialkoxycarbonylation of terminal alkynes, carried out with oxygen as the external oxidant, with the formation of maleic diesters and their cyclic tautomers in high yields and excellent TONs (Scheme 2) [31,32]. Later on, we found that, using water as the nucleophile under suitable conditions, it was also possible to effectively synthesize maleic anhydrides or acids [33]. The excess of KI was necessary to solubilize PdI_2 in the alcoholic solvent and to stabilize the catalytically active species PdI_4^{2-}. The main reason for the high efficiency shown by this complex was related to a very efficient reoxidation of Pd(0), through a mechanism involving the initial oxidation of the 2 equiv of HI (ensuing from the carbonylation process) to I_2 followed by the oxidative addition of the latter to Pd(0) (Scheme 3; in this and in all the following Schemes in this account, unreactive iodide ligands are omitted for clarity). The formation of maleic diesters can be rationalized by triple bond *syn* insertion into an alkoxycarbonylpalladium iodide complex (formed by the reaction between PdI_2, R'OH, and CO) followed by carbon monoxide insertion and nucleophilic displacement by R'OH (Scheme 3) [32,34–36].



Scheme 2. Synthesis of maleic diesters by PdI_2/KI-catalyzed oxidative dialkoxycarbonylation of terminal alkynes (DMA = *N*,*N*-dimethylacetamide) [32].

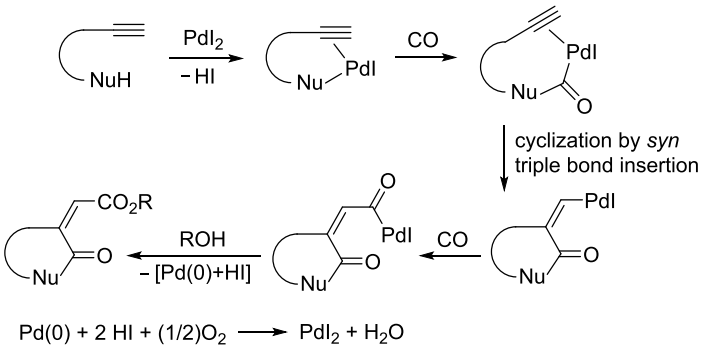


Scheme 3. Mechanism of the formation of maleic diesters by PdI_2/KI-catalyzed oxidative dialkoxycarbonylation of terminal alkynes [32].

2.2. PdI_2-Catalyzed Oxidative Cyclocarbonylation-Alkoxycarbonylation of Functionalized Alkynes

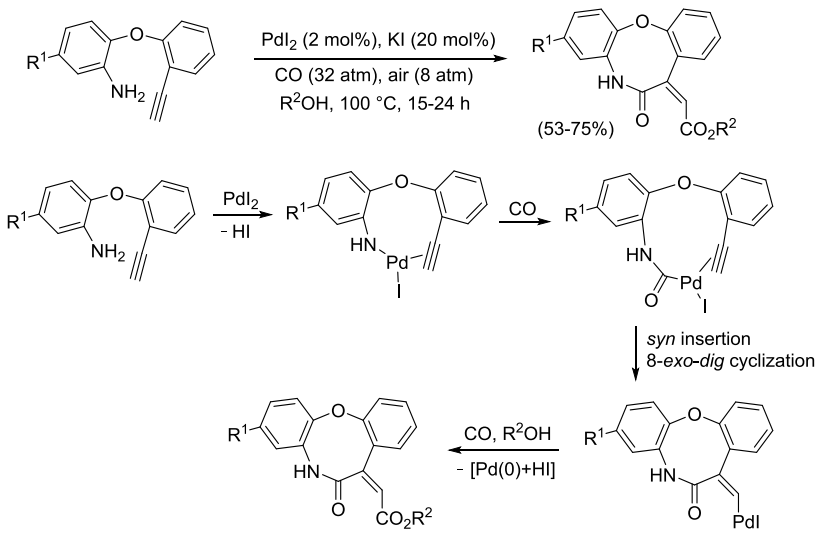
The PdI_2-catalyzed oxidative carbonylation of the triple bond described in Section 2.1 was successively exploited to synthesize a variety of carbonylated heterocycles (such as β-lactones [37,38], γ-lactones [38], β-lactams [39], indolones [40], and pyridinones [41]), starting from suitably

functionalized alkynes bearing a nucleophilic group in appropriate position for cyclization. In these reactions, heterocyclization occurred with CO incorporation into the cycle (cyclocarbonylation) and was accompanied by exocyclic alkoxycarbonylation, as outlined in Scheme 4. Thus, the formation of a triple bond-stabilized complex [–Nu(CO)PdI; from the reaction between the substrate, PdI_2, and CO] takes place, followed by cyclization by *syn* intramolecular triple bond insertion, CO insertion, and nucleophilic displacement by the external alcohol (Scheme 4). This kind of reactivity usually occurs with substrates bearing a terminal triple bond (because the intramolecular triple bond insertion step is quite sensitive to steric hindrance) and with relatively strong nucleophiles (such as amino groups), able to readily afford a carbamoylpalladium iodide species [–N(R)(CO)PdI]. On the other hand, with weaker nucleophilic groups (such as the hydroxyl), the cyclocarbonylation-alkoxycarbonylation mechanism is generally observed when the direct nucleophilic attack to the triple bond coordinated to palladium (see Section 2.3) is not allowed by Baldwin's rules.



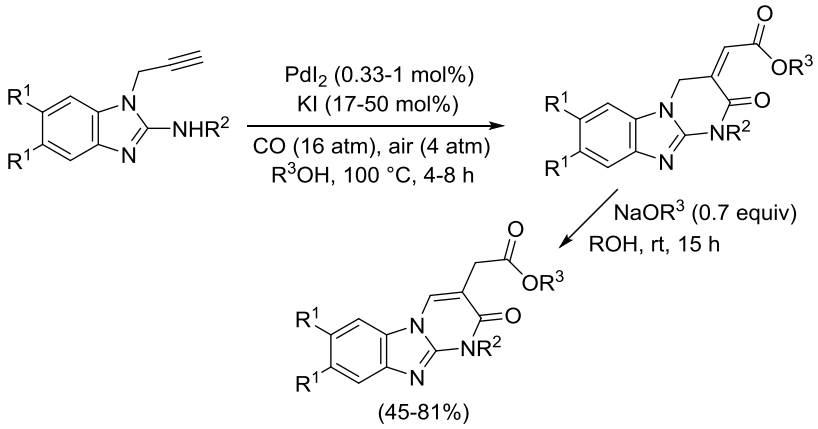
Scheme 4. Mechanism of the formation of carbonylated heterocycles by PdI_2/KI-catalyzed oxidative cyclocarbonylation-alkoxycarbonylation of terminal alkynes bearing a suitably placed nucleophilic group.

Recently, ζ-lactams with antitumor activity against breast cancer cells were also successfully synthesized, as shown in Scheme 5 [42]. In this reaction, the formation of a carbamoylpalladium iodide intermediate is followed by a remarkable intramolecular *syn* 8-*exo-dig* triple bond insertion and nucleophilic displacement by an alcohol (Scheme 5) [42].



Scheme 5. Synthesis of ζ-lactams by PdI_2/KI-catalyzed oxidative cyclocarbonylation-alkoxycarbonylation of 2-(2-ethynylphenoxy)anilines [42].

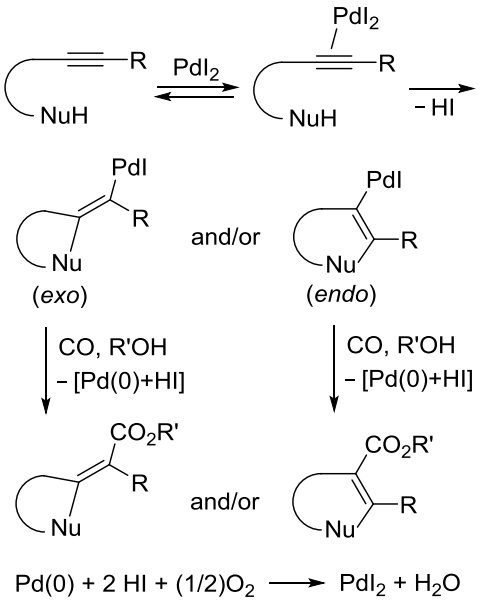
The nucleophile may also be bonded to a heterocyclic ring, leading to fused heterocycles, as shown in the synthesis of benzimidazopyrimidinones from propynylbenzimidazolamines (Scheme 6) [43].



Scheme 6. Synthesis of benzimidazopyrimidinones by PdI_2/KI-catalyzed oxidative cyclocarbonylation-alkoxycarbonylation of propynylbenzimidazolamines [43].

2.3. PdI_2-Catalyzed Oxidative Heterocyclization-Alkoxycarbonylation of Functionalized Alkynes

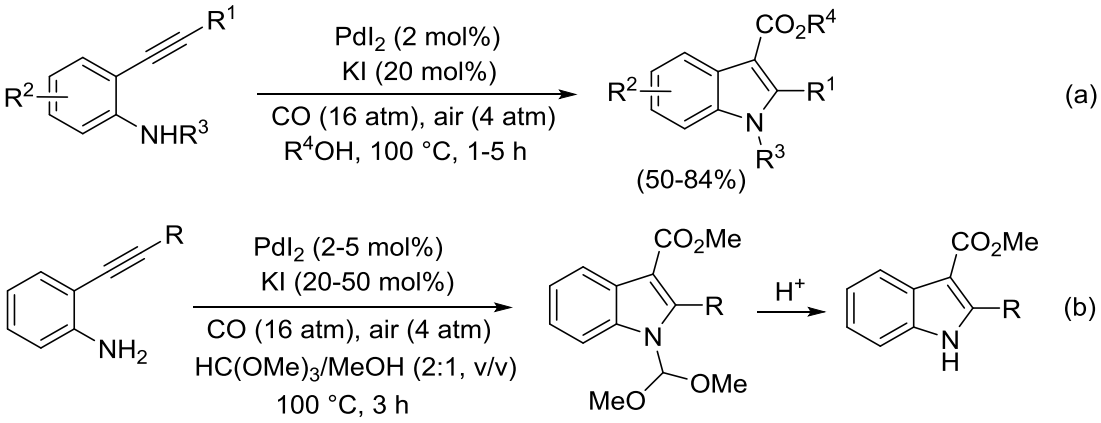
With alkynes bearing less nucleophilic groups (such as hydroxyl or amido groups), an initial *exo* or *endo* heterocyclization without CO incorporation into the cycle generally occurs, as long as it is allowed by Baldwin's rules. Cyclization, which may take place with the terminal as well as with internal triple bonds, is then followed by alkoxycarbonylation of the ensuing vinylpalladium moiety, to afford the final monocarbonylated heterocycle (Scheme 7). This mechanism is particularly favored when the initially formed heterocyclic ring may further undergo aromatization. Furans [44,45], tetrahydrofurans [46–48], oxazolidinones [49,50], oxazolines [39,47,51,52], pyrroles [41,53], dihydroisobenzofurans [48,54], isochromenes [54,55], isoquinolines [55], benzoxazines [56,57], quinolines [58], and indoles [59] were synthesized by this approach.



Scheme 7. Mechanism of the formation of carbonylated heterocycles by PdI_2/KI-catalyzed oxidative heterocyclization-alkoxycarbonylation of terminal alkynes bearing a suitably placed nucleophilic group.

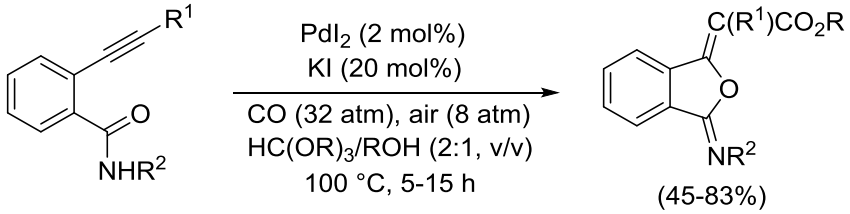
More recently, we have applied this kind of reactivity to the synthesis of other important heterocyclic derivatives. Thus, indole-3-carboxylic esters were prepared in good yields

(50–84%) from 2-alkynylanilines bearing an internal triple bond and a secondary amino group (Scheme 8a) [60]. With a primary amino group, and in the presence of trimethyl orthoformate, 1-(dimethoxymethyl)indole-3-carboxylates were obtained, which could be easily converted under acidic conditions into the corresponding unprotected indoles (Scheme 8b) [60]. It is worth noting that the latter could not be obtained by the direct oxidative carbonylation of 2-alkynylanilines bearing a primary amino group under the usual conditions (i.e., in the absence of trimethyl orthoformate) [60].



Scheme 8. Synthesis of alkyl indole-3-carboxylates by PdI_2-catalyzed oxidative *endo* heterocyclization-alkoxycarbonylation of 2-alkynylanilines bearing a secondary (**a**) or a primary (**b**) amino group [60].

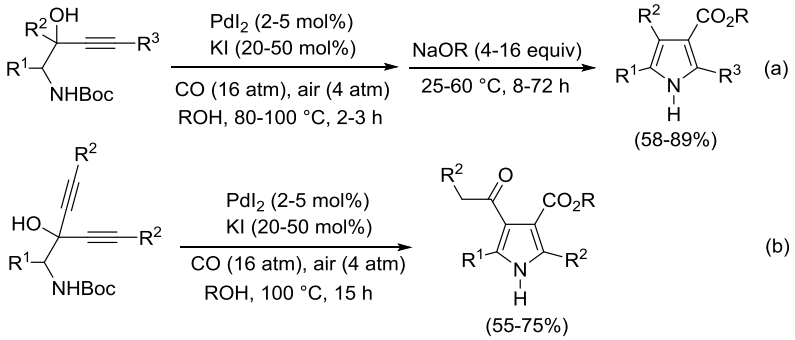
Using an ROH/$HC(OR)_3$ mixture as the solvent, 2-alkynylbenzamides were also subjected to PdI_2-catalyzed oxidative carbonylation conditions and were selectively converted into isobenzofuranimine derivatives through 5-*exo-dig* *O*-heterocyclization followed by alkoxycarbonylation (Scheme 9) [61]. These derivatives have shown a promising herbicidal activity [62].



