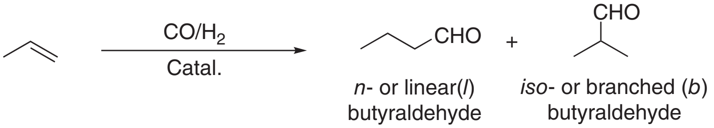
1

Carbon Monoxide

1.1 Hydroformylation of Alkenes and Alkynes

Hydroformylation is one of the most important reactions for the preparation of aldehydes and alcohols from alkenes and synthesis gas [1]. In 1938, Roelen (1897–1993) discovered the reaction between alkenes and an equimolar mixture of carbon monoxide (CO) and hydrogen to form aldehydes [2, 3]. It is called “hydroformylation” and was originally called “oxo-reaction.” Nowadays, homogeneous metal complexes commercially based on cobalt and rhodium are used as catalysts. With more than 10 million metric tons of oxo products per year, hydroformylation represents one of the most important industrial applications and achievements of homogeneous catalysis in the chemical industry [4].

The key consideration of hydroformylation is the selectivity of “normal” vs. “iso.” For example, the hydroformylation of propylene can afford two isomeric products, butyraldehyde or isobutyraldehyde (Scheme 1.1).

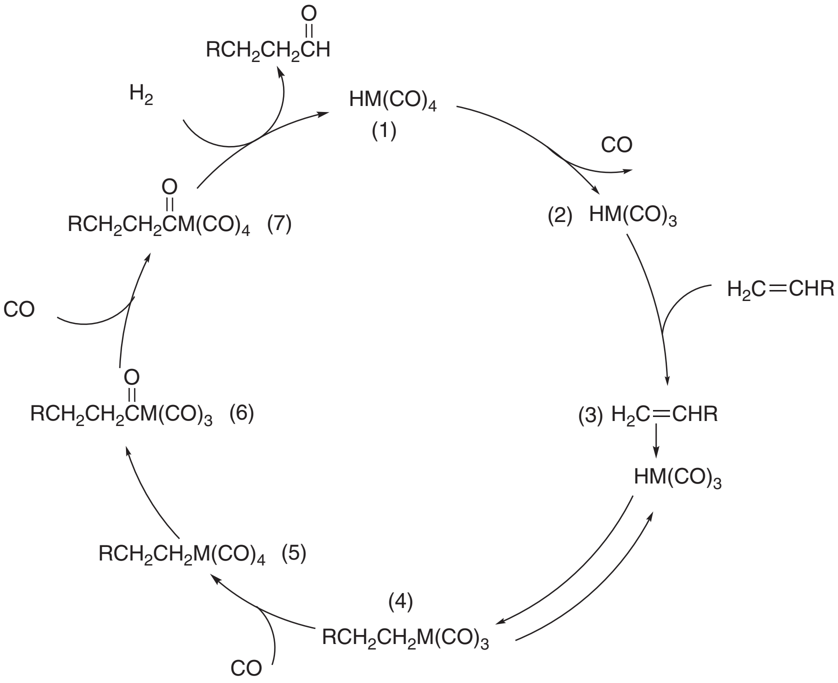


Scheme 1.1 Example of hydroformylation.

These isomers are related to steric hindrance and the rate of CO migration insertion. In addition, they also reflect the regiochemistry of the insertion of alkene into the M–H bond. For example, the reaction mechanism begins with dissociation of CO from hydrido-metal–tetracarbonyl complex (1) to give the 16-electron species $HM(CO)_3$ (2). Then, the alkene starts to coordinate with the $HM(CO)_3$ complex. The π-complex (3) is converted into the corresponding σ-complex (4); the 18 electron species are formed by adding CO (5). In the next step of the reaction cycle, the CO is inserted into the carbon–metal bond (6). Once again, CO is associated to end up in the 18 electron species (7). In the last step of the reaction cycle, the catalytically active hydrido-metal–tetracarbonyl complex (1) is released by adding hydrogen. Moreover, the aldehyde is formed by a final reductive elimination step

Carbonyl Compounds: Reactants, Catalysts and Products, First Edition.
Feng Shi, Hongli Wang and Xingchao Dai.

(Scheme 1.2) [5]. In this section, we will summarize the history and recent advances of catalysts for hydroformylation.



Scheme 1.2 Mechanism of metal-catalyzed hydroformylation. Source: Based on Heck and Breslow [5].

1.1.1 Co Catalysts

A generally accepted rough order of active metals in hydroformylation is given in Table 1.1 [6].

Roelen first discovered and patented hydroformylation of straight-chain 1-olefins under the $HCo(CO)_4$ catalyst system which generally leads to the formation of linear aldehydes and large amounts of branched aldehydes [7]. This laid a good foundation for all hydroformylation studies.

As early as in 1958, the heterogeneous cobalt catalyst for hydroformylation was reported by Aldridge et al. [8] With 0.879 wt% insoluble cobalt as a catalyst system, the conversion of C_7 olefin (mixed isomers) using CO and H_2 (about 1 : 1, 2750–2900 psig) at 177 °C is 83%. But, it was soon recognized that the real active species is the homogeneous complex hydridocobaltcarbonyl. $HCo(CO)_4$ is a yellow liquid and strong acid, which is stable only under CO/H_2 pressure above the melting point (−26 °C) [9]. Therefore, the mechanism of hydroformylation has been extensively studied.

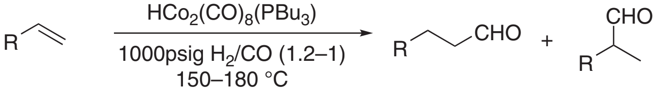
In 1968, the hydroformylation of propene and 1-hexene has been investigated in a tertiary organophosphine–cobalt hydrocarbonyl catalyst system $HCo_2(CO)_8(PBu_3)$

Table 1.1 Activity of metals in hydroformylation.

Active metal	Rh	Co	Ir	Ru	Os	Tc	Mn	Fe	Re
Log(relative activity)	3	0	−1	−2	−3	−3	−4	−6	<−6

Source: Beller [6]. © 2006, Springer Nature.

by Tucci (Scheme 1.3) [10]. Trialkylphosphine complexes yielded 73% less branched isomer formation than the conventional $HCo(CO)_4$ system. The activity of the cobalt hydrocarbonyl-catalyzed branched isomer formation decreases in the order $HCo(CO)_4 > HCo(CO)_3(PAr_3) > HCo(CO)_3(PR_3)$.

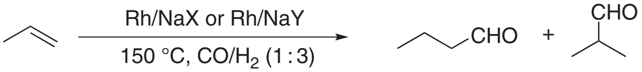


Scheme 1.3 Ligand modification of the catalyst-catalyzed hydroformylation of olefins. Source: Based on Tucci [10].

There has been an important breakthrough in the development of cobalt catalysts recently. Stanley's group found the $[HCo(CO)_n(P_2)]^+$ catalyst showed nice activity at lower pressures for hydroformylation [11]. For example, using $[Co(acac)(depe)](BF_4)$ under standard conditions (1 mM catalyst, 1 M 1-hexene, dimethoxytetraglyme solvent, activate at 140 °C under 34 bar of 1 : 1 H_2 : CO, then reduced to 100 °C and 10 bar), *n*/*iso* aldehyde ratio of 0.8% and 15.1% alkene isomerization can be obtained.

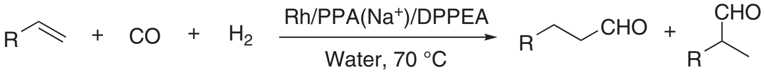
1.1.2 Rh Catalysts

Since the 1970s, most hydroformylation reactions rely on catalysts based on rhodium catalysts [12]. For example, Hanson and coworkers described the Rh/NaX and Rh/NaY catalyst system in a fixed bed reactor consisting of propylene : H_2 : N_2 : CO (3 : 3 : 2 : 1) at 1 atm [13]. The selectivity of *n*-butyraldehyde vs. *iso*-butyraldehyde is 2.0 : 1 and 1.9 : 1 for Rh/NaX and Rh/NaY at 150 °C, respectively (Scheme 1.4).



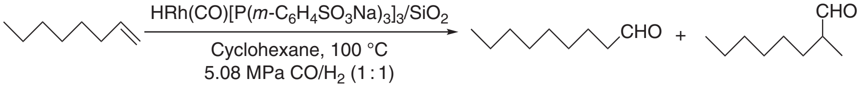
Scheme 1.4 Zeolite-catalyzed hydroformylation of propylene.

Water-soluble catalysts have been developed. They facilitate the separation of the products from the catalyst [14]. For example, Herrmann et al. reported the novel Rh(I)/BISBIS catalyst for hydroformylation of propene and 1-hexene [15]. The high activity (97.7) and productivity (1.26) at low phosphane/rhodium ratios (6.7 : 1) can be obtained in the hydroformylation of propene. Alper and coworker reported the first polymeric water-soluble metal complex Rh/PPA(Na^+)/DPPEA for hydroformylation of aliphatic olefins (Scheme 1.5) [16]. For the hydroformylation of vinyl arenes, the complete conversion, high selectivity (>97%) and *iso*/*n* ratio (7.3–24) can be observed.



Scheme 1.5 Rh/PPA(Na^+)/DPPEA-catalyzed hydroformylation of olefins. Source: Based on Ajjou and Alper [16].

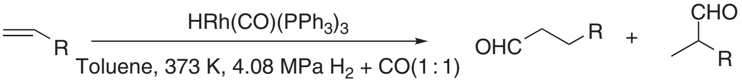
In 1989, Arhancet et al. described a novel supported aqueous-phase catalyst $HRh(CO)[P(m\text{-}C_6H_4SO_3Na)_3]_3/SiO_2$ (SAPC) for hydroformylation (Scheme 1.6) [17]. The hydroformylation of 1-octene yielded a nonanal/2-methyl octanal (*n*/*iso*) ratio ranging from 1.8 to 2.9 depending on the water content and ligand/rhodium ratio (which varied from 7 to 30).



Scheme 1.6 Hydroformylation of 1-octene using SAPC. Source: Based on Arhancet et al. [17].

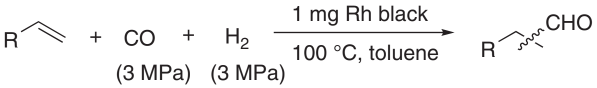
In 2000, Arya and Alper found a solid-phase synthetic approach to obtain dendritic ligands anchored onto beads for the hydroformylation of several olefins [18]. For example, the complete conversion of styrene (>99%) with a high selectivity for the branched isomer (branched : linear, 16 : 1) was obtained at 65 °C. The catalyst can be recycled five times without deactivation.

Chaudhari and coworkers reported $HRh(CO)(PPh_3)_3$ encapsulated and anchored in NaY, MCM-41 and MCM-48 for hydroformylation of olefins to aldehydes in 2003 (Scheme 1.7) [19]. 99.4% conversion of 1-octene and a 1.7 *n*/*iso* ratio of regioselectivity were obtained when using Rh-MCM-48 at 80 °C. This catalyst is recyclable and can be reused six times without obvious deactivation.



Scheme 1.7 Hydroformylation of olefins using $HRh(CO)(PPh_3)_3$-encapsulated catalysts. Source: Based on Mukhopadhyay et al. [19].

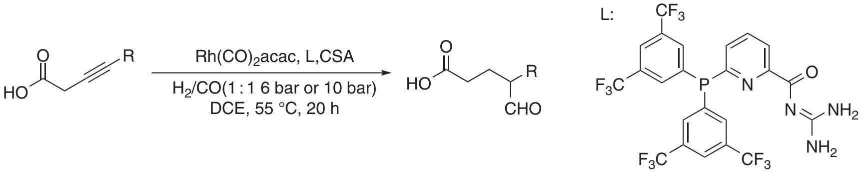
Recently, Shi's group described the simple Rh black as a heterogeneous catalyst for hydroformylation of olefins [20]. This catalyst system has a broad substrate scope including the aliphatic and aromatic olefins, affording the desired aldehydes in good yields (Scheme 1.8). For example, 86% yield of propanal and 200 h^{-1} turnover



Scheme 1.8 Rh black-catalyzed hydroformylation of olefins.

frequency (TOF) were obtained when ethylene is the reactant. The catalyst could be recycled five times without loss of activity.

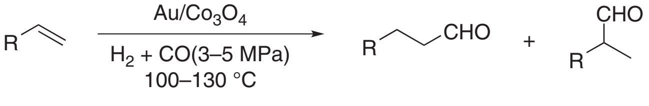
For hydroformylation of alkynes, Breit and coworker designed and synthesized a series of new supramolecular ligands containing a functional guanidine group with increasing p-acceptor ability of the phosphine donor ligands in 2018 [21]. The desired aldehydes were obtained in 51–94% yields with regioselectivities up to 25 : 1 (Scheme 1.9).



Scheme 1.9 Hydroformylation of alkynes.

1.1.3 Au Catalysts

In 2008, Tokunaga and coworkers presented Au/Co_3O_4 heterogeneous catalysts prepared by coprecipitation for hydroformylation (Scheme 1.10) [22]. Aldehydes were prepared with 99.5% conversion of 1-hexene and 1.2 regioselectivity at 130 °C. The Au/Co_3O_4 catalysts can be recycled by simple decantation with slight decrease in catalytic activity. The role of Au may promote in situ reduction of Co_3O_4 to Co^0 which is the active site for the hydroformylation reaction.

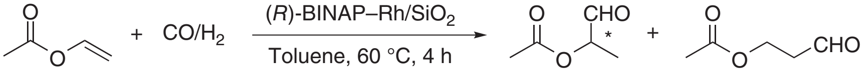


Scheme 1.10 Au/Co_3O_4-catalyzed hydroformylation of 1-olefins. Source: Based on Liu et al. [22].

1.1.4 Ligand-Modified Heterogeneous Catalysts

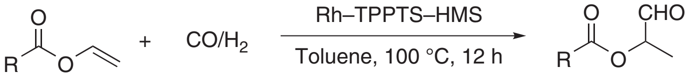
Subsequent work demonstrated that the ligand modification of the catalyst system can influence the catalytic activity and selectivity of the hydroformylation process. In 2006, Li and coworkers prepared heterogeneous chiral ligand-modified silica-supported rhodium (Rh/SiO_2) with chiral phosphorus ligands [23]. Up to 72% enantiomeric excess (ee) and 100% selectivity of branched aldehyde for the hydroformylation of vinyl acetate at 60 °C were obtained by (*R*)-BINAP-Rh/SiO_2 catalysts

(BINAP = 1,1′-binaphthyl-2,2′-diphenyl phosphine) (Scheme 1.11). Reviews on active cobalt and rhodium complexes, also ligand-modified, and on methods for the necessary spectroscopic in situ methods are reported [24, 25].



Scheme 1.11 Asymmetric hydroformylation of vinyl acetate.

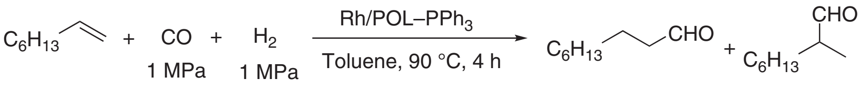
In 2011, Shukla and coworkers prepared the Rh-TPPTS-hexagonal mesoporous silica (HMS) catalyst that $RhCl(TPPTS)_3$ (TPPTS = *m*-trisulfonato triphenyl phosphine) was in situ encapsulated into the mesopores of HMS for hydroformylation of vinyl esters [26]. The synthesized heterogeneous catalyst evaluated for hydroformylation of vinyl esters gave 100% conversion and 88–94% selectivity to *iso*-aldehyde at 100 °C (Scheme 1.12).



Scheme 1.12 Hydroformylation of vinyl esters.

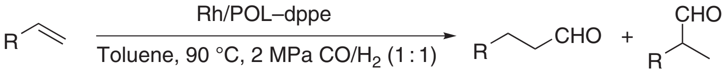
To enhance the activity and stability of the heterogeneous catalyst, a nice method of organic phosphine ligand functionalized support via ligand immobilization or polymerization was developed and applied in the preparation of heterogeneous hydroformylation catalysts [27–29].

In 2014, Xiao, Ding, Chen, and Meng reported the POL (porous organic ligand) bearing a triphenylphosphine-supported rhodium catalyst (Rh/POL–PPh_3) for hydroformylation of 1-octene [30]. Good conversion (>99%) of 1-octene, regioselectivity (*n*/*iso* = 0.87–1.35), and selectivity (89.0–92.1%) were afforded at 90 °C (Scheme 1.13). The catalyst could be recycled at least six times with negligible loss of activity.



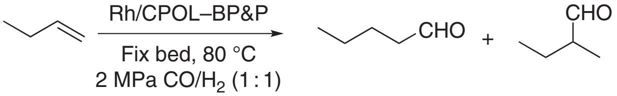
Scheme 1.13 Rh/POL–PPh_3-catalyzed hydroformylation of 1-octene.

Then, Xiao's group synthesized Rh/POL–dppe catalyst for hydroformylation (dppe = 1,2-bis(diphenylphosphino)ethane) [31]. For example, using Rh/POL–dppe as a catalyst, 1-octene in the presence of CO (1 MPa) and H_2 (1 MPa) at 90 °C can give corresponding aldehydes in high conversion of up to 96.9% with regioselectivities of *n*/*iso* up to 2.46 (Scheme 1.14). Meanwhile, the catalyst can be easily separated and recycled five times from the reaction systems without losing any activity and selectivity.



