Review

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Review

Recent Progress in Pd-Catalyzed Tandem Processes

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Abstract: In recent years Pd-containing catalytic systems for tandem processes has drawn special attention due to the enhanced catalytic properties and possibility to perform several reactions without the necessity to separate the intermediates. In this review, recent progress in Pd-catalyzed tandem processes is considered. Three types of catalytic systems were described: homogeneous catalysts (including immobilized Pd complexes); heterogeneous catalysts supported on oxides, MOFs, COFs, etc. with particular attention to the supports containing acid/base sites; metal-enzyme catalysts for chemoenzymatic tandem processes applied in fine organic synthesis and biotechnology. For homogeneous Pd-catalyzed reactions different tandem reactions were considered, i.e. cross-coupling, cyclization, carbonylation, isomerization, alkylation, arylation, etc.

Keywords: tandem catalysis; one-pot processes; palladium; bifunctional catalysts; chemoenzymatic catalysis

1. Introduction

Multiple catalytic processes in a one reactor are of high importance due to the time-space economy and global tendency to greener sustainable processes [1]. However, at present there are a lot of misinterpretations in used terminology. As was mentioned by Camp et al. [2], such processes havedifferent names: single-pot catalysis, one-pot catalysis, domino-catalysis, dual catalysis, tandem-catalysis and multifaceted catalysis. Many papers use the term "tandem" for different processes proceeding just one after another. Fogg and dos Santos [3] defined one-pot catalytic processes that are not tandem catalysis as bicatalytic reaction, in which the second catalyst is added after the first one completes the reaction. When all the catalytic species are present in the reactor all together, it can be defined as either domino or tandem catalysis. If all the reagents and catalysts are simultaneously present in the reactor, and functionality formed in the previous step undergoes subsequent transformation, such process can be classified as domino catalysis. It is important to emphasize that in the case of domino/cascade catalysis, multiple transformations proceed via a single catalytic mechanism (Figure 1) [3].

In the instance of tandem catalysis, the substrate is sequentially transformed through a number of mechanistically distinct mechanisms. Moreover, the tandem catalysis can be divided in orthogonal, assisted, and auto-tandem catalysis [3]. The difference between auto-tandem and assisted tandem processes is that in the latter case an additional compound is added in the reactor, switching the second mechanistically distinct reaction. As it was mentioned by different authors [4–6], auto-tandem catalysis is an effective method for generating complex molecules from basic starting materials since it can support several mechanistically distinct reactions in a single reactor. When sequential C–C bond-forming processes take place in the reactions, the adoption of the auto-tandem catalysis technique has a very significant effect [6]. In contrast to auto-tandem catalysis, a linear synthetic method would not be able to produce unstable or sensitive organic intermediates in situ. Although auto-tandem processes have many benefits, it might be challenging to control them. Moreover, interference from side reactions might make them more difficult, particularly when the optimal conditions for certain catalytic cycles differ from one another [4].

Tandem catalysis is a powerful tull for the production of a wide range of organic compounds via a variety of synthetic transformations, among which are arylation, alkylation, cyclization, cycloaddition, carbonylation, cross-coupling, amination, isomerisation and other processes. Different metals such as Co [7], Cu [8], Ag [9,10], Au [11], Ni [12], Ru [13], Pt [14,15], Pd [16] in composition of both homogeneous [17,18] and heterogeneous [19] systems can catalyze tandem reactions.

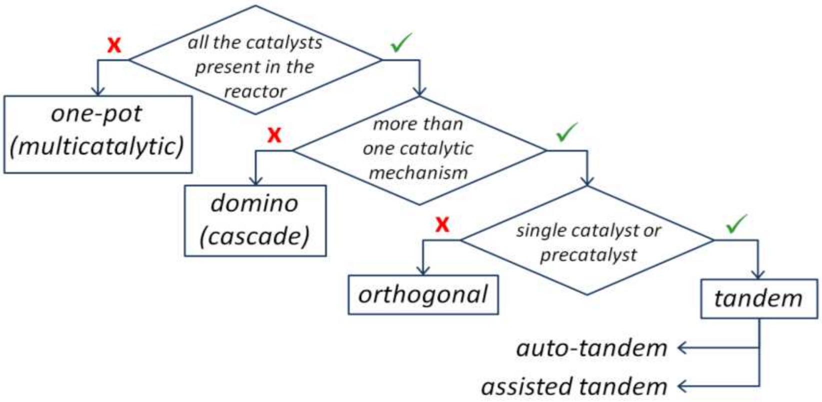

Figure 1. Distinguish between one-pot, domino, and tandem processes (based on ref. [3]).

Moreover, bimetallic catalytic systems (Cu-Zn [20], Cu-Ni [21], Pd-Cu [22,23], Au-Pd [24,25],Ir-Pd [25], Pd-Ru [26,27], Pd-Rh [28], Ag-Pd [29], Pd-Ni [30], Au-Cu [31], Cu-Ag [10,32], Cu-Bi [10], etc.), can be also used.

Among the transition metals applied for tandem processes, palladium is one of the most widely used. Thus, this review is devoted to the recent advances (for the last five years) in tandem reactions catalyzed by Pd complexes and nanoparticles (NPs), including those catalyzed by bimetallic systems and metal-enzyme catalysts.

2. Pd-Catalyzed Homogeneous Tandem Catalysis

At present, homogeneous Pd-catalyzed processes, including the tandem ones, are the most widespread in fine organic synthesis for production of active pharmaceutical ingredients (APIs) and polymers.

2.1. Coupling Tandem Processes

Palladium is known as a catalyst for the cross-coupling processes [33,34]. Both sequential and iterative Pd-catalyzed reactions can be carried out in tandem cross-coupling reactions, and the order of C–C bond forms can be regulated by either the attenuated leaving groups of the multireactive substrate or certain catalyst/ligand combinations [35–37]. Both the nucleophilic and electrophilic sites may be coupled in a specific manner. Additionally, in addition to halogen and metal leaving groups, the C–H bond can be used as an appealing leaving group [35].

In the catalytic cycle of cross-coupling reactions the palladium constantly changes its oxidation state from Pd(0) to Pd(II) and vice versa, hence the process can be catalyzed by any form of the metal [38,39]. Lamb et al. [40] employed Pd(II) to catalyze in one-pot the dehydrogenation of 2,2-disubstituted cyclopentane-1,3-diones and the oxidative Heck coupling (Figure 2). It was postulated that Pd(II) was an active form, which underwent partial decomposition during the reaction if the ligand loading was unsufficient. However, it was difficult to create the ideal one-pot conditions since the optimal conditions for the dehydrogenation stage were inappropriate for the oxidative Heck process.

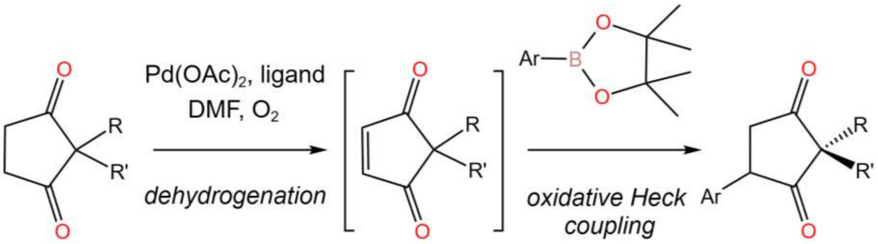

Figure 2. Scheme of the dehydrogenation of 2,2-disubstituted cyclopentane-1,3-diones and the oxidative Heck coupling in a one-pot.

Due to the presence of unligated Pd, which was likely formed during the aerobic dehydrogenation stage, the established one-pot reaction allowed achieving a reasonable yield of 60% at moderate enantioselectivity at 74:26 e.r. In order to study the telescoped reaction, the reaction mixture was filtered to remove any unligated Pd before the cross-coupling partner was added. Such treatment enabled the e.r. comparable to the separate oxidative Heck step (88:12 vs. 90:10 e.r.) and good 70% yield [40].

The improved synthesis of indolines via tandem decarboxylative amination/Heck/annulation reaction was carried out by Wang et al. [41] (Figure 3).

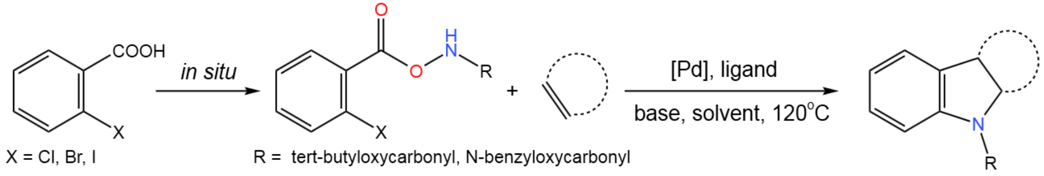

Figure 3. Scheme of the synthesis of indolines via tandem decarboxylative amination/Heck/annulation reaction [41].

Different palladium compounds ($Pd(OAc)_2$, $Pd(TFA)_2$,$Pd_2(dba)_3$, $PdCl_2$) and ligands ((t-Bu)$_3$P·BF_4, Ph_3P, etc.) were used. $PdCl_2$and (t-Bu)$_3$P·BF_4 revealed the best performance. Among the bases (Cs_2CO_3, K_2CO_3, t-BuOK, DBU, and Et_3N), Cs_2CO_3 was optimum. Moreover, different solvents were used (benzene, toluene, xylene, MeCN, $CHCl_3$, and DMF), and benzene was the most preferable one. Depending on the halogen, protecting group, substituent and nature of the second substrate and also on the reaction conditions, up to 78% yield of target product was achieved [41].The reaction mechanism was proposed to proceed via formation of the intermediate of an intramolecular decarboxylation process. The cyclization product was then synthesized by reacting this intermediate with norbornadiene using a tandem Heck-type reaction and nitrogen nucleophilic route. The reaction followed a similar tandem Heck/intramolecular Tsuji-Trost pathway when the 1,3-diene substrate was used [41].

Song et al. [42] developed synthesis of 2-(1-phenylvinyl)-indoles via novel Pd(0)-catalyzed intermolecular coupling reaction of 2-*gem*-dibromovinylanilines and *N*-tosylhydrazones (Figure 4).

Novel Pd(0)-catalyzed intermolecular coupling process between 2-gem-dibromovinylanilines and N-tosylhydrazones was proposed by Song et al. [42] to obtain 2-(1-phenylvinyl)-indoles (Figure 4).

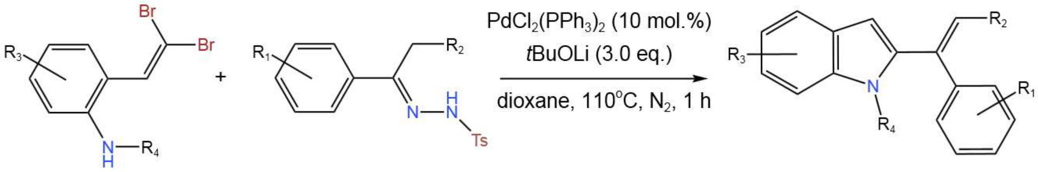

Figure 4. Scheme of tandem reaction of 2-*gem*-dibromovinylanilines and N-tosylhydrazones [42].

Reaction conditions were optimized ($PdCl_2(PPh_3)_2$ was chosen as a catalyst, and tBuOLi as a base (other bases were DMAP, tBuOK, TEA, $CsCO_3$, and CsF)). Using 2-*gem*-dibromovinylanilines as a substrate, the scope of *N*-tosylhydrazones was studied. The reaction products were obtained in moderate to good yields (from 42% up to 90%) depending on the substituents: electron-donating (*m*-OMe, *p*-OMe and -OCH_2O-) or electron-withdrawing (NO_2 and CN). The substitutions on 2-*gem*-dibromovinylaniline were also studied (-CO_2Me, Br, F, Ns, Ph, 4-F-Ph, 4-Cl-Ph, 4-OMe-Ph, 4-tBu-Ph, 4-Me-Ph, N-Ac, N-Ms) giving good yields (> 80% in most of cases).

In situ produced vinyl fluorosulfate intermediates were coupled with electron-deficient olefin partners (Figure 5) by Revathi et al. [43] to create a protocol for the one-pot conversion of alcohols to 1,3-dienes. Broad substrate scopes of alcohols were examined for the SO_2F_2 mediated dehydrative cross-coupling. Different starting compounds containing both electron-donating groups (alkyl, aryl, trifluoromethoxy, methoxy, ether, thioether) and electron-withdrawing groups (nitro, trifluoromethyl) including halogens were investigated. Corresponding products were synthesized with the yields varied from 40% up to 99%. Besides, the substrate scope of electron-deficient olefin coupling partners was studied. The best results were obtained with acrylamide, which provided the corresponding product in 82% yield, and ethyl vinyl ketone, which produced the corresponding 1,3-diene in 88% yield [43].

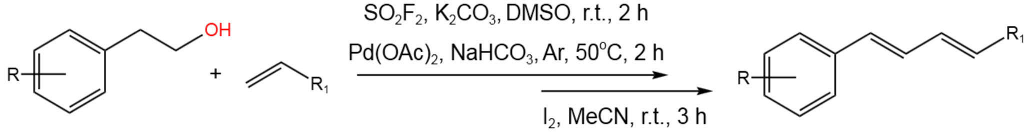

Figure 5. Scheme of dehydrative cross-coupling[43].

The C–C/C–N bond formation in the reaction between N-methyl benzamide and aryl boronic acid was catalyzed by the dinuclear palladium(II) complex, resulting in the direct synthesis of phenanthridinone (Figure 6) [44].

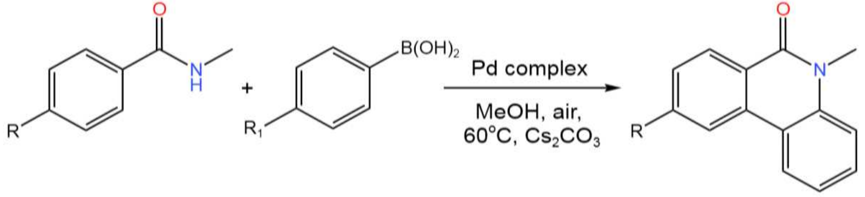

Figure 6. Scheme of the synthesis of phenanthridinones [44].

Broad range of phenanthridinones was synthesized in good to excellent yields (from 79% up to 96%) using 1 mol.% of the catalyst. It was proposed that the reaction proceeds via ortho-arylation [44].

Pd pincer complex supported by 2,6-bis(pyrrolyl)pyridine ligands was shown [45] to be an efficient catalytic system for one-pot tandem Heck alkynylation(copper-free Sonogashira coupling)/cyclization reaction (Figure 7). It was shown that a wide range of benzofuran derivatives can be obtained using 0.1 mol.% of catalysts loading for 10 h with high yields (up to 96%).

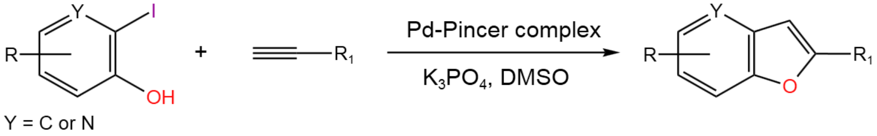

Figure 7. Scheme of benzofuran derivatives via Heck alkynylation/cyclization reaction [45].

In a similar way, microwave assisted domino [Pd]-catalyzed Heck cyclization followed by intermolecular Sonogashira coupling was carried out by Karu and Gedu [46] for the synthesis of substituted dihydrobenzofurans with the yields up to 99% (Figure 8).

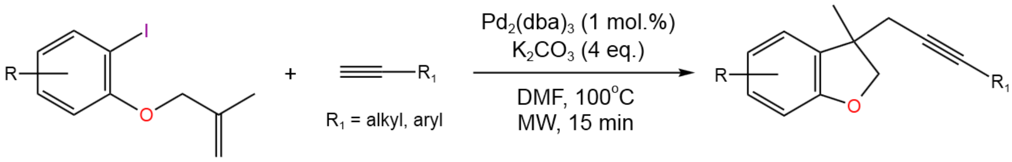

Figure 8. Scheme of benzofuran derivatives via Heck alkynylation/cyclization reaction [46].