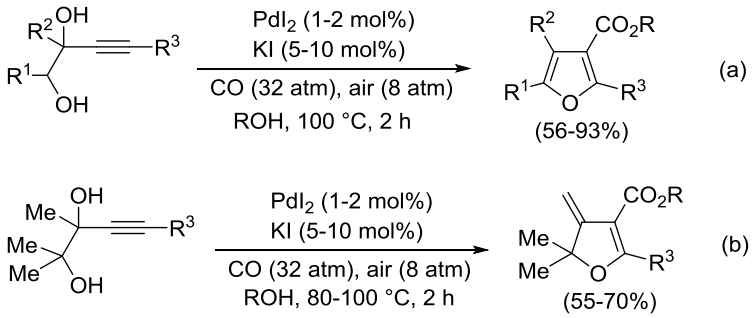
Scheme 9. Synthesis of 3-[(alkoxycarbonyl)methylene]isobenzofuran-1(3*H*)imines by PdI_2-catalyzed oxidative *exo* *O*-heterocyclization-alkoxycarbonylation of 2-alkynylbenzamides [61,62].

Pyrrole-3-carboxylates were synthesized starting from *N*-Boc-1-amino-3-yn-2-ols [63]. In this case, the 5-*endo-dig* heterocyclization-alkoxycarbonylation process was accompanied by dehydrative aromatization, and led to a mixture of Boc-protected and *N*-unsubstituted pyrrole derivatives. This mixture could be easily converted into *N*-unsubstituted pyrrole-3-carboxylic esters by a basic treatment with NaOR (Scheme 10a) [63]. Starting from substrates bearing geminal alkynyl groups, 4-acyl-3-pyrrolecarboxylates were directly obtained, from *N*-deprotection in situ and regioselective water addition to the triple bond of the second alkynyl moiety (Scheme 10b) [63].

In a similar manner, 3-yne-1,2-diol derivatives were smoothly converted into furan-3-carboxylates (Scheme 11a) [64,65] or 4-methylene-4,5-dihydrofuran-3-carboxylates (Scheme 11b) [65], depending on whether dehydration from the alcoholic function at C-2 occurred in an endocyclic (with substrates bearing a secondary alcoholic group at C-1) or exocyclic (tertiary alcoholic group at C-1) way, respectively.

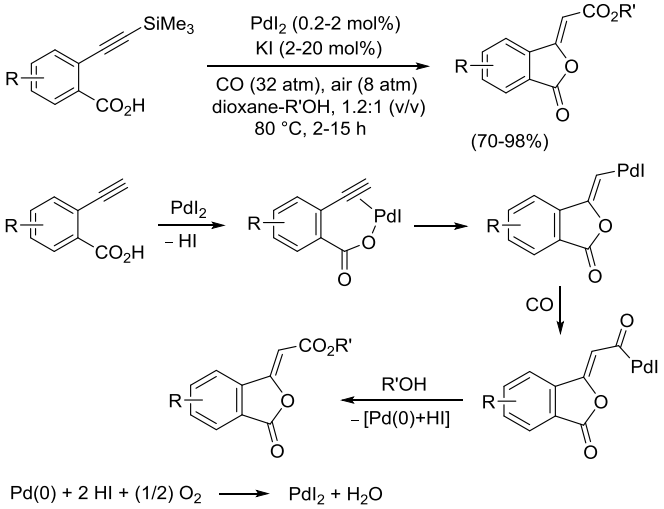


Scheme 10. Synthesis of pyrrole-3-carboxylates (**a**) and 4-acyl-3-pyrrolecarboxylates (**b**) by PdI_2-catalyzed *endo* heterocyclization-alkoxycarbonylation of *N*-Boc-1-amino-3-yn-2-ols and *N*-Boc-2-alkynyl-1-amino-3-yn-2-ols, respectively [63].



Scheme 11. Synthesis of furan-3-carboxylates (**a**) [64,65] or 4-methylene-4,5-dihydrofuran-3-carboxylates (**b**) [65] by PdI_2-catalyzed oxidative *endo*-heterocyclization- alkoxycarbonylation of 3-yne-1,2-diol derivatives.

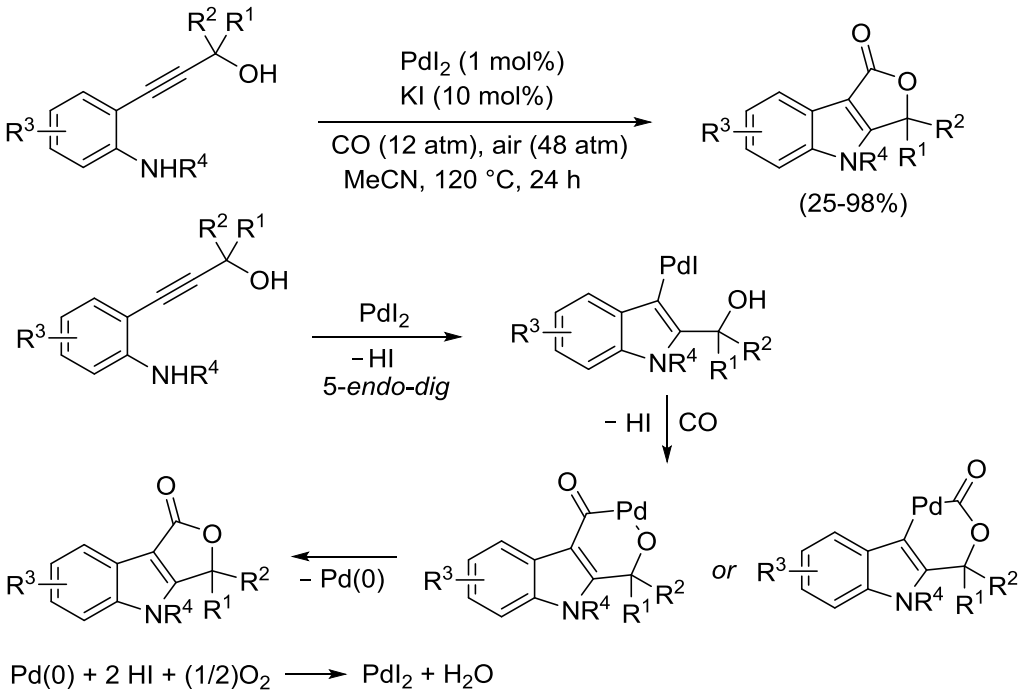
Very recently, we found that 2-(ethynyl)benzoic acids (obtained in situ by desilylation of 2-[(trimethylsilyl)ethynyl]benzoic acids) can be stereoselectively converted into (*Z*)-2-[oxoisobenzofuran-1-(3*H*)-ylidene]acetates in high to excellent yields (70–98%) (Scheme 12) [66]. In this case, to account for product stereochemistry (which was confirmed by XRD analysis), the formation of a palladium carboxylate can be assumed, followed by 5-*exo-dig* intramolecular insertion of the triple bond and alkoxycarbonylation (Scheme 12) [66].



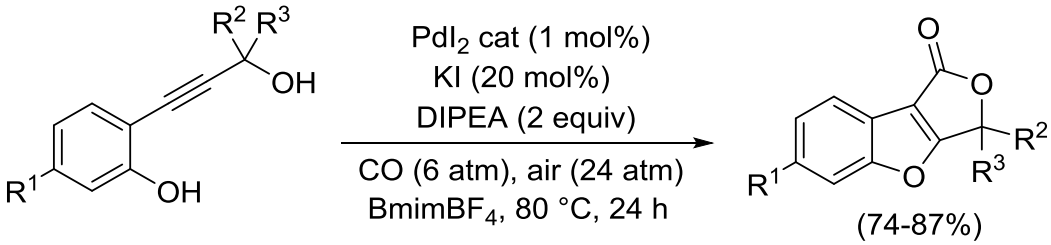
Scheme 12. Synthesis of (*Z*)-2-[oxoisobenzofuran-1-(3*H*)-ylidene]acetates by PdI_2-catalyzed oxidative heterocyclization-alkoxycarbonylation of 2-(ethynyl)benzoic acids [66].

2.4. PdI_2-Catalyzed Oxidative Carbonylative Double Cyclization of Functionalized Alkynes

With acetylenic substrates bearing two suitably placed nucleophilic groups, a cascade double cyclization process may take place, ensuing from an initial heterocyclization followed by intramolecular cyclocarbonylation. This reactivity was observed with 2-(hydroxypropyn-1-yl)anilines, which were converted into 3,4-dihydrofuro[3,4-*b*]indol-1-ones by 5-*endo-dig* *N*-cyclization followed by carbon monoxide insertion and intramolecular nucleophilic displacement by the alcoholic group (Scheme 13) [67]. In a similar way, furobenzofuranone derivatives were synthesized in 74–86% yields starting from 2-(hydroxypropyn-1-yl)phenols, in $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) as unconventional solvent (Scheme 14) [68].

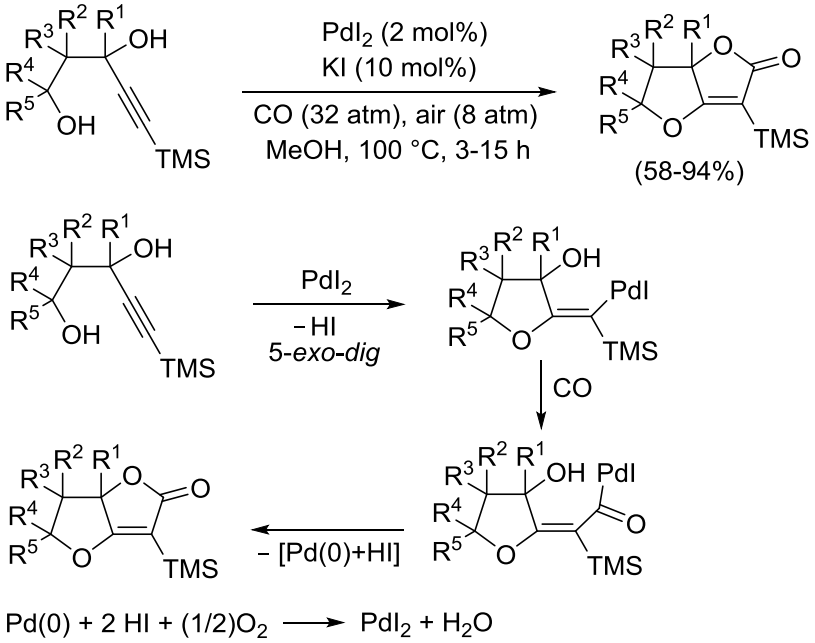


Scheme 13. Synthesis of 3,4-dihydrofuro[3,4-*b*]indol-1-ones by PdI_2-catalyzed oxidative carbonylative double cyclization of 2-(hydroxypropyn-1-yl)anilines: 5-*endo-dig* *N*-cyclization followed by cyclocarbonylation [67].



Scheme 14. Synthesis of furo[3,4-*b*]benzofuran-1(3*H*)-ones by PdI_2-catalyzed oxidative carbonylative double cyclization of 2-(hydroxypropyn-1-yl)phenols in $BmimBF_4$ [68].

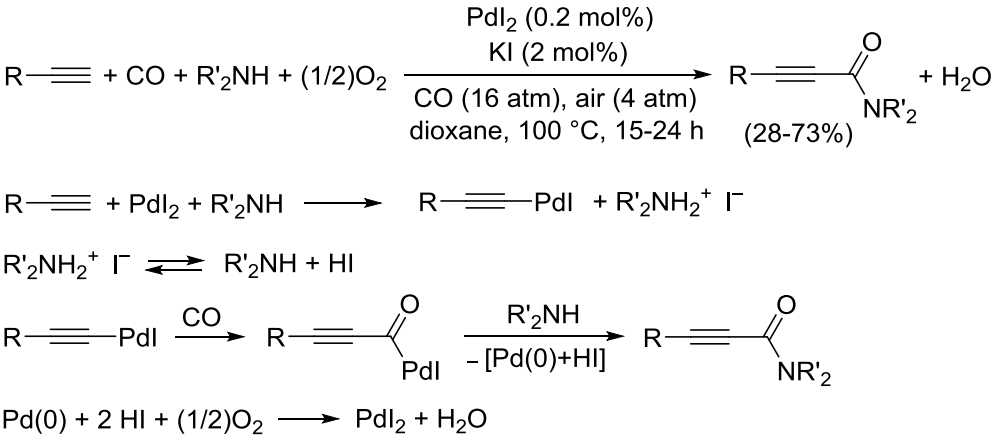
In the case of 5-trimethylsilyl-4-yne-1,3-diols, an initial 5-*exo-dig* *O*-cyclization was followed by cyclocarbonylation to afford dihydrofurofuranone derivatives, which have shown significant antitumor activity in vitro against breast cancer cells, including the most aggressive MDA-MB-231 and MDA-MD-468 cells (Scheme 15) [69].