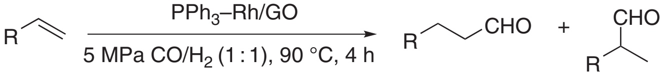
Scheme 1.14 Rh/POL–dppe-catalyzed hydroformylation of olefins.

Ding and Li reported porous organic copolymer (denoted as CPOL–BP&P) which was prepared by copolymerization of vinyl biphephos and tris(4-vinylphenyl) phosphine monomers under solvothermal conditions, and followed with impregnation method provided a highly efficient Rh/CPOL–BP&P catalyst with high activity (TOF = 11 200 h^{-1}) and regioselectivity (the ratio of linear to branched aldehydes, *n*/*iso* = 62.2) for hydroformylation of 1-butene (Scheme 1.15) [32]. High regioselectivity was also obtained in the hydroformylation of butene mixture (2-butene: *n*/*iso* = 55.8, isomeric mixture of butenes: *n*/*iso* = 56.0). Later, they found the hydroformylation of propene to linear butaldehyde by employing single atom dispersed Rh/CPOL–BP&P catalysts in a continuous fixed-bed reactor [33]. In the presence of CO/H_2 (0.5 MPa, 1 : 1) at 70 °C, high regioselectivity (*n*/*iso* > 24), activity (TOF > 1200 h^{-1}) and stability (over 1000 h) were obtained.



Scheme 1.15 Rh/CPOL–BP&P-catalyzed hydroformylation of 1-butene.

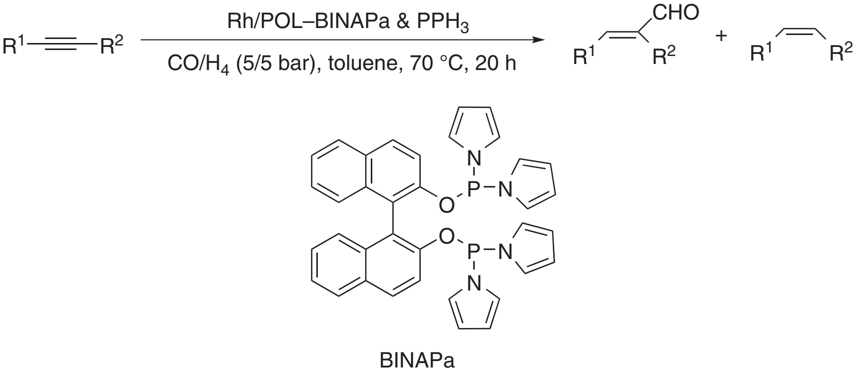
Tsubaki and Yang prepared PPh_3-Rh/GO heterogeneous catalyst by triphenylphosphine (PPh_3)-reduced graphene oxide (rGO) and a rGO-supported Rh–ligand complex catalyst simultaneously [34]. This catalyst system is applied in 1-olefins hydroformylation to form normal aldehyde, exhibiting remarkable catalytic activity and selectivity (Scheme 1.16). For example, the conversion of 1-hexane is 99.9% and the regioselectivities of *n*/*iso* is 2.10. This catalyst could be recycled five times without significant decrease in activity.



Scheme 1.16 PPh_3–Rh/GO-catalyzed hydroformylation of olefins.

In addition, Yang and coworkers presented an efficient heterogeneous catalytic system about IL-in-oil (IL = ionic liquid) Pickering emulsion constructed with Rh-sulfoxantphos as the catalyst and surface-modified dendritic mesoporous silica nanospheres as the stabilizer for hydroformylation of long-chain alkenes in 2018 [35]. 1-Dodecene could be converted to the corresponding aldehyde with an *n*/*iso* ratio of 98 : 2, chemoselectivity of 94% and TOF of 413 h^{-1}, among the highest ever reported for IL-oil biphase hydroformylation of long-chain alkenes. The high efficiency of IL-in-oil Pickering emulsion was primarily attributed to the increased interface area and unique properties of ILs.

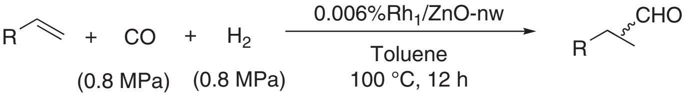
Jia and Zong recently developed a novel Rh/POL–BINAPa&PPh$_3$ catalyst by porous organic polymer-supported rhodium for the hydroformylation of various alkynes (Scheme 1.17) [36]. It can afford the corresponding α,β-unsaturated aldehydes with good to excellent yields (61–89%) with high *E* stereoselectivity (>40 : 1), excellent catalytic activity and good reusability (10 cycles).



Scheme 1.17 Rh/POLBINAPa&PPh$_3$-catalyzed hydroformylation of alkynes. Source: Modified from Liang et al. [36].

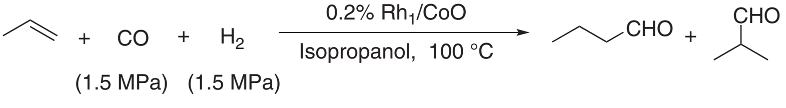
1.1.5 Single-Atom Catalysts

With the development of single-atom catalysis (SAC), it has also been successfully applied in hydroformylation. Zhang and coworkers synthesized a Rh SAC supported on ZnO nanowires for the hydroformylation reaction (Scheme 1.18). As a result, a complete conversion of styrene, a TON of about 40 000 and 99% selectivity can be obtained [37].



Scheme 1.18 Rh$_1$/ZnO-catalyzed hydroformylation of olefins.

Wang and Zhang developed CoO-supported Rh single-atom catalysts (Rh$_1$/CoO) for hydroformylation of propene [38]. The optimal selectivity of 94.4% for butyraldehyde and the highest TOF number of 2065 h^{-1} among the atomic-scale Rh-based catalysts were obtained (Scheme 1.19).



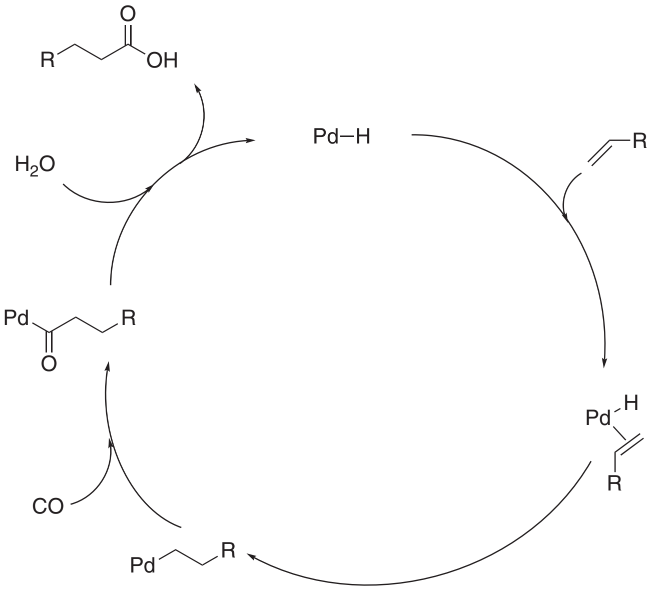
Scheme 1.19 Rh$_1$/CoO-catalyzed hydroformylation of propene.

1.2 Hydroxy-, Alkoxy-, and Aminocarbonylation of Alkenes and Alkynes

Transition metal-catalyzed carbonylation of alkenes and alkynes with nucleophiles such as water, alcohols or amines are called hydroxycarbonylation, alkoxycarbonylation, or aminocarbonylation, respectively. As the importance of carboxylic acid derivatives, transition metal-catalyzed hydroxyl, alkoxy-, and aminocarbonylation reactions are important transformations in organic synthesis. Several palladium-catalyzed alkoxycarbonylations and aminocarbonylations have also been applied on an industrial scale, such as the carbonylation of 1,2-xylyldichloride to give isochroman-3-one, aminocarbonylation of 2,5-dichloropyridine to give Lazabemide and so on.

1.2.1 Hydroxycarbonylation of Alkenes

In 1969, Von Kutepow et al. patented phosphine-containing palladium complexes for the hydroxycarbonylation of a terminal alkene [39]. Further studies by Fenton [40] showed that palladium–phosphine was a good precursor and the reaction parameters were optimized to combine high conversion and a good selectivity in the linear ester. At pressures ranging from 7 to 55 bar, temperatures near to 150 °C, with an excess of PPh_3, linear to branched ratios as high as 3.5 can be reached. As the conversion is largely improved when a hydrogen partial pressure is introduced, the active catalytic species is presumably $[Pd(H)Cl(PPh_3)_2]$ and the catalytic cycle is shown in Scheme 1.20, in which “Pd” represents $[PdCl(PPh_3)_2]$.



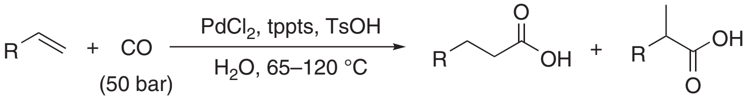
Scheme 1.20 Catalytic cycle of the Pd−H-catalyzed hydroxycarbonylation of alkenes.

In 1983, Alper et al. discovered that the selectivity of the carbonylation reaction can be turned toward the branched acid by adding copper(II) chloride and hydrochloric acid to the palladium catalyst system (Scheme 1.21) [41]. The reaction conditions become very mild since the reaction is performed at room temperature and at 1 bar of CO; the yields in 30–100% can be obtained. By addition of the BNPPA ((*R*)- or (*S*)-1,1-binaphthyl-2,2-diylhydrogenophosphate) chiral ligand, it was possible to reach an ee as high as 91% [42]. It is thus possible to transform *p*-isobutylstyrene into (*S*)-ibuprofen and 2-vinyl-6-methoxynaphthalene into (*S*)-naproxen, which both possess nonsteroidal anti-inflammatory properties [43].

$$\mathrm{RCH{=}CH_2} + \mathrm{CO} + \mathrm{H_2O} \xrightarrow[\mathrm{O_2,\ r.t.,\ 1\ atm}]{\mathrm{PdCl_2,\ CuCl_2,\ HCl}} \mathrm{RCH(CO_2H)Me}$$

Scheme 1.21 Pd-catalyzed hydroxycarbonylation of alkenes. Source: Alper et al. [41].

Hydroxycarbonylation has been performed in biphasic media, maintaining the catalyst in the aqueous phase using water-soluble mono- or diphosphine ligands. For example, Sheldon and coworkers reported the sodium salt of TPPTS ($P(C_6H_4\text{-}m\text{-}SO_3Na)_3$) with palladium was shown to synthesize carbonylate efficiently propene and light alkenes in acidic media (Scheme 1.22) [44, 45]. By applying propene as a starting material, the TOF was >2800 h^{-1} with 99% selectivity to *n*- and isobutyric acid.



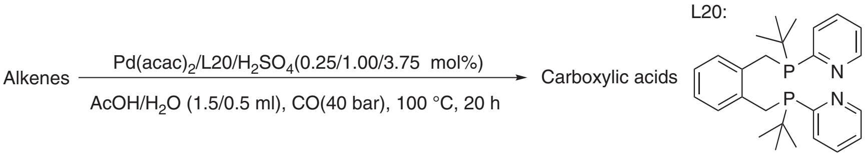
Scheme 1.22 The hydrocarboxylation of olefins in the aqueous phase. Source: Papadogianakis et al. [44]; Verspui et al. [45].

Monflier and coworkers introduced an inverse phase transfer agent particularly dimethyl-β-cyclodextrin to overcome the mass transfer problems between the aqueous and organic phases for heavy alkenes [46, 47]. For instance, the selectivity obtained during 1-decene hydroxycarbonylation reached 90% with per(2,6-di-*O*-methyl)-β-cyclodextrin as ligand.

In 1998, van Leeuwen and coworkers presented a dicationic palladium center coordinated by the bidentate diphosphine ligand 2,7-bis(sulfonato)xantphos catalyzes, in the presence of tolylsulfonic acid, the hydroxycarbonylation of ethylene, propene, and styrene can provide a ca. 0.34 : 0.66 molar ratio for the linear and branched acids [48].

Alper and coworker reported that a mixture of palladium acetate $Pd(OAc)_2$, 1,4-bis(diphenylphosphino butane) (dppb), and formic or oxalic acid is possible to promote high selectivity in linear acid synthesis. For instance, under roughly 7 bar pressure of CO and at 150 °C, α-methylstyrene gives 82% conversion and 100% linearity or 2,4,6-trimethylstyrene gives 98% conversion and 100% linearity, respectively [49].

Recently, Beller and coworkers reported a new state-of-the-art palladium catalyst containing L20 as a ligand for mild and versatile hydroxycarbonylation of olefins (Scheme 1.23) [50]. For industrially relevant olefins, for example, ethylene, excellent catalyst turnover numbers and frequencies are obtained (TON > 350 000, TOF > 15 000 for propionic acid). The catalyst shows outstanding stability and can be easily recycled (>25 runs) without measurable loss of reactivity.

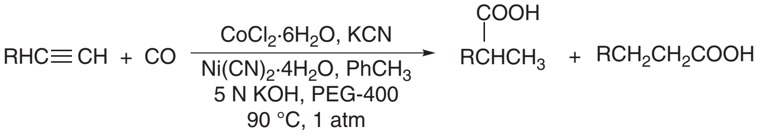


Scheme 1.23 Hydroxycabonylation of olefins. Source: Based on Sang et al. [50].

1.2.2 Hydroxycarbonylation of Alkynes

The pioneering work of Reppe and coworkers reported the industrial preparation of acrylic acid by carbonylation of acetylene as early as 1938 [51]. The reaction was conducted at 200–230 °C and 100 bar of CO and catalyzed by $Ni(CO)_4$ in the presence of a copper halide. Selectivity of 90% and 85% was reached in acrylic acid with regard to acetylene and CO, respectively [52].

Later, Alper and his group reported that hydroxycarbonylation of alkynes can be performed under mild conditions (90 °C, 1 bar of CO), provided that a phase transfer agent is added to the biphasic medium. In the presence of cetyltrimethylammonium bromide, various substituted alkynes or diynes are converted into the corresponding unsaturated carboxylic acids in 50–95% yields by using $Ni(CN)_2$ [53]. When using the bimetallic system $CoCl_2$ and $Ni(CN)_2$ with KCN, saturated carboxylic acids are obtained with a good selectivity for the branched isomer (Scheme 1.24) [54].

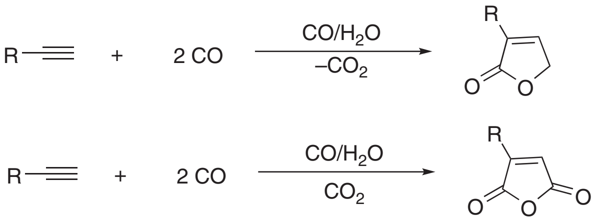


$$RHC{\equiv}CH + CO \xrightarrow[\substack{Ni(CN)_2{\cdot}4H_2O,\ PhCH_3 \\ 5\ N\ KOH,\ PEG\text{-}400 \\ 90\ °C,\ 1\ atm}]{CoCl_2{\cdot}6H_2O,\ KCN} \underset{}{\overset{COOH}{\overset{|}{RCHCH_3}}} + RCH_2CH_2COOH$$

Scheme 1.24 Hydroxycarbonylation of alkynes. Source: Lee and Alper [54].

Similarly, allenes [55] and alkynols [56] were used as starting materials, and their carbonylation provides β,γ-unsaturated acids and unsaturated diacids, respectively.

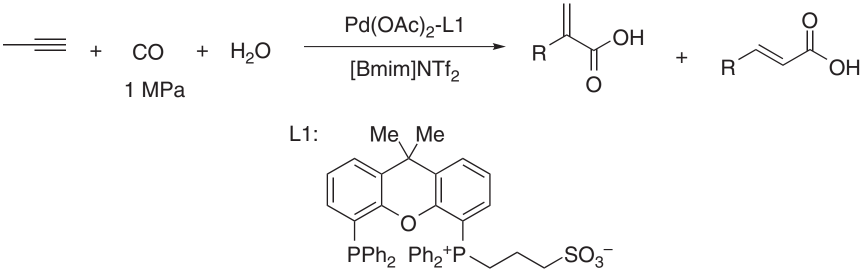
Gabriele et al. mentioned that some precursors easily catalyze the reductive carbonylation of alkynes from the CO/H_2O couple [57, 58]. The main role of water is to furnish hydrogen through the water–gas-shift (WGS) reaction, as evidenced by the co-production of CO_2. In the presence of PdI_2/KI, terminal alkynes have been selectively converted into furan-2-(5*H*)-ones or anhydrides. Two CO building



Scheme 1.25 Incorporation of two CO building blocks into alkynes under water–gas-shift conditions.

blocks are incorporated, and the cascade reactions that occur on palladium result in a cyclization together with the formation of an oxygen–carbon bond furnish (Scheme 1.25).

Recently, Liu and coworkers reported an L1-based Pd catalyst for the hydroxycarbonylation of terminal alkynes containing aromatic and aliphatic toward α,β-unsaturated carboxylic acids (Scheme 1.26) [59]. The high conversion (68–91%) and B/L ratio (68 : 32–91 : 9) can be obtained at 120 °C. This catalyst could be recycled for six times in IL $[\text{Bmim}]\text{NTf}_2$ without obvious activity loss and detectable metal leaching.