Yokoya et al. [47] suggested fabricating the benzo[de]chromene ring followed by its oxidation in order to produce benzo[de]chromene-7,8-dione derivatives, which are known to have significant biological and pharmacological effects (Figure 9). Pd- and Cu-catalyzed Sonogashira coupling and cyclization was applied to produce benzo[de]chromene-7,8-dione derivatives with the yields up to 69%. It was found that the coupling process was catalyzed by Cu and Pd complexes while the cyclization was catalyzed by CuI alone.

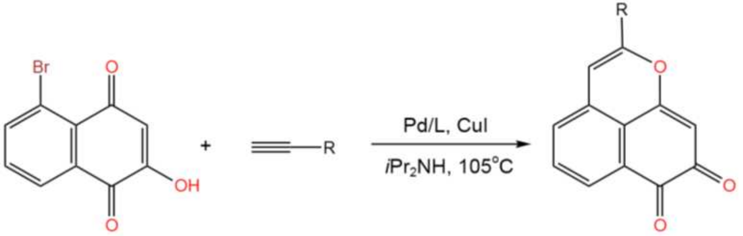

Figure 9. Tandem Sonogashira coupling and intramolecular cyclization with terminal alkynes [47].

For the one-pot synthesis of alkenyl-substituted boron dipyrromethene (BODIPY) from Cl-BODIPY and alkyne, coupling-reduction tandem process (Figure 10) was reported [48]. In comparison to traditional approaches, this synthesis enabled higher yields (up to 80%), a wider range of substrates, and a faster reaction rate by combining the Sonogashira coupling and the reduction process avoiding the use of a reductant.

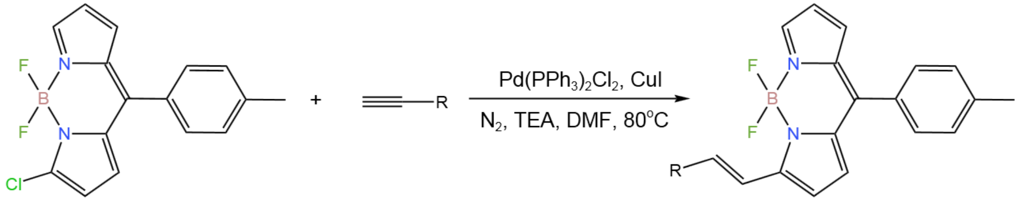

Figure 10. Synthesis of alkenyl-substituted BODIPYs [48].

One of the reactions attributed to the tandem Pd-catalyzed catalytic processes is the synthesis of imidazole derivatives [49–51]. The tandem synthesis of imidazole-fused polyheterocycles (Figure 11) from 2-vinyl imidazoles and aryl halides was reported by Li et al. [49] and involved intermolecular Heck arylation of 2-vinyl imidazoles, followed by an intramolecular aerobic oxidative C−H amination reaction. In this tandem reaction, the Pd(0)↔Pd(II) catalytic cycle was used to simultaneously break two or three C−H bonds, one C−X bond, and one N−H bond.

A tandem reaction involving boronic acids and 2-(bromobenzylsulfenyl)-1-propargyl benzimidazoles catalyzed by Pd was developed [50] (Figure 12). This process involved three different reactions: (i) Suzuki debrominative cross-coupling; (ii) Cu-free desulfenylative coupling at the 2-position of the benzimidazole; and (iii) intermolecular regioselective and stereoselective hydrothiolation of the triple C–C bond of the N-propargyl benzimidazole.

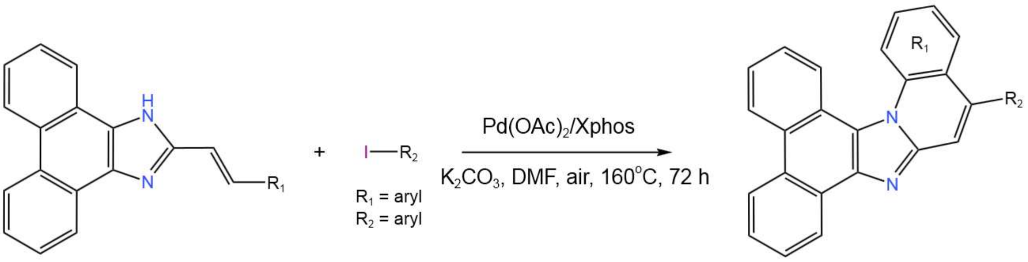

Figure 11. Pd-Catalyzed annulation of phenanthroimidazoles with aryl iodides [49].

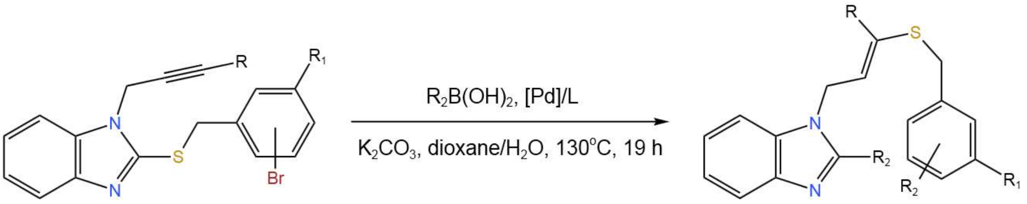

Figure 12. Tandem Pd-catalyzed reaction between boronic acids and 2-(bromobenzylsulfenyl)-1-propargyl benzimidazoles [50].

The whole procedure resulted in an alkenyl benzyl sulfide and doubled the amount of boronic acid partner that was incorporated into the final structure. The developed tandem process proceeded with moderate up to high yields (82%) depending on the substituents and ligands [50].

Luo et al. [51] developed the cross-coupling reaction of aliphatic isocyanides with *α*-diazoacetates catalyzed by palladium to form ketenimines, which were subsequently underwent the DABCO-catalyzed aza-Mannich type reaction (Figure 13) under mild reaction conditions (80^{o}C, CH_3CN – solvent). Different 2-mercaptoimidazoles or 1*H*benzo[*d*]imidazol-2-oles were transformed to 1,3-bis(β-aminoacrylate)-substituted 2-mercaptoimidazoles and 2-benzimidazolinones with the yields up to 68%.

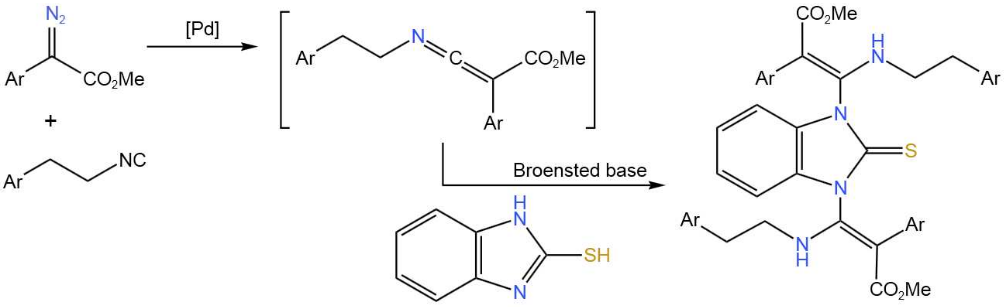

Figure 13. Scheme of the synthesis of 1,3-bis(β-aminoacrylate)-substituted 2-mercaptoimidazole derivatives synthesized in one pot using sequential Pd and Brønsted base catalysis [51].

2.2. Isomerization Tandem Processes

Isomerization tandem reactions catalyzed by Pd are possible due to the simultaneous existence of two oxidation states of this metal. Thus, there is double terminology for these reactions: some authors attribute them to orthogonal catalysis [52], others – to tandem catalysis [53]. Arroniz et al. [52] demonstrated tandem orthogonal process of conversion of alkynyl epoxides to furans (Figure 14).The developed procedure allowed high yields (up to 93%) of furan' derivatives.

It was found that the reaction proceeded through the formation of allenyl ketone and β,γ-alkynyl ketone as intermediates. Porposed reaction mechanism involved oxidative addition of Pd(0) into the alkynylepoxide resulting in formation of allenylpalladium(II) species, which underwent reductive elimination to enol. The latter tautomerized to alkynyl ketone and to allenyl ketone. Furanylpalladium complex was formed by the Pd(II)-activated cyclization of allenyl ketone. After the protodepalladation, the target furan's derivatives were produced under mildly acidic conditions. Moreover, a possible alternate mechanism for the conversion of the alkyne to the furan was suggested [52].

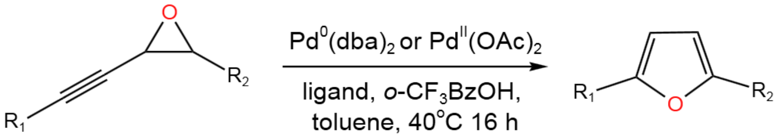

Figure 14. Dual catalytic isomerization of alkynyl epoxides [52].

The synthesis of furans and pyrroles was carried out via the Pd-catalyzed tandem addition/ring-opening/cyclization reaction of 2-(3-aryloxiran-2-yl)acetonitriles with arylboronic acids in aqueous medium (Figure 15) [53].

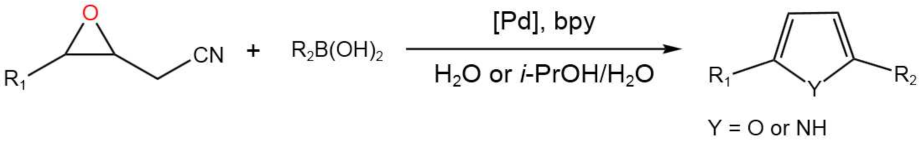

Figure 15. Tandem reaction of epoxynitriles with arylboronic acids [53].

Yu et al. [53] noticed that despite the advances in the Pd-catalyzed ring-opening of epoxides with nonpolar multiple bonds (such as vinyl and alkynyl), the reactions of boronic acids with epoxides with polar groups are less studied due to the lower reactivity.

As a result of the study, an efficient approach for the synthesis of furans and pyrroles with high selectivity was developed allowing, depending on the catalyst and additive (*p*-toluenesulfonic acid, trifluoromethanesulfonic acid, D-camphorsulfonic acid, methanesulfonic acid, etc.), the yields up to 73% of furan derivatives in aqueous medium at 80°C under air. It is noteworthy that the replacement of air to the oxygen allowed noticeably increasing the yield of target product (up to 86%). In the case of the synthesis of 2,5-diarylpyrroles at 100°C under nitrogen using *i*-PrOH/H_2O mixture as a solvent, up to 84% yield was achieved depending on the substituents. Moreover, it was found that the steric effects of arylboronic acids primarily controlled the chemo-selectivity of the developed tandem process: when 2-(3-aryloxiran-2-yl)acetonitriles were reacting with the less sterically hindering arylboronic acids, the only products produced were furans, whereas when reacting with the more sterically bulky arylboronic acids, pyrroles were selectively produced [53].

Another one example of isomerization tandem processes is the tandem isomerization/hydrothiolation of allylbenzenes (Figure 16) [54]. It was demonstrated that the highly regioselective catalytic system composed of a Pd(II) precursor, bidentate phosphine ligand, and strong Brønsted acid may convert a wide range of 3-arylpropenes and thiols to branched benzylic thioethers. The reaction was facilitated by an *in situ* generated Pd hydride.

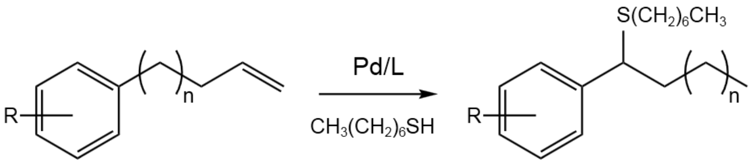

Figure 16. Tandem isomerization/hydrothiolation of allylarenes [54].

2.3. Carbonylation Tandem Processes

Over 80% of all the APIs are known to have heterocyclic aromatic rings, with *N*-containing aromatic heterocycles predominating. Many APIs have the carbolinone ring system as a substructure [55]. Thus, carbolylation reactions are highly demanded by modern chemical industry. These reactions can be carried out in tandem with such processes as cross-coupling, dealkylation, dehydrogenation, etc.

A tetracyclic isoindoloindole skeleton with three new C–C/C–N bonds simultaneously generated, for instance, could be constructed in a one step using tandem Pd-catalyzed carbonylation and C–C cross-coupling via C–H activation (Figure 17) [56]. In more detail, the production of *6H*-isoindolo[2,1-*a*]indol-6-ones from commercially accessible substrates involved the carbonylation of aryl dibromides with indoles and the C–H activation of in situ produced *N*-(2′-bromoaroyl)-indole. It is noteworthy that glyoxylic acid monohydrate was used as an eco-friendly CO surrogate in the aminocarbonylation stage of the proposed tandem process. As a result, a number of *6H*-isoindolo[2,1-*a*]indol-6-ones were produced in yields of 40-64%.

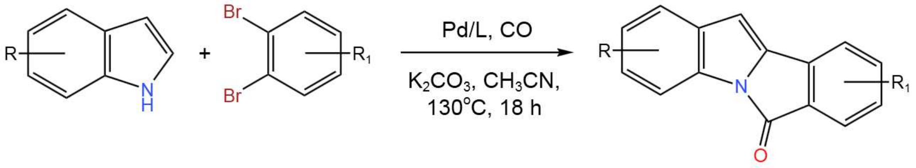

Figure 17. Tandem Pd-catalyzed carbonylation and C-C cross-coupling[56].

Wang et al. [57] developed the Pd-catalyzed multi-step tandem carbonylation/N-dealkylation/carbonylation reaction with alkyl as the leaving group and tertiary anilines as the nitrogen nucleophile, which allowed for the effective production of isatoic anhydride derivatives (Figure 18). Moderate to good (>80%) yields were obtained depending on the substituents. Moreover, the developed approach was successfully used to synthesize Evodiamine – biologically active alkaloid – with 70% yield.

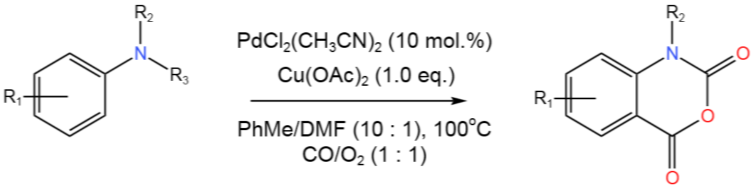

Figure 18. Tandem Pd-catalyzed carbonylation/N-dealkylation/carbonylation reaction of *N*,*N*-dialkyl anilines [57].

For the synthesis of a variety of carbolinones under mild reaction conditions, Han et al. [55] proposed an effective tandem oxidative C–H aminocarbonylation and dehydrogenation reaction co-catalyzed by Pd and Cu (Figure 19). Carbolinones, tetrahydro-β-carbolinones, and tetrahydro-γ-carbolinones were selectively obtained with the yields of up to 90% by simply changing the reaction conditions. Strychnocarpine, a natural alkaloid, and its analogs were also produced.

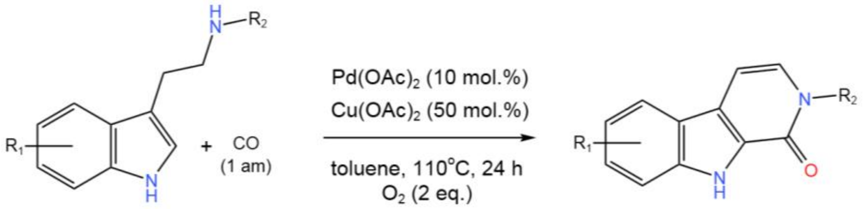

Figure 19. The scheme of synthesis of β-carbolinones via the Pd/Cu co-catalyzed tandem C–H aminocarbonylation and dehydrogenation [55].