Scheme 15. Synthesis of 6,6*a*-dihydrofuro[3,2-*b*]furan-2(5*H*)-one derivatives by PdI_2-catalyzed oxidative carbonylative double cyclization of 5-trimethylsilyl-4-yne-1,3-diols: 5-*exo-dig O*-cyclization followed by cyclocarbonylation [69].

2.5. PdI_2-Catalyzed Oxidative Monoaminocarbonylation of Terminal Alkyne Derivatives

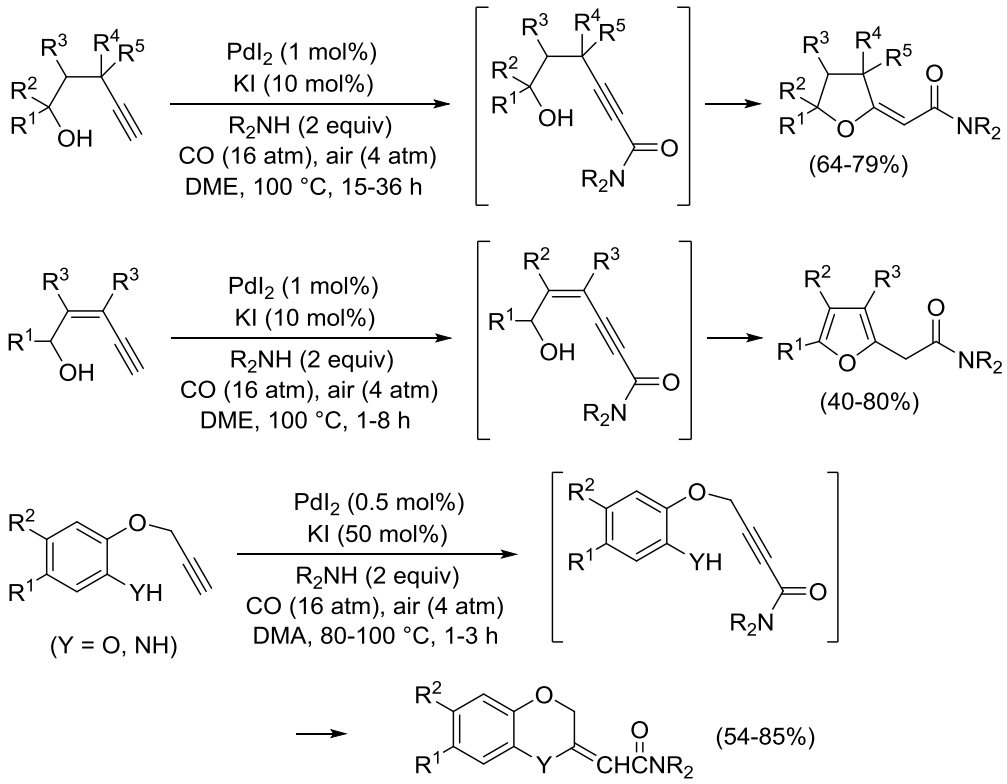
When carried out in the presence of a nucleophilic secondary amine as external nucleophile instead of an alcohol, the PdI_2-catalyzed oxidative carbonylation of terminal alkynes selectively led to 2-ynamides, corresponding to a monocarbonylation of the triple bond ensuing from *sp* C-H activation (Scheme 16) [70]. In fact, under these conditions, the amine may initially act as a base, promoting the formation of an alkynylpalladiumiodide species. Carbon monoxide insertion is then followed by nucleophilic displacement by the same amine to afford the final product (Scheme 16) [70].



Scheme 16. PdI_2-catalyzed oxidative monoaminocarbonylation of terminal alkynes leading to 2-ynamides [70].

This reactivity may lead to the formation of heterocyclic derivatives when applied to suitably substituted terminal alkynes, because the initially formed 2-ynamide compounds present a triple bond conjugated to the amido group and are therefore susceptible to nucleophilic attack (either intermolecular or intramolecular). Thus, furanone [71,72] and pyrrolone [73] derivatives were formed starting from

propargyl alcohols or amines, respectively, ensuing from intermolecular conjugate addition by the secondary amine and intramolecular alcoholysis [71–73]. In other cases, the nucleophilic function in the 2-ynamide intermediate was already placed in a suitable position for the occurrence of an intramolecular conjugate addition, in agreement with Baldwin's rules. By this latter approach, different kinds of carbonylated heterocycles, including tetrahydrofurans [72,74], dihydrobenzodioxines [75], dihydrobenzoxazines [75], and furans [72,76] were synthesized, as exemplified in Scheme 17.

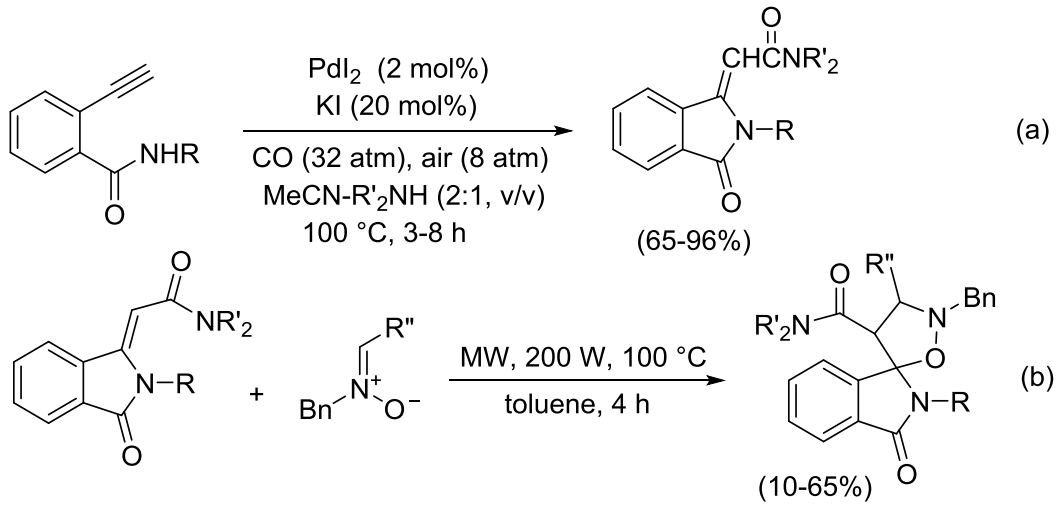


Scheme 17. Synthesis of various functionalized heterocycles by PdI_2-catalyzed oxidative monoaminocarbonylation of terminal alkynes followed by intramolecular conjugate addition [72,74–76].

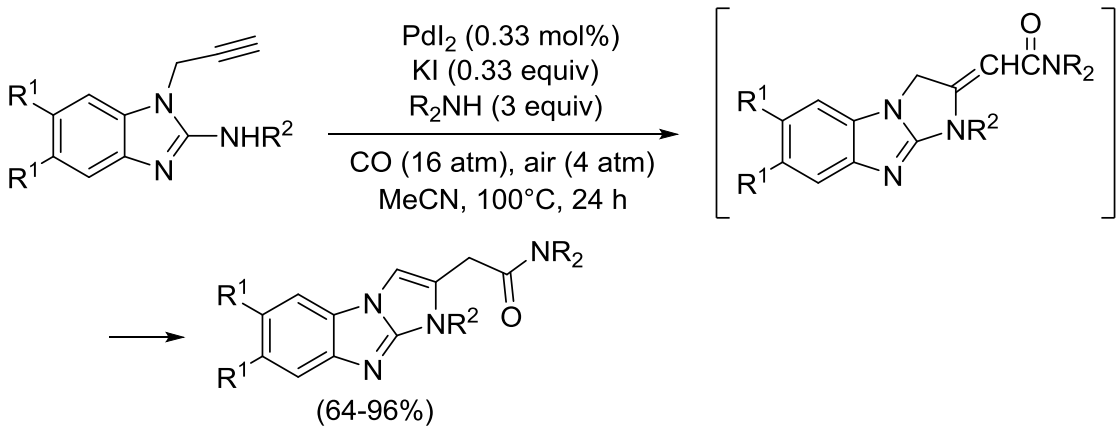
More recently, isoindolinones were conveniently prepared by sequential oxidative aminocarbonylation-intramolecular conjugate addition of 2-ethynylbenzamides, as shown in Scheme 18a [61,77]. The heterocyclic derivatives thus obtained were used for preparing new spiro[isoindole-1,5′-isoxazolidin]-3(2*H*)ones with antitumor activity against neuroblastoma SH-SY5Y, colorectal HT-29, and hepatocellular HepG2 cell lines (Scheme 18b) [78].

Propynylbenzimidazolamines, already successfully employed for the synthesis of benzimidazopyrimidinones under oxidative alkoxycarbonylation conditions (Scheme 6, Section 2.2) [43], were also used as substrates under aminocarbonylation conditions, to produce benzimidazoimidazoles in good to excellent yields after a final isomerization process (Scheme 19) [79]. In a similar way, benzimidazothiazoles were synthesized from propynylsulfanylbenzimidazoles, obtained in situ from the corresponding benzimidazolium bromide salts (Scheme 20) [80]. In this latter case, the internal heteronucleophile corresponded to the nitrogen of an imidazole ring.

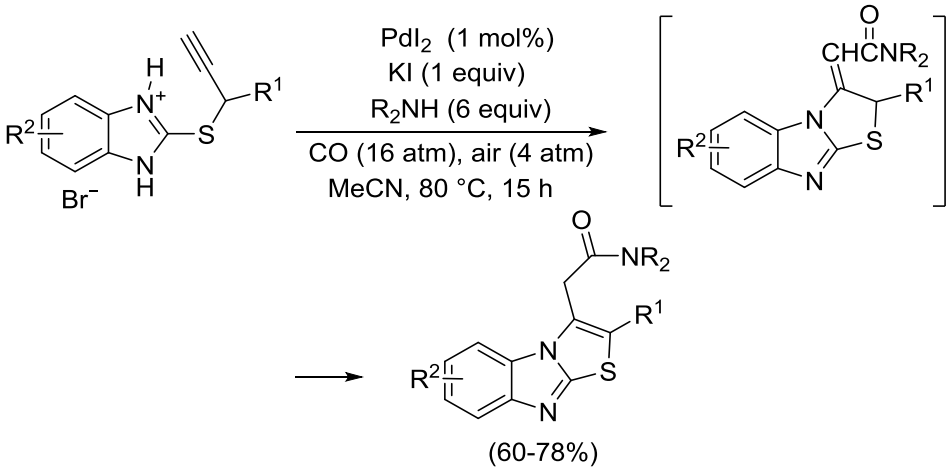
Aminocarbonylation followed by carbocyclization is also possible, with substrates leading in situ to stabilized carbonucleophiles (by carbon deprotonation under the basic reaction conditions) in a suitable position with respect to the triple bond. Thus, 2-(2-ethynylbenzyl)malonates were converted into functionalized indanes in one single procedure, as shown in Scheme 21 [81].



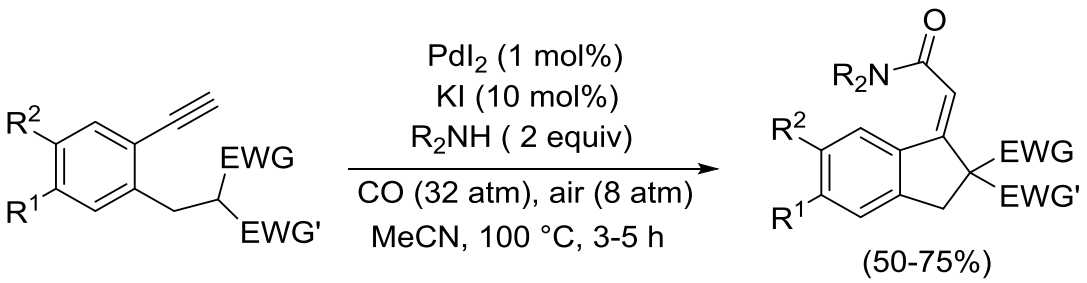
Scheme 18. (**a**) Synthesis of isoindolinones by sequential PdI_2-catalyzed oxidative aminocarbonylation-*N*-cyclization of 2-ethynylbenzamides [61,77] and (**b**) their use for the preparation of spiro[isoindole-1,5′-isoxazolidin]-3(2*H*)ones with antitumor activity [78].



Scheme 19. Synthesis of benzimidazoimidazoles by sequential oxidative PdI_2-catalyzed aminocarbonylation-*N*-cyclization-isomerization of propynylbenzimidazolamines [79].

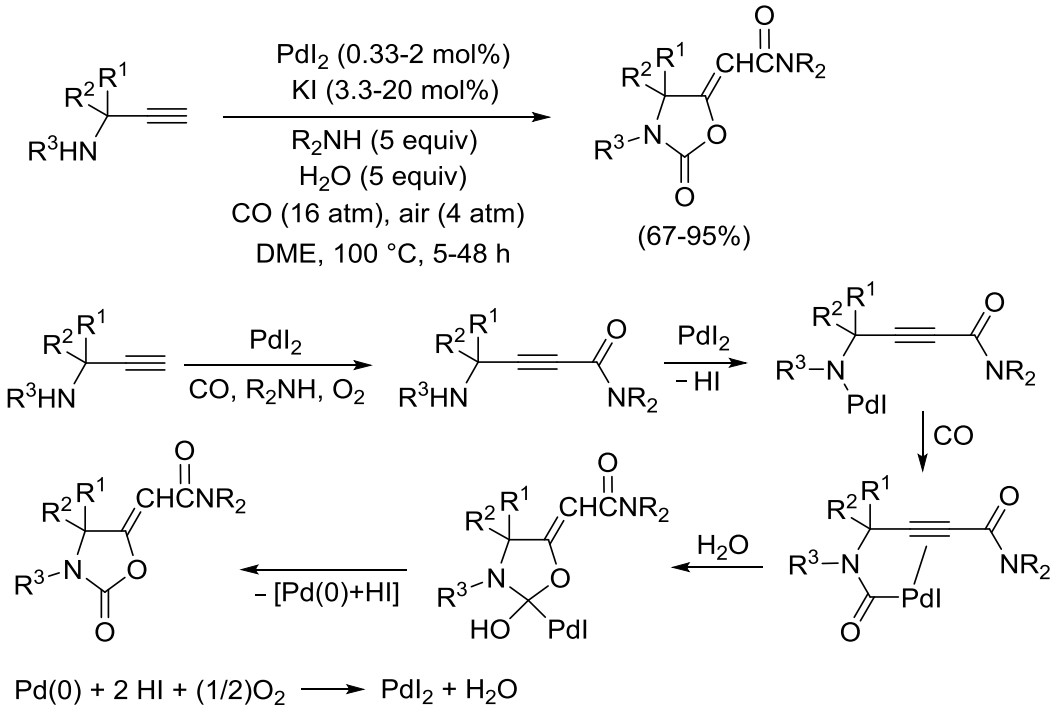


Scheme 20. Synthesis of benzimidazothiazoles by sequential PdI_2-catalyzed oxidative aminocarbonylation-*N*-cyclization-isomerization of propynylsulfanylbenzimidazoles [80].