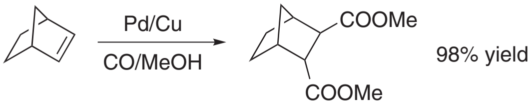


Scheme 1.26 Pd catalyst for the hydroxycarbonylation of terminal alkynes. Source: Based on Yang et al. [59].

1.2.3 Alkoxycarbonylation of Alkenes

Since the first observation by Heck that $Pd(OAc)_2$ can substitute a hydrogen atom in ethylene by a carbomethoxy group [60], Stille and James have discovered that the [Pd–Cu] couple catalyzes the incorporation of a COOMe group arising from CO and methanol [61]. Most of the reactions with an alkene end up with a diester or a methoxyester, copper being used in stoichiometric quantities. For example, in the presence of 3 atm of CO at 28 °C, norbornene yielded 98% diesters products (Scheme 1.27).

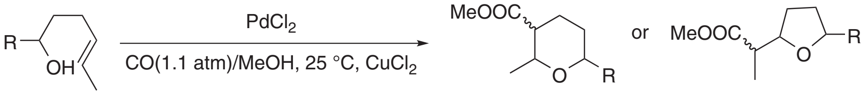
Other Pd catalyst systems have been used for the bisalkoxycarbonylation of alkenes; however, the formation of by-products in the Pd-reoxidation process decreases ester yields dramatically [51]. In the absence of an oxidation agent, the reaction is derived to monoalkoxycarbonylation provided the Pd metal center is



Scheme 1.27 An example of methoxycarbonylation of a cyclic alkene leading to a diester.

stabilized by surrounding ligands. This strategy, first illustrated in 1976 by Knifton with the complex [$PdCl_2(PPh_3)_2$], has been extensively developed since then [62, 63].

In 1984, Semmelhack and coworker reported the first attempts applying mild conditions (25 °C) in intramolecular alkoxycarbonylation of alkenes (Scheme 1.28) [64]. Reactions were under 1 bar of CO in the presence of $PdCl_2$ with $CuCl_2$ as a stoichiometric oxidant; the high yields in 65–88% can be obtained.

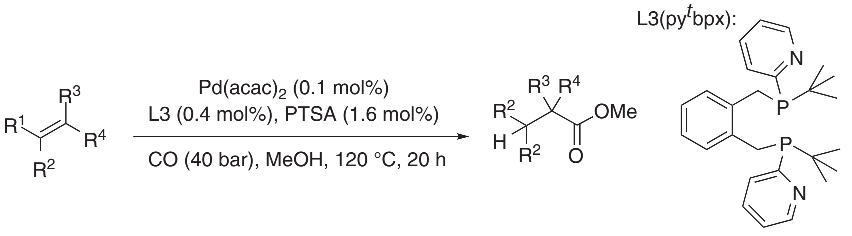


Scheme 1.28 Intramolecular alkoxycarbonylation of alkenes. Source: Based on Semmelhack and Bodurow [64].

The use of heterogeneous catalysts in this reaction has also been achieved: palladium–montmorillonite clays [65] or palladium/activated carbon [66] in the presence of dppb transformed 2-allylphenols into lactones and the regioselectivity of the reaction being largely dependent on the nature of the support.

In 2005, Alper and Touzani used palladium complexes immobilized onto silica-supported (polyaminoamido) dendrimers as catalysts in the presence of dppb for the cyclocarbonylation of 2-allylphenols, 2-allylanilines, 2-vinylphenols, and 2-vinylanilines affording five-, six-, or seven-membered lactones and lactams [67]. Good conversions (up to 100%) are realized at 120 °C, and the catalyst can be recycled 3–5 times.

In 2017, Beller's group designed and synthesized palladium catalyst based on 1,2-bis((*tert*-butyl(pyridin-2-yl)phosphanyl)methyl)benzene L3 (py^{t}bpx) for alkoxycarbonylation of alkenes (Scheme 1.29) [68]. Under 40 bar CO and at 120 °C, the isolated yields in 65–99% can be obtained. In addition, industrially relevant bulk ethylene is functionalized with high activity (TON: >1 425 000; TOF: 44 000 h^{-1} for initial 18 h) and selectivity (>99%).



Scheme 1.29 Methoxycarbonylation of various alkenes. Source: Modified from Dong et al. [68].

1.2.4 Alkoxycarbonylation of Alkynes

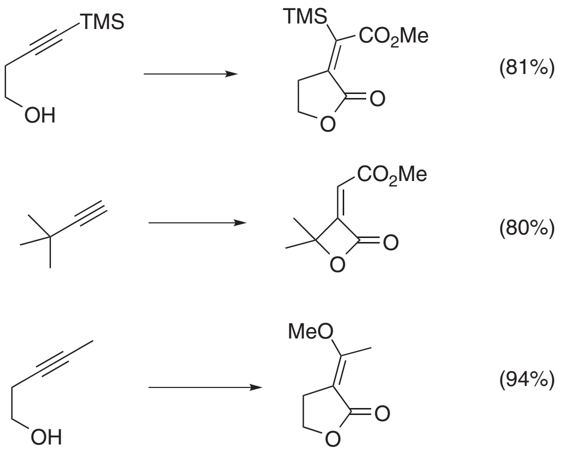
The first observations, done by Tsuji et al. in 1980 on substituted acetylenes (Scheme 1.30) [69], were reinvestigated by Brandsma and coworkers in 1994 and concern the alkoxycarbonylation of these substrates to product acetylenic esters [70]. The yields in 55–84% can be obtained at room temperature.

$$\mathrm{RC{\equiv}CH} + \mathrm{CO} + \mathrm{R'OH} \xrightarrow[\text{NaOAc, r.t.}]{\mathrm{PdCl_2(catal.), CuCl_2}} \mathrm{RC{\equiv}C{-}COOR'}$$

Scheme 1.30 Alkoxycarbonylation of alkynes. Source: Modified from Tsuji et al. [69].

In 1997, Alper and coworker reported that CO insertion occurs prior to allene insertion leading to methylene- or vinyl-benzopyranone derivatives [71]. On the contrary, insertion of alkynes precedes insertion of CO, affording coumarine derivatives, as reported by Larock. This unusual selectivity can be explained by the inability of the acyl palladium species to further react with the alkyne; hence, the decarbonylation step occurs preferentially [72–74].

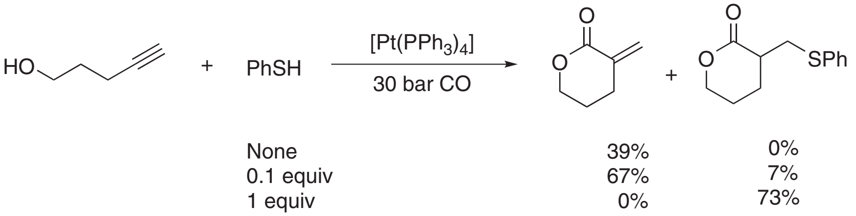
Dialkoxycarbonylation has been reported using a Pd-catalyst/oxidant system on propynols or butynols furnishing, respectively, β- or γ-lactone derivatives with α-(alkoxycarbonyl)ethylene chains (Scheme 1.31) [75–77].



Scheme 1.31 Double carbonylation of various butynols or propynols. Source: Bonardi et al. [75]; Gabriele et al. [76]; Tamaru et al. [77].

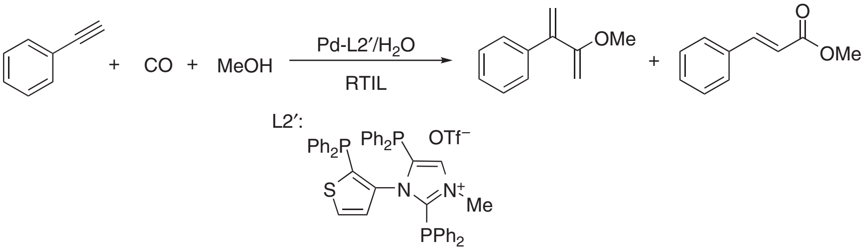
This reaction occurs in a stereospecific way leading exclusively to cis-dicarbonylated products in fair to excellent yields (25–97%). Noteworthy, a butynol bearing an alkyl or an aryl substituent instead of a tetramethylsilane one undergoes a different course of reaction under the same conditions that trans-alkoxycarbonylation takes place selectively (Scheme 1.32).

Recently, Liu and coworkers developed ionic tri-dentate phosphine (L2′) enabled Pd-catalyzed alkoxycarbonylation of alkynes with H_2O as an additive instead of acid



Scheme 1.32 Cyclocarbonylation of an alkynol in the presence of thiols.

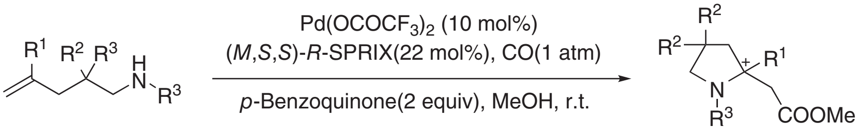
(Scheme 1.33) [78]. High conversion (64–90%), complete selectivity, and B/L ratio (83 : 17–95 : 5) can be obtained at 110 °C. This catalyst could be recycled for seven runs without obvious activity loss or metal leaching.



Scheme 1.33 Methoxycarbonylation of phenylacetylene. Source: Yang et al. [78].

1.2.5 Aminocarbonylation of Alkenes

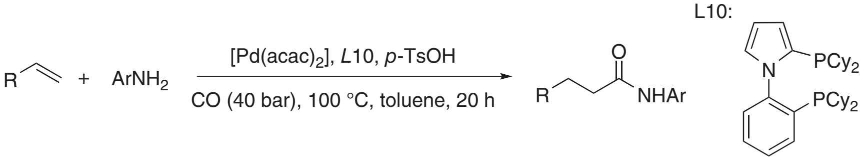
In 2003, Sasai and coworkers reported the first report of an enantioselective intramolecular aminocarbonylation (Scheme 1.34) [79]. The reaction of alkenyl amine derivatives in the presence of Pd(II)-SPRIX catalyst and *p*-benzoquinone (BQ) in methanol under a CO atmosphere affords ester compounds in good yield (47–95%) with moderate enantioselectivity (10–65%).



Scheme 1.34 Intramolecular aminocarbonylation of alkenyl amine derivatives promoted by Pd(II) catalyst. Source: Shinohara et al. [79].

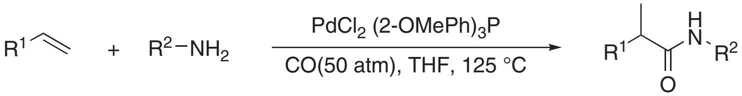
In 2013, Beller and coworkers developed $Pd(acac)_2$ catalyst system for aminocarbonylation of alkenes with (hetero)aromatic amines to alkanamides (Scheme 1.35) [80]. For example, aminocarbonylation of ethylene with aniline can get 98% yield of *N*-phenylpropionamide in the presence of 40 bar CO at 100 °C.

In 2014, Liu et al. described a simple, homogeneous PdX_2/tris(2-methoxyphenyl) phosphine system (X = Cl or Br) for the aminocarbonylation of alkenes



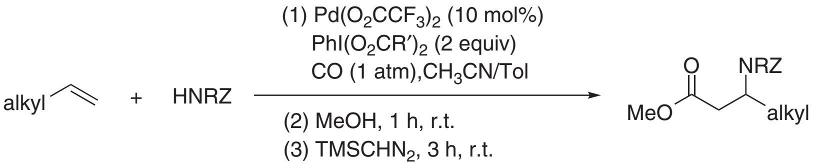
Scheme 1.35 Pd(acac)$_2$ catalyzed aminocarbonylation of alkenes with amines. Source: Fang et al. [80].

(Scheme 1.36) [81]. The wide range of aromatic amines can be efficiently transformed in good yield (27–98%) and usually with high regioselectivity (>99%) for branched carboxamides. Notably, the catalyst does not require acid, base, or any other promoters and employs a commercially available bulky monophosphine ligand thus facilitating reaction scale-up.



Scheme 1.36 PdCl$_2$ catalyzed aminocarbonylation of alkenes with amines. Source: Liu et al. [81].

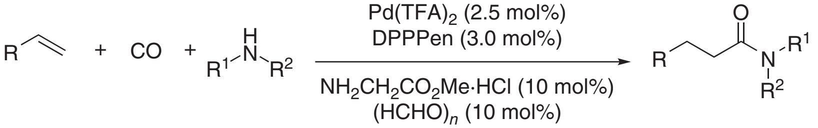
Later, a novel convenient methods to generate β-amino acid derivatives from simple alkenes was developed (Scheme 1.37) [82]. The palladium catalyst can be used in the intermolecular aminocarbonylation of broad substrate scope with 1 atm CO at room temperature, providing their corresponding products in excellent yields (41–92%).



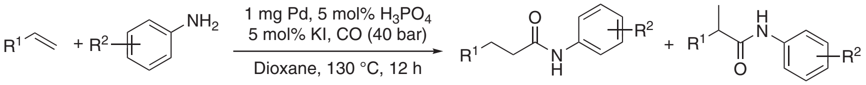
Scheme 1.37 Pd(O$_2$CCF$_3$)$_2$ catalyzed aminocarbonylation of alkenes with amines. Source: Modified from Cheng et al. [82].

In 2015, a cooperative catalytic system combining of Pd(TFA)$_2$/ligand, paraformaldehyde, and acid was established for hydroaminocarbonylation of alkenes by Huang and coworkers (Scheme 1.38) [83]. This catalyst system allows the synthesis of a wide range of *N*-alkyl linear amides in 66–88% yields with high regioselectivity ($n/iso = 80:20–97:3$) and overcomes the difficulty of using aliphatic amines.

In 2018, Shi and Wang described a bulk Pd catalyst for aminocarbonylation of a wide range of olefins with amines under organic ligand-free conditions (Scheme 1.39) [84]. Several kinds of aromatic and aliphatic alkenes with aromatic amines were converted into desired products in 70–99% yields and moderate



Scheme 1.38 $Pd(TFA)_2$ catalyzed aminocarbonylation of alkenes with amines. Source: Zhang et al. [83].

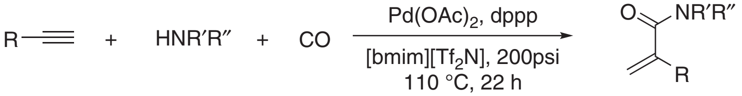


Scheme 1.39 Bulk Pd catalyzed aminocarbonylation of alkenes with amines. Source: Liu et al. [84].

regioselectivities (*n*/*iso* = 50 : 50–71 : 29). The bulk Pd catalyst can be reused at least three times without deactivation. This catalyst can also be applied to the aminocarbonylation reaction of aryl iodides with amines and the oxidative carbonylation reaction of a variety of amines for symmetric urea synthesis.

1.2.6 Aminocarbonylation of Alkynes

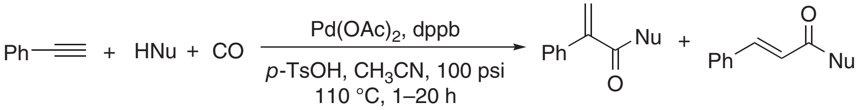
Since the pioneering work of Reppe [85], various organometallic catalysts and synthetic procedures have been explored for the carbonylation of alkynes. For example, Yu and Alper reported $Pd(OAc)_2$-catalyzed aminocarbonylation of alkynes in IL [bmim][Tf_2N] without any acid additive under relatively mild conditions in 2006 (Scheme 1.40) [86]. Acrylamides were obtained in 26–85% yields and the catalyst system can be reused five times without loss of catalytic activity. The IL was used as the reaction medium and also acted as a promoter.



Scheme 1.40 Palladium-catalyzed aminocarbonylation of alkynes in the IL. Source: Li et al. [86].

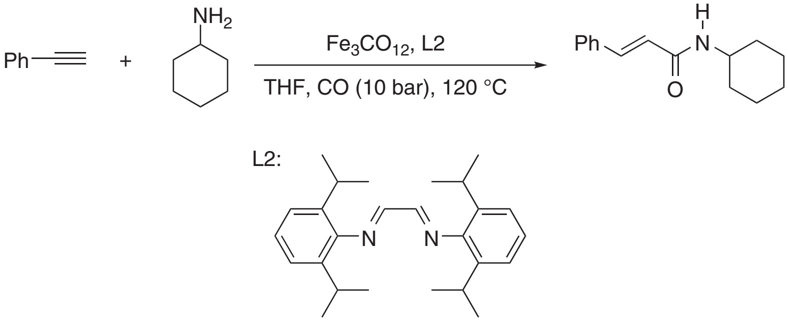
In 2010, El Ali and coworkers reported the aminocarbonylation reaction of terminal alkynes using a catalyst system $Pd(OAc)_2$–dppb–*p*-TsOH–CH_3CN–CO under relatively mild conditions [87]. Phenylacetylene and various amines can be successfully transformed into the corresponding products with up to 88% yield (Scheme 1.41). The obtained DFT/B3LYP results indicate the formation of trans ester isomer via palladium–hydride cycle, while palladium–amine mechanism is the key for the formation of gem isomer [88]. The results prove the role of acetonitrile solvent in improving the stability of catalytic intermediates.

In 2011, Beller and coworkers developed the first general iron-catalyzed aminocarbonylation of alkynes [89]. Starting from commercially available amines and alkynes, a range of structurally diverse amides are obtained smoothly in the



Scheme 1.41 Palladium(II)-catalyzed aminocarbonylation of phenylacetylene using various amines.