New P,O-hybrid ligand was developed by Zhao et al. [58] for the Pd-catalyzed bis-hydroaminocarbonylation of alkynes allowing the effective production of N-aryl substituted succinimides with the isolated yield of 57-90% (Figure 20) in the presence of methanesulfonic acid (MSA) as an additive. The catalyst L1-Pd(CH_3CN)$_2$$Cl_2$ system was reused for 5 runs without the precipitation of Pd-black.

One of the widespread reactions for the synthesis of cyclic compounds is the Diels-Alder reaction, which can be also combined with the carbonylation process [59]. Such approach can provide a variety of functionalized carbocycles with complex architectures. Most of the methods of the synthesis of lactone-containing bridged polycyclic compounds are based on a stepwise protocol restricting the overall scope and practicality of these transformations.

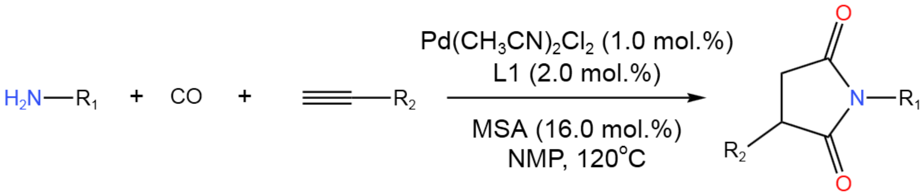

Figure 20. Pd-catalyzed bis-hydroaminocarbonylation of alkynes [58].

Therefore, Pd-catalyzed tandem carbonylative Diels-Alder process was developed by Wang et al. [59] (Figure 21).

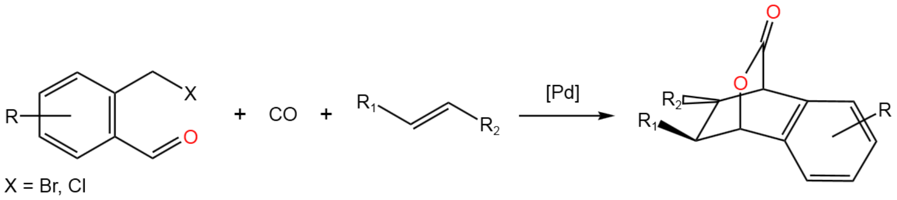

Figure 21. Scheme of the reaction of aldehyde-tethered benzylhalides and alkenes via the Pd-catalyzed tandem carbonylative lactonization and Diels-Alder cycloaddition [59].

It was proposed that the use of the aldehyde functionality as the reactive directing group resulted in good chemo- and stereoselectivity. Moderate up to high (93%) yields were achieved depending of the palladium source, base and nature of substituents in the initial compounds [59].

2.4. Cyclization Tandem Processes

Cyclization is another type of reactions widely used in fine synthesis [60–64]. Such reactions can proceed with the *in situ* generated active species as a part of tandem catalytic transformations. For example, in order to produce EGFR (epidermal growth factor receptor) inhibitors, Ansari et al. [65] established a four-component procedure for the synthesis of pyrazolo[1,5-*c*]quinazolines with a small polar substitution of the pyrazole ring (Figure 22). In this tandem process, azomethine imine was generated in situ. Then, acetonitrile having the electron withdrawing group (EWG) at α-position (malononitrile, α-cyanocaboxyalate or β-ketonitrile) participated in the reaction.

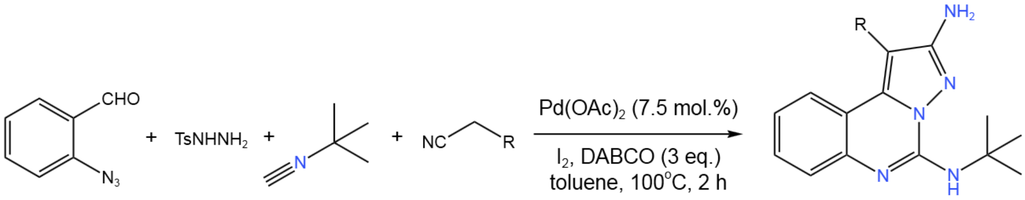

Figure 22. Four-component one-pot synthesis of pyrazolo[1,5-*c*]quinazoline [65].

In order to create 6-fluoroalkyl-phenanthridines in the absence of an oxidant, Bao et al. [66] developed a Pd-catalyzed tandem cyclization of fluorinated imidoyl chlorides using 2-bromophenylboronic acid (Figure 23). The developed procedure allowed high yields (up to 97%) of target compounds using fluorinated imidoyl chlorides as fluorine-containing synthons.

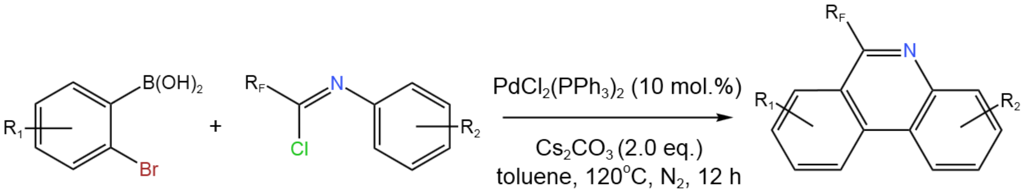

Figure 23. Synthesis of 6-fluoroalkyl-phenanthridines [66].

Another example of cyclization reactions proceeding with participation of organic cyanides – Pd-catalyzed tandem reaction of cyanomethyl benzoates with arylboronic acids developed by Dai et al. [67]. According to this approach, the selective synthesis of oxazoles and isocoumarins was found to depend strongly on substitution at the 2-position of starting cyano-compounds. Thus, 2,4-diaryloxazoles were selectively produced from cyanomethyl benzoates (3-benzoyl-4-aryl-isocoumarins – from 2-benzoyl-substituted cyanomethyl benzoates) with the yields of up to 93% (Figure 24).

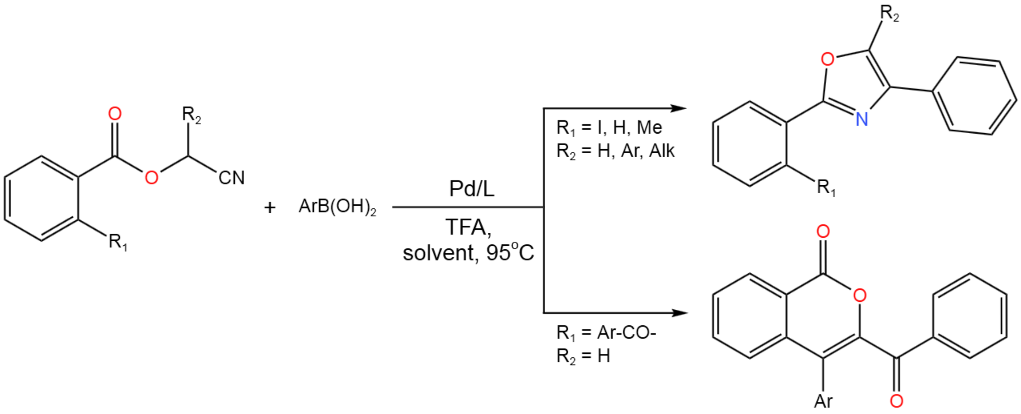

Figure 24. Four-component one-pot synthesis of pyrazolo[1,5-*c*]quinazoline [67].

By using the Pd-catalyzed tandem reaction of 2-aminostyryl nitriles with arylboronic acids, Xu et al. [68] developed new protocol for the synthesis of 2-arylquinolines (Figure 25). The proposed procedure is an alternative synthetic route as compared to common condensation reaction of (*E*)-2-aminostyryl ketones.

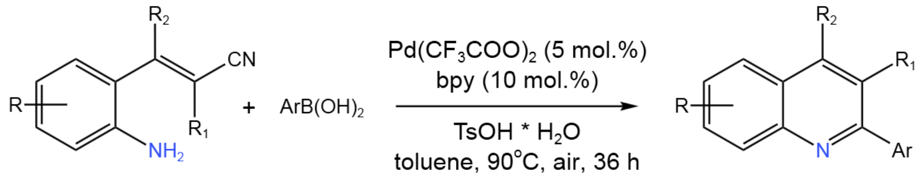

Figure 25. Pd-catalyzed tandem reaction of 2-aminostyryl nitriles with ArB(OH)2 [68].

Ye et al. [69] established a palladium-catalyzed approach for the tandem reaction of 2-(arylamino)benzonitrile with arylboronic acids in water to produce 9-arylacridine derivatives posessing estrogenic biological activity (Figure 26). High yields of the desired products (up to 93%) were achieved via proposed tandem process, involving the nucleophilic addition of aryl Pd species to the nitrile to produce an aryl ketone intermediate, which was then underwent an intramolecular Friedel-Crafts acylation and dehydration to produce acridines.

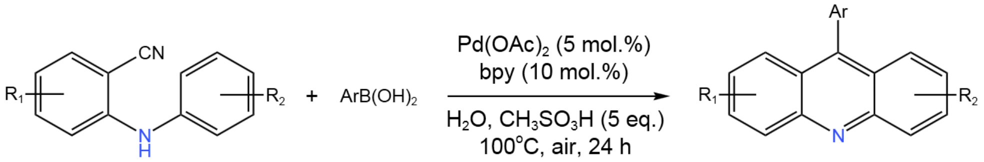

Figure 26. Tandem reaction of 2-(arylamino)benzonitrile with arylboronic acids[69].

A method for the production of benzoxazinones or quinazolinones was reported by Lang et al. (Figure 27) [70]. It was mentioned that other protocols are carried out under harsh conditions restricting the functional group tolerance. According to the proposed strategy, benzoxazinone skeletons were synthesized via utilizing an oxidative carbene-catalyzed tandem isomerization/cyclisation process, which, under mild conditions, allowed producing a number of valuable benzoxazinones or quinazolinones from a wide range of substrates.

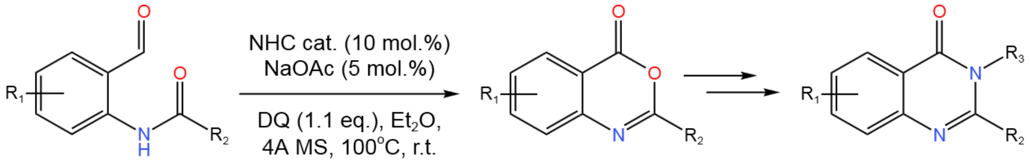

Figure 27. Carbene-catalyzed tandem isomerization/cyclisation [70].

By using a one-pot intramolecular C–N coupling cyclization reaction, Patel et al. [71] created promising catalytic process to incorporate four membered ring systems between the benzimidazole and 4-phenyl quinoline cores (Figure 28). This protocol was proposed to be an attractive route for the synthesis of different heterocycles, considering its high efficiency (yields up to 94%), wide substrate scope and mild reaction conditions [71].

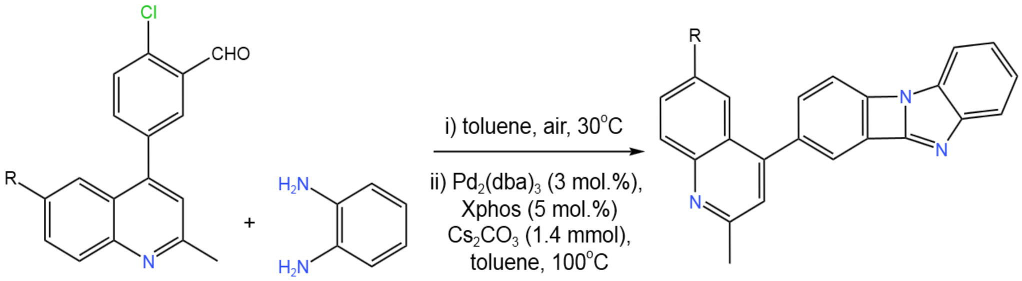

Figure 28. Scheme of Pd-catalyzed intramolecular C–N coupling cyclization reaction [71].

Pd-catalyzed cascade addition/cyclization/aromatization of heteroarenes (e.g., thiophenes, furans, pyrroles, and indoles) with 2-(cyanomethoxy)chalcones was shown to be a promising approach for the synthesis of various benzofuro [2,3-c]pyridines with the yields up to 86% [72].

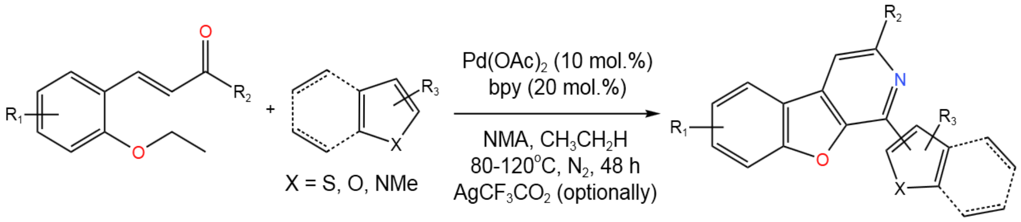

Figure 29. Pd-catalyzed cascade reaction of 2-(cyanomethoxy)chalcones with heteroarenes [72].

A novel procedure for the tandem intramolecular addition of active methylene compounds to internal alkynes, followed by coupling with aryl and heteroaryl bromides, was described by Błocka et al. [73] (Figure 30). This method allowed obtaining a variety of vinylidenecyclopentanes with the yields up to 90%, provided high regio- and stereoselectivity and tolerance to the wide range of substituents. Thus, the the *5-exo-dig* intramolecular addition proceeded with high efficiency.

Figure 30. Tandem Pd-catalyzed carbocyclization-coupling of methylene compounds bearing internal alkyne group with aryl and heteroaryl bromides [73].

The mechanism involving oxidative addition, cyclization, and reductive elimination was also confirmed by the computational study. The rate- and configuration-determining step was found to be the 5-*exo-dig* intramolecular nucleophilic addition of the enol intermediate to the alkyne activated via coordination with Pd(II) [73].

2.5. Other Tandem Processes

There are many other tandem reactions homogeneously catalyzed by palladium. Below we will provide several examples, among which are: alkylation, alkenylation arylation, cycloaddition, carboannulation, etc.

Novel procedure of arylation-cyclization was developed for the synthesis of 3-aryl-2-quinolone and 4-aryl-2-quinolone derivatives from simple isomeric precursors using oxygen as a co-oxidant (Figure 31) [74].

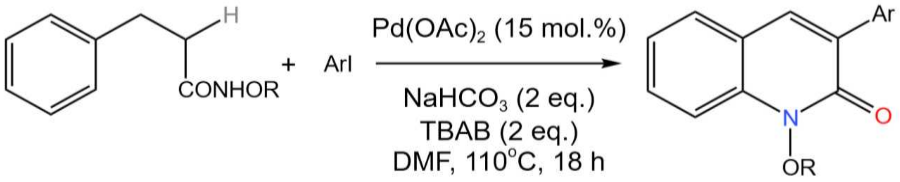

Figure 31. Tandem arylation-cyclization [74].

Ghosh and Chattopadhyay [74] identified the following Pd-catalyzed tandem procedures, which can be applied for the synthesis of 4-aryl-2-quinolones:

intramolecular hydroarylation of yanamides;
hydroarylation-heterocyclization of 2-aminophenyl propiolate;
Heck-heterocyclization;
oxidative Heck-heterocyclization;
arylation of ortho-halo-cinnamides followed by Buchwald-type intramolecular amidation.

In the developed approach, the unusual complementary regioselectivity was found in the tandem C–H-arylation C–H-amidation of isomeric substrates. The origin of selectivity was proposed at the C–H-arylation step [74].