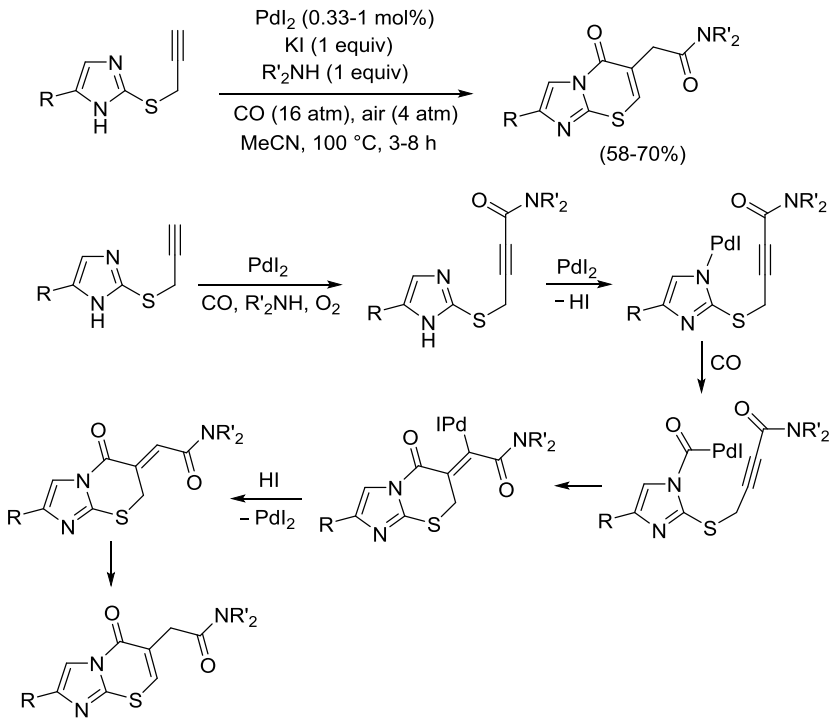
Scheme 21. Synthesis of indanes by PdI_2-catalyzed by oxidative aminocarbonylation-carbocyclization of 2-(2-ethynylbenzyl)malonates (EWG = CO_2Me, EWG′ = CO_2Me, COMe, CN) [81].

In some cases, and under suitable conditions, the initial PdI_2-catalyzed aminocarbonylation of the terminal triple bond is followed by PdI_2-catalyzed cyclocarbonylation through the concatenation of two different catalytic cycles, both catalyzed by the same species (auto-tandem catalysis). We observed this reactivity with propargyl amines, when the oxidative carbonylation reactions were carried out in the presence of water as a promoter [82]. The cyclocarbonylation process started with palladation of the nitrogen of the 2-ynamide intermediate (deriving from the aminocarbonylation process) and was followed by CO insertion, *O*-cyclization triggered by water attack, and β-H elimination from the HO-C-PdI moiety (Scheme 22) [82]. More recently, we also found that it is possible to carry out the process in the ionic liquid (IL) $EtSO_4$ (1-ethyl-3-methylimidazolium ethyl sulfate) as a nonconventional solvent, with the possibility to recycle the catalyst-IL medium [83].



Scheme 22. Synthesis of oxazolidinones from propargylic amines by PdI_2-promoted auto-tandem catalysis: PdI_2-catalyzed oxidative aminocarbonylation followed by PdI_2-catalyzed, water-promoted oxidative cyclocarbonylation [82].

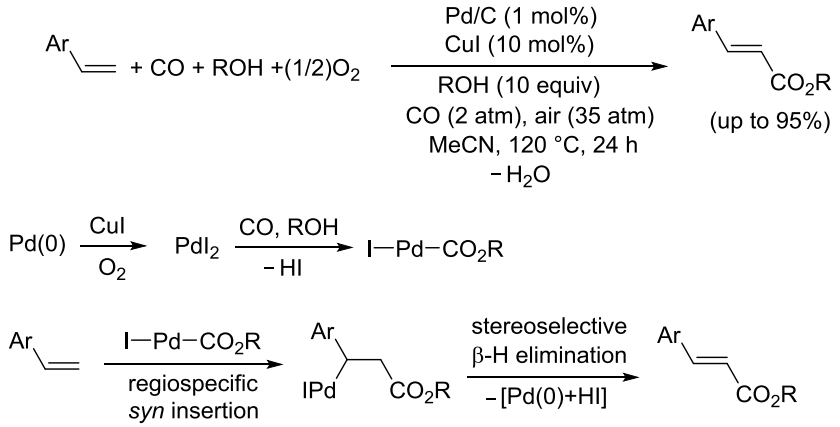
Aminocarbonylation followed by cyclocarbonylation was also observed in the case of monosubstituted propynylthioimidazoles, which led to imidazothiazinones in one step and in satisfactory yields. In this case, in the cyclocarbonylation cycle, nitrogen palladation was followed by CO insertion, intramolecular triple bond insertion, protonolysis, and isomerization (Scheme 23) [84].



Scheme 23. Synthesis to imidazothiazinones by PdI_2-catalyzed oxidative aminocarbonylation–cyclocarbonylation of propynylthioimidazoles [84].

2.6. PdI_2-Catalyzed Oxidative Monoalkoxycarbonylation of α-Olefins

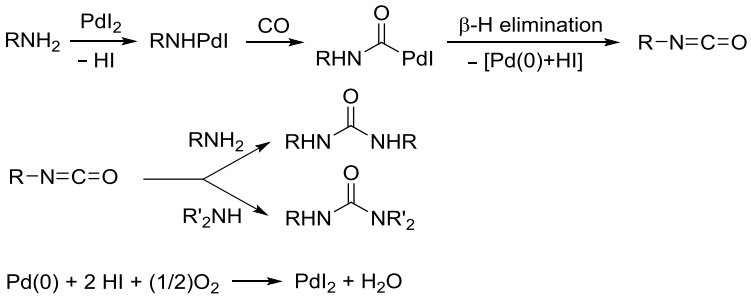
In combination with CuI as co-catalyst, PdI_2-based catalysts are also able to promote the monoalkoxycarbonylation of α-olefins to give (*E*)-α,β-unsaturated esters, under relatively mild conditions (120 °C and under 2 atm of CO and 35 atm of air). Pd/C was used as the catalytic precursor in this process, leading in situ to PdI_2 by the combined action of CuI and oxygen. Interestingly, the direct use of PdI_2/KI or PdI_2/CuI catalytic systems led to less satisfactory results (both in terms of product yield and selectivity) with respect to Pd/C-CuI, perhaps also suggesting the involvement, in the last case, of Pd-Cu bimetallic species, more active toward olefin carbonylation. The formation of an alkoxycarbonylpalladium iodide species was then followed by regiospecific double bond insertion and stereoselective β-H elimination to give the final product (Scheme 24). The reaction worked nicely with several arenes, leading to the corresponding cinnamates in yields up to 95% (Scheme 24). In the case of aliphatic α-olefins, however, a mixture of isomeric α,β- and β,γ-unsaturated esters were obtained [85].



Scheme 24. Synthesis of alkyl cinnamates by PdI_2/CuI-catalyzed oxidative monoalkoxycarbonylation of arenes [85].

2.7. PdI_2-Catalyzed Oxidative Carbonylation of Amines, β-Amino Alcohols, and 2-Aminophenols to Ureas, Oxamides, Oxazolidinones, and Benzoxazolones

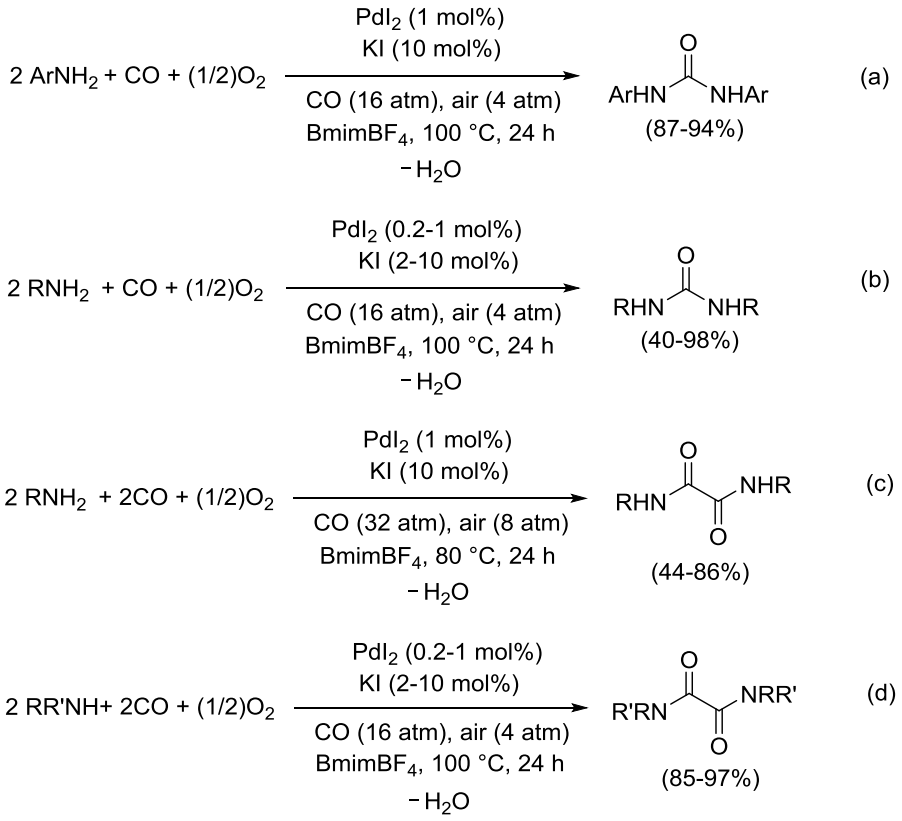
We have seen in Sections 2.2 and 2.5 that PdI_2 can easily react with amino groups to form carbamoylpalladiumiodide intermediates. This reactivity can be conveniently exploited for the synthesis of ureas, when applied to simple primary amines. In fact, in this case, the initially formed RNH(CO)PdI intermediate may undergo β-H elimination from the HN-CO-Pd moiety, with the formation of an isocyanate and palladium(0). While the latter is readily reoxidized to PdI_2 in the presence of oxygen, the isocyanate may be attacked by a second molecule of amine (either the same primary amine or a secondary amine, used as additional substrate) to yield a symmetrical 1,3-disubstituted or a trisubstituted urea, respectively (Scheme 25) [86,87]. We originally developed this process using 1,2-dimethoxyethane (DME) as the solvent, using, in some cases, an excess of CO_2 to ensure better catalytic performances [87]. In the synthesis of symmetrically 1,3-disubstituted ureas, carbon dioxide could even be used as the reaction solvent, reaching, in the conversion of aniline to 1,3-diphenylurea (DPU), an unprecedented catalytic efficiency of 43,500 mol of DPU per mol of palladium employed [88,89].



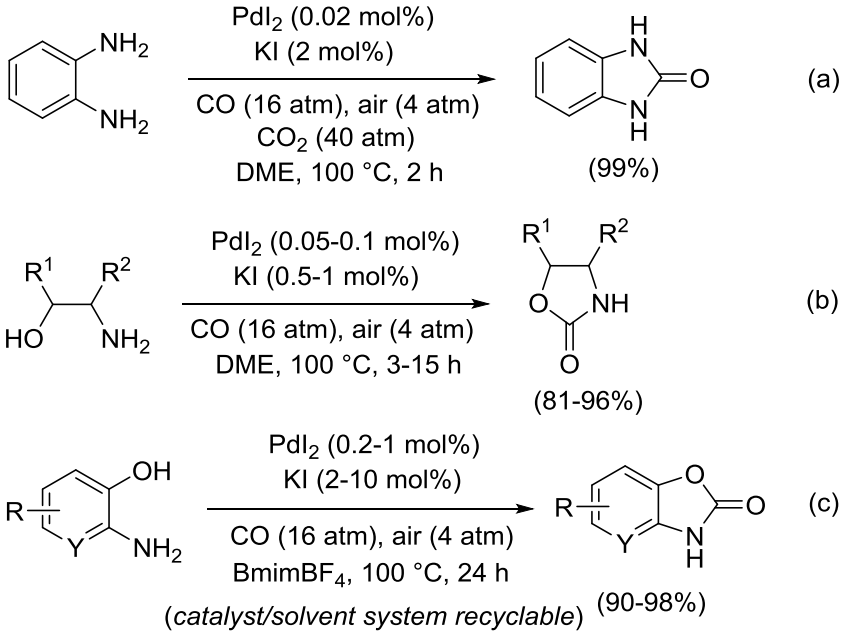
Scheme 25. Formation of symmetrically 1,3-disubstituted and trisubstituted ureas by PdI_2-catalyzed oxidative carbonylation of amines [86–89].