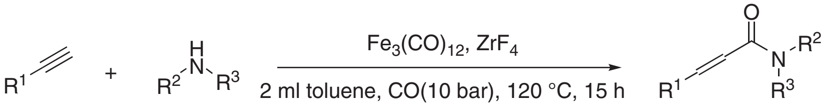
presence of catalytic amounts of $[Fe_3(CO)_{12}]$ and L2. For example, mono carbonylation of phenylacetylene with cyclohexylamine can get 66% yield of product at 120 °C (Scheme 1.42). Notably, the method is highly chemo- and regioselective, and no expensive catalyst is required for this novel environmentally friendly reaction.



Scheme 1.42 Iron-catalyzed mono carbonylation of phenylacetylene.

In 2017, Alper and coworker reported $Pd(OAc)_2$/dppp-catalyzed aminocarbonylation reactions of alkynes and aminophenols provide direct OH-substituted α,β-unsaturated amides [90]. By a simple change of the ligand and the additives, branched or linear amides were formed in excellent chemo- and regioselectivities (up to b/l > 99 : 1) and in good to excellent yields.

In 2019, Li and coworkers utilized ZrF_4 to promote efficiently iron-catalyzed aminocarbonylation between alkynes and amines without the use of extra ligands (Scheme 1.43) [91]. In the presence of cheap and readily prepared ZrF_4 at 120 °C, various aromatic and aliphatic alkynes including internal alkynes were transformed into the desired α,β-unsaturated amides in 65–93% yields.



Scheme 1.43 ZrF_4 as co-catalyst promoted iron-catalyzed aminocarbonylation. Source: Modified from Huang et al. [91].

1.3 The Pauson–Khand Reaction

The transition metal-mediated conversion of alkynes, alkenes, and CO in a formal [2 + 2 + 1] cycloaddition process, commonly known as the Pauson–Khand reaction

(PKR), is an elegant method for the construction of cyclopentenone scaffolds. During the last decade, significant improvements have been achieved in this area [92, 93]. For instance, catalytic PKR variants are nowadays possible with different metal sources. In addition, new asymmetric approaches were established, and the reaction has been applied as a key step in various total syntheses. Recent work has also focused on the development of CO-free conditions, incorporating transfer carbonylation reactions. This section attempts to cover the most important developments in this area.

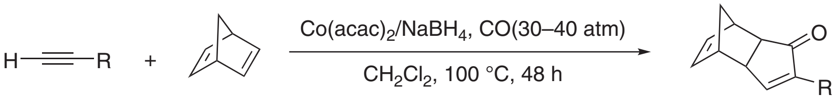
1.3.1 The Catalytic Pauson–Khand Reaction

In 1973, Pauson and Khand reported the first successful example for the conversion of norbornene with the phenylacetylene–hexacarbonyldicobalt complex to give the corresponding cyclopentenone in 45% yield (Scheme 1.44) [94]. With regard to environmental friendliness, catalytic procedures are desirable.

Scheme 1.44 Conversion of norbornene with the phenylacetylene–hexacarbonyldicobalt complex. Source: Modified from Khand et al. [94].

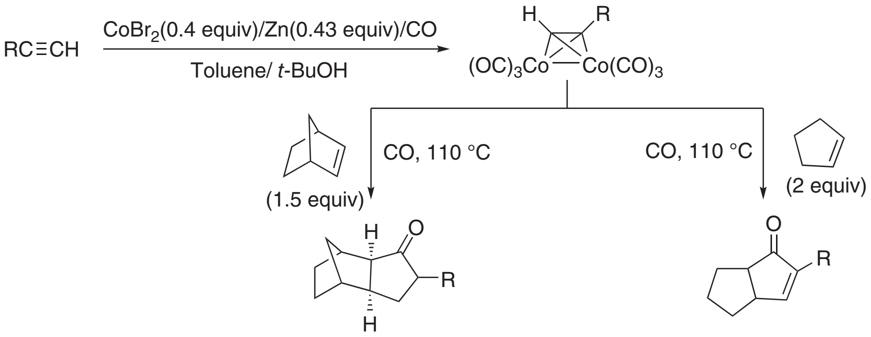
In 1990, Rautenstrauch et al. reported the first catalytic PKR using $Co_2(CO)_8$ as a catalyst [95], who described the conversion of heptyne using a mixture of 40 bar ethylene and 100 bar CO to form the resulting cycloaddition adduct in a yield of 48%. A more practicable procedure was later reported by Jeong et al. [96]. With triphenylphosphite as a ligand, the PKR in 51–94% yields can be obtained at 3 atm of CO and 100 °C by stabilization of the cobalt catalyst.

Apart from $Co_2(CO)_8$, other Co sources, i.e., $Co_3(CO)_9(\mu^3\text{-CH})$, were also successfully applied within the reaction [97]. Lee and Chung [98] examined the use of $Co(acac)_2/NaBH_4$ as a cycloaddition catalyst (Scheme 1.45). In this case, yields were observed in a range of 33–85%. Successful conversions need high CO pressures (40 atm) and long reaction times (up to several days).



Scheme 1.45 Use of $Co(acac)_2/NaBH_4$.

The first example of a catalytic conversion under atmospheric pressure CO was reported by Rajesh and Periasamy (Scheme 1.46) [99]. A combination of 0.4 equiv

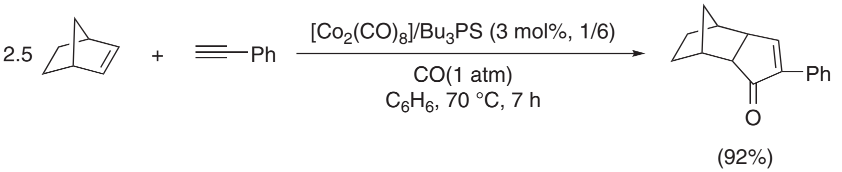


Scheme 1.46 Catalytic conversion under atmospheric pressure of carbon monoxide. Source: Rajesh and Periasamy [99].

$CoBr_2$ and 0.43 equiv Zn was chosen to facilitate the intermolecular PKR. Isolated yields were obtained in the range of 30–88% at 110 °C.

Supplementary to reactions in organic solvents, procedures applying supercritical fluids have become more and more attractive in industry and academic research. Jeong's group reported the use of supercritical CO_2 as an alternative solvent [100]. Using $Co_2(CO)_8$ as a catalyst, 112 atm of CO_2 and 15–30 atm of CO were required at 37 °C to obtain cyclopentenones in yields up to 91%.

In addition to the accelerating effect of sulfides and amines in the stoichiometric $Co_2(CO)_8$-mediated procedure, Hashimoto and coworkers showed that phosphane sulfides are able to promote the $Co_2(CO)_8$-catalyzed reaction [101]. For example, at atmospheric CO pressure and moderate temperature of 70 °C, the desired product was isolated in 92% yield (Scheme 1.47).



Scheme 1.47 Phosphane sulfides promoted the $Co_2(CO)_8$-catalyzed reaction.

Chung and coworkers developed an easy system that is based on the immobilization of 12 wt% metallic cobalt on commercially available charcoal [102]. The resulting yields were obtained in the range of 61–98%. The catalyst was reused up to 10 times without significant loss of activity after simple filtration.

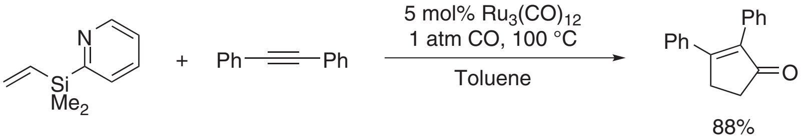
Although Co carbonyl complexes have been used most often in catalytic PKR, a variety of other transition metal complexes are able to catalyze this reaction. Buchwald and coworkers has shown that 5–20 mol% $Cp_2Ti(CO)_2$ facilitates the PKR at 18 psi CO and 90 °C, giving yields in between 58% and 95% [103].

Mitsudo and coworkers [104] and Murai and coworkers [105] reported independently on the employment of $Ru_3(CO)_{12}$ as an active catalyst. Cyclopentenones were isolated in 41–95% yields. In addition, rhodium catalysts were successfully examined for use in the PKR.

Narasaka and coworkers [106] carried out reactions at atmospheric CO pressure using the dimeric $[RhCl(CO)_2]_2$ complex. Also, in the presence of other rhodium complexes like Wilkinson catalyst $RhCl(PPh_3)_3$ and $[RhCl(CO)(dppp)]_2$ [107] in combination with silver salts, cyclopentenones were obtained in yields in the range of 20–99%.

The pioneering work of Krafft and coworkers revealed that the introduction of coordinating heteroatoms, such as nitrogen or sulfur, attached to the alkene leads to a strong enhancement of reactivity and regioselectivity [108–110]. Hence, further work was dedicated to developing an easily removable directing group, which would open the way to increasing the synthetic potential of the intermolecular PKR.

In this connection, Itami et al. developed an interesting system, which included a 2-pyridyldimethylsilyl group tethered to the alkene part (Scheme 1.48) [111, 112]. As a major advantage, this directing group enabled the regioselective synthesis of cyclopentenones at the 4- and 5-position. The pyridylsilyl group is removed after product formation caused by residual water. $Ru_3(CO)_{12}$ gave the best results even under low pressure of 1 atm CO. Yields were obtained in the range of 40–91%.

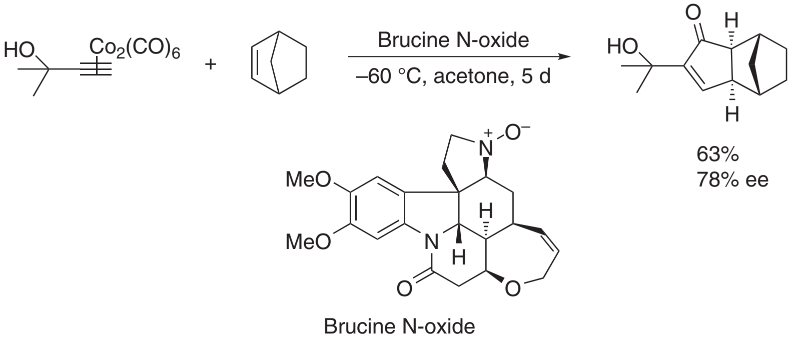


Scheme 1.48 2-Pyridyldimethylsilyl group tethered to the alkene part. Source: Itami et al. [111]; Itami et al. [112].

Because of the remarkable increase of molecular complexity, the PKR serves as a useful methodology for various natural product syntheses. Numerous examples of synthetic applications have been reported. For instance, the PKR was successfully employed in the total syntheses of β-cupraenone [113], loganin [114], hirsutene [115], and (+)-epoxydictymene [116].

1.3.2 Stereoselective Pauson–Khand Reactions

The virtue of performing the PKR in an enantioselective manner has been extensively elaborated. Different powerful procedures were developed, spanning both auxiliary-based approaches and catalytic asymmetric reactions. For instance, the use of chiral N-oxides was reported by Kerr and coworkers, who examined the effect of the chiral brucine N-oxide in the intermolecular PKR of propargylic alcohols and norbornadiene [117]. Under optimized conditions, ee values up to 78% at −60 °C have been obtained (Scheme 1.49). Chiral sparteine N-oxides are also able to induce chirality, but the observed enantioselectivity was comparatively lower [118]. The application of chiral auxiliaries is an alternative route to obtain enantiomerically



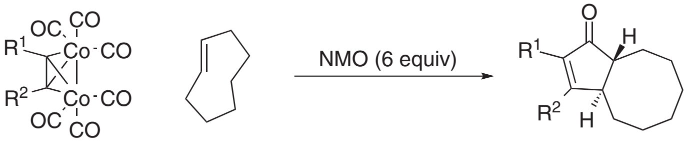
Scheme 1.49 Chiral brucine N-oxide in the intermolecular PKR of propargylic alcohols and norbornadiene.

pure compounds. This approach has been frequently used in the total syntheses of natural products like hirsutene [115] and (+)-15-norpentalene [119].

In 1996, Buchwald and Hicks reported the first successful results that the chiral titanocene complex (*S*,*S*)-(EBTHI)Ti$(CO)_2$ is a useful system for the synthesis of enantiomerically pure cyclopentenones [120, 121]. Various enynes were converted into corresponding product in 72–96% yields with 70–94% ee under 14 psig CO pressure at 90 °C. In addition, $RhCl(CO)_2$ in combination with AgOTf and (*S*)-BINAP was reported to facilitate enantioselective PKR [122]. Values of ee were observed in between 22% and 99%, and isolated yields were in the range of 22–96%.

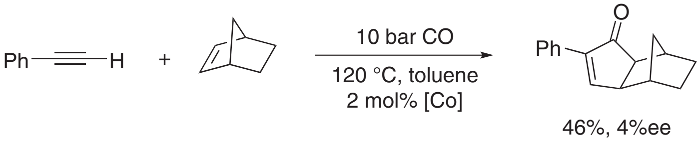
Moreover, it was shown that chiral iridium diphosphine complexes catalyze such cycloaddition reactions [123]. Using a comparatively large amount of 10 mol% $[Ir(cod)Cl]_2$, reactions afforded enantiomerically enriched cyclopentenones when (*S*)-tolBINAP was employed as a ligand. The corresponding cyclopentenones were obtained in yields up to 85% and ee values ranging from 82% to 98%. Interestingly, $Co_2(CO)_8$ in combination with a chiral bisphosphite also gives access to chiral Pauson–Khand products [124]. Although yields were observed up to 97%, in most cases, the ee was rather low (<20%).

An interesting advance in expanding the scope of the alkene component of the PKR came from Lledo and Riera [125]. The team developed a cobalt-mediated PKR between alkynes and *trans*-cycloalkenes. The scope was established for the reaction between symmetric and terminal alkynes and medium-sized *trans*-cyclooalkenes (Scheme 1.50).



Scheme 1.50 Application of (*E*)-cyclooctene in the PKR.

In 2016, Nordlander and coworkers applied tris-μ carbyne cobalt pre-catalysts to the intermolecular PKR. While they were able to use the catalyst in 2 mol%, yields were modest and enantioselectivity was poor (Scheme 1.51) [126]. Additionally, they used dicobalt octacarbonyl and tetracarbonyl dodecacarbonyl within the PKR and exogenous chiral phosphine ligands and obtained excellent yields, though again no ee.



Scheme 1.51 Trinuclear cobalt–WalPHOS-catalyzed coupling of phenylacetylene and norbornene. Source: Modified from Mottalib et al. [126].

1.3.3 Pauson–Khand Transfer Carbonylation Reactions

The PKR has been developed as a straightforward and practicable method for the synthesis of highly substituted cyclopentenones. But for many synthetic chemists, the employment of poisonous CO still represents a disadvantage. Hence, different strategies focused on the replacement of CO within the reaction sequence (Scheme 1.52).

conditions:

a: 5 mol% $[RhCl(cod)]_2$, 11 mol% dppp, 2 equiv C_6F_5CHO, xylene, 4h, 130 °C [127]

b: 5 mol% $Rh(dppp)_2Cl$, 20 equiv cinnamaldehyde, 2 h, 120 °C [128]

c: 5 mol% $[RhCl(cod)]_2$, 10 mol% dppp, 10 mol% TPPTS, 2 equiv SDS, 10 eq HCHO, 2 h, refluxing water [129]

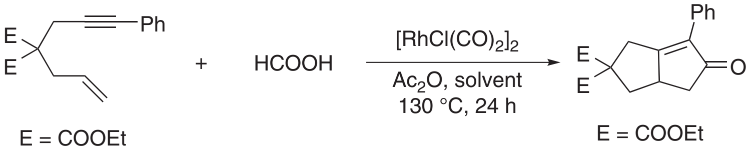
Scheme 1.52 Pauson–Khand transfer carbonylation reactions.

Morimoto, Kakiuchi, and coworkers were the first to show that aldehydes are a useful source of CO in the catalytic PKR [127]. Based on ^{13}C-labeling experiments, it was proposed that after decarbonylation of the aldehyde, an active metal catalyst is formed. The best results were obtained using C_5F_5CHO and cinnamaldehyde as a CO source in combination with $[RhCl(cod)]_2$/1,3-bis(diphenylphosphino)propane (dppp) as the catalyst system. In the presence of an excess of aldehyde, the corresponding products were isolated in the range of 52–97%.

Later, Shibata et al. reported PK-type transfer carbonylation reactions in the absence of solvent and employing a large excess of aldehyde [128]. Also in this case, the reactions went smoothly yielding cyclopentenones in the range of 56–96%. Interestingly, it was also demonstrated that this methodology provides access to chiral products. By applying the chiral catalyst system $[RhCl(cod)]_2$/tolBINAP, ee values of 45–90% were observed.

Another convincing approach to carrying out PK-type transfer carbonylation reactions was again reported by Kakiuchi and coworkers [129]. Formaldehyde was employed as a decarbonylating agent in the presence of a micelle-containing aqueous system. It was proposed that the decarbonylation and carbonylation reactions take place in different phases. More precisely, the water-soluble formaldehyde is decarbonylated in the aqueous phase, enabled by the $[RhCl(cod)]_2$/triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt (TPPTS) system, while carbonylation takes place in a micelle formed by the surfactant sodium dodecyl sulfate. Also, in this case, the yields obtained were good to quantitative (67–96%).