Domański et al. [75] described the tandem Pd-catalyzed three-component reaction that allowed regio- and stereoselective perfluoroalkylative borylation of a variety of terminal and internal alkynes in the presence of perfluoroalkyl iodide and $(Bpin)_2$. Thus, the first example of anti-addition across a C–C multiple bonds of groups originating from two separate electrophiles to functionalize alkynes by reductive dicarbofunctionalization was shown. Iodoperfluoroalkylation, borylation, and coupling are the three fundamental processes responsible for this sequential transformation, and mechanistic studies have shown that their rates significantly differ (Figure 32).

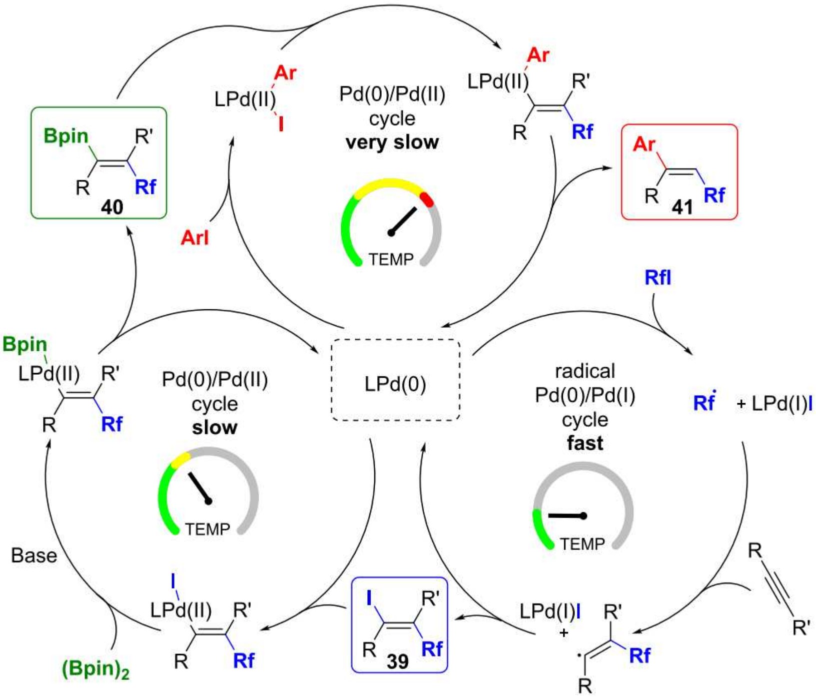

Figure 32. Proposed reaction mechanism of perfluoroalkylative borylation. Reproduced with permission from [75]. Copyright 2019 American Chemical Society.

According to the developed tandem process, from the same reaction mixture and under the same reaction conditions the fluoroalkyl-substituted vinyl iodides, vinyl boronates, or olefins can be produced by changing the temperature program [74].

The Pd-catalyzed direct tandem C–O/C–H activation method for C–C bond formation was described by Fernández et al. [76]. To accomplish base-free direct C–H alkenylation, the novel approach combined coordinated metalation-deprotonation of functionalized heterocycles with C–O oxidative addition at enol pivalates (Figure 33). According to mechanistic studies, the C–O oxidative addition to Pd(0) was shown to be reversible, and the product of Pd(II) C–O oxidative addition directly resulted to C–H activation.

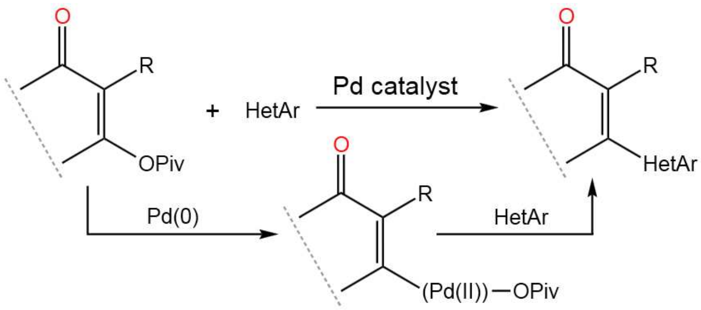

Figure 33. General scheme of Pd-catalyzed tandem C–O/C–H activation [76].

Zhang et al. [77] developed a prospective route for the synthesis of poly-substituted quinolines via a three-component tandem reaction. 2-Aminobenzonitriles, arylboronic acids and ketones were used as the substrates. Pd-catalyzed aryl addition to the cyano group was followed by hydrolysis and Friedländer-type cyclization to produce the quinoline compounds, with the yields up to 96%. The described above cyclization tandem process developed by Xu et al. [68] resulted in the lower yields, while comparing the same structures of target products.

Through the three-component tandem arylation and allylic etherification of 2,3-allenol with aryl iodides and alcohols, an effective approach for the synthesis of arylated allylic ethers was implemented [78]. By this method, functionalized 1-arylvinylated 1,2-diol derivatives were produced with the yields up to 83% and complete selectivities.

Tang et al. [79] reported Pd-catalyzed tandem reaction of 3-allyloxybenzocyclobutenols that involved proximal C–C bond cleavage, C–O bond cleavage, and allylic alkylation of the C–H bond. Thus, novel approach to meta-β-keto phenols bearing an allylic group with 100% atom economy was developed. It is noteworthy that, by adjusting substituents on various positions of benzocyclobutenols, sequential proximal or distal C-C bond cleavage/deallylation could be implemented.

Li et al. [80] developed a tandem process for the selective assembly of tri- or tetrasubstituted vinylsilanes. It was shown that using this method, *ortho*-vinyl bromobenzenes can be formed in situ from 1-bromo-2-iodobenzenes and N-tosylhydrazones and disilylated to produce two C–Si bonds and two C–C bonds (Figure 34).

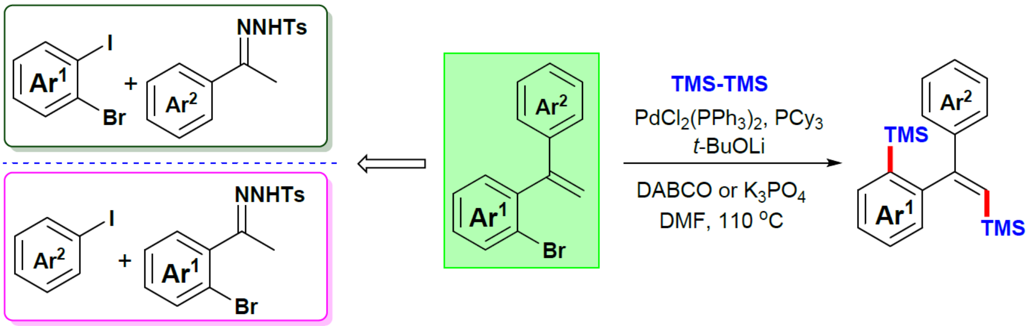

Figure 34. General scheme of the disilylation of C(aryl),C(vinyl)-palladacycles. Reproduced with permission from [80], RCS, 2020.

It was determined that the *ortho*-vinyl bromobenzenes produced from 1-bromo-2-iodobenzenes and N-tosylhydrazones are the crucial intermediates needed to manufacture vinylsilanes by disilylating the C(aryl),C(vinyl)-palladacycle, which is formed by a direct vinylic C-H bond activation [80].

By the reaction with aldehydic N-tosylhydrazones, the treansformation of 1-aryl- and 2-aryl-1,2-dihydro-3H-indazol-3-ones into 1,2-di(hetero)aryl- and 2,3-di(hetero)aryl-2,3-dihydroquinazolin-4(1H)-ones was carried out [81]. The method involved a cascade process that included base-mediated Pd-carbenoid production via the decomposition of N-tosylhydrazones, nucleophilic attack of indazolone on the Pd-carbenoid complex, and intramolecular ring expansion by N-N bond cleavage.

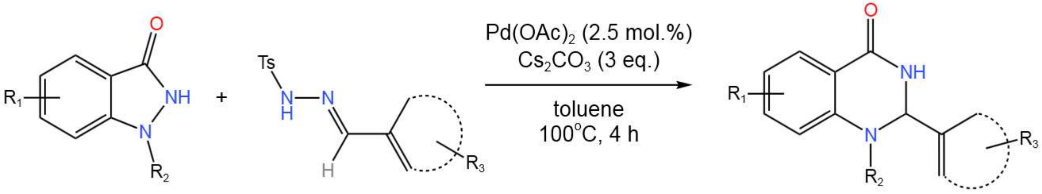

Figure 35. General scheme of Pd-catalyzed tandem C–O/C–H activation [81].

Activated tetrasubstituted alkenes made from phthalides or butyrolactone were combined with vinylethylene carbonates in an unprecedented [5 + 2] cycloaddition/ring-contraction tandem process by Xiong et al. [82] under Pd(0) catalysis (Figure 36). Proposed approach was practical and mechanistically novel. In contrast to the traditional spirolactonization method, benzo-[5,5]-spiroketal lactones and [5,5]-spiroketal lactones bearing two vicinal tetrasubstituted centers can be obtained by this tandem [5 + 2] cycloaddition/ring-contraction mechanism with moderate to high yields.

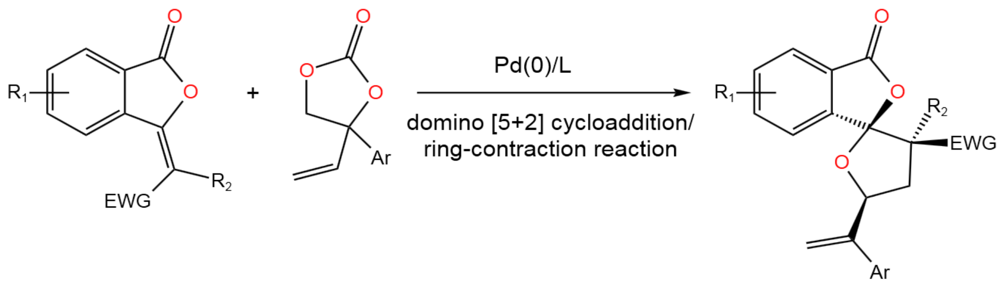

Figure 36. Pd-catalyzed[5 + 2] cycloaddition/ring-contraction tandem process [82].

The first example of transition-metal catalyzed multicomponent carboannulation reaction of [60]fullerene was reported by Liu et al. [83]. In a Pd-catalyzed three-component tandem coupling-carboannulation process, [60]fullerene, 2-(2,3-allenyl)-malonates, and (hetero)aryl iodides were converted into a variety of polysubstituted [60]fullerene-fused cyclopentanes with a wide range of substrates and excellent functional group compatibility (Figure 37).

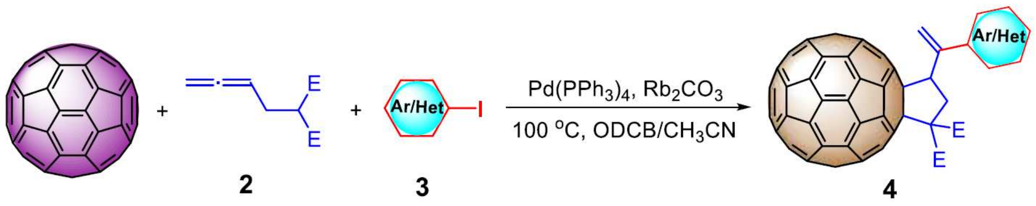

Figure 37. Scheme of Pd-catalyzed tandem coupling-carboannulation for the regioselective synthesis of polysubstituted C_{60}-fused cyclopentanes. Reproduced with permission from [83]. Copyright 2020 American Chemical Society.

Zhang et al. [84] developed the Pd-catalyzed tandem synthesis of 2-trifluoromethylthio-(seleno)-substituted benzofurans, benzothiophenes and indoles (Figure 38) in acceptable to good yields (up to 93%).

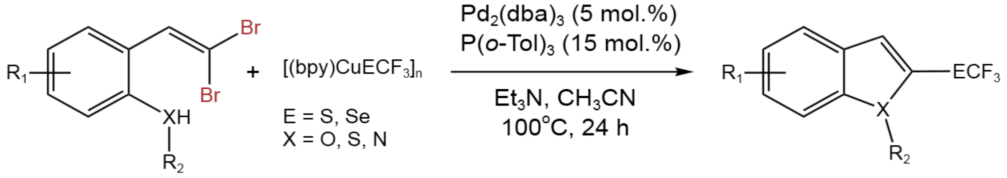

Figure 38. Pd-catalyzed tandem synthesis of 2-trifluoromethylthio-(seleno)-substituted benzofurans, benzothiophenes and indoles [84].

Yang et al. [85] reported the asymmetric tandem C−C bond activation/Cacchi reaction between cyclobutanones and *o*-ethynylanilines (Figure 39). The chiral σ-alkylpalladium intermediates were formed via enantioselective C(sp^3)−C(sp^2) bond activation of cyclobutanones and then promoted cyclization of *o*-ethynylanilines, leading to one-carbon-tethered chiral indanone-substituted indoles. An all-carbon quaternary stereocenter was simultaneously formed along with the two C−C bonds and one C−N bond. Moreover, indanones substituted indoles with both central and axial stereogenic elements were synthesized with good yields and excellent enantioselectivity.

The borrowing hydrogen (BH) reaction (hydrogen autotransfer) is another example of Pd-catalyzed tandem processes that can be mentioned [86] as a powerful strategy that combines transfer hydrogenation (avoiding the direct use of molecular hydrogen) with one or more intermediate reactions to synthesize more complex molecules without the need for time-consuming separation or isolation processes. The strategy of BH process relies on three steps, (i) dehydrogenation, (ii) intermediate reaction, and (iii) hydrogenation, among which the intermediate reaction works in tandem with the metal-catalyzed hydrogenation/dehydrogenation step.

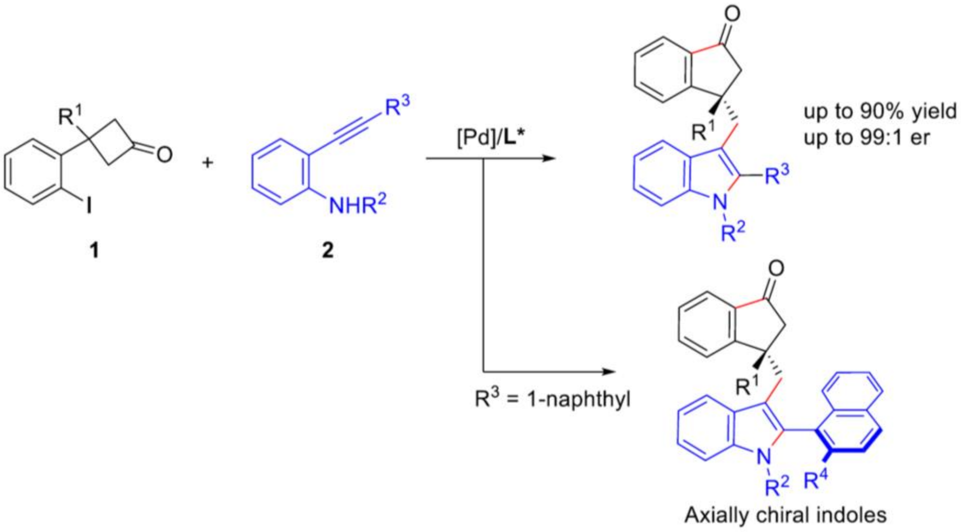

Figure 39. Pd-catalyzed enantioselective tandem ring-opening/Cacchi reaction. Reproduced with permission from [85]. Copyright 2021 American Chemical Society.

3. Heterogenized Pd-Complexes in Tandem Processes

Homogeneous Pd complexes can be anchored to the different organic or inorganic supports. Such heterogenized complexes can be also used in tandem catalytic processes.

As the examples of heterogenized Pd-complexes reported for the last five years for application in tandem reactions, the works of Fan et al. [87] and Esfandiary et al. [88] can be mentioned. In both cases Pd catalyzed the chosen tandem process homogeneously, while the support facilitated the separation and reuse of the catalysts.