More recently, we found that it is also possible to carry out this transformation in the ionic liquid (IL) $BmimBF_4$ (1-butyl-3-methylimidazolium tetrafluoroborate) as an unconventional solvent, with the possibility to recycle the catalyst-IL system (Scheme 26) [90]. Interestingly, while aromatic primary amines led to 1,3-diarylureas (Scheme 26a), aliphatic primary amines could be divergently converted into 1,3-dialkylureas (Scheme 26b) or *N*,*N*′-dialkyloxamides (deriving from a double carbonylation process; Scheme 26c), depending on reactions conditions [90]. On the other hand, secondary amines (normally unreactive under the "classical" conditions [86–88]) selectively afforded tetrasubstituted oxamides (Scheme 26d) [90].

The isocyanate intermediate deriving from a primary amine under PdI_2-catalyzed oxidative carbonylation conditions can also be trapped intramolecularly by a second nucleophilic group. Thus, cyclic ureas [87], 2-oxazolidinones [90–93], and benzoxazolones [90,92] were obtained in excellent yields from aromatic diamines, β-amino alcohols, and 2-aminophenols, respectively, as exemplified in Scheme 27.



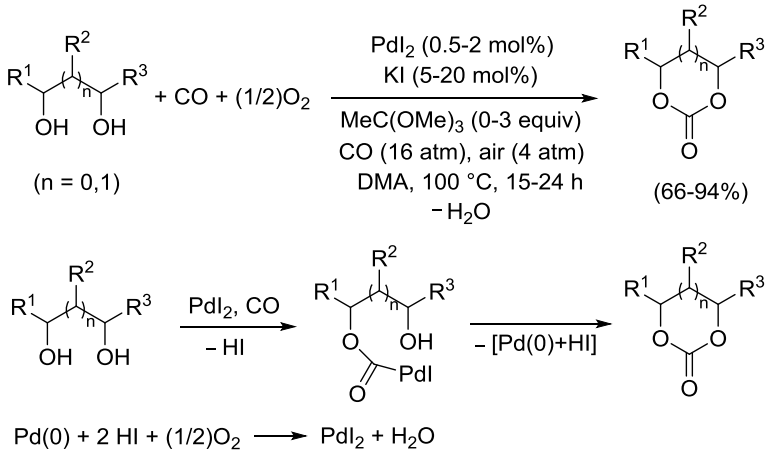
Scheme 26. Synthesis of (**a**) 1,3-diarylureas; (**b**) 1,3-dialkylureas; (**c**) *N*,*N*′-dialkyloxamides; and (**d**) tetraalkyloxamides by PdI_2-catalyzed oxidative carbonylation of amines in $BmimBF_4$ [90].



Scheme 27. Synthesis of (**a**) benzimidazolone [87]; (**b**) 2-oxazolidinones [92]; and (**c**) benzoxazolones (Y = CH,N) [90] by PdI_2-catalyzed oxidative carbonylation of 1,2-benzenediamine, β-amino alcohols, and 2-aminophenols, respectively.

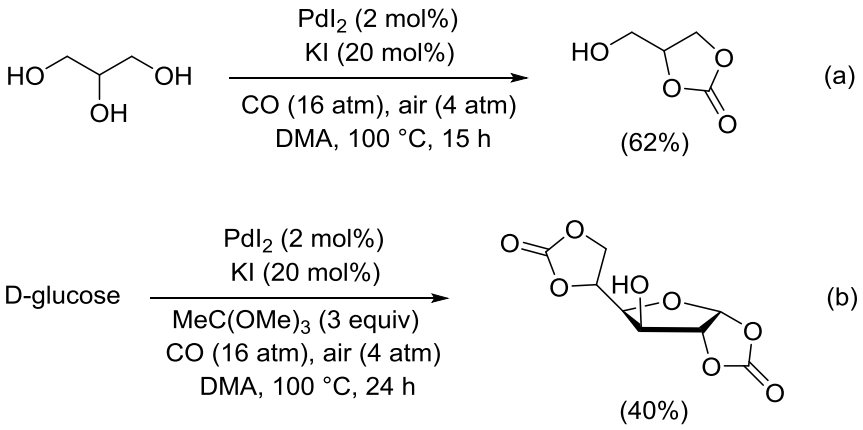
2.8. PdI_2-Catalyzed Oxidative Carbonylation of 1,2- and 1,3-Diols to Cyclic Carbonates

Under PdI_2-catalyzed oxidative carbonylation conditions 1,2- and 1,3-diols, were also reactive and led to the corresponding cyclic carbonates in good to excellent yields (66–94%, Scheme 28) [94,95]. In some cases, the use of a dehydrating agent, such as trimethyl orthoacetate, was necessary to achieve more satisfactory product selectivities. In this case, the alkoxycarbonylpalladiumiodide intermediate deriving from the reaction between the first hydroxyl group, PdI_2 and CO, was intramolecularly trapped by nucleophilic displacement by the second hydroxyl (Scheme 28) [94,95].



Scheme 28. Synthesis of 5-membered and 6-membered cyclic carbonates by PdI_2-catalyzed oxidative cyclocarbonylation of 1,2- and 1,3-diols, respectively [94,95].

Notably, the reaction could also be applied to glycerol, affording, under suitable conditions, glycerol carbonate (a very important derivative, used in many applicative fields, including industrial, pharmaceutical, and material chemistry) in 62% yield (Scheme 29a) [95]. More complex polyols, such as D-glucose, underwent a double cyclocarbonylative process leading to bicyclic carbonates (Scheme 29b) [95].



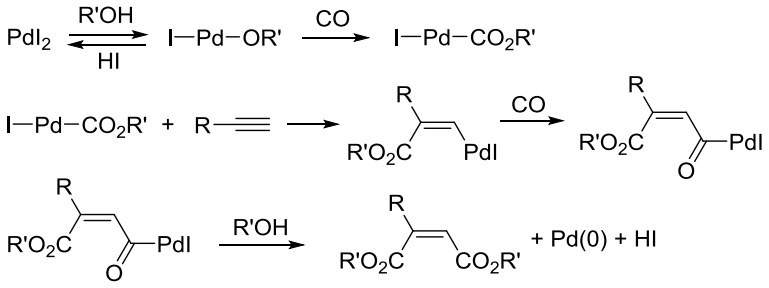
Scheme 29. Synthesis of (**a**) glycerol carbonate and (**b**) α-D-glucofuranose 1,2:5,6-dicarbonate by PdI_2-catalyzed oxidative cyclocarbonylation of glycerol and D-glucose, respectively [95].

3. PdI_2-Catalyzed Non-Oxidative Carbonylations

3.1. Combination Between Oxidative and Reductive Carbonylation and Additive Carbonylation of Terminal Alkynes

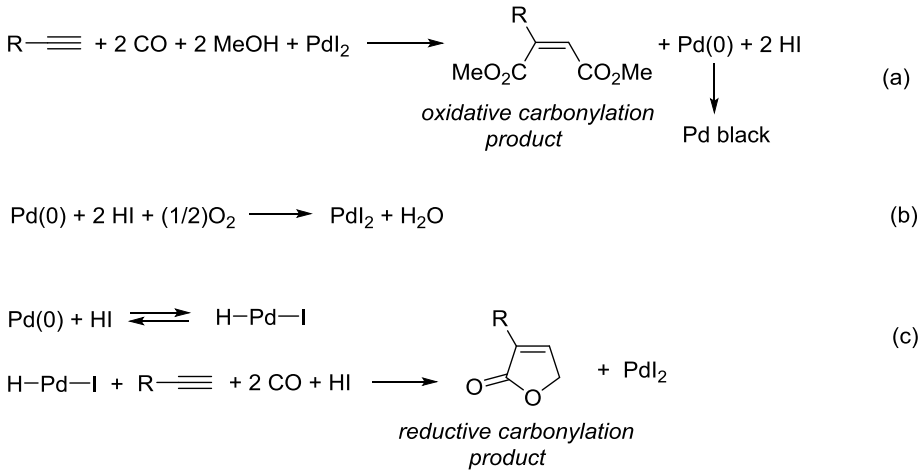
As we have seen in Section 2.1, the palladium-iodine bond of PdI_2 is particularly prone to undergo alkoxycarbonylation in the presence of carbon monoxide and an alcohol, to give an

alkoxycarbonylpalladiumiodide intermediate with the elimination of HI. In the presence of an alkyne substrate, triple bond insertion may take place, usually in a regioselective manner, leading to an alkoxycarbonylvinylpalladium species, as depicted in Scheme 30. Under suitable conditions (depending on solvent, temperature, and CO pressure), this intermediate may further insert CO to give the corresponding acylpalladium complex, which undergoes nucleophilic displacement by the alcohol to give maleic diesters, HI, and Pd(0) (Section 2.1 and Scheme 30).



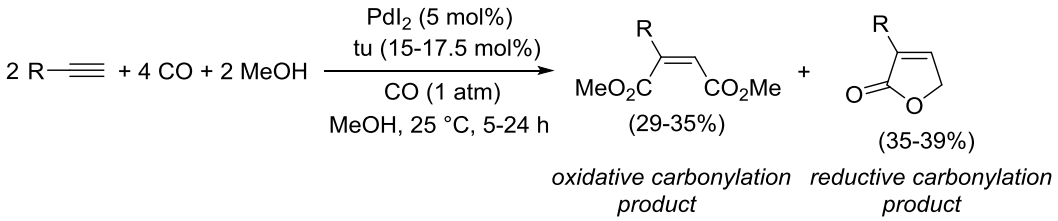
Scheme 30. Formation of alkoxycarbonylvinylpalladium iodide from PdI_2, an alcohol, CO, and a terminal alkyne, and subsequent CO insertion and nucleophilic displacement leading to maleic diesters and Pd(0).

In particular, in highly polar MeOH as the solvent and nucleophile, maleic dimethyl esters are formed even at room temperature and under atmospheric pressure of CO, with reduction of PdI_2 to Pd(0), which readily decomposes to palladium black (stoichiometric oxidative dimethoxycarbonylation reaction) (Scheme 31a). As we have seen in Section 1, one way to achieve a catalytic process, affording maleic diesters, is to operate under oxidative conditions, that means, in the presence of an external oxidant (such as oxygen), able to reconvert Pd(0)+2HI into PdI_2 (Schemes 3 and 31b). In principle, however, a catalytic process can also take place under non-oxidative conditions, if the dialkoxycarbonylation process leading to maleates takes place under conditions able to stabilize the H-Pd-I species that can be in equilibrium with Pd(0)+HI. In this manner, in fact, palladium does not decompose to palladium black, while the H-Pd-I species may promote a parallel reduction process, leading to a second product corresponding to reductive carbonylation (a 2(5*H*)furanone, for example), with the regeneration of PdI_2 (Scheme 31c).



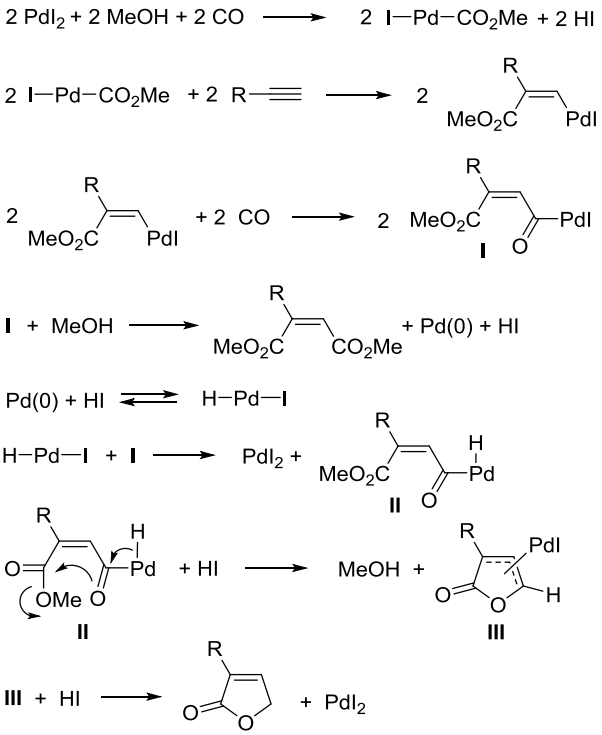
Scheme 31. (**a**) PdI_2-promoted stoichiometric oxidative dimethoxycarbonylation of terminal alkynes, leading to maleic diesters and Pd(0); (**b**) possible reconversion of Pd(0) to PdI_2 under oxidative conditions (with oxygen as external oxidant); (**c**) possible reconversion of Pd(0) to PdI_2 under non-oxidative conditions, with concomitant formation of a reductive carbonylation product.

Many years ago we found that, in MeOH as the solvent and under particularly mild conditions (25 °C and 1 atm of CO), an appropriate ligand able to stabilize the H-Pd-I species deriving from the oxidative dimethoxycarbonylation of terminal alkynes could be thiourea (tu) [96]. In fact, using PdI_2 in conjunction with 3–3.5 equiv tu to PdI_2, a catalytic process under non-oxidative conditions took place, corresponding to the combination between oxidative dimethoxycarbonylation (leading to maleic diesters) and reductive dicarbonylation (leading to 2(5*H*)-furanones). Accordingly, the maleic diesters and furanones were obtained in a ca. 1:1 molar ratio (Scheme 32) [96].