In 2019, He and coworkers have shown the feasibility of the rhodium-catalyzed PK-type reaction using formic acid for the conversion of CO_2 to CO to prevent the arduous management of gaseous reagents (Scheme 1.53) [130]. A variety of 1,6-enyne substrates bearing electron-withdrawing or electron-donating substituents were smoothly converted to the corresponding cyclopentenones in 49–86% yields.



Scheme 1.53 Pauson–Khand transfer carbonylation reactions. Source: Lang et al. [130].

1.4 Synthesis of Acetic Acid

Acetic acid (AA) synthesis via the carbonylation of methanol is one of the most important industrial applications of catalysis using organometallic compounds. The processes based on cobalt, rhodium, and iridium have been developed since the 1960s. Methanol carbonylation comprises more than 60% of the world AA production [131]. The most significant development is the commercialization by BP Chemicals of the iridium-based Cativa™ process. Enhanced stability of iridium catalysts also allows operation at lower water concentration.

1.4.1 Process Considerations

The carbonylation reaction (1) involves formal insertion of CO into the C–O bond of methanol. In a working catalytic system, however, the principal solvent component is AA, so esterification (2) leads to substantial conversion of the substrate into methyl acetate. Methyl acetate is activated by reaction with the iodide co-catalyst (3). Transition metal-catalyzed carbonylation of methyl iodide then gives acetyl iodide (4), which is rapidly hydrolyzed to the product AA (5). The net result of the reactions is described (Scheme 1.54).

As well as playing a role in some of the organic transformations, excess water is also present as a significant component of the solvent mixture, which helps

$$(1)\quad MeOH + CO \longrightarrow MeCO_2H$$

$$(2)\quad MeOH + AcOH \longrightarrow MeOAc + H_2O$$

$$(3)\quad MeOAc + HI \longrightarrow MeI + AcOH$$

$$(4)\quad MeI + CO \longrightarrow MeCOI$$

$$(5)\quad MeCOI + H_2O \longrightarrow AcOH + HI$$

$$(6)\quad H_2O + CO \longrightarrow CO_2 + H_2$$

Scheme 1.54 Process of catalytic carbonylation of methanol for the synthesis of acetic acid.

to maintain catalyst stability. It is found that catalyst solubility is enhanced at high water concentrations, but these results in a more costly separation process to dry the product. The presence of water also results in the occurrence of the WGS reaction (6), which can be catalyzed by Rh and Ir iodocarbonyls, in competition with the desired carbonylation process, resulting in a lower utilization of CO.

From a commercial viewpoint, potential benefits can accrue from operating the methanol carbonylation process at low water concentration, provided that catalyst stability can be maintained. Strategies to achieve this include (i) addition of iodide salts to stabilize the Rh catalyst, (ii) heterogenization of the Rh catalyst on a polymer support to restrict the catalyst to the reactor and (iii) replacement of Rh by a more robust Ir catalyst. These strategies, along with others for improving catalyst activity, will be discussed in the following sections.

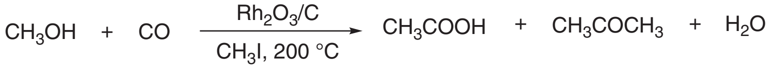
1.4.2 Rhodium-Catalyzed Carbonylation

The first process for the carbonylation of methanol to AA commercialized by BASF in 1960 with cobalt/iodide catalyst under a high temperature of 250 °C and 680 bar pressure [132, 133]. The selectivity to AA of the BASF process is about 90% based upon methanol.

In 1968, Paulik and Roth of Monsanto Company announced the discovery of a low-pressure carbonylation of methanol using an iodide-promoted rhodium catalyst [134]. Under CO pressures as low as 1 atm, the selectivity to AA is virtually quantitative (>99%) at 175 °C. Then, scientists began to study the performance and reaction mechanism of rhodium catalysts or iridium catalysts.

In order to overcome the catalyst recycle step, the immobilization of the rhodium complex on a support has been the subject of considerable investigation [135]. These works include activated carbon, inorganic oxides, zeolites, polymeric materials, and so on.

Schultz prepared thermal decomposition of rhodium nitrate impregnated on activated carbon for vapor-phase carbonylation of methanol in the presence of CH_3I promoter (Scheme 1.55) [136]. The 93% conversion of methanol and 91% selectivity to AA can be obtained at 200 °C and 215 psia pressure under this catalyst system (3% rhodium content).



$$CH_3OH + CO \xrightarrow[CH_3I,\ 200\ ^\circ C]{Rh_2O_3/C} CH_3COOH + CH_3COCH_3 + H_2O$$

Scheme 1.55 Rhodium-catalyzed carbonylation of methanol. Source: Modified from Schultz [136].

In 1988, Miessner and Luecke reported the Rh/zeolite (NaX, NaY) catalyst for carbonylation of methanol to AA [137]. The good conversion (about 55%) and the high selectivity (about 90%) can be obtained at 350 °C with a maximum carbonylation activity in the range of the Si/Al ratio of 1.3–1.5.

In 2017, Bae and coworkers investigated a novel heterogeneous Rh-g-C_3N_4 catalyst for a liquid-phase carbonylation of methanol to AA to overcome disadvantages of the commercialized Rh-based homogeneous catalysts [138]. The catalyst system showed a superior catalytic activity in a liquid-phase carbonylation with AA yield above 82% under the reaction conditions of 140 °C and 4.0 MPa CO pressure.

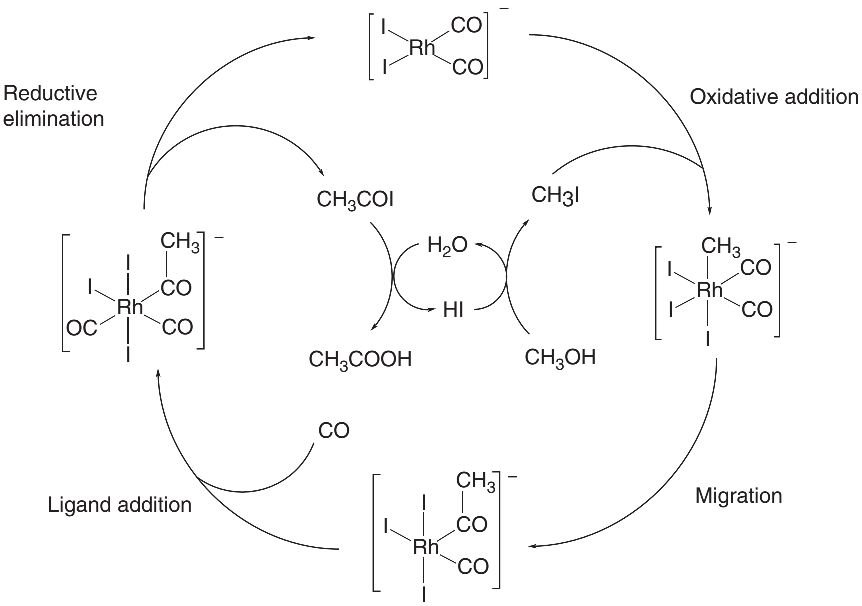
In 2019, Christopher and coworker reported an atomically dispersed Rh catalyst on an acidic support (Al_2O_3, ZrO_2) for methanol carbonylation to AA under halide-free and gas-phase conditions [139]. When operating at 300 °C and 1 : 1 methanol to CO molar feed ratio, 0.2 wt% atomically dispersed Rh loaded on 5%Na–ZrO_2 exhibited stable reactivity over the course of 50 h with 54% selectivity to AA. It is demonstrated that active site pairs consisting of atomically dispersed Rh and support acid sites enable highly selective AA production, whereas Rh clusters drive methanol decomposition to CO and CO_2.

Ding and Lyu prepared single-atom Rh–POL–2BPY catalyst by impregnation of $Rh_2(CO)_4Cl_2$ solution of dichloromethane for methanol carbonylation [140]. Under 195 °C and 2.5 MPa, this catalyst behaved excellent carbonylation activity ($\mathrm{TOF} > 1400\ h^{-1}$).

The catalytic cycle and mechanism of classic example of homogeneous catalytic rhodium-catalyzed carbonylation was studied (Scheme 1.56) [141]. The Monsanto catalyst system has been the subject of numerous studies [142–145]. The kinetics of the overall carbonylation process are zero order in both reactants (MeOH and CO) but first order in rhodium catalyst and methyl iodide co-catalyst. The active catalyst (identified by in situ high-pressure infrared spectroscopy [146]) is the square-planar Rh(I) complex, *cis*-$[Rh(CO)_2I_2]^-$. Oxidative addition of methyl iodide to this complex is the rate-determining step of the cycle, consistent with the observed kinetics. Rate measurements on the stoichiometric reaction of $[Rh(CO)_2I_2]^-$ with MeI have confirmed this to be second-order, with activation parameters comparable to those for the overall carbonylation process [147].

1.4.3 Iridium-Catalyzed Carbonylation

It was discovered by Monsanto that methanol carbonylation could be promoted by an iridium/iodide catalyst [134]. However, Monsanto chose to commercialize the



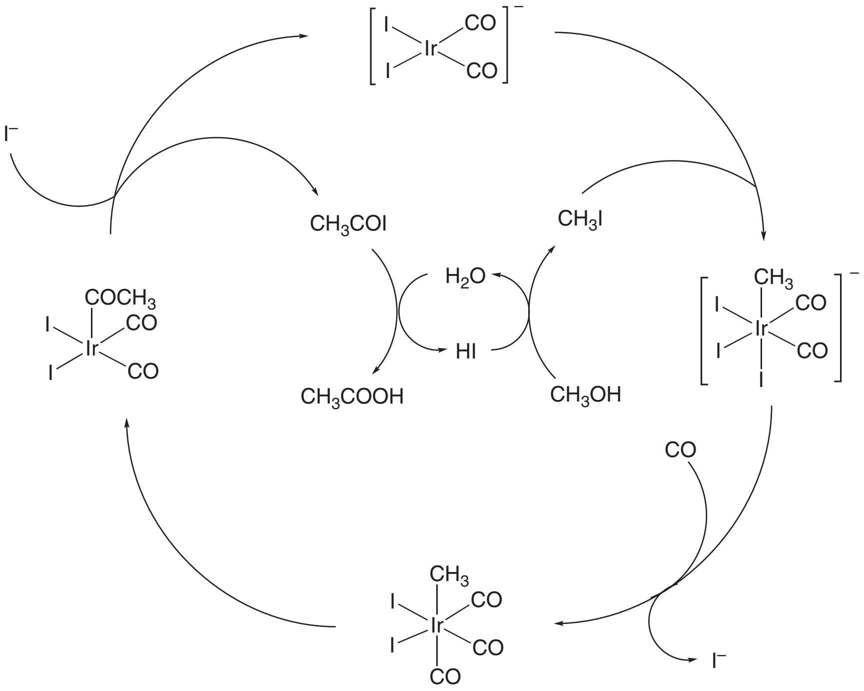
Scheme 1.56 Catalytic cycle of the rhodium-catalyzed methanol carbonylation (Monsanto process). Source: Modified from Forster [141].

rhodium-based process due to its higher activity under the conditions used. In 1996, BP Chemicals announced a new methanol carbonylation process, Cativa™, based upon a promoted iridium/iodide catalyst which now operates on a number of plants worldwide [148–150].

In 2006, Kalck and coworkers discovered $[PtI_2(CO)]_2$ or $[PtI_2(CO)_2]$ has a pronounced synergistic effect for low water content $[Ir(CH_3)I_3(CO)_2]^-$-catalyzed methanol carbonylation to AA [151]. When Pt/Ir ratio is 33 : 67, 35 $mol\,l^{-1}\,h^{-1}$ AA can be observed under 30 bar and at 190 °C.

In 2019, Ding and Song investigated the stability of a heterogeneous single-site Ir_1–La_1/AC catalyst for vapor methanol carbonylation [152]. In the presence of CO/H_2 with 240 °C and 2.4 MPa pressure, TOF about 3700 mol_{acetyl}/mol_{Ir} h can be obtained. The La promoter could protect the Ir^+ species from reduction by H_2, favor the single-atom dispersion of Ir metal, and also increase the reaction rate of methanol carbonylation.

Mechanistic studies of iridium/iodide-catalyzed methanol carbonylation have been reported by Forster [153] and others (Scheme 1.57) [154, 155]. The catalytic cycle involves the same fundamental steps as the rhodium system: oxidative addition of MeI to Ir(I), followed by migratory CO insertion to form an Ir(III) acetyl complex. Of course, there are differences between them, the iridium-based cycle involving neutral iridium complexes, and rhodium-based cycle predominantly involving anionic species. Model kinetic studies [156, 157] have shown that the oxidative addition of methyl iodide to the iridium center is about 150 times faster than the analogous reaction with rhodium. The rate-determining step involves



Scheme 1.57 Catalytic cycle of the iridium-catalyzed methanol carbonylation (Cativa process). Source: Matsumoto et al. [154]; Haynes et al. [155].

dissociative substitution of I^- by CO in $[Ir(CO)_2I_3Me]^-$, followed by migratory CO insertion in the tricarbonyl, $[Ir(CO)_3I_2Me]$.

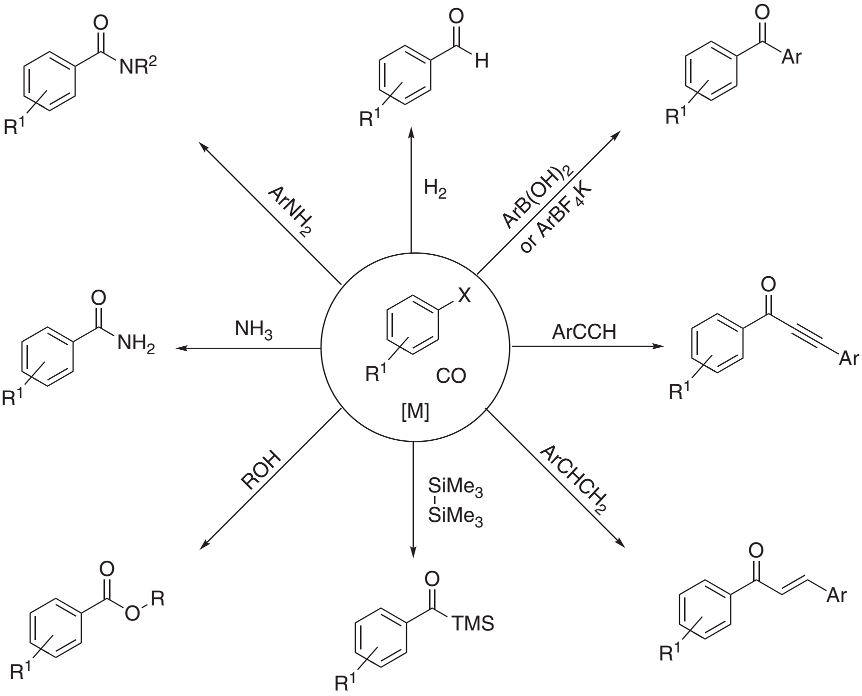
A great advantage of iridium, compared to rhodium, is that a broad range of conditions are accessible for the Ir catalyst without precipitation of IrI_3 occurring. The greater stability of the iridium catalyst can be ascribed to stronger metal–ligand bonding for the third-row metal, which inhibits CO loss from the Ir center.

1.5 Carbonylation of C–X Bonds

Carbonylations of C–X bonds is the insertion of CO into C–X (X = Cl, Br, I) in the presence of nucleophiles. In Scheme 1.58, alcohols, amines, ethers, carboxylic acids, and halides can be converted into acids, amides, esters, ketones, alkynones, alkenones, anhydrides, and acid halides with the assistance of transition metal catalysts in the presence of CO source [158, 159].

1.5.1 Hydroxy-, Alkoxy-, and Aminocarbonylations of C–X Bonds

Transition metal-catalyzed carbonylative activation of C–X bonds with nucleophiles such as water, alcohols, or amines are called hydroxycarbonylation, alkoxycarbonylation, or aminocarbonylation, respectively. From a mechanism point of few, the

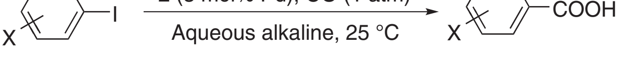


Scheme 1.58 Transition metal-catalyzed carbonylation reactions of C–X bonds.

catalytic cycles for these reactions end with the nucleophilic attack of nucleophiles with an acylpalladium complex and produce carboxylic acids, esters, and amides as their terminal products.

As early as in 1988, Bumagin et al. utilized palladium catalyst ($Pd(OAc)_2$, K_2PdCl_4, $PdCl_2(PPh_3)_2$, and $Pd(NH_3)_4Cl_2$) for hydroxycarbonylation of ArI with CO and H_2O [160]. In the presence of palladium catalyst and base (K_2CO_3 or NaOAc) under 1 atm CO at 25 °C, the product of yield with up to 100%.

In 1999, Uozumi and coworker reported palladium-catalyzed hydroxycarbonylation of aryl or alkenyl halides, which was performed in water in the presence of an amphiphilic solid-supported phosphine–palladium complex (Pd–PEP) [161]. For example, aryl halides can get the corresponding carboxylic acids in 45–100% yields under mild reaction conditions and an atmospheric pressure of CO (Scheme 1.59).



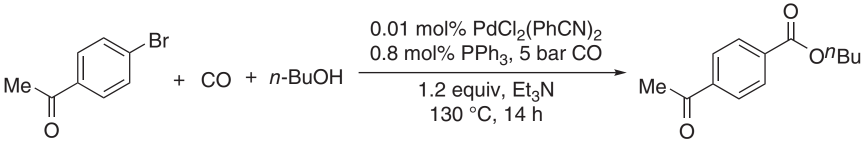
Scheme 1.59 Hydroxycarbonylation of aryl halides in water.