Fan et al. [87] synthesized polyethyleneimine(PEI)-capped microcrystalline cellulose(MCC)-supported polyamidoamine (PAMAM) dendrimer (MCC-PAMAM$_{G2.5}$-PEI) was synthesized for loading of Pd^{2+} and Cu^{2+} ions. In this catalytic system, PAMAM$_{G2.5}$ served as the carrier to immobilize Pd^{2+} ions, and PEI provided the coordinating sites to selectively chelate Cu^{2+} species. The Pd/Cu@MCC-PAMAM$_{G2.5}$-PEI was tested in Sonogashira-cyclization tandem reaction, and revealed excellent catalytic activity, recyclability and robustness. The synergetic effect between Pd and Cu was observed.

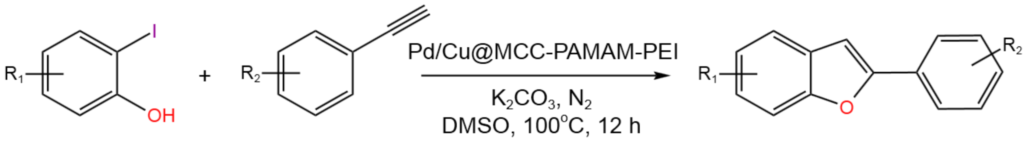

Figure 40. Scheme of Pd/Cu@MCC-PAMAM$_{G2.5}$-PEI-catalyzed Sonogashira-cyclization tandem reaction[87].

Novel magnetic γ-Fe_2O_3@Cu-LDH@Cysteine-Pd dual nanocatalyst system was designed by Esfandiary et al. [88]. The surface of magnetic NPs was modified by substitution of Cu(II) metal cations with layered double hydroxide (LDH) cations. Then the Pd(II) complex was immobilized on the interface defect structure of LDH (Figure 41). Using the synthesized catalyst, the A^3-coupling followed by C-N coupling and intramolecular cyclization was carried out for the synthesis of quinolines (yields up to 94%) from 2-bromobenzaldehyde as low cost simple starting material (Figure 42). The suggested nanocatalyst easily activated terminal alkynes in the absence of base using recyclable choline azide as a green solvent and reagent. The catalyst could be reused up to four times without significant loss of activity [88].

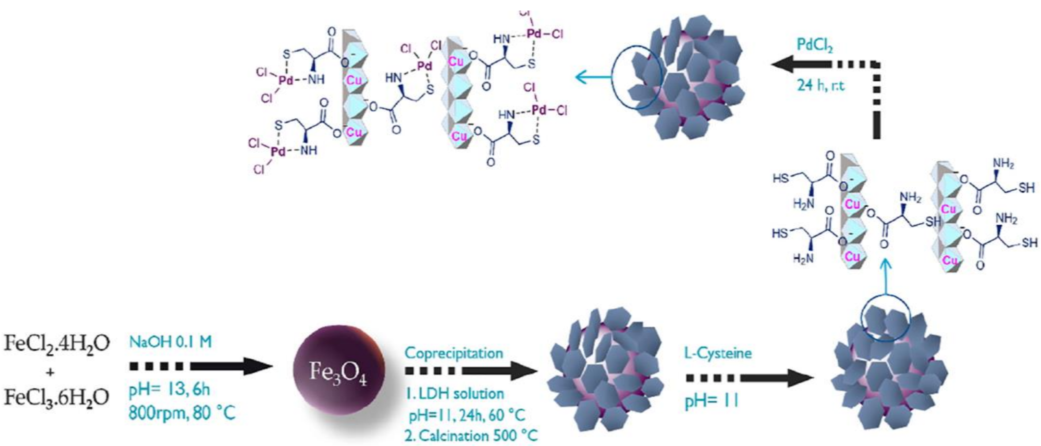

Figure 41. Schematic procedure of synthesis γ-Fe_2O_3@Cu-LDH@Cysteine-Pd. Reproduced with permission from [88], Elsevier, 2020.

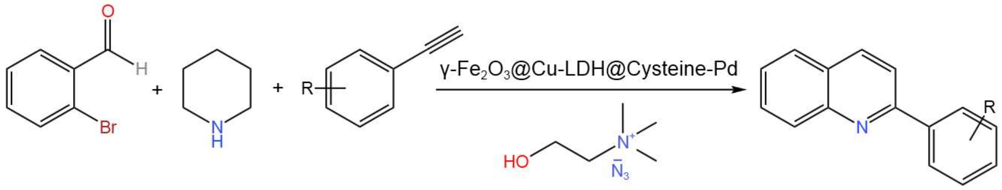

Figure 42. Scheme of the synthesis of 2-substituted quinolines in the presence of γ-Fe_2O_3@Cu-LDH@Cysteine-Pd [88].

Rajabi et al. [89] developed new environmentally friendly universal protocol for the one-pot conversion of aliphatic, aromatic, and unsaturated aldehydes into esters under ambient conditions in the presence of oxygen using palladium nanocatalyst supported on mesoporous organosilica (SBA-15). Palladium bearing a functionalized cytosine (Cyt) on the surface of mesoporous silica (Pd-Cyt@SBA-15) allowed selective large-scale conversion of a broad range of short chain alcohols with aldehydes including aromatic and aliphatic aldehydes to the corresponding ester products with the yields up to 98% and TON (98000). The catalyst Pd-Cyt@SBA-15 revealed high stability and reusability over ten reaction runs.

4. Heterogeneous Pd-Catalyzed Tandem Processes

Aiming the implementation of tandem catalysis, multiple reactions can be carried out in one pot by using bifunctional heterogeneous systems for the simultaneous activation of substrates and reagents in various Lewis/Brønsted acid, acid/base, metal/base, metal/acid, or metal/metal-catalyzed processes. Bifunctional catalyst can be designed in such a way that the two different catalytic functions (e.g., acidic and basic site) act in a collaborative way in the transition state, or each one catalyzes a different reaction in a multistep process [19].

Besides the common approaches to the desingof multifunctional catalyst, Cho et al. [15] defined the following additional directions in the desing of tandem processes:

size and shape selectivity with active sites only accessible to substrates and intermediates with specific sizes and shapes;

surface and solvent engineering that exploits differences in the hydrophobicity, hydrophilicity, and other properties of the catalizate' components;

metal site engineering through controlled size, exposed facets, composition, and their spatial distribution;

reactor and process engineering (i.e. chemical looping, reactive separations and multiple sequential catalyst beds in flow reactors) [15].

For example, Sheetal et al. [90] developed the direct one pot carbonylation of iodobenzene and NaN_3as N-atom source under Pd@PS catalyzed conditions utilizing $(CO_2H)_2$ as an environmentally benign CO surrogate in DMF solvent system. Proposed approach was based on the use of two vials with different solvents: (i) outer vial with $(CO_2H)_2$ and DMF; (ii) inner vial containing iodobenzene, NaN_3 along with catalyst in xylene solvent conditions (Figure 43).

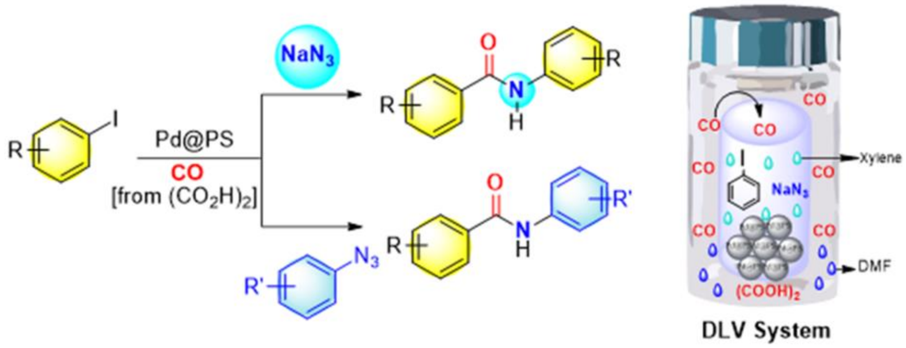

Figure 43. Tandem approach to the synthesis of N-aryl benzamides through bifunctional transformation of aryl iodides in a double layer vial (DLV) system. Reproduced with permission from [90], Elsevier, 2021.

Thus, the use of aryl iodides as bifunctional reactants under base, ligand and additive free conditions allowed carrying out the simultaneous C–C and C–N bond formation to obtain the desired products (N-phenyl benzamide derivatives) with good to moderate yields (up to 70%) at 140°C for 24 h [90].

Heterogeneous catalysts with acid sites in the composition of supports are widely used in catalysis, especially in biomass processing. Zeolites are a common example of such supports since they have high thermal and hydrothermal stabilities, homogeneous porosity, shape-selective properties, and tunable acidities [91]. Amoo et al. [91] in their review have mentioned that the design of metal-zeolite composite catalysts is prospective for syngas conversion. For example, alkali surfaces are known to favor the adsorption and subsequent conversion of CO to olefins over Fe-based catalysts due to the preffered formation of Fe-C over a high pH surface. The acid sites of zeolites might alter the intrinsic pH of the Fe-zeolite composite catalyst, thus the interaction between these two active components located in proximity will benefit in tandem catalysis (such as oligomerization, isomerization, alkylation, hydrocracking, etc.) [91].

Mesoporous silica materials, which have ordered pore size, a high specific surface area, a large pore volume, and the ability to synthesize a wide range of morphologies and shapes, can be utilized as an alternative to zeolites [92–98]. Mesoporous silica, usch as MCM-41 and SBA-15, used as supports for metal NPs and widely applied in catalysis, including tandem processes. Recently, propylamine, diethylamine, and pyrrolidine were used by Hernández-Soto et al. [97] to create the single basic sites in organic-inorganic hybrid bifunctional organosiliceous catalysts with pendant amine groups in addition to Pd NPs. In the developed catalysts, heterogenized amine groups and palladium NPs were found to be homogeneously distributed and stabilized in the mesochannels of the MCM-41. The steric effects around the amine groups in mesochannels was proposed to have stron influence on the catalytic activity. Moreover, longer amines exhibited higher interaction with the silica surface, decreasing the catalytic activity [97].

In the presence of Pd/MCM-41 bearing the propylamine groups, furfural and methyl isobutyl ketone underwent a tandem aldol condensation/crotonization reaction in a single reactor, followed by hydrogenation (Figure 44). At 100°C in the presence of toluene almost complete conversion of furfural and 82% yield of 1-(furan-2-yl)-5-methylhexan-3-ol was achieved. It was shown that in a dual fixed-bed reactor, the catalyst robustness may be improved, providing 20% furfural conversion for 12 hours on stream with the preferential production of 1-(furan-2-yl)- 5-methylhexan-3-one [97]. It is noteworthy that the reaction products can be used as renewable biosolvent and biofuel precursors.

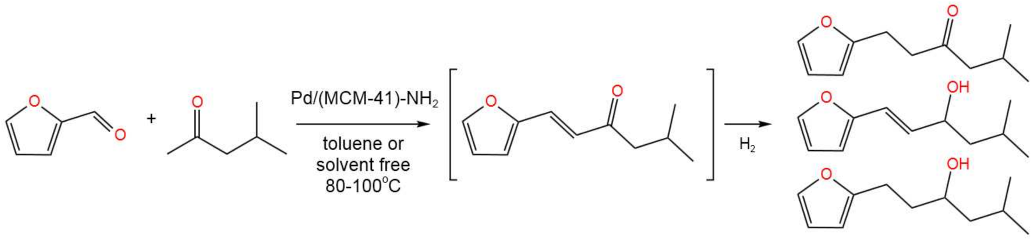

Figure 44. Scheme of tandem aldol condensation/crotonization of furfural and methyl isobutyl ketone, followed by hydrogenation [97].

Maties et al. [98] synthesized Pd-containing Al-SBA-15 materials for the valorization of trans-ferulic acid into stilbenes via tandem decarboxylation/Mizoroki-Heck coupling (Figure 45). Under mild reaction conditions (100°C, 3-6 h), quantitative product yields were obtained with over 90% selectivity to target stilbene products. The sizes of Pd NPs were found to be an important factor with a significant impact on the catalytic activity. The catalyst deactivation via sintering of Pd NPs was also observed.

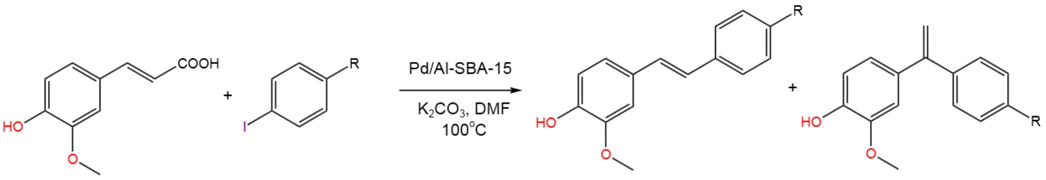

Figure 45. Stilbene synthesis by decarboxylative C-C coupling of trans-ferulic acid and iodoanisoleover Pd/Al-SBA-15 catalyst [98].

Tungsten oxide (WOx) is one of the well-known and widely used oxides with surface acid-base properties, which oftenly combined with other oxydes (ZrO_2 [99–101], SiO_2 [102–104], Al_2O_3 [105,106]) and zeolites [103,107]. Chu et al. [108] reported the synthesis of multifunctional Pd-Cu-WO_x/SiO_2 catalyst for the one-pot conversion of cellulose to ethanol. This catalyst allowed an ethanol yield of 42.5% at 300°C under 4 MPa H_2 in aqueous medium. It was shown that the cellulose conversion to ethanol followed the consecutive steps: (i) cellulose hydrolyzed to glucose over acid sites; (ii) glucose then converted to glycolaldehyde over W species; (iii) glycolaldehyde hydrogenated to ethylene glycol over Pd; (iv) ethylene glycol hydrolyzed to ethanol over Cu. It was shown that the three metal components Pd, Cu, and WOx were in appropriate balance allowing to achieve an ethanol formation rate of 0.163 g/($g_{cat} \cdot$ h).

The versatility of MOFs as highly porous acidic supports for metal NPscan be used for one-pot tandem processes [16,109–111].

MIL-101(Cr) (Figure 46) contining Pd NPs (about 3 nm) at 0.2-1.0 wt.% was used to catalyse one-pot tandem reductive amination of 4′-fluoroacetophenone with benzylamine (Figure 47) under 10 bar of H_2 [16]. The MOF's Lewis acidity and the Pd NPs' capacity for catalytic hydrogenation are combined in the bifunctional catalyst. The selectivity in the reductive amination reaction was found to be significantly influenced by altering the Pd loading within the MOF to tune the ratio of active sites. Higher metal loadings led to a significant amount of undesired product (4′-fluoro-α-methylbenzenemethanamine). Higher selectivity was achieved by decreasing the total number of Pd sites compared to Lewis acidic sites; the 0.4 wt.% Pd MIL-101 allowed nearly 90% of the target amine (4′-fluoro-methyl-N-(phenylmethyl)benzenemethanamine) after 7 hours. Moreover, synthesized catalysts were reusable and maintained crystallinity and small highly dispersed NPs after reaction.

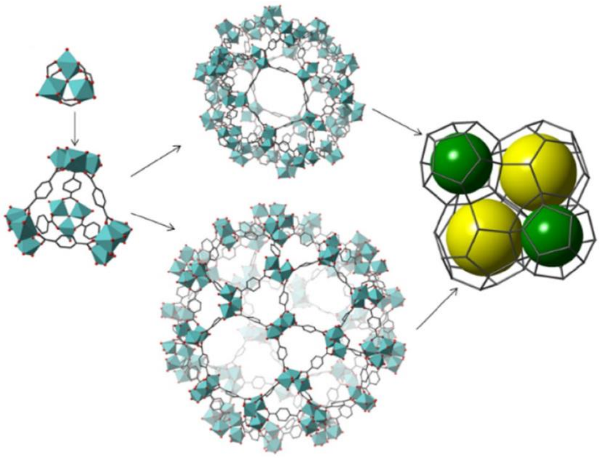

Figure 46. Scheme of MIL-101(Cr), showing the $Cr_3O(O_2C–)_6$ cluster, the super-tetrahedral building units and the smaller (green spheres) and larger cages (yellow spheres). Reproduced with permission from [16], Springer Nature, 2018.