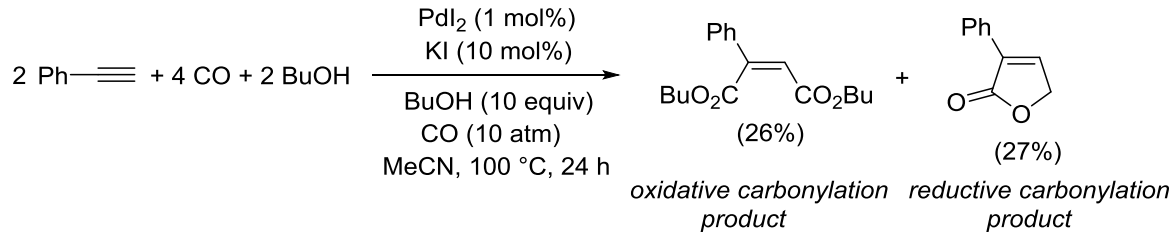
Scheme 32. PdI_2-catalyzed carbonylation of terminal alkynes under non-oxidative conditions: combined oxidative dimethoxycarbonylation and reductive dicarbonylation of terminal alkynes leading to maleic diesters and 2(5*H*)-furanones, respectively [96].

In a simplified version of the mechanism, the tu-stabilized H-Pd-I species ensuing from the dimethoxycarbonylation of the triple bond may interact with the acylpalladium intermediate **I**, leading, after hydride exchange, to acylpalladiumhydride species **II**. The final furanone product would then be formed after the intramolecular nucleophilic attack of the hydride to the acyl moiety with simultaneous cyclization to give π-allylcomplex **III** followed by protonolysis, with the regeneration of PdI_2 (Scheme 33) [96].



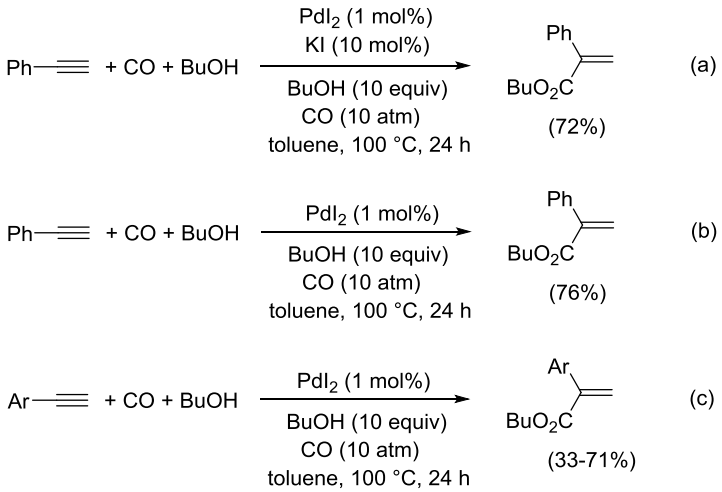
Scheme 33. Simplified mechanistic proposal for the PdI_2/tu-catalyzed combined oxidative dimethoxycarbonylation and reductive dicarbonylation of terminal alkynes leading to maleic diesters and 2(5*H*)-furanones, respectively [96].

Interestingly the same kind of reactivity was also observed in the butoxycarbonylation of terminal alkynes, when it was carried out with BuOH as a nucleophile (10 equiv with respect to the alkyne) in a polar aprotic solvent, such as MeCN [97]. In this case, the addition of tu as a ligand was not necessary, as the combination between the oxidative carbonylation and reductive carbonylation took place with PdI_2 in conjunction with KI as the catalyst (Scheme 34) [97]. This is likely due to the fact that, in the aprotic solvent, the equilibrium between H-Pd-I and Pd(0)+HI is much less shifted to the right with respect to MeOH, where HI is much more stabilized by hydrogen bonding.

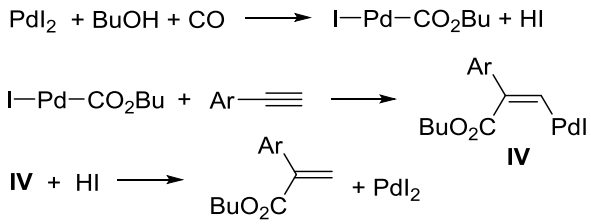


Scheme 34. PdI_2/KI-catalyzed combined oxidative dibutoxycarbonylation and reductive dicarbonylation of phenylacetylene leading to dibutyl 2-phenylmaleate and 3-phenylfuran-2(5*H*)-one, respectively [97].

Even more interesting was the observation that, shifting from polar MeCN (ε = 37.5) to apolar toluene (ε = 2.4), the reaction course changed dramatically, with the predominant formation of the hydrobutoxycarbonylation product (Scheme 35a) [97]. This product clearly derives from an additive carbonylation process, ensuing from protonolysis of the butoxycarbonylpalladium intermediate **IV**, with direct regeneration of PdI_2 (Scheme 36). The process worked even better in the absence of KI, as shown in Scheme 35b, and could also be generalized to other arylacetylenes (Scheme 35c) [97]. Apparently, in low-polar solvents, protonolysis by HI is much more favored with respect to further alkoxycarbonylation of **IV** (Scheme 36) [97].



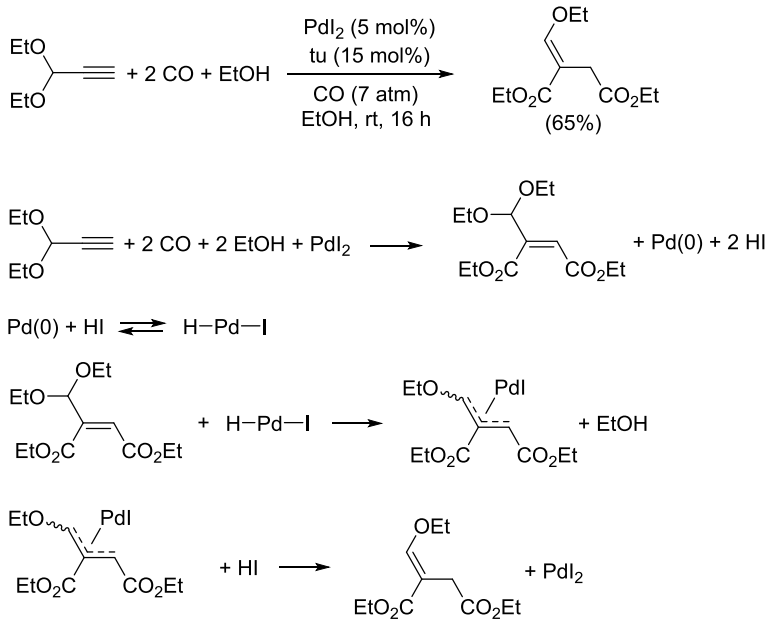
Scheme 35. PdI_2-catalyzed additive hydrobutoxycarbonylation reactions in toluene as the solvent: (**a**) of phenylacetylene with PdI_2/KI as the catalytic system; (**b**) of phenylacetylene with PdI_2 alone as catalyst; (**c**) of arylacetylenes with PdI_2 as catalyst [97].



Scheme 36. Mechanism of the PdI_2-catalyzed additive hydrobutoxycarbonylation of terminal alkynes in toluene as the solvent [97].

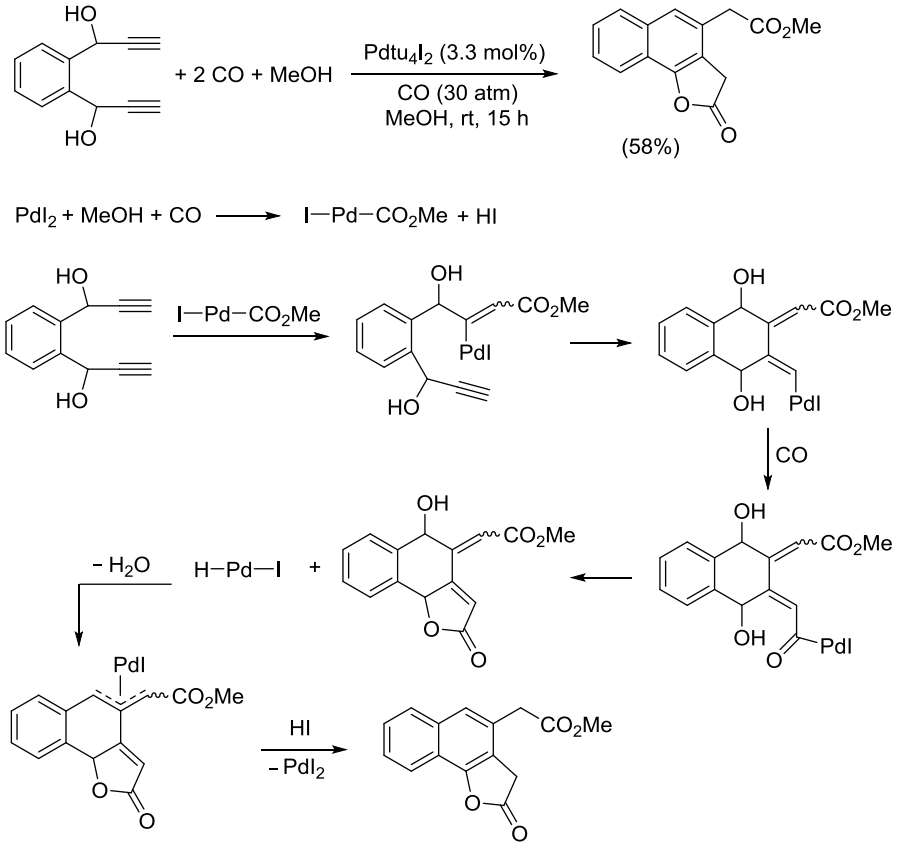
3.2. Combination Between Oxidative and Reductive Carbonylation within the Same Molecule and Sequential Homobimetallic Catalysis

Of particular interest is the possible combination between an oxidative carbonylation process and a reductive process within the same molecule, because this may result in the selective formation of a single molecule, under PdI_2-catalyzed non-oxidative conditions. This kind of concept was successfully verified in the case of 3,3-diethoxyprop-1-yne, containing, besides the terminal triple bond, an acetalic moiety potentially reducible. This substrate was selectively converted into diethyl (*E*)-2-(ethoxymethylene)succinate in 65% yield in the presence of PdI_2+3tu as the catalytic system under mild conditions (rt and 7 atm of CO), in EtOH as the solvent (Scheme 37). The initially formed maleate derivative reacted with H-Pd-I to give a π-allyl complex with the elimination of EtOH from the acetal function, and then protonolysis by HI afforded the final product (Scheme 37) [98].



Scheme 37. Synthesis of diethyl (*E*)-2-(ethoxymethylene)succinate from 3,3-diethoxyprop-1-yne by the combination between PdI_2-catalyzed oxidative dialkoxycarbonylation and reduction within the same molecule [98].

Similar to an acetalic function, an allylalcoholic moiety can also serve as "internal" reducible function, with the elimination of water, thus allowing the occurrence of catalytic carbonylation under non-oxidative conditions leading to a single product. Thus, 1,1′-(1,2-phenylene)bis(prop-2-yn-1-ol) was converted into methyl 2-(2-oxo-2,3-dihydronaphtho[1,2-*b*]furan-4-yl)acetate in 58% yields, by reduction of both the allylalcoholic groups formed in the initial dimethoxycarbonylation process, under the catalysis of the $Pdtu_4I_2$ complex (Scheme 38) [99]. The X-ray structure of this catalyst confirmed that tu coordinates through the sulfur atom [100].

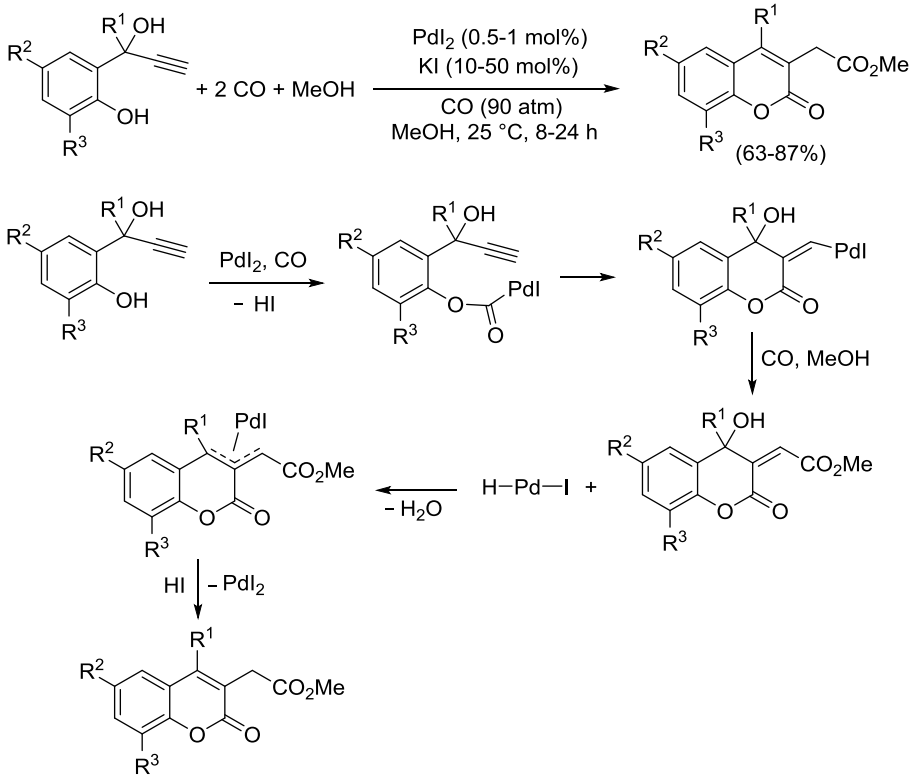


Scheme 38. $Pdtu_4I_2$-catalyzed synthesis of methyl 2-(2-oxo-2,3-dihydronaphtho[1,2-*b*]furan-4-yl)acetate from 1,1′-(1,2-phenylene)bis(prop-2-yn-1-ol) by the combination between oxidative dialkoxycarbonylation and reduction within the same molecule [99].