In 2010, Reiser and coworkers developed the reversible immobilization of pyrene-tagged palladium NHC complexes on highly magnetic, graphene-coated cobalt nanoparticles for hydroxycarbonylation of aryl halides in water (100 °C)

[162]. For example, hydroxycarbonylation of 4-iodophenol can yielded 95% product in the presence of K_2CO_3 and 1 atm CO. This catalyst can be recycled 10 times without the significantly decrease amount of nanoparticle-bound palladium.

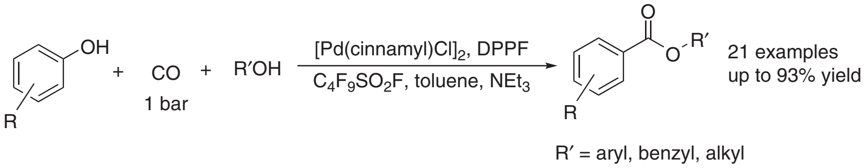
Heck and colleagues described the first palladium-catalyzed alkoxycarbonylation reaction in 1974 [163]. Carboxylic acid *n*-butyl esters were synthesized from aryl and vinyl iodides and bromides after they reacted with CO (1 bar) in *n*-butanol at 60–100 °C. In the presence of $Pd(OAc)_2$ or $PdX_2(PPh_3)_2$ complexes with a slight excess of tri-*n*-butylamine as a base, 4–83% yields of the corresponding esters were obtained.

Notable progress with regard to catalyst productivity was achieved by Beller's group [164]. Butyl ester was achieved at low pressure (5 bar CO) and 100 °C in the presence of only 0.3 mol% $Pd(PPh_3)_4$ and 3 equiv of Et_3N in *n*-butanol. The optimization resulted in the high turnover (TON up to 7000) for alkoxycarbonylation of aryl halides (Scheme 1.60)



Scheme 1.60 Palladium-catalyzed alkoxycarbonylation of aryl bromides.

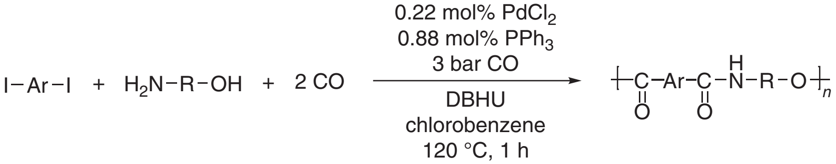
Beller's group developed a general palladium-catalyzed carbonylation of aryl and heteroaryl bromides with phenols. The reaction proceeds smoothly in the presence of di-1-adamantyl-*n*-butylphosphine under 2 bar of CO in 1,4-dioxane at 100 °C. Later on, the same group developed a one-pot alkoxycarbonylation of phenols with alcohols and phenols via the in situ formation of ArONf. The reaction proceeds selectively to the desired benzoates in good yields (Scheme 1.61) [165, 166].



Scheme 1.61 Palladium-catalyzed carbonylation of phenols. Source: Wu et al. [165]; Wu et al. [166].

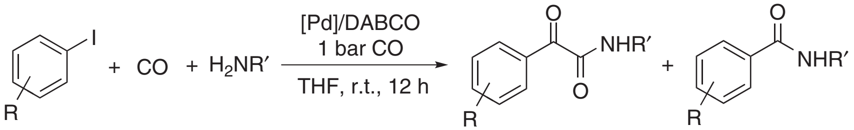
Chaudhari and colleagues reported a palladium-catalyzed carbonylation–polycondensation reaction of aromatic diiodides and aminohydroxy compounds [167]. With their methodology, alternating polyesteramides were prepared in chlorobenzene with 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) as a base under 3 bar of CO at 120 °C (Scheme 1.62).

Palladium-catalyzed double carbonylation as a more special carbonylation variant usually requires high CO pressures in order to compete with the corresponding monocarbonylation reactions. In 2001, Uozumi et al. reported



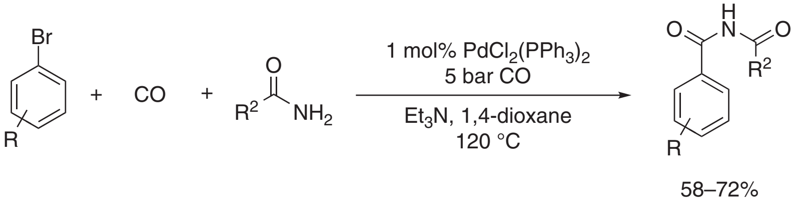
Scheme 1.62 Palladium-catalyzed polycondensations.

a procedure that significantly improved the existing protocols. They found 1,4-diaza-bicyclo[2.2.2]octane to be a superior base for the highly selective double carbonylation of aryl iodides with primary amines (Scheme 1.63) [168]. The desired a-keto amides were prepared under atmospheric pressure of CO at room temperature in the presence of a simple palladium–triphenylphosphine complex.



Scheme 1.63 Palladium-catalyzed double carbonylation of aryl iodides. Source: Modified from Uozumi et al. [168].

Schnyder and Indolese proved that the carbonylation of aryl bromides with primary amides or sulfonamides can lead to asymmetrical aroyl acyl imides. When the reactions were carried out under mild conditions, Et_3N was found to be the best base and the desired products were produced in 58–72% yields (Scheme 1.64) [169].



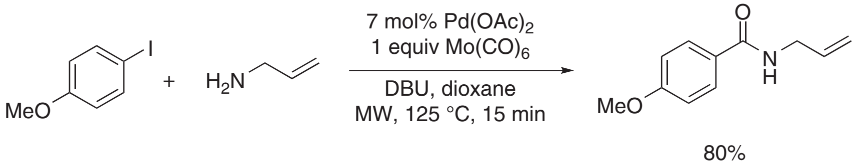
Scheme 1.64 Palladium-catalyzed aminocarbonylation with amides. Source: Modified from Schnyder and Indolese [169].

Beller's group developed several novel methodologies for the primary amides synthesis [170–173]. In the presence of palladium catalysts, aryl halides, phenyl triflates, benzyl chlorides, and even phenols were transformed into the corresponding primary amides in good to excellent yields. Ammonia gas was used directly as an amine source and also as a base. These were the primary reports on using NH_3 and CO for primary amides synthesis (Scheme 1.65).

A microwave-promoted palladium-catalyzed aminocarbonylation of (hetero)aryl halides (X = I, Br, Cl) using $Mo(CO)_6$ and allylamine as a nucleophile was also described [174, 175]. Remarkably, no side products resulting from the competing Heck reaction were detected. Importantly, this was the achievement that

Scheme 1.65 Procedures for carbonylative synthesis of primary amides.

aminocarbonylation was realized on a larger laboratory scale (25 mmol) starting from 4-iodoanisole (Scheme 1.66).



Scheme 1.66 Mo(CO)$_6$-mediated carbonylation of aryl iodides.

1.5.2 Reductive Carbonylations

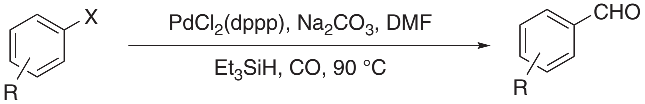
Reductive carbonylation (also called formylation) catalyzed by transition metal offers a straightforward procedure for aryl aldehyde preparation. Starting from the corresponding aryl–X (X = I, Br, Cl, OTf, etc.), in the presence of catalyst and CO, aromatic aldehydes can be easily prepared (Scheme 1.67).

Scheme 1.67 Reductive carbonylation.

The palladium-catalyzed reductive carbonylation reaction was originally discovered by Schoenberg and Heck in 1974 [176]. In the presence of [$PdX_2(PPh_3)_2$] as a catalyst under 80–100 bar of CO/H_2 and at 80–150 °C, aryl and vinyl bromides or iodides were converted into the corresponding aldehydes in 34–95% yields. This pioneering work was improved by using metal hydrides as reducing agents later.

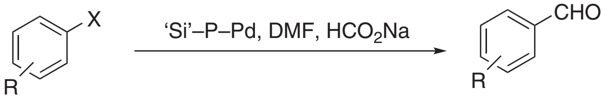
Baillargeon and Stille [177, 178] established the use of tributyltin hydride (Bu_3SnH) in reductive carbonylation reactions. Under mild conditions (50 °C, 1–3 bar CO), aryl iodides, benzylic halides, vinyl iodides, triflates, and allylic halides were successfully carbonylated in 2.5–3.5 h reaction time. Since then, tin hydrides have been applied for reductive carbonylations in several natural product syntheses. Because of the toxicity and waste generation of tin hydrides, it should no longer be used despite the general application of tin hydrides in the past.

Organosilanes [179–181] are certainly a better choice to be based in conjunction with CO. Ashfield and Barnard recently took up this concept by testing the practicability of various R_3SiH systems for assorted known palladium catalysts [182]. When Et_3SiH was used under mild conditions (3 bar CO, 60–120 °C), the $[PdCl_2(dppp)]/DMF/Na_2CO_3$ system produced good results for most of the substrates (Scheme 1.68). In general, the desired aldehydes were obtained in 79–100% yields.



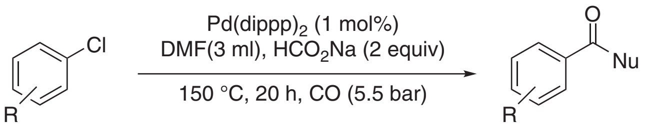
Scheme 1.68 Palladium-catalyzed reductive carbonylation of aryl halides.

The use of readily available and cheap formate salts is an economically attractive variant for performing palladium-catalyzed reductive carbonylations [183, 184]. For example, Cai and his associates developed a silica-supported phosphine palladium complex ("Si"–P–Pd) for the formylation of aryl bromides and iodides with sodium formate (1 bar CO, 90–110 °C) [185]. The polymeric catalyst could be recovered afterward and shown in simple model reactions comparable catalytic activity than homogeneous $PdCl_2(PPh_3)_2$ (Scheme 1.69).



Scheme 1.69 "Si"–Pd-catalyzed reductive carbonylation of aryl halides.

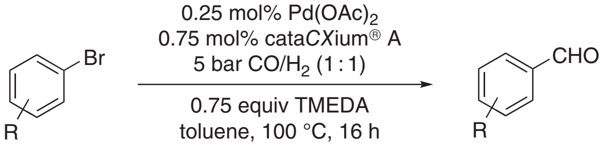
In 1989, Milstein and colleagues realized the reductive carbonylation of aryl chlorides [186]. Under the assistant of $Pd(dippp)_2$ complex, aryl chlorides were transformed into the corresponding aldehydes in good yields in the presence of CO and sodium formate (Scheme 1.70).



Scheme 1.70 Palladium-catalyzed reductive carbonylation of aryl chlorides.

Hydrogen is an inexpensive, atom-economic, and environmentally friendly reductant, and it is desirable to use syngas as a source of CO and H_2 for reductive carbonylation of C–X. Beller's group has developed the general and efficient palladium-catalyzed formylation procedure for the synthesis of aromatic and heteroaromatic aldehydes [187, 188]. Various (hetero)aryl bromides were successfully carbonylated with the cheap and environmentally benign formyl source, synthesis gas, in the presence of $Pd(OAc)_2$/cata*CX*ium A [189] and *N*,*N*,*N*′,*N*′-

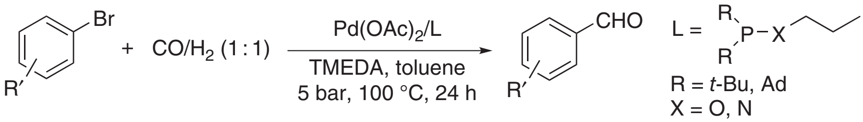
tetramethylethylenediamine at 100 °C (Scheme 1.71). Advantageously, the catalyst system was active at low concentrations (0.25 mol% $Pd(OAc)_2$, 0.75 mol% cata*CX*ium A) and at much lower pressures (5 bar) than those previously reported in the literature. Besides, it was shown that vinyl halides could be formylated under similar conditions to form α, β-unsaturated aldehydes in 41–98% yield [190].



Scheme 1.71 $Pd(OAc)_2$-catalyzed reductive carbonylation.

In 2007, Beller and his colleagues developed the first general palladium-catalyzed carbonylation of aryl triflates with synthesis gas [191]. In contrast to aryl bromides, only the bidentate ligands dppe and dppp led to significant conversion and aldehyde formation. Under mild conditions, various aromatic aldehydes were obtained in a 50–92% yield in the presence of 1.5 mol% $Pd(OAc)_2$, 2.25 mol% dppp, and pyridine in DMF.

Later on, the same group developed an efficient phosphinite ligand for the palladium-catalyzed reductive carbonylation of aryl bromides to aromatic aldehydes based on phosphinite ligands [192]. Several aryl bromides with electron-donating and electron-withdrawing substituents reacted to produce aldehydes in good to excellent yields (Scheme 1.72).



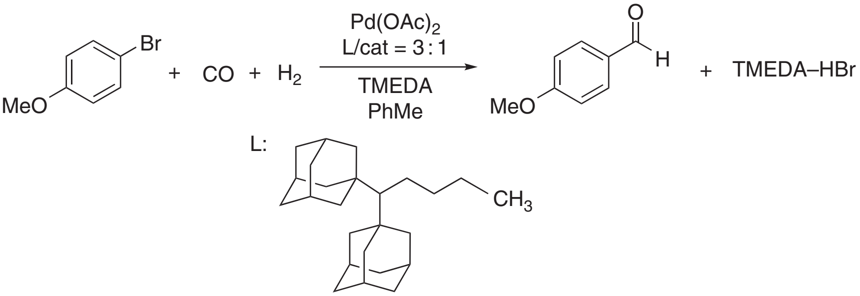
Scheme 1.72 Palladium phosphinite-catalyzed reductive carbonylation of ArBr.

Kappe and coworkers lately developed a continuous-flow protocol for Pd-catalyzed reductive carbonylation of (hetero)aryl bromides to aldehydes, with syngas as an inexpensive, atom-economic, and environmentally friendly source of CO and H_2 [193]. Relatively low catalyst loadings (0.5–1 mol%) and ligand loadings (1.5–3 mol%) provided 55–100% product yields (Scheme 1.73).

Reductive carbonylation offers an interesting pathway for aromatic aldehyde synthesis. Starting from the easily available corresponding parent molecules, aldehydes are selectively produced in good yields. For reductive carbonylation, the choice of hydrogen donor and ligand is important for the success of the transformation.

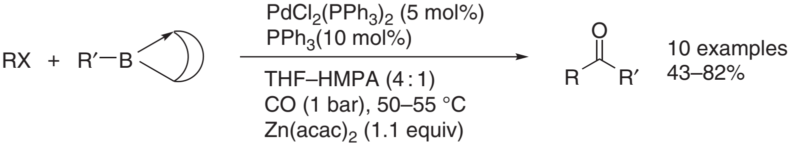
1.5.3 Carbonylative Coupling Reactions with Organometallic Reagents

In carbonylative coupling with organometallic reagent reactions, transmetalation is normally involved in advance of reductive elimination. As early as 1986, Kojima and



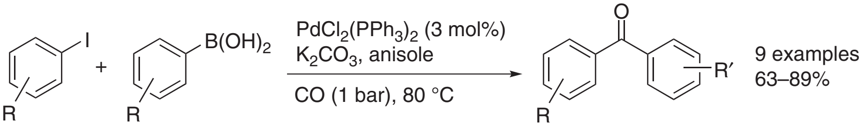
Scheme 1.73 Reductive carbonylation of 4-bromoanisole.

colleagues reported on the carbonylative coupling of aryl iodides or benzyl halides with organoboranes in the presence of dichlorobis(triphenylphosphine)-palladium catalyst [194]. This was the first application of organoboranes in carbonylative coupling reactions mediated by 1.1 equiv of $Zn(acac)_2$ to favor the transmetalation. Various ketones have been produced in good yields starting from aryl iodides and benzyl chloride (Scheme 1.74).



Scheme 1.74 The first Pd-catalyzed carbonylative coupling of organoboranes.

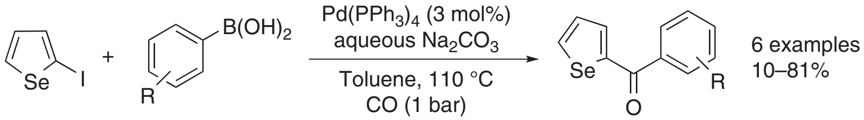
In 1993, Suzuki and colleagues described the palladium-catalyzed carbonylative coupling of aryl iodides with aryl boronic acids [195]. Various diarylketones were produced in high yields (Scheme 1.75). The choice of base and solvent was essential to obtain the desired ketones without biaryl by-products.



Scheme 1.75 Pd-catalyzed carbonylative Suzuki coupling of aryl iodides with aryl boronic acids.