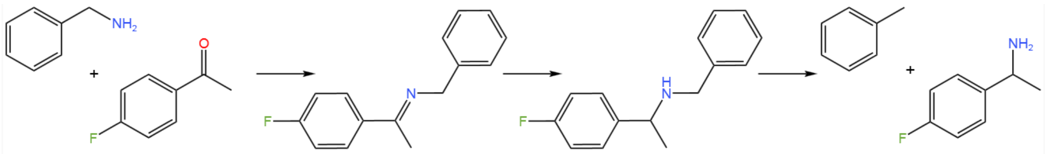

Figure 47. Synthesis of 4′-fluoro-α-methyl-*N*-(phenylmethyl)benzenemethanamine via the reductive amination reaction [16].

Bifunctional catalyst Pd@MIL-101-SO_3H was developed by Liu et al. [109] and applied in the one-pot oxidation-acetalization reaction (Figure 48), the products of which are widely utilized as fuel additives, perfumes, pharmaceuticals and polymer chemistry.

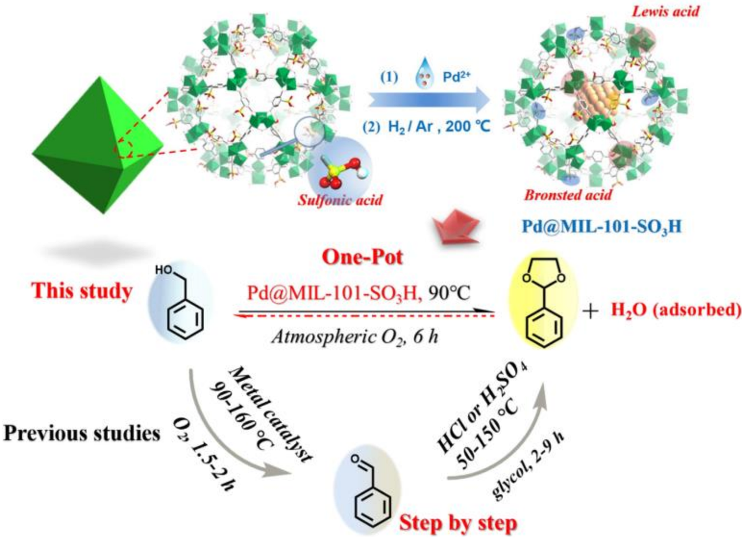

Figure 48. Scheme of the synthesis of Pd NPs immobilized in MIL-101-SO_3H and one-pottransformation of benzaldehyde glycol acetal. Reproduced with permission from [109], Elsevier, 2019.

High yields (>99%) were ascribed to the combined actions of Pd NPs, responsible for oxidation, and Lewis and Brønsted acid sites, responsible for acetalization, which were encapsulated in sulfonated MIL-101(Cr). The high capacity of MIL-101(Cr) for water adsorption aided the shift in equilibrium by impeding the reversible process. Thus, the nonpolar solvents were demonstrated to be the optimum ones.The reaction mechanism is presented in Figure 49. Moreover, the Pd@MIL-101-SO_3H could be reused for at least eight times without loss of catalytic activity [109].

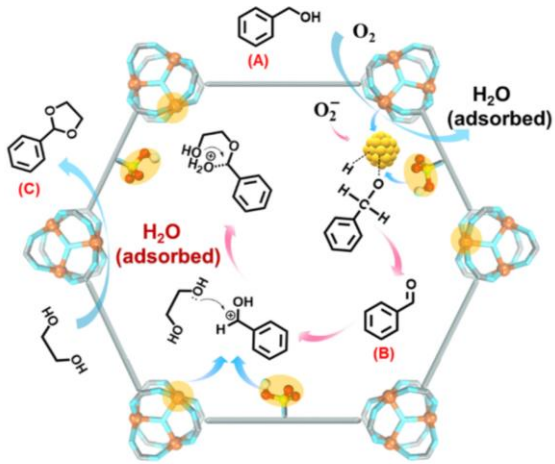

Figure 49. Proposed mechanism of the one-pot oxidation-acetalization. Reproduced with permission from [109], Elsevier, 2019.

Tandem heterogenous catalysis of bimetallic Cu-Pd on aminofunctionalized Zr-based metal-organic framework (UiO-66(NH2)) incorporated into sulfonated graphene oxide (Cu-Pd/UiO-66(NH2)@SGO) was investigated by Insyani et al. [110] for the one-pot conversion of disaccharides and polysaccharides into 2,5-dimethylfuran (2,5-DMF) (Figure 50).

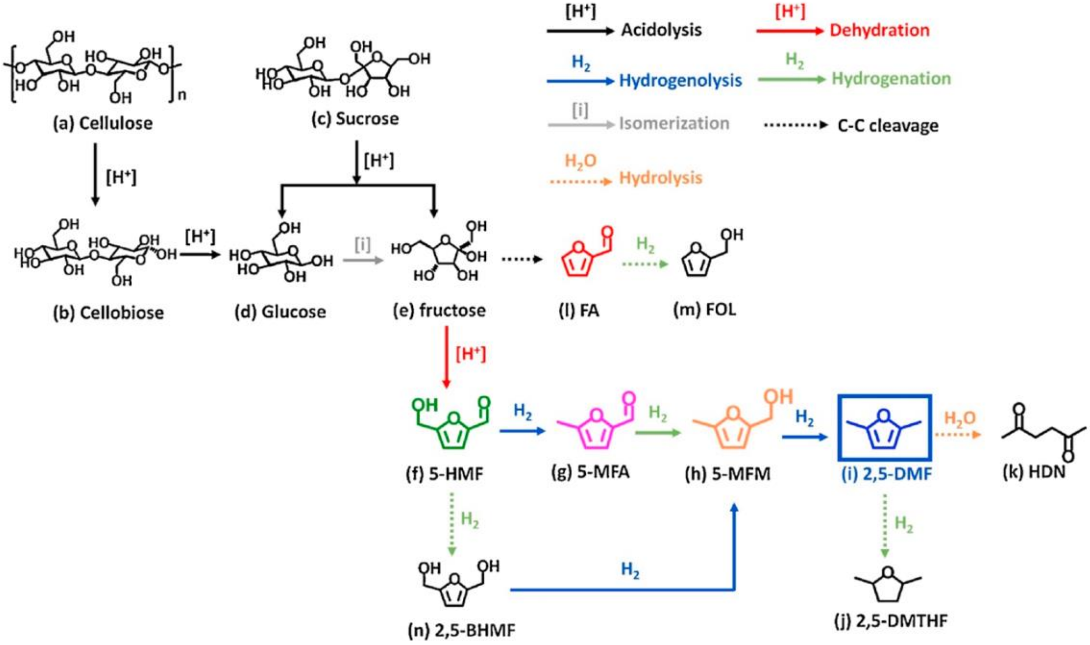

Figure 50. Reaction pathway for di- and polysaccharide conversion into 2,5-DMF. Reproduced with permission from [110], Elsevier, 2019.

Sequential glycosidic bond cleavage, isomerization, and dehydration of sucrose led to a high yield (75.8%) of 5-(hydroxymethyl)furfural (5-HMF) by altering the strength and ratio of the Lewis and Brønsted acid sites by varying the ratios of UiO-66(NH_2) to SGO. Bimetallic Cu-Pd, in contrast to monometallic Cu and Pd, favored sequential C–OH hydrogenolysis and C=O hydrogenation of the intermediates, resulting in the production of 2,5-DMF with a high yield of 73.4% during the one-pot conversion of sucrose at 200°C and 1 MPa H_2 for 3 h. 2,5-DMF was produced during the conversion of starch with the 53.6% yield. In the presence of 0.01 M HCl, cellulose was converted into 2,5-DMF with the yield of 29.8% [110].

Another example of tandem catalytic processes is one-pot three-step Deacetalization–Knoevenagel–Hydrogenation (D–K–H) reaction (Figure 51), requiring the synergetic catalysis and the close location of the acid, basic and metal sites. D–K–H can be successfully carried using trifunctional integrated catalyst (Pd@HPW@HP-UiO-66-NH_2): phosphotungstic acid (HPW) immobilized on the hierarchically porous UiO-66-NH_2acting as a support for Pd NPs [111].

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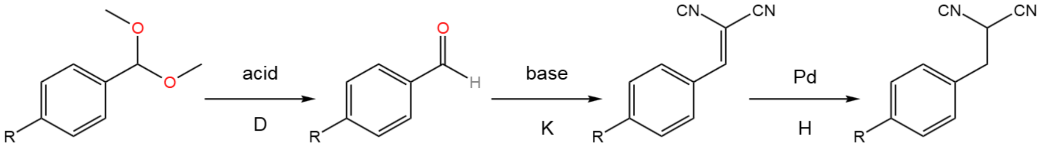

Figure 51. Proposed mechanism of the one-pot oxidation-acetalization [111].

While controlling the ratio of immobilized HPW and amino groups, acidic and basic properties can be easily tuned, thus the catalytic performance of Pd NPs and its stability can be controlled. The as-prepared catalyst revealed good catalytic activity in the one-pot D-K-H tandem processes, allowing up to 99% substrate conversion and 97% yield of the target product (toluene, 80°C, 12+24 h). Moreover, due to the strong interaction between the MOF (HP-UiO-66-NH_2) and the guest molecules, the catalyst could be reused at least five times without noticeable loss of its activity [111].

By using a straightforward two-step post-synthetic modification, Lee et al. [112] sunthesized an acid-base bifunctional zeolitic imidazolate framework catalyst (ZIF-8-A61-SO_3H) with amine and sulfonic acid groups. First, amine-functionalized ZIF-8 with amine contents of 61% (ZIF-8-A61) was obtained by the ligand exchange of 2-mIM with 3-amino-1,2,4-triazole (Atz). Then the sulfonic acid functionalization by the ring-opening reaction of 1,3-propanesultone with –NH_2 groups in ZIF-8-A61 was carried out. Different amine-functionalized ZIF-8-A materials (15%, 34%, and 61% of amine content) were prepared by controlling the synthesis time. The catalysts were used for one-pot deacetalization-Knoevenagel (D-K) condensation tandem reaction (the reaction is similar to the one presented in the Figure 51). ZIF-8-A61-SO_3H catalyst allowed 100% conversion of the reactant and 98% selectivity of the final Knoevenagel product at mild conditions (0.1 g of catalyst, 1,4-dioxane/H_2O, 80°C, 4 h) [112]. The developed ZIF-8-A61-SO_3H [112] seems to be possess higher efficiency in the D-K process as compared to HPW@HP-UiO-66-NH_2 [111]. Thus, the immobilization of Pd NPs in ZIF-8-A61-SO_3H may result in the further improvement of D-K-H tandem reaction.

As an another example of bifunctional catalyst, a double-shelled hollow polymer microsphere were developed [113]. Pd NPs were found mostly in the outer shell of catalytic material and stabilized by pyrrolidone groups. The inner shell P(EGDMA-co-AA) contained the acid sites. The resulting bifunctional catalytic system (void@PAA/PNVP@Pd) was applied for the deacetalization-hydrogenation tandem process (Figure 52), demonstrating the viability of the plan to load distinct catalytic sites onto the walls of double-shelled hollow polymer microspheres. Deacetalization of benzaldehyde dimethyl acetal was followed by hydrogenation with formation of benzyl alcohol. As a result, conversion of benzaldehyde dimethyl acetal reached 99% with 96% yield of the benzyl alcohol [113].

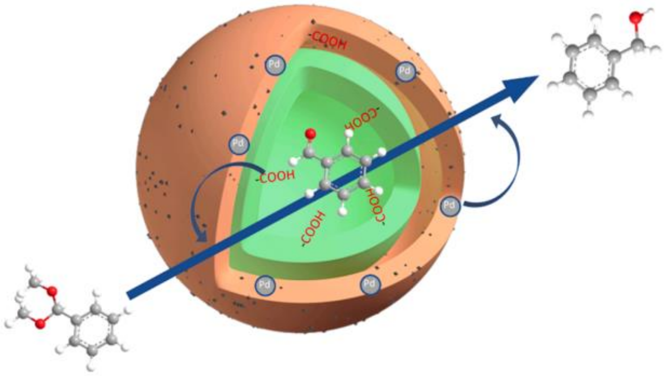

Figure 52. The void @PAA/PNVP@Pd hollow multishell microspheres as a nanoreactor for the tandem reaction. Reproduced with permission from [113], Elsevier, 2023.

Bifunctionalcatalytic system of Pd/C and water tolerant Lewis acid (i.e., $Sm(OTf)_3$, $La(OTf)_3$, $Cu(OTf)_2$) were applied for the synthesis of fuel precursors from biomass liquefaction with high efficiency in both water and ethanol [114]. The maximum yield of bio-oil (49.71 wt.%) was achieved for 30 min at supercritical ethanol (300°C) in the presence of Pd/C and $La(OTf)_3$.

Raza et al. [115] synthesized highly dispersed Pd NPs immobilized over covalent triazine polymer (CTP) functionalized with sulfonic acid groups (CTP-SO_3H/Pd). The sulfonic acid groups were shown to be responsible for the uniform dispersion of palladium NPs over the CTP. Obtained bifunctional catalyst was used in one-pot hydrogenation-esterification (OHE) reaction and revealed promising catalytic activity with 94% yield of target product at 95% conversion (Figure 53).

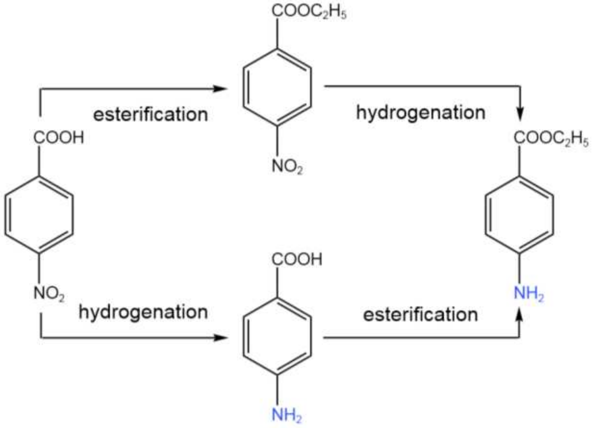

Figure 53. Scheme of OHE reaction [115].

After the reaction the catalyst was separated by simple filtration. It was shown that the CTP-SO_3H/Pd catalyst could be reused for at least five times with a slight loss of catalytic activity, indicating its potential usage in OHE reactions. The cooperative effect of functional acidic and metal sites was proposed [115].

Covalent organic frameworks (COFs) are widely used as support for catalytic applications [116–119], including tandem one-pot processes [120]. The COFs possess a variety of chemical structures, which may be precisely tuned to control the surrounding coordination environment and electronic interaction between metal NPs and supports, in contrast to other materials used for NPs immobilization. The uniform porous structure in COFs allows numerous metal active sites, which enhances the catalytic activity [121]. A simple hydrothermal synthesis was recently used by Wang et al. [121] to produce COF. Noble metals (Pt, Pd, and Rh) were introduced to the COF matrix for further application in the reductive amination of benzaldehyde. The optimum Pd/COF catalyst revealed 91% yield of secondary amines at 1.2 : 1 M ratio of aldehyde and ammonia under mild reaction conditions (2 MPa of H_2 and 90°C, 15 h) [121].