More recently, we applied this concept in the non-oxidative carbonylation of 2-(1-hydroxyprop-2-ynyl)phenols, which, under suitable conditions, afforded coumarinacetate derivatives (Scheme 39) [101], which have shown an interesting potential herbicidal activity [102]. In this case, the initial oxidative cyclocarbonylation-methoxycarbonylation process was followed by reduction of the HO-C-C=C-CO_2Me moiety to give the final coumarinic derivative with the regeneration of PdI_2. Notably, in this process, iodide was the only ligand used for palladium (no tu was needed), owing to the high reactivity of the HO-C-C=C-CO_2Me toward H-Pd-I to give a particularly stable β-allyl complex (Scheme 39) [101].

The possibility to combine oxidative carbonylation with a reduction within the same molecule was also assessed with 2-(1-hydroxylalk-2-ynyl)phenols, bearing an internal rather than a terminal triple bond. These substrates, however, turned out to be unstable, so we decided to start with 1-(2-allyloxyphenyl)-2-yn-1-ols, with the phenolic oxygen protected with the allyl group. In order to achieve the allyl deprotection in situ, we carried out the carbonylation experiments in the presence of two different kinds of catalysts: $Pd(PPh_3)_4$ (able to promote substrate deallylation) and PdI_2/KI (able to promote the oxidative carbonylation-reduction sequence). The use of these two catalysts simultaneously caused the selective formation of the desired product deriving from an ordered deallylation-oxidative carbonylation-reduction sequence, as shown in Scheme 40 [103,104]. For a process like this, consisting of two cycles catalyzed by the same metal, but in two different oxidation states, we coined the term "sequential homobimetallic catalysis" [103–105]. In more detail, the first cycle, catalyzed by Pd(0), relates to substrate deallylation, while the second cycle, catalyzed by Pd(II), corresponds to 5-*exo-dig* heterocyclization followed by oxidative alkoxycarbonylation and reduction of the HO-C-C=C-CO_2Me moiety (Scheme 40) [103–105]. No cyclocarbonylation product was observed,

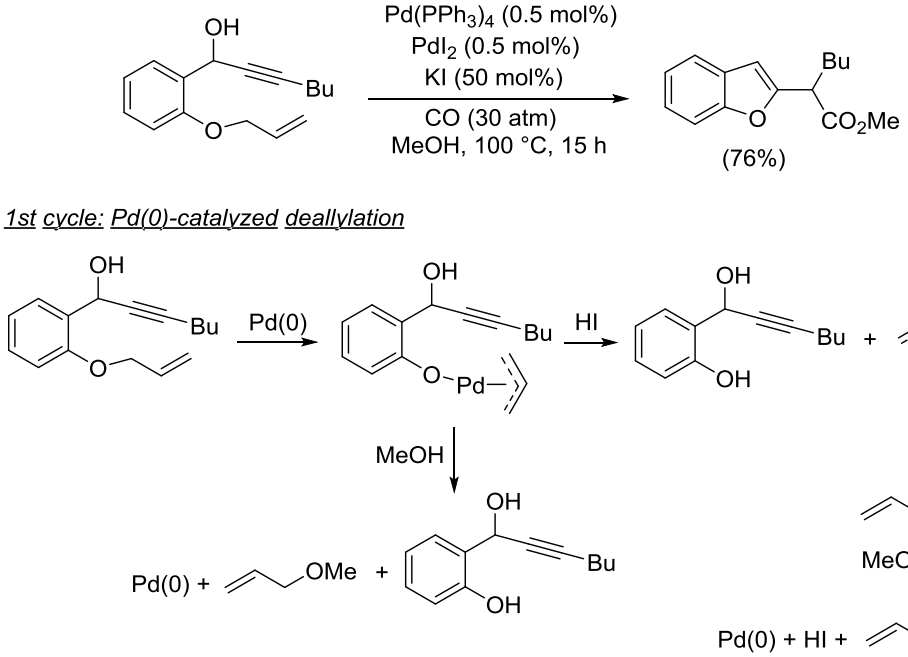
because the intramolecular triple bond insertion into a phenoxycarbonylpalladium intermediate was much less favored with an internal triple bond with respect to a terminal one. The benzofuran derivatives thus obtained were of particular interest, as they showed important antitumor activity against breast cancer cell lines [106]. Moreover, very recently, we have shown that it is possible to improve the delivery of this bioactive scaffold in vitro by chemically anchoring it (through the formation of amide bond) to suitably functionalized graphene quantum dots [107].



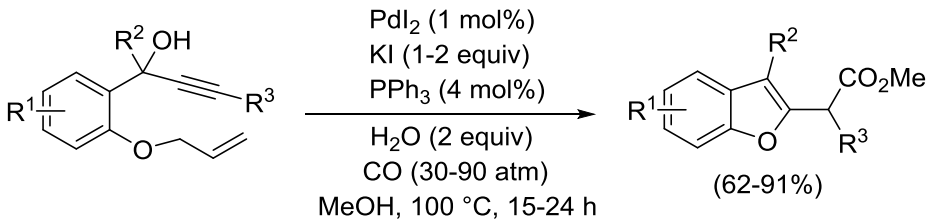
Scheme 39. Synthesis of methyl 2-(2-oxo-2*H*-chromen-3-yl)acetates from 2-(1-hydroxyprop-2-ynyl)phenols by the combination between PdI_2-catalyzed oxidative alkoxycarbonylation and reduction within the same molecule [101].

Interestingly, the PPh_3-stabilized Pd(0) complex could also be formed starting from PdI_2+PPh_3+H_2O (Scheme 41) [103–105], since it is known that PdI_2 may be reduced to Pd(0) by the action of water and CO, through decarboxylation of the I-Pd-CO_2H intermediate formed by the reaction between PdI_2, CO, and H_2O (Scheme 42) [33,108,109].

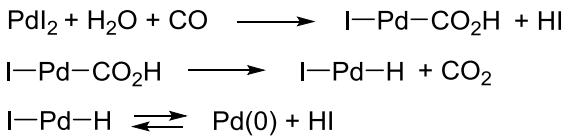
Amines could also be used as nucleophiles in this reaction, leading to the corresponding 2-benzofuran-2-ylacetamides in good to high yields (Scheme 43) [110]. More recently, we have also found that it is possible to carry out the sequential homobimetallic catalytic process in an unconventional solvent, such as $BmimBF_4$, with the possibility to recycle the solvent-catalyst system [111].



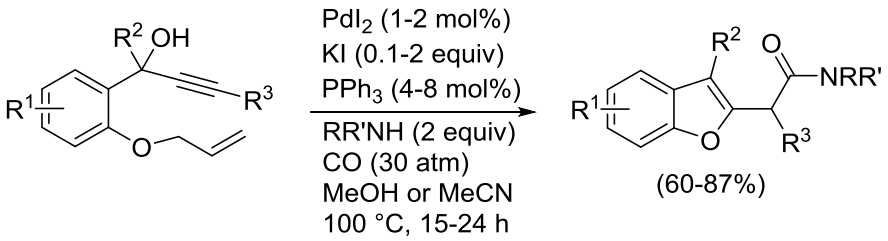
Scheme 40. Sequential homobimetallic catalysis: synthesis of methyl 2-(benzofuran-2-yl)hexanoate from 1-[2-(allyloxy)phenyl]hept-2-yn-1-ol by the concatenation between Pd(0)-catalyzed deallylation – PdI_2-catalyzed carbonylative heterocyclization [103–105].



Scheme 41. Synthesis of methyl 2-benzofuranacetates from 1-(2-allyloxyphenyl)-2-yn-1-ols by sequential homobimetallic catalysis, using PdI_2 as both the catalytic precursor for Pd(0) and as Pd(II) catalyst [103–105].

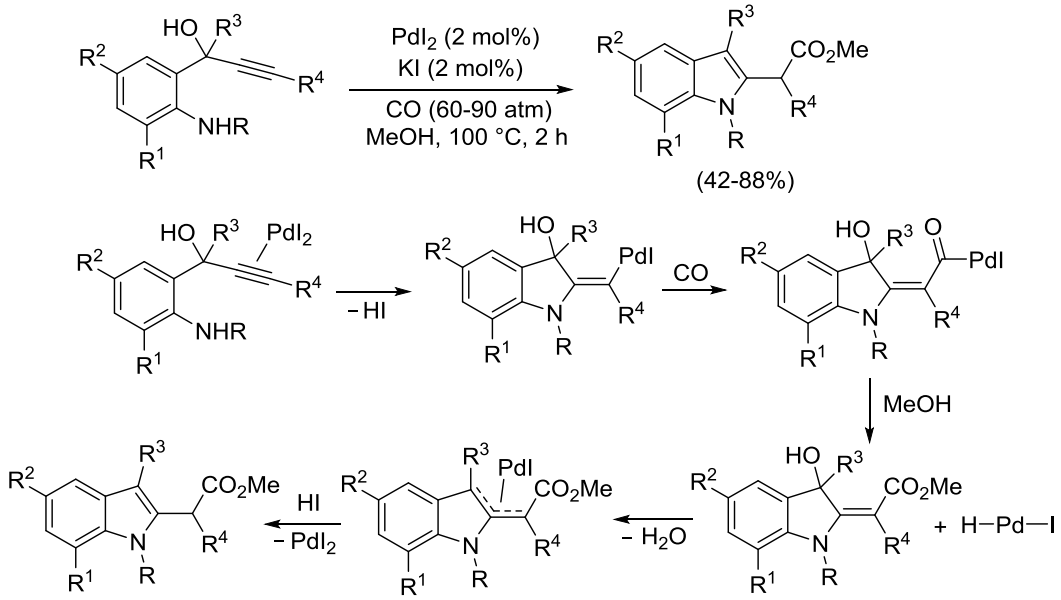


Scheme 42. In situ formation of Pd(0) from PdI_2, CO, and H_2O [33,108,109].



Scheme 43. Synthesis of 2-benzofuran-2-ylacetamides from 1-(2-allyloxyphenyl)-2-yn-1-ols by sequential homobimetallic catalysis using amines as nucleophiles [110].

The mechanistic sequence heterocyclization-oxidative alkoxycarbonylation-reduction of an HO-C-C=C-CO_2Me moiety was also observed in the formation of indol-2-acetic esters starting from 1-(2-aminoaryl)-2-yn-1-ols, as shown in Scheme 44 [58].



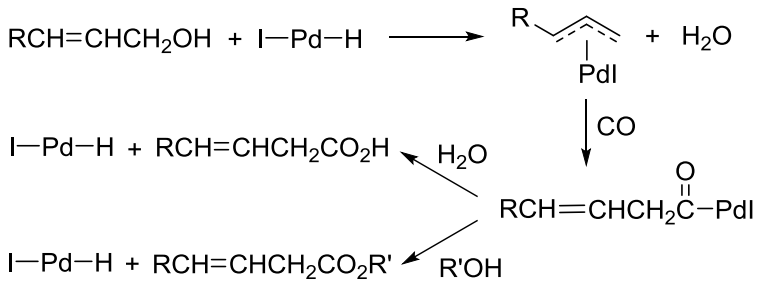
Scheme 44. Synthesis of indol-2-acetic acids from 1-(2-aminoaryl)-2-yn-1-ols [58].