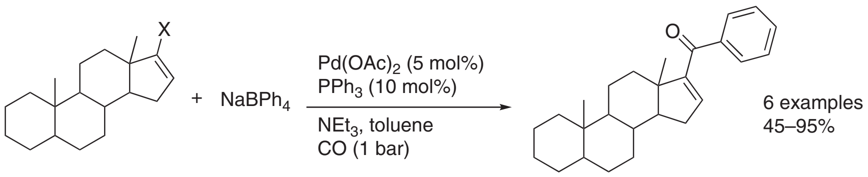
Zeni and colleagues described the coupling of 2-iodoselenophenes with arylboronic acids and CO in 2006 (Scheme 1.76) [196]. Interestingly, the reaction proceeded with aqueous Na_2CO_3 as base under 1 bar of CO. Concerning the variation of arylboronic acids, strong electron-withdrawing substituted or ortho-substituted arylboronic acids gave low or no yields.

Steroidal phenyl ketones were synthesized by Skoda-Foeldes and colleagues via a related carbonylation pathway [197]. The ketones were produced in high yields by



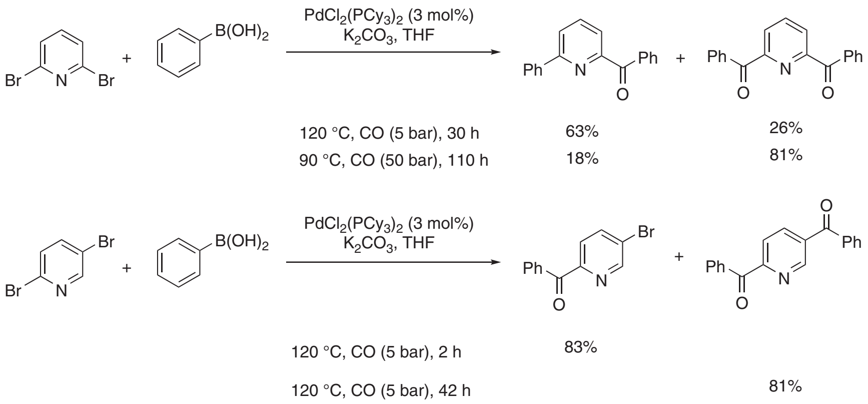
Scheme 1.76 Pd-catalyzed carbonylative coupling of 2-iodoselenophenes. Source: Modified from Prediger et al. [196].

the carbonylation of 17-iodo-androst-16-ene derivatives in the presence of $NaBPh_4$ (Scheme 1.77).



Scheme 1.77 Pd-catalyzed carbonylative synthesis of steroidal ketones.

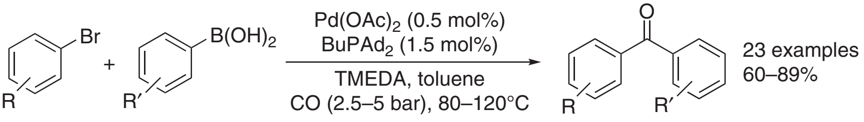
Castanet and his team demonstrated a palladium-catalyzed carbonylative Suzuki reaction of pyridine halides in 2001. Under their conditions, pyridine halides reacted with aryl boronic acids to 2-pyridyl ketones in 81–95%yields (Scheme 1.78). Later on, they extended this methodology to pyridine chlorides by applying an NHC ligand and Cs_2CO_3 as a base [198–201].



Scheme 1.78 Pd-catalyzed Suzuki carbonylation of halopyridines.

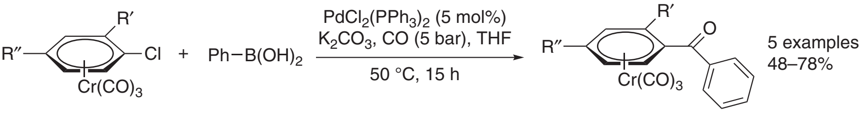
In 2008, Beller's group developed a general method for diaryl ketone synthesis by palladium-catalyzed carbonylative coupling of aryl bromides with arylboronic acids [202]. The combination of $Pd(OAc)_2$ and $BuPAd_2$ allowed the coupling of aryl/heteroaryl bromides with arylboronic acids to produce a wide range of ketones in 60–89% yields (Scheme 1.79).

Schmalz and his colleagues investigated the carbonylative Suzuki reaction of their chloroarene–$Cr(CO)_3$ complexes with phenyl boronic acid [203]. Using



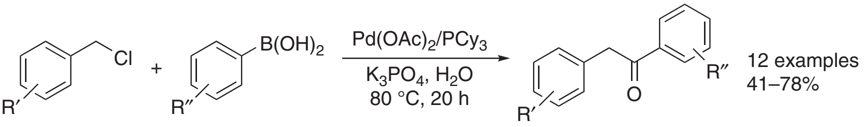
Scheme 1.79 Pd-catalyzed carbonylative Suzuki reaction of aryl bromides.

$PdCl_2(PPh_3)_2$ as a catalyst precursor, benzophenone derivatives were achieved in 48–78% yields (Scheme 1.80).



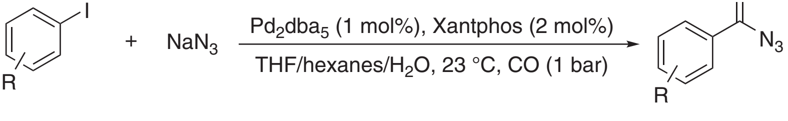
Scheme 1.80 Pd-catalyzed carbonylative coupling of chloroarene–$Cr(CO)_3$ complexes.

Later, Beller and colleagues described a novel carbonylative coupling of benzyl chlorides with aryl boronic acids [204]. This was the first report on carbonylative Suzuki couplings of benzyl chlorides with arylboronic acids (Scheme 1.81). The reaction was carried out using a commercially available $Pd(OAc)_2/PCy_3$ catalyst in the presence of K_2CO_3 and water as the solvent. Twelve ketones have been synthesized in 41–78% yields. Later on, they succeeded in extending their reaction to $ArBF_3K$, a more stable class of borane compounds [205].



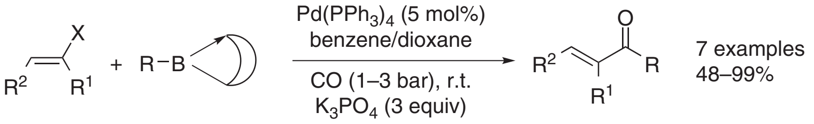
Scheme 1.81 Pd-catalyzed carbonylative Suzuki coupling of aryl boronic acids with hypervalent iodonium salts.

Grushin's team developed a palladium-catalyzed carbonylative coupling of aryl iodides with sodium azide [206]. This catalytic reaction occurs smoothly at temperatures as low as 25–50 °C and 1 bar to cleanly produce aroyl azides from the corresponding aryl iodides, CO, and NaN_3 (Scheme 1.82).



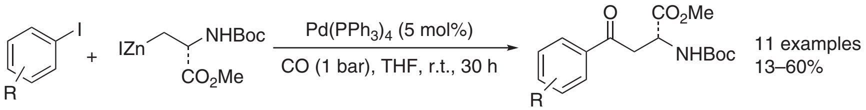
Scheme 1.82 Palladium-catalyzed carbonylative coupling of ArI and NaN_3.

Suzuki and colleagues developed another methodology for the carbonylative coupling of vinyl halides with organoboranes using $Pd(PPh_3)_4$ and K_3PO_4 as a base [207] to synthesize vinyl ketones in moderate to excellent yields (Scheme 1.83).



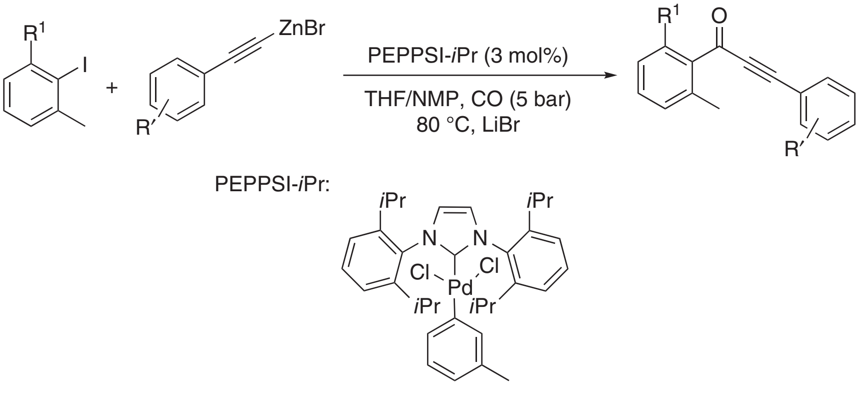
Scheme 1.83 Pd-catalyzed carbonylative Suzuki coupling of organoboranes with vinyl halides.

Jackson and colleagues reported $Pd(PPh_3)_4$ catalyzed an amino acid-derived organozinc reagent with aryl iodides under 1 atm of CO for the synthesis of Kynurenine derivatives [208]. The yields in 13–60% can be obtained at room temperature (Scheme 1.84).



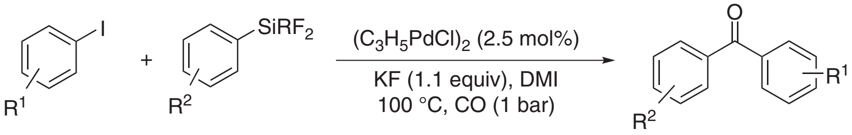
Scheme 1.84 Pd-catalyzed carbonylative coupling of an amino acid-derived organozinc reagent.

In 2008, Martin and colleagues investigated the [1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride (PEPPSI-IPr)-catalyzed carbonylative Negishi coupling of ortho-disubstituted aryl iodides with an alkynyl zinc reagent [209]. Alkynones were produced in 67–79% yields under mild conditions (Scheme 1.85).



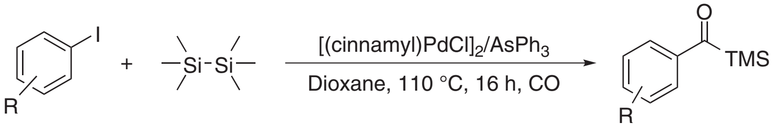
Scheme 1.85 Pd-catalyzed carbonylative Negishi reaction of 2,6-disubstituted aryl iodides.

The first example of Hiyama reactions that palladium-catalyzed C–C bond formation between aryl, alkenyl, or alkyl halides with organosilanes was published in 1989 [210, 211]. In the presence of KF, diaryl ketones were produced in 38–91% yields via the $(C_3H_5PdCl)_2$-catalyzed carbonylative coupling of arylfluorosilanes with aryl iodides (Scheme 1.86).



Scheme 1.86 Pd-catalyzed carbonylative Hiyama coupling of aryl iodides.

In 2012, Beller's group reported Pd-catalyzed reaction of aryl iodides and hexamethyldisilane (HMDS) for the synthesis of acyl silanes [212]. In the presence of 10 bar CO, various benzoyl silanes were produced in 41–88% yields (Scheme 1.87).

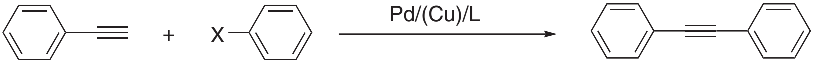


Scheme 1.87 Palladium-catalyzed carbonylative synthesis of acyl silanes.

Aryl iodide, aryl bromide, aryl chloride, and alkenyl halides have been partially discussed. In addition, there are other electrophilic reagents, such as hypervalent iodonium salts [213, 214] and 1-aryltriazene [215], which can also undergo carbonylation with organometallic reagents.

1.5.4 Carbonylative Sonogashira Reactions

The Sonogashira reaction is generally known as a coupling reaction of terminal alkynes with aryl or vinyl halides. This reaction was first reported by Sonogashira and Hagihara in 1975 (Scheme 1.88) [216]. If the Sonogashira reaction is carried out in a CO atmosphere, the reactions are called Carbonylative Sonogashira Reactions, which will give alkynone as an interesting structural motif found in numerous biologically active molecules [217, 218].

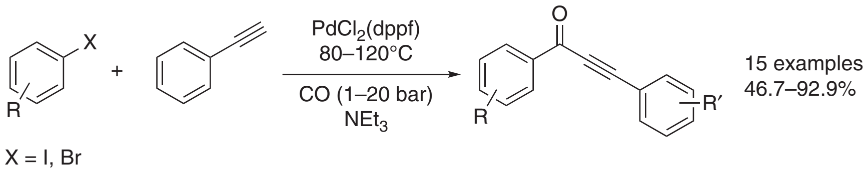


X = I, Br, Cl, OTf, N_2BF_4, etc.

Scheme 1.88 Palladium-catalyzed Sonogashira coupling reaction. Source: Modified from Sonogashira et al. [216].

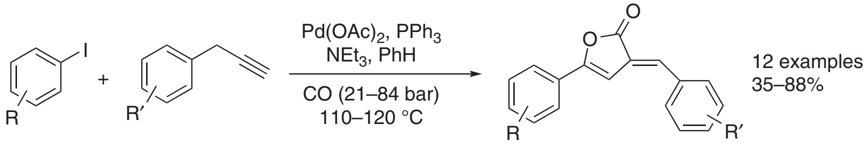
The first palladium-catalyzed carbonylative Sonogashira coupling was reported in 1981 by Kobayashi and Tanaka [219]. Aryl, heterocyclic, and vinylic halides reacted with CO and terminal acetylenes at 120 °C and 80 bar in the presence of NEt_3 and $PdCl_2$(1,1′-bis(diphenylphosphino)ferrocene, dppf) to form alkynones in 46–93% yields (Scheme 1.89).

In 1991, Alper and Huang interestingly described another type of palladium-catalyzed carbonylative Sonogashira coupling of aryl iodides with benzyl acetylenes



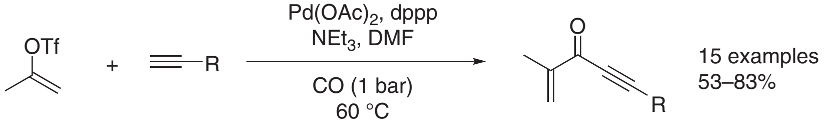
Scheme 1.89 First Pd-catalyzed carbonylative Sonogashira coupling of organic halides.

[220]. In the presence of $Pd(OAc)_2/PPh_3$, aryl iodides and benzyl acetylenes were transformed into furanones in 33–88% yields (Scheme 1.90). Furanones were isolated as the terminal products and not the predicted alkynones.



Scheme 1.90 Pd-catalyzed carbonylation of benzyl acetylenes to fuanones.

Ortar and colleagues published a general procedure for the carbonylative Sonogashira couplings of vinyl triflates with terminal acetylenes in 1991 [221]. Various alkynyl ketones were produced in 53–83% yields (Scheme 1.91).

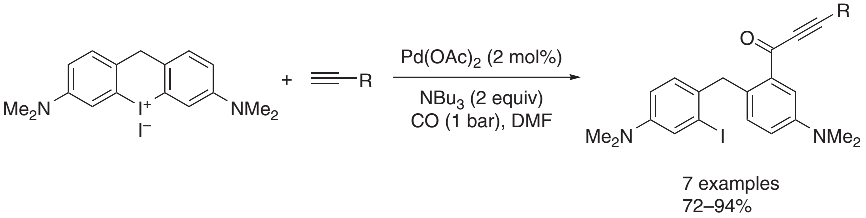


Scheme 1.91 Pd-catalyzed carbonylative Sonogashira coupling of vinyl triflates with 1-alkynes.

The catalytic ability of dimeric palladium hydroxide in carbonylative Sonogashira coupling was demonstrated by Alper and his team in 1994 [222]. Terminal alkynes and alkynols were coupled with aryl iodides in the presence of CO in moderate to good yields.

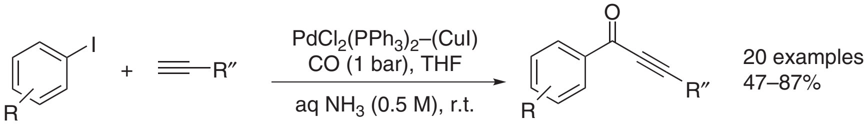
Kang and colleagues described the carbonylative Sonogashira reaction of iodonium salts with terminal alkynes [223]. Both $Pd(OAc)_2$/CuI and $Pd(OAc)_2$ systems alone could be used, and various alkynones were synthesized in 61–89% yields with 1 bar CO at room temperature in aqueous media. In 2001, another example of carbonylative Sonogashira coupling reactions with iodinium iodide and 1-alkynes was published by Ma and colleagues [224]. Under atmospheric pressure of CO, iodine-substituted alkynones were produced in 72–94% yields (Scheme 1.92). Aromatic, aliphatic, and heterocyclic terminal acetylenes can be applied as their substrates.

An interesting room-temperature carbonylation using a palladium/copper-catalyst system was published by Mori and Ahmed in 2003 [225–227]. As shown in



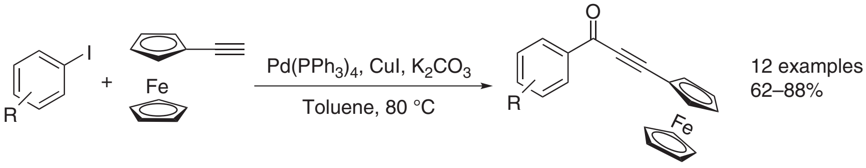
Scheme 1.92 Pd-catalyzed carbonylative Sonogashira coupling of iodinium iodide.

Scheme 1.93, various aromatic alkynones were produced in 47–87% yields using aqueous ammonia as a base.