5. ChemoenzymaticProcesses

At present the enzymatic catalysis is considered a powerful tool for synthetic chemists, providing access to a wide range of compounds. Advances in the field of immobilization, molecular biology and bioinformatics have paved the way for biotransformation in various environments, improving the stability and activity of biocatalysts, opening up new enzymatic pathways. The capacity of enzymes is attracting more and more attention, since they can be successfully combined with other types of catalysts, as shown by recent achievements in their joint action with metals [122–124]. This section is devoted to the consideration of the combination of palladium and enzymatic catalysts for chemoenzymatic processes. This combination gives the advantages of conducting tandem processes in a single reactor, which simplifies the complex routes, avoiding the separation of unstable intermediates to obtain final products with a higher yield.

In the recent review by Gonzalez-Granda et al [122], the combination of enzymes and transition metals in catalysis for asymmetric synthesis was considered. Such reactions as Suzuki cross-coupling [125–127], Wacker-Tsuji oxidation [128–130], Buchwald-Hartwig cross-coupling [131–133], etc. were discussed.

Metal-enzymatic parallel and sequential transformations were described involving Pd, Ru, Au, Ir and Fe, which catalyze numerous organic transformations (C-C coupling, isomerization, hydrogenation, etc.). The combination of catalytically active metals with enzymes in the chemoenzymatic processes allows obtaining chiral products due to the action of stereospecific enzymes, including alcohol oxidases, aldolases, alcohol dehydrogenases, amine dehydrogenases, amino acid dehydrogenases, aminotransaminases, arylmalonate decarboxylase, enreductase, iminoreductase, nitrile hydratase or phenylalanine monialiases, etc. It was noticed [122] that incompatibilities between chemical and enzymatic steps can be often found, such as cross-prohibitions due to the presence of cofactors, reagents or intermediates, or preference for different solvents or temperatures, so these protocols must be accomplished sequentially.

A stereoselective one-pot tandem reduction of 3-methyl-2-cyclohexenone to 3-(1S,3S)-methylcyclohexanol (Figure 54) was carried out by Coccia et al. [134] using Pd and Pt NPs as the metal precatalyst and a NAD^+-dependent thermostable alcohol dehydrogenase, isolated from *Thermus* sp. ATN1 (TADH).

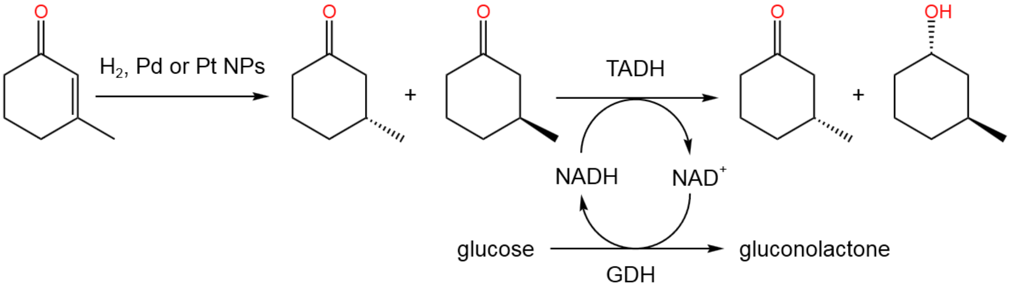

Figure 54. Scheme of the tandem selective reduction of the C=C bond with metal (Pd or Pt) NPs and asymmetric reduction of the keto group by TADH (GDH – glucose dehydrogenase) [134].

The Pd and Pt NPs possess high surface-to-volume ratio, simple preparation, and good “solubility” in water. Moreover, the metal NPs can work without significant pH or temperature limitations and can be used in different reactions such as oxidation, reduction, etc. TADH revealed a broad substrate scope including aldehydes, aliphatic ketones, cyclic ketones, and double-ring systems [134].

The assumptions were made on the interactions between the chemo- and the bio-catalyst. The sizes of NPs were demonstrated to be a crucial parameter for mutual inhibition: the larger the NPs the higher the enzyme inhibition, and vice versa the smaller the NPs, the lower the TADH denaturation. In general, the chemocatalysts possessed high deactivation sensitivity, which was highly dependent on the amount of enzyme utilized, i.e. the inhibition of the biocatalyst could be greatly decreased by reducing the NPs/TADH ratio. In order to avoid the direct binding of NPs to TADH, the use of large Pd NPs protected with a silica shell is promising: the yield of 3-(1S,3S)-methylcyclohexanol was increased up to 36% [134].

Combining metal ions or NPs with biocatalysts in a single system is a promising strategy for implementation in the one-pot chemoenzymatic cascade reactions [135], especially for asymmetric syntheses. For example, Li et al. [136] developed a one-pot chemoenzymatic cascade reaction to asymmetric synthesize (*R*)-1-(4-biphenyl) ethanol (Figure 55) while using highly active and selective enzyme-metal-single-atom catalyst. To facilitate the production of chiral biaryl alcohols, the Pd single atoms anchored lipase (Pd1/CALB-P) may effectively drive one-pot cascade reactions in aqueous solution at 30°C. The production rate was 30 times higher than that catalyzed by the commercial Pd/C and CALBP.

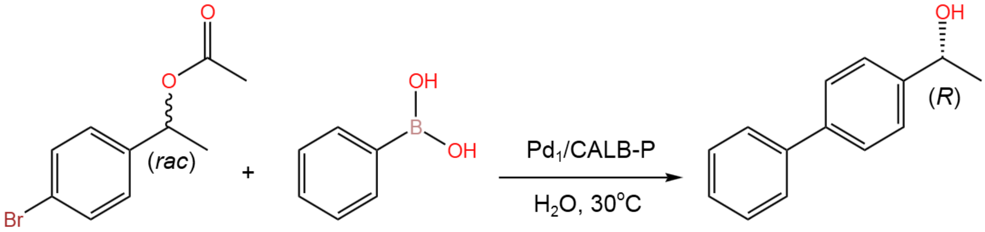

Figure 55. Synthesis of (*R*)-1-(4-biphenyl)ethanol by one-pot chemoenzymatic reaction [136].

In other recent work of Li et al. [137], bimetallic PdCu/CALB CLEAs hybrid catalyst was synthesized by the in situ reduction of PdCu nanoclusters immobilized on cross-linked lipase aggregates (CALB CLEAs).

Cross-linked enzyme aggregates (CLEAs) were prepared from *Candida antarctic* lipase B (CALB) by their precipitation and subsequent cross-linking with the glutaraldehyde. The bimetallic PdCu nanoclusters were formed in situ on CALB CLEAs (Figure 56) by the reduction of Pd^{2+} and Cu^{2+} ions in an aqueous solution contained 20% (v/v) methanol, which served as an additional reducing agent. Obtained PdCu nanoclusters were highly dispersed (sizes of 1.5 ± 0.2 nm). The strong synergistic effect between Pd and Cu in PdCu/CALB CLEAs allowed high activities in the Sonogashira cross-coupling reaction and one-pot chemoenzymatic reaction resulting in the synthesis of (*R*)-N-[1-(4-(phenylethynyl)phenyl)ethyl]acetamide (Figure 57) [137].

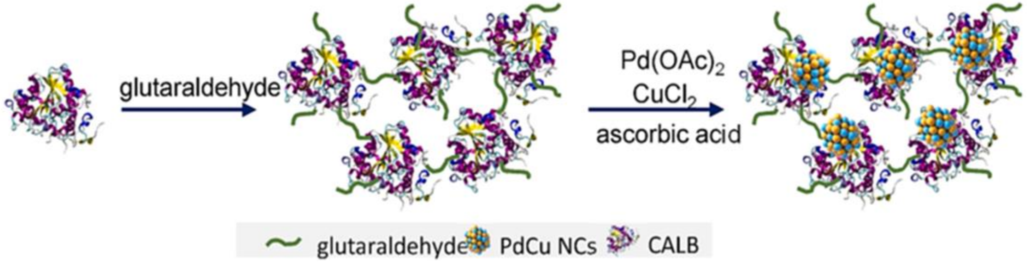

Figure 56. Schematic illustration of the strategy used to synthesize PdCu/CALB CLEAs via in situ reduction. Reproduced with permission from [137], Elsevier, 2021.

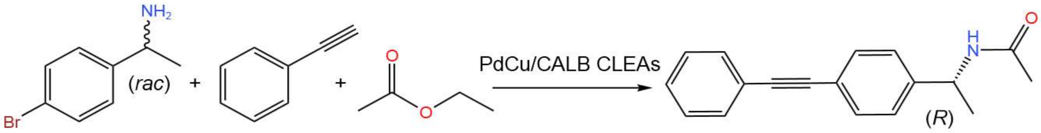

Figure 57. Synthesis of (*R*)-N-[1-(4-(phenylethynyl)phenyl)ethyl]acetamide by one-pot chemoenzymatic reaction [137].

In this reaction (Figure 57), CALB catalyzed the acylation of (*R*)-enantiomer of the amine, while PdCu nanoclusters were responsible for the Sonogoshira cross-coupling and the racemization of (*S*)-enantiomer of the amine. It was proposed that Cu-alkynyl and Pd-arylparticles were formed simultaneously by surface coordination. The coordinated Pd and Cu particles were then subjected to the transmetalation stage, which facilitated the cross-coupling reaction. Catalytic activity increased with the increase of the content of PdO [137]. It is noteworthy that the higher activity of PdO as compared to metallic palladium was described earlier for the reaction of Suzuki cross-coupling by Collins at al. [138].

Deiana et al. [139] developed the bioinspired multicatalytic system based on an artificial plant cell wall (APCW) containing the lipase and Pd NPs for transformation of racemic amine into the corresponding enantiomerically pure amide with the yield up to 99% (Figure 58), which involves synergistic interaction between the racemization reaction catalyzed by Pd(0) and the enantioselective amidation catalyzed by CALB.

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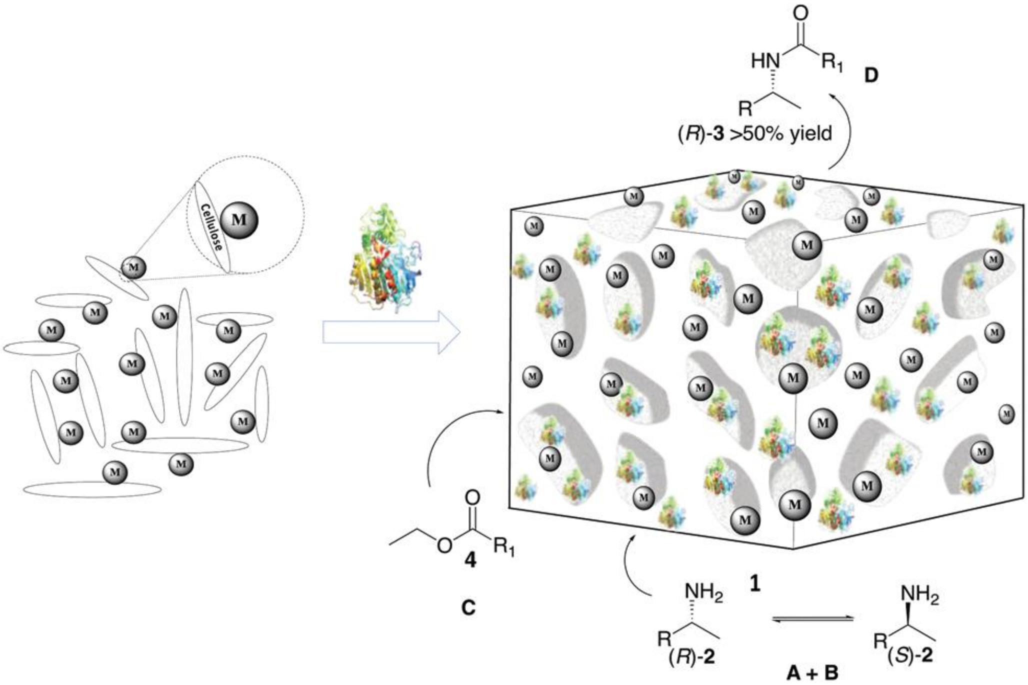
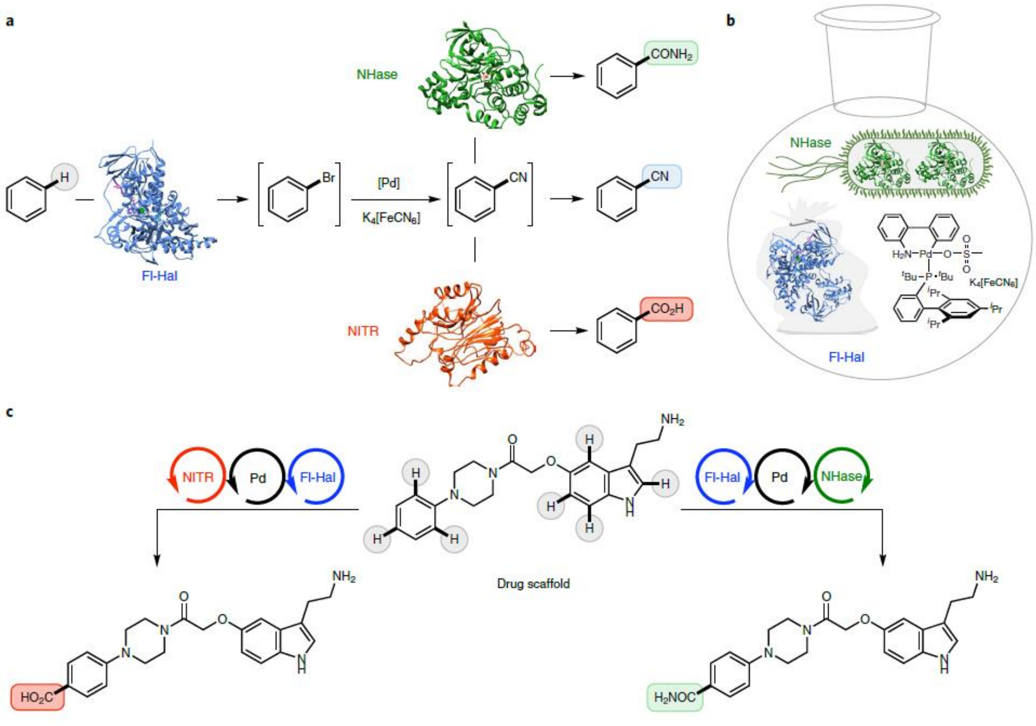


Figure 58. Simplified scheme of self-assembly of components to create an APCW, which simultaneously catalyzes racemization and amidation of racemic amines. M = metal. Reproduced with permission from [139], RSC, 2021.

The main component of the developed multicatalytic system is MCC or nanofibrillated cellulose, the surface of which is modified with aminopropylsilane, which allows the retention of Pd NPs. The best approach for the self-assembly of the resulting hybrid catalyst was a non-covalent modification of CALB with surfactant polyethylene glycol hexadecyl ether (Brij) in a phosphate buffer. TEM data confirmed formation of Pd NPswith a narrow size distribution (from 1.6 nm up to 2.8 nm). The hybrid heterogeneous multicatalytic system APCW9 was more efficient and chemoselective as compared to the mixture of Pd NPs on MCC and CALB on MCC [139].

By the example of different aryl and heteroaryl scaffolds, Craven et al. [140] showed that flavin adenine dinucleotide (FAD)-dependent halogenases (Fl-Hal) can be used in combination with Pd-catalyzed cyanation to effect the C-H functionalization cascades that deliver nitriles in a highly regioselective manner. As a non-toxic cyanation reagent, $K_4[Fe(CN)_6]$ was used. It was shown that this approach can be extended by including nitrile hydratase (NHase) or nitrilase (NITR) to create integrated cascades of three catalysts for regioselective installation of amide and carboxylic acid groups (Figure 59).



- Selective C–H functionalization of similar C–H challenging for chemocatalysis
- Cyanation, aryl C–C bond formation, impractical for biocatalysis
- Cyano hydrolysis under mild conditions very difficult for chemocatalysis
- Integrated chemobiocatalysis enables sought-after transformations.

Figure 59. Overview of site-selective C–H functionalization cascades. Reproduced with permission from [140], Springer Nature, 2021.