3.3. Substitutive Carbonylation of Allylic Alcohols to β,γ-Unsaturated Acids or Esters

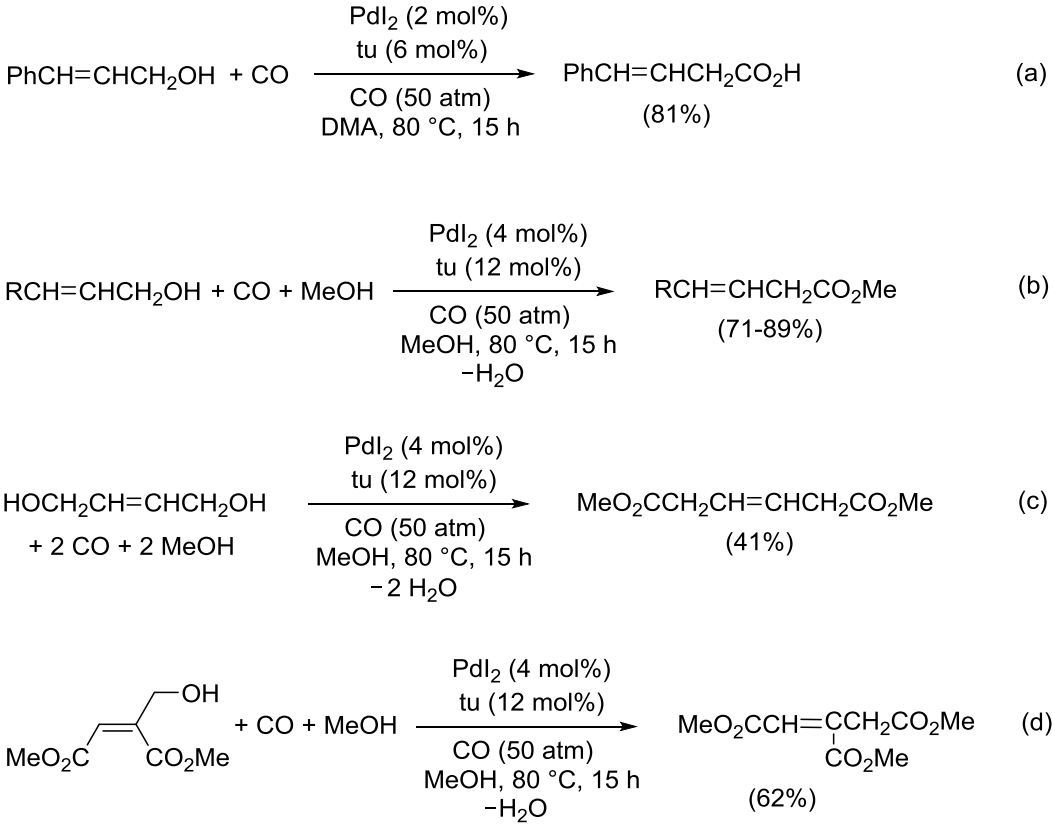
We have seen in Section 3.2 that the H-Pd-I species obtained from PdI_2, possibly stabilized by tu, can efficiently promote the reduction of allylalcoholic moieties through the formation of a π-allylpalladium complex with the elimination of water (Schemes 37–40 and 44). Under suitable conditions, the π-allylpalladiumiodide complex obtained from H-Pd-I and an allylic alcohol may undergo, instead of protonolysis, carbon monoxide insertion followed by nucleophilic displacement by water or an alcohol. This leads to the formation of a β,γ-unsaturated acid or ester, respectively, together with regeneration of H-Pd-I (Scheme 45). As we have described in Section 3.2 (Scheme 42), the easiest way to generate H-Pd-I from PdI_2 is to work in the presence of small amounts of water (either present as an impurity in the reaction solvent or added in the reaction mixture). Moreover, we have seen in Section 3.1 that the H-Pd-I species can be stabilized by the ligand tu.

Based on these concepts, we were able to directly convert (*E*)-3-phenylprop-2-ene-1-ol into 4-phenylbut-3-enoic acid in 81% yield, working in *N*,*N*-dimethylacetamide (DMA) as the solvent in the presence of water, using PdI_2 in conjunction with 3 equiv of tu as the catalytic system (Scheme 46a) [112]. Using methanol as the nucleophile under similar conditions, different allylic alcohols were also efficiently converted into the corresponding β,γ-unsaturated esters (Scheme 46b) [112]. The method also worked

nicely for the preparation of high value-added dimethyl hex-3-ene-1,6-dioate from but-2-ene-1,4-diol (Scheme 46c) and trimethyl aconitate from dimethyl hydroxymethylmaleate (Scheme 46d) [31,112].



Scheme 45. Formation of β,γ-unsaturated acids or esters by the reaction between allylic alcohols and H-Pd-I followed by CO insertion and nucleophilic displacement by water or an alcohol, respectively.

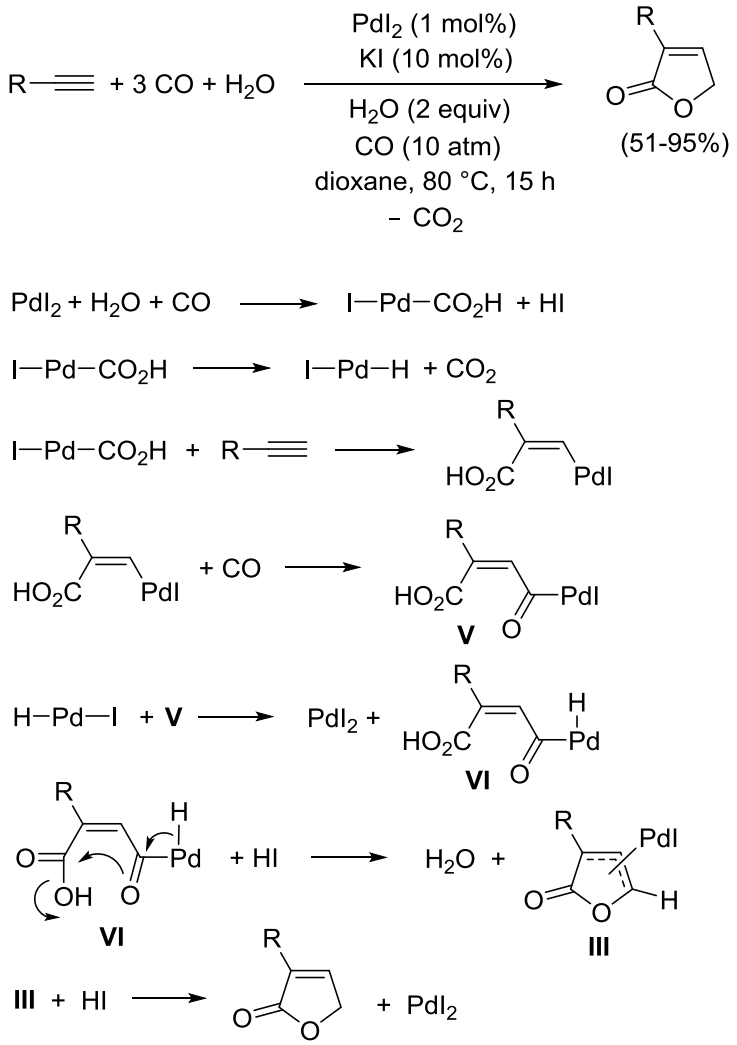


Scheme 46. PdI_2/tu-catalyzed substitutive carbonylation of (**a**) cinnamic alcohol to cinnamic acid; (**b**) allylic alcohols to β,γ-unsaturated esters; (**c**) but-2-ene-1,4-diol to dimethyl hex-3-ene-1,6-dioate; (**d**) hydroxymethylmaleate to trimethyl aconitate [31,112].

3.4. Reductive Carbonylation of Terminal Alkynes

We have seen in Section 3.1 that, in MeOH as the solvent, the H-Pd-I species, ensuing from the dimethoxycarbonylation of the triple bond, and stabilized by thiourea as a ligand, is able to reduce the acylpalladium intermediate **I** (Scheme 33). This probably occurs through the formal formation of an acylpalladiumhydride species **II**, eventually leading (via the formation of π-allylpalladiumiodide complex **III**) to a furanone product, corresponding to reductive carbonylation of the triple bond (Scheme 33). We then also noticed that an H-Pd-I species can be relatively stable, even in the absence of tu as a ligand, in an aprotic solvent, such as MeCN (Scheme 35 and related text). On the other hand, in Section 3.2, we have seen that an H-Pd-I species, besides ensuing from oxidative alkoxycarbonylation

of acetylenic substrates (Section 3.1, Scheme 33), can also be easily formed from PdI_2, CO, and H_2O (Section 3.2, Scheme 42). Taken these considerations in mind, the reactivity that we observed with terminal alkynes when we allowed them to react with CO in the presence of the PdI_2/KI catalytic system and small amounts of water in aprotic dioxane as the solvent can be easily interpreted (Scheme 47) [108,109,113]. Under these conditions, in fact, 2(5*H*)-furanones, corresponding to reductive carbonylation of the triple bond, were selectively obtained in good yields, with simultaneous oxidation of one equiv of CO to CO_2 [113] (Scheme 47). This transformation may be interpreted as occurring through a sequence of mechanistic steps involving the following: (a) formation of H-Pd-I from PdI_2, CO, and H_2O, with elimination of one equiv of HI and CO_2; (b) formation of acylpalladium intermediate **V** from the terminal alkyne, PdI_2, CO, and H_2O; (c) formal reduction of **V** by H-Pd-I with formation of acylpalladiumhydride species **VI**; (d) lactonization of **VI** by intramolecular hydride attack to the carbonyl to give **III**; and (e) protonolysis of **III** by HI with regeneration of PdI_2 (Scheme 47) [108,109].

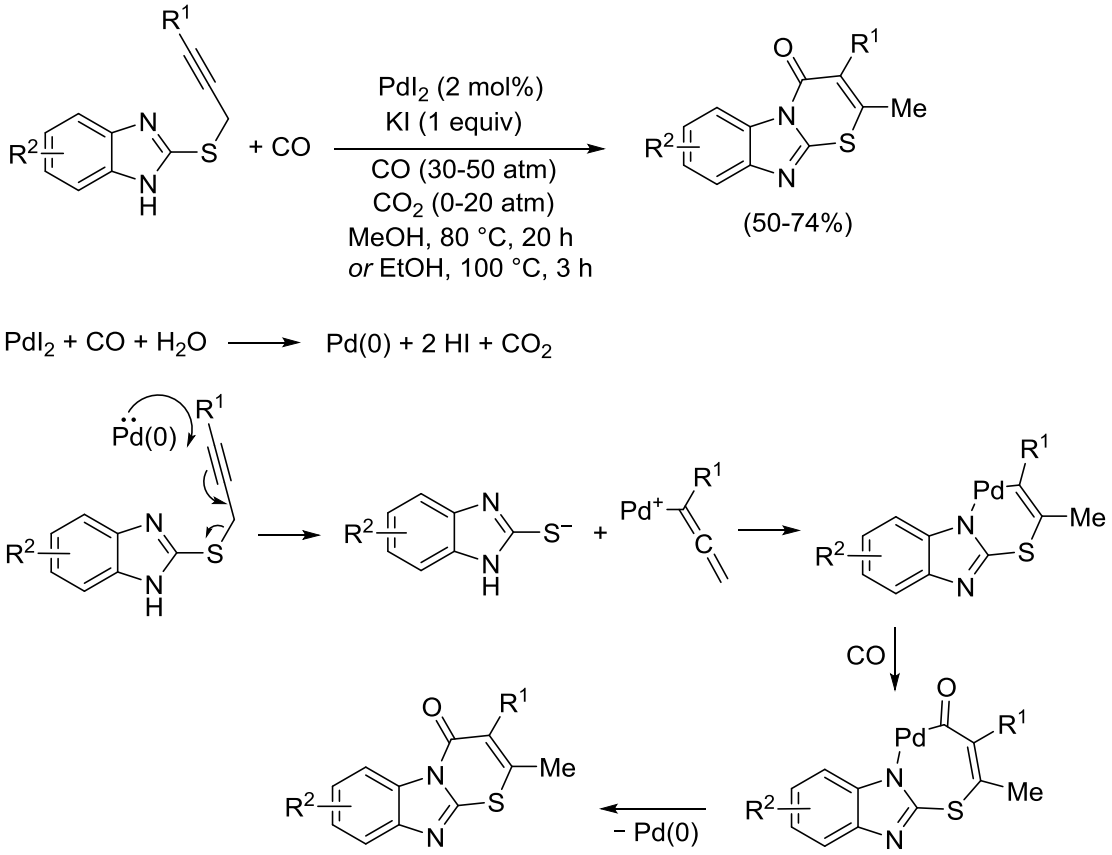


Scheme 47. Synthesis of 2(5*H*)-furanones by PdI_2-catalyzed reductive carbonylation of terminal alkynes [108,109,113].

It is worth noting that we were able to observe the Pd-H bond by NMR in dioxane-d_8 (broad signal at −4.3 ppm) [109]. Moreover, an interesting phenomenon was observed when the same process was carried out in the presence of added CO_2 in excess (40 atm); in this case, in fact, the H-Pd-I species was partly reconverted to PdI_2 (through CO_2 insertion into the Pd-H bond, followed by protonolysis), with formation of maleic anhydrides besides furanones [108,109].

3.5. Propargylic Rearrangement Followed by Heterocyclization

Recently, an interesting process was realized by carbonylating 2-(alkynylthio)benzimidazoles under non-oxidative conditions, with the selective formation of 2-methyl-1-thia-4a,9-diazafluoren-4-ones (Scheme 48) [114,115]. Product formation corresponded to some kind of structural rearrangement, most likely occurring through Pd(0)-promoted propargyl-allene rearrangement. Palladium(0), under the reaction conditions, could be easily formed by the reaction of PdI_2 with CO and traces of water, as we have already seen in Section 3.3 (Scheme 42). The propargyl-allene rearrangement of the substrate was favored by the possibility to eliminate a thiolate as a leaving group, as shown in Scheme 48. The thiolate group then attacked the allenylpalladium intermediate to give a palladacycle, from which the final product was formed by reductive elimination (Scheme 48) [115].



Scheme 48. Synthesis of 2-methyl-1-thia-4a,9-diazafluoren-4-ones by PdI_2-catalyzed carbonylation of 2-(alkynylthio)benzimidazoles [114,115].

4. Conclusions

In conclusion, we have seen how PdI_2-based catalysis is very effective and versatile for realizing a variety of important carbonylation reactions, including oxidative carbonylations (of simple and functionalized alkynes, amines, diamines, β-amino alcohols, 2-aminophenols, 1,2- and 1,3-diols), additive carbonylations (of simple and functionalized alkynes), substitutive carbonylation of allylic alcohols, and reductive carbonylation of terminal alkynes.

PdI_2-based catalysis works very nicely in different classical organic solvents, either nucleophilic (such as alcohols) or non-nucleophilic (such as *N*,*N*-dimethylacetamide, 1,2-dimethoxyethane, and 1,4-dioxane). Moreover, it can also efficiently occur, under suitable circumstances, in water as the cosolvent and in nonconventional solvents, such as ionic liquids.

The results achieved so far make this kind of catalysis one of the most important and versatile methods in carbonylation chemistry, and its use in the future, possibly in combination with

other cocatalysts or promoters, will allow achieving novel and even more complex carbonylative organic transformations.

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

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