It was emphasized [140] that the recent advances in the discovery, engineering, and synthesis of Fl-Hal biocatalysts can significantly broaden the application of this strategy. New Fl-Hals with improved catalytic characteristics, modified substrate specificities, and altered regioselectivity are continuously emerging from genome mining and directed-evolution programs. The inclusion of the Fl-Hals will boost the potential of the proposed programmable integrated cascades, enabling the integration of rich functionality into a variety of candidate scaffolds and facilitating the manufacturing of target molecules.

PdCu hydrogel nanozymes with a hierarchically porous structure were synthesized by Huang et al. [141] to immobilize horseradish peroxidase (HRP) (PdCu@HRP).The 3D porous nanowire networks of resulting hydrogels with high porosity served as a biocompatible supports for immobilizing HRP. The affinity of Cu and Pd to proteins simplified the procedures of the enzyme immobilization without the addition of other cross-linking agents. The immobilization of HRP on PdCu hydrogels enhanced the thermal and chemical stabilities of HRP, realizing the reuse of the enzyme. Moreover, PdCu@HRP exhibited synergistically enhanced HRP activity as compared to native HRP and PdCu hydrogel nanozymes. The improved catalytic activity was likely due to specific interactions between PdCu hydrogel nanozymes and enzymes as well as the enrichment of substrates around enzymes by electrostatic adsorption of hydrogels. Using catalytic cascade reactions, colorimetric biosensing of the carcinoembryonic antigen (CEA) was carried out while applying the PdCu@HRP and the glucose oxidase encapsulated in ZIF-8. The obtained biosensor allowed the quantitative probing of the CEA concentration in a wide range from 5 to 1000 pg/mL with a LOD of 1.4 pg/mL and nearly 6.1-fold increase of the detection sensitivity as compared to the conventional HRP-based enzyme-linked immunosorbent assay [141].

It is important to highlight the work of Ming et al. [142], who developed a novel tandem Pd-Ru/Uricase@RBC nanoreactor, including Pd-Ru nanosheets, uricase and red blood cell (RBC) membranefor hyperuricemia treatment. New highly active 2D nanozyme Pd-Ru was covalently bounded with the uricase and immobilized on the surface of RBC. It is noteworthy that the RBC membrane coating is a new biomimetic technique that gives nanomaterials a natural surface and can significantly increase the time that they circulate in the bloodstream [142].

The prepared Pd-Ru/Uricase@RBC demonstrated high catalase-like activity (Pd-Ru nanosheets decomposed H_2O_2 to rapidly generate O_2) and stability against various extreme pH, temperature, and proteolytic degradation during biological transport. Moreover, Pd-Ru nanozyme and uricase in close proximity to each other allowed achieving the efficient cascade reactions: degradation of the uric acid by uricase to allantoin and H_2O_2 and removal of H_2O_2 by Pd-Ru nanosheets. The generated O_2even facilitated the catalytic degradation of the uric acid [142]. Thus, the cascade reactions based on the nanozymeswere shown to be an effective strategy for the treatment of diseases due to its high efficiency and low level of side effects.

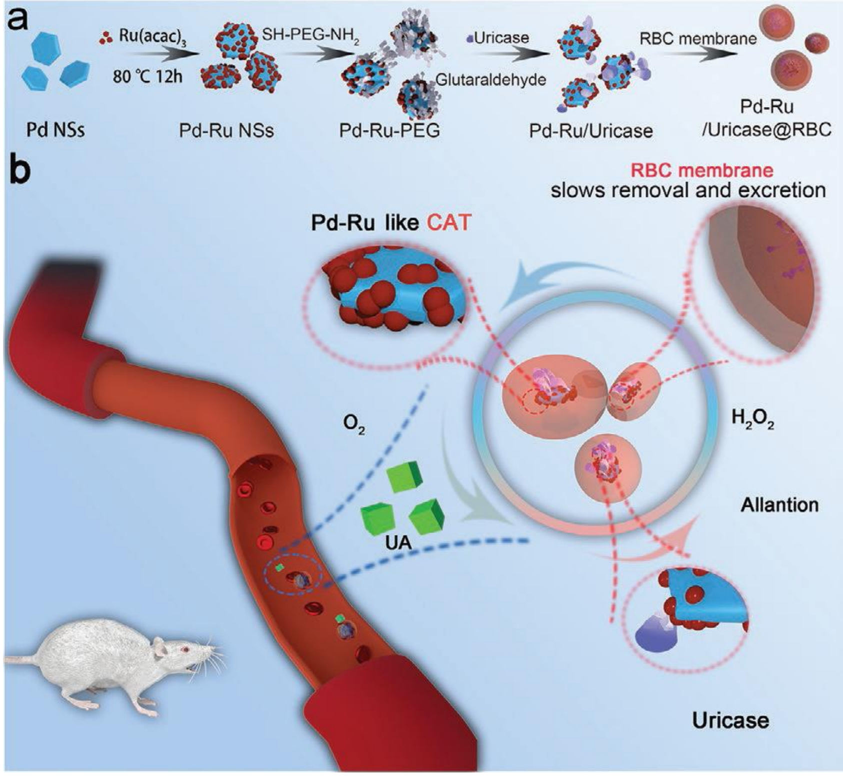


Figure 60. Schematic illustration of the construction procedure of Pd-Ru/Uricase@RBC (**a**) and its treatment of hyperuricemia (**b**). Reproduced with permission from [142], John Wiley and Sons, 2021.

Zhang et al. [143] developed bifunctional biocatalysts based on mesoporous silica NPs (MSN), the surface hydrophobicity of which was created via alkylation.Pd NPs and the enzyme CALB were separately loaded into compartmentalized locations (Figure 61). Pd(0) NPs were loaded into the MSN by in situ reduction of Pd acetate with $NaBH_4$. Then the surface of Pd@MSN was modified with long-chain alkanes (obtaining Pd@mMSN). Subsequently, CALB was immobilized via hydrophobic interactions (bifunctional biocatalyst was denoted as CalB@Pd@mMSN) [143].

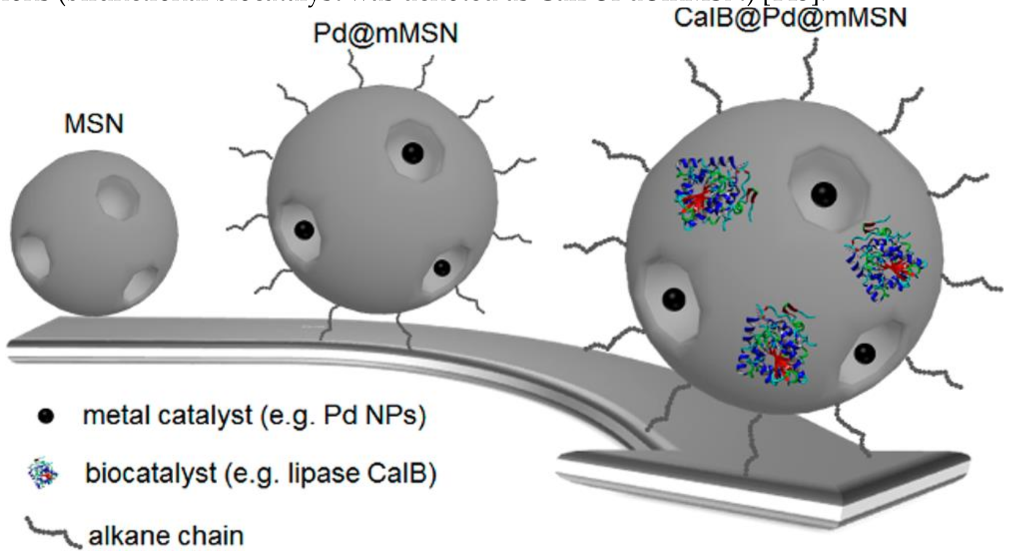


Figure 61. Schematic illustration of the construction of CalB@Pd@mMSN. Reproduced with permission from [143], Copyright 2018 American Chemical Society.

The CalB@Pd@mMSN was tested in a one-pot cascade reaction, in which Pd NPs first reduced the benzaldehyde and then the immobilized CalB converted the benzyl alcohol into benzyl hexanoate (Figure 62). The developed catalyst was highly active and reusable: after four times of reuse, reaction yield (4 h) remained higher than 80%.

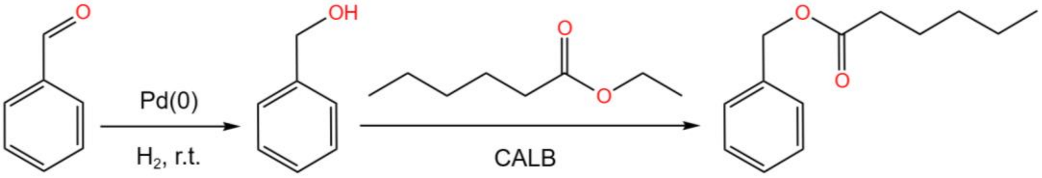
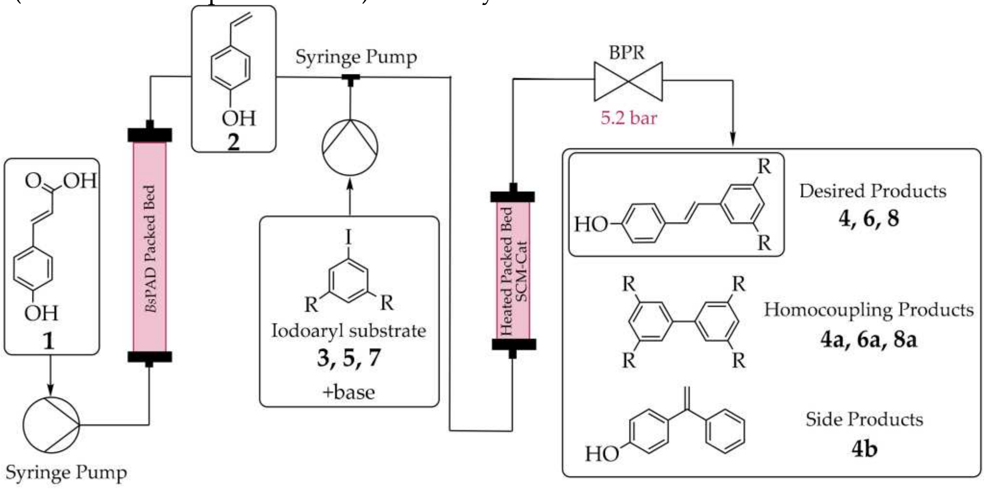


Figure 62. Scheme of the one-pot cascade reaction of benzaldehyde with ethyl hexanoate[143].

The developed bifunctional biocatalyst provides a universal platform with a large surface area for the transfer of catalysts to various organic solvents. Thus, it can be developed as a tool for adding other chemical and biocatalysts (such as glucose oxidase and other proteins) to the reaction medium of interest [143].

As it was shown in the review by Metzger et al. [144], the combination of inorganic supports and catalysts into tandem systems is an actively developing area of tandem catalysis, since the durability of the systems allows their application in industrial processes. Compartmentalization was shown to be a method for overcoming the difficulties associated with mixing several incompatible catalysts into a one-pot system. Compartmentalization can decrease side reactions, inhomogeneity, and catalyst deactivation that are often experienced when incompatible catalysts are in close proximity. Thus, the application of MSNs and MOFs as supports in tandem chemoenzymatic processes is promising

Chemoenzymatic tandem reactions for the synthesis of pharmacologically active compounds in continuous flow was developed by Lackner et al. [145]. While using two sequential packed bed reactors hosting encapsulated phenolic acid decarboxylase from *B. subtilis* (*Bs*PAD) facilitating enzymatic decarboxylation as well as a heterogeneous Pd catalyst for Heck coupling, stilbene derivativeswere synthesized (Figure 63). Varyling the reaction conditions of the cross-coupling step (pH, carbonate concentration, temperature) allowed obtaining the 4-hydroxystilbene and other products (resveratrol and pterostilbene) with the yield 32-54%.



Residue [1]	Product	Iodoaryl substrate	Homoproduct
R = H	4-hydroxystilbene **4**	**3**	**4a**
R = OH	resveratrol **6**	**5**	**6a**
R = OMe	pterostilbene **8**	**7**	**8a**

[1] All compounds in the same row have the same residue

Figure 63. Scheme of the chemoenzymatic cascade for the synthesis of stilbenes in continuous flow. Reproduced with permission from [145], MDPI, 2020.

By changing the substrate being subjected to enzymatic decarboxylation and using more complex iodoaryl coupling partners, this chemoenzymatic cascade is likely to be further expanded to the production of other valuable stilbenes [145].

6. Conclusions

Tandem processes is a hot area of catlytic reasearch aimed to to perform the traditional stepwise reactions in one-pot mode. Palladium, as one of the most abundat metal-catalysts, is oftenly used in tandem processes.

In many homogeneously-catalyzed reactions, the tandem processes can be implemented due to the known ability of palladium to change constantly its oxydation state during the reaction course. This ability of Pd to catalyze the reactions while being in different oxidation states generated from a single precatalyst is effectively used in those tandem processes, which include, for example, the C–C coupling (Heck, Suzuki, Sonogashira, etc.), isomerization, cyclization, carbonylation as one of the reactions in tandem. Thus, some authors refer such processes to the orthogonal catalysis, considering Pd(II) and Pd(0) as two different catalysts. Since, in homogeneously-catalyzed tandem processes the catalysts are rather ordinar (Pd salts or complexes), the current trends are in development of new routes to the one-pot tandem syntheses of certain structures, which would allow higher efficiency at milder reaction conditions.

In heterogeneous catalysis for tandem processes, two or more active sites are required with their rational desing to act independently or synergistically. Many of such processes are not truly tandem and rather can be attributed to orthogonal catalysis, especially those realted to the biomass processing in the presence supported Pd-containg catalytic systems bearing acid sites (Figure 64). For the last years, such materials, as zeolites, oxides (especially mesoporous), MOFs and COFs attained attention as supports for the development of heterogeneous Pd-containing materials for tandem processes.

The third type of prospective catalysts for tandem processes is the systems combining the action of metals and enzymes (chemoenzymatic catalysis). Such mulifunctional metal-enzyme catalysts are highly perspective for asymmetric catalysis due to the known extremely high substrate sensitivity and selectivity of enzymes as compared to inorganic catalysts.

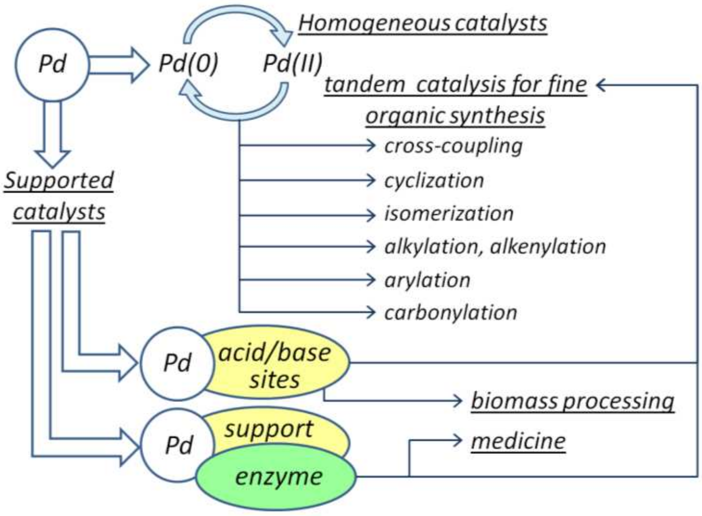


Figure 64. General scheme of the application of Pd-catalyzed tandem processes.

In spite of some existing difficulties due to the different reaction conditions required for the optimum reactivity of inorganic and organic parts as well as the possibility of enzyme inactivation with metal NPs, chemoenzymatic tandem processes are highly demanded by modern organic synthesis and biotechnology.

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