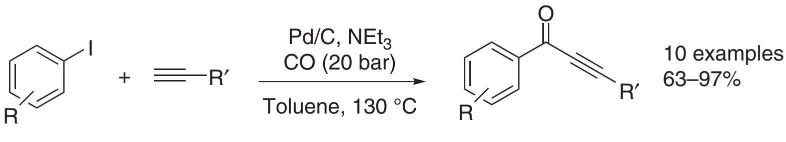
Scheme 1.93 Carbonylative room-temperature Sonogashira reaction in aqueous ammonia.

In 2006, Chen and his colleagues described a convenient, effective method for the carbonylative Sonogashira coupling of aryl iodides with ethynyl ferrocene under one atmosphere of CO [228]. Various aryl ferrocenylethynyl ketones have been synthesized in a 62–88% yields (Scheme 1.94).



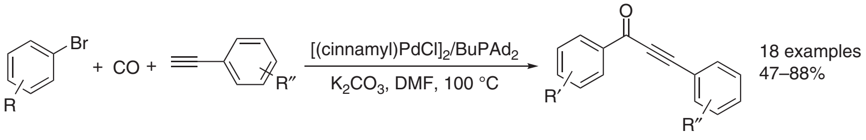
Scheme 1.94 Pd-catalyzed carbonylative Sonogashira coupling of ethynyl ferrocene with aryl iodides.

In 2008, Xia and Chen described a recyclable phosphine-free catalyst system for alkynone synthesis [229]. Using palladium on charcoal (Pd/C) and NEt_3, the carbonylative Sonogashira coupling of aryl iodides with alkynes was smoothly carried out and the desired products were isolated in 63–97% yields (Scheme 1.95). Pd/C could be recycled at least 10 times with only a slight decrease in efficiency.



Scheme 1.95 Pd/C-catalyzed carbonylative Sonogashira reaction of aryl iodides.

In 2010, Beller's group discovered a general and convenient palladium-catalyzed carbonylative Sonogashira coupling of aryl bromides [230]. The key to success was the application of $BuPAd_2$ (di-1-adamantyl-*n*-butylphosphine) as a ligand in the presence of K_2CO_3. Alkynones have been generated in 47–88% yields from the corresponding aryl bromides and terminal alkynes (Scheme 1.96).



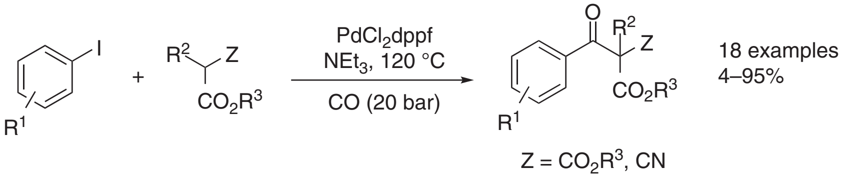
Scheme 1.96 Pd-catalyzed carbonylative Sonogashira coupling of aryl bromides.

In 2019, Li and Zhang reported $PdCl_2(PPh_3)_2$-catalyzed carbonylative Sonogashira coupling in tandem with double annulation reaction to synthesize benzannulated [6,6]-spiroketals [231]. Under mild conditions (under 1 atm pressure of CO at room temperature), a wide range of benzannulated [6,6]-spiroketals in 45–90% yields can be obtained with good functional group tolerance and excellent diastereoselectivities (dr > 20 : 1).

1.5.5 Carbonylative C–H Activation Reactions

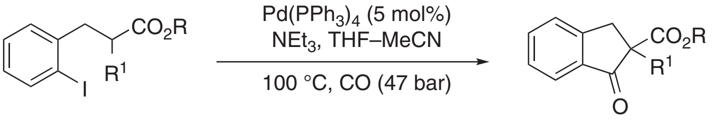
Transition metal-catalyzed carbonylation reactions represent an enormous toolbox for CO–X bond formation (X = C, N, O, etc.). While most coupling reactions take place with heteronucleophiles nowadays, carbonylations including C–H activation are attracting more and more attention because the use of stoichiometric amounts of organometallic reagents can be avoided.

In 1986, Kobayashi and Tanaka published the first report of carbonylative C–H activation by $PdCl_2$ [232]. In the presence of NEt_3 under 20 bar of CO, the carbonylation of organic halides with activated methylene compounds produces various ketones in 4–95% yields (Scheme 1.97).



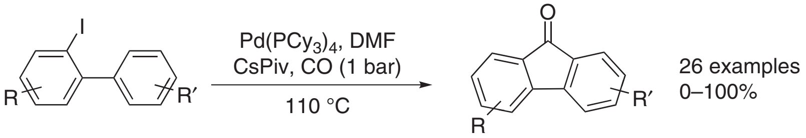
Scheme 1.97 Pd-catalyzed carbonylative coupling with activated methylene compounds.

Later on, Negishi and colleagues reported intramolecular coupling reactions of internal enolates [233] and five- or six-membered rings were synthesized by using the carbonylative C–H activation methodology (Scheme 1.98). In 1998, this group proved that the same reaction can also be catalyzed by $Cl_2Ni(PPh_3)_2$, $Ni(COD)_2$, or Li_2CuCl_4 [234].



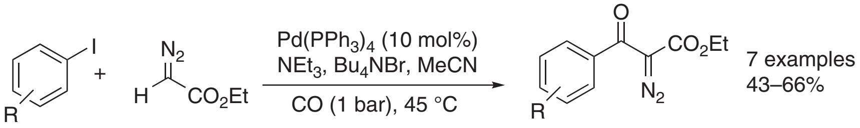
Scheme 1.98 Pd-catalyzed intramolecular carbonylative C–H activations.

In 2002, Larock and Campo reported the palladium-catalyzed cyclocarbonylation of *o*-halobiaryls [235, 236], giving various substituted fluorenones in high yields (Scheme 1.99). The authors succeeded in extending the reaction to polycyclic fluorenones, fused isoquinoline, indole, pyrrole, thiophene, benzothiophene, and benzofuran rings.



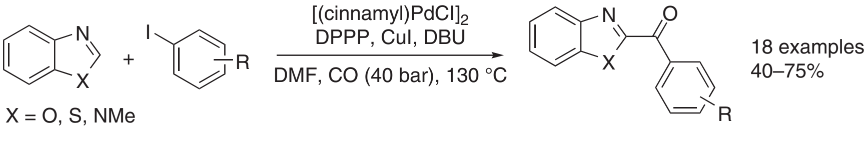
Scheme 1.99 Pd-catalyzed carbonylative synthesis of fluorenones.

In 2007, Wang and his team found the Pd(PPh$_3$)$_4$-catalyzed coupling of aryl or vinyl iodides with ethyl diazoacetate [237]. Under 1 bar CO, the products yielded in 43–66% at 45 °C. It was the first example of using α-diazocarbonyl compounds as a coupling partner in a palladium-catalyzed carbonylation reaction (Scheme 1.100).



Scheme 1.100 Pd-catalyzed carbonylative coupling reactions of aryl iodides with α-diazocarbonyl compound.

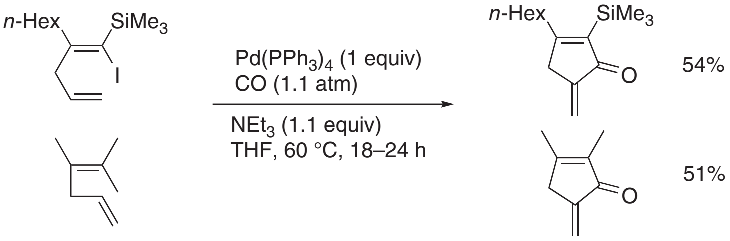
In 2010, Beller's group developed an efficient methodology for the carbonylative coupling between aryl iodides and heteroarenes [238]. In the presence of a Pd/Cu system, using various aryl iodides and different heterocycles, such as oxazoles, thiazoles, and imidazole, the corresponding coupling products are obtained in 40–75% yields at 130 °C (Scheme 1.101). This is the first carbonylative C–H activation reactions of heteroarenes to form diarylketones.



Scheme 1.101 Pd-catalyzed carbonylative coupling of ArI with heteroarenes.

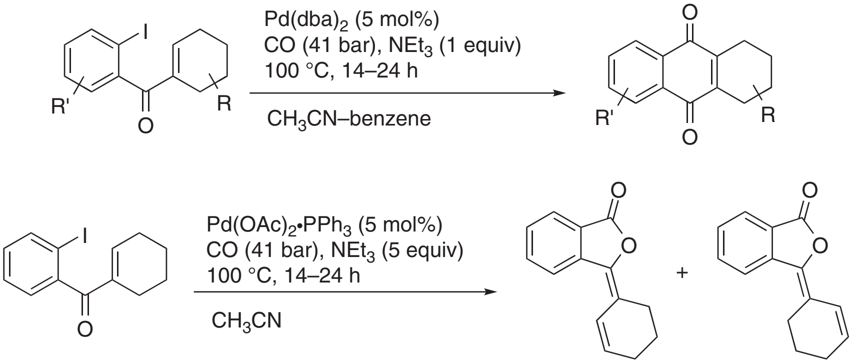
1.5.6 Carbonylative Heck Reactions

The catalytic insertion of olefins into acylpalladium complexes is called a "Carbonylative Heck reaction." The first palladium-catalyzed copolymerization of CO with olefins was described in 1982 [239], and as a consequence, carbonylative coupling reactions with alkenes were reported soon after. In 1983, Negishi and Miller discovered two examples of intramolecular carbonylative Heck reactions of 1-iodopenta-1,4-dienes by applying $Pd(PPh_3)_4$ [240]. 5-Methylenecyclopent-2-enones as the products were produced in moderate yields (Scheme 1.102).



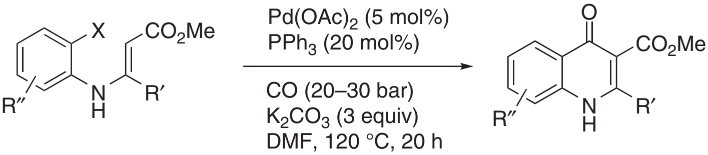
Scheme 1.102 The first examples of palladium-mediated intramolecular carbonylative Heck reactions.

Negishi synthesized various quinones using *o*-iodoaryl cyclohexyl ketones as the starting materials [241]. In the presence of bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) as a catalyst (5 mol%) and under CO pressure (41 bar), quinones were produced in good yields with 100% regioselectivity (Scheme 1.103). In this catalytic system, 58% of furanones were formed instead of quinones if $Pd(OAc)_2/PPh_3$ was used. In 1996, this group published a full account using various vinyliodides [242–244].

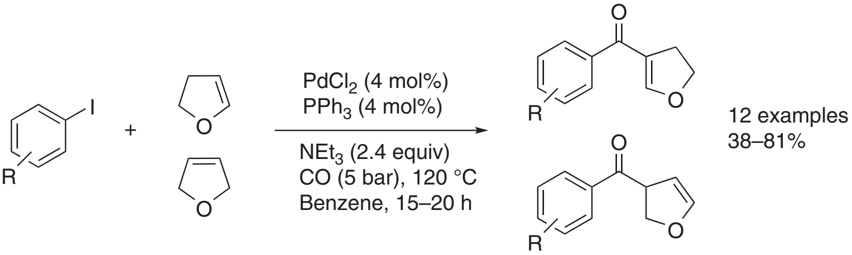


Scheme 1.103 First palladium-catalyzed intramolecular carbonylative Heck reaction.

Notably, Torii and colleagues reported the intramolecular carbonylative Heck coupling of 3-(2-haloarylamino)prop-2-enoates to the corresponding quinolinone



Scheme 1.104 Palladium-catalyzed carbonylative Heck reaction to quinolinones.

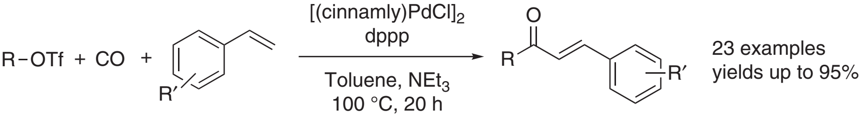


Scheme 1.105 Palladium-catalyzed carbonylative cross-coupling of ArI with cyclic olefins.

derivatives [245]. In the presence of a catalytic amount of $Pd(OAc)_2$ under 20 bar of CO at 120 °C, quinolinones were synthesized in good yields (Scheme 1.104).

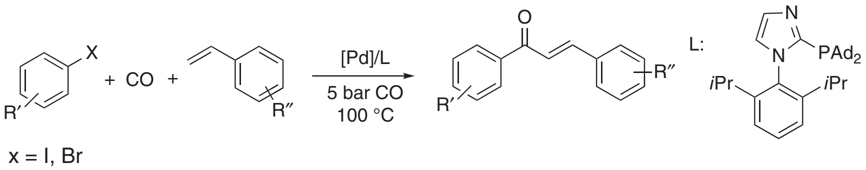
In 1995, Miura and colleagues described a palladium-catalyzed carbonylative cross-coupling of aryl iodides with five-membered cyclic olefins [246]. This represents the first palladium-catalyzed intermolecular carbonylative cross-coupling of aryl iodides with olefins. Various benzoylated cyclic olefins were isolated in 38–81% yields (Scheme 1.105).

In 2010, Beller's group reported carbonylative Heck couplings of aryl triflates with styrenes that is a general intermolecular carbonylative coupling of aryl halides or triflates with terminal olefines [247]. The corresponding unsaturated ketones can be obtained in good yields starting from easily available aryl and alkenyl triflates (Scheme 1.106).



Scheme 1.106 Palladium-catalyzed carbonylative Heck reaction of ArOTf with styrenes.

Then, Beller's group developed a more general $[(cinnamyl)PdCl]_2$-catalyzed carbonylative Heck reaction of aryl halides [248]. Various aromatic and aliphatic alkenes were used successfully in this system for the first time, and 41–90% yields of the corresponding a,b-unsaturated ketones were obtained. When using aryl iodides and bromides, interesting building blocks were obtained at 100 °C (Scheme 1.107).



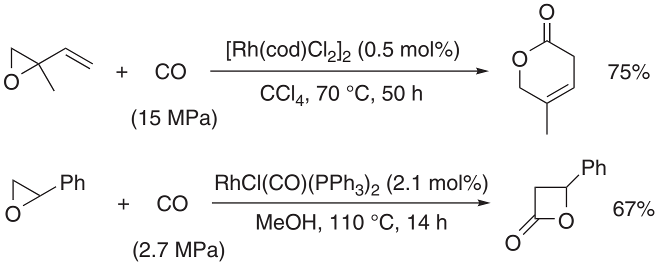
Scheme 1.107 Palladium-catalyzed carbonylative Heck reaction of aryl halides.

1.6 Carbonylation of Epoxides

Carbonylation of epoxides provides direct access to a large variety of hydroxy carbonyl compounds, such as β-lactones, useful synthons in organic synthesis, and poly(3-hydroxyalkanoate), important biodegradable polyesters. Thus, the development of efficient catalysts for such carbonylations has been widely studied.

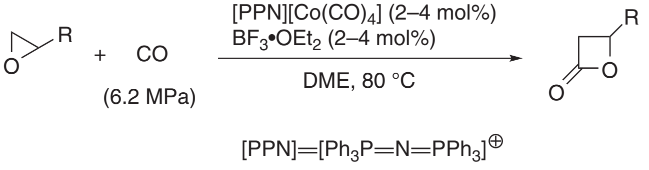
1.6.1 Ring-expansion Carbonylation of Epoxides

The first successful example of a catalytic ring-expansion carbonylation was reported by Aumann and coworkers in 1970s [249, 250]. Isoprene oxide was allowed to react with CO in the presence of $[Rh(cod)Cl]_2$ to give lactone 67–75% yields (Scheme 1.108).



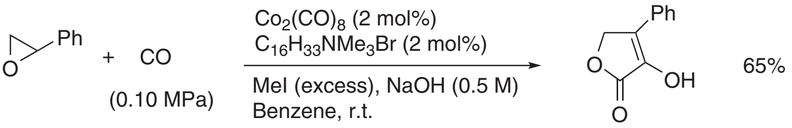
Scheme 1.108 Catalytic ring-expansion carbonylation.

Alper and coworkers reported the regioselective carbonylation of epoxides by using $[PPN][Co(CO)_4]$ [PPN = bis(triphenylphosphine)iminium] in conjugation with a Lewis acid such as $BF_3{\cdot}OEt_2$ or $SnCl_4$ in DME (Scheme 1.109) [251].



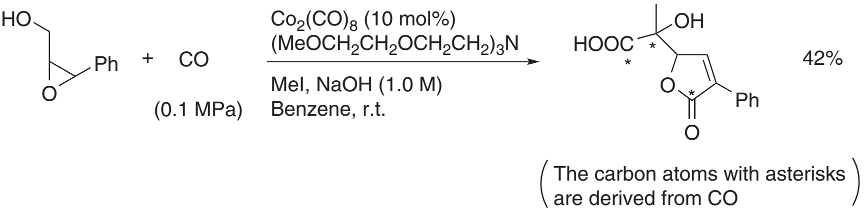
Scheme 1.109 Regioselective carbonylation of epoxides. Source: Modified from Lee et al. [251].

Two molecules of CO were successively incorporated into an epoxide in the presence of a cobalt catalyst and a phase transfer agent [252]. When styrene oxide was treated with CO (0.1 MPa), excess methyl iodide, NaOH (0.50 M), and catalytic amounts of $Co_2(CO)_8$ and hexadecyltrimethylammonium bromide in benzene, 3-hydroxy-4-phenyl-2(5*H*)-furanone was produced in 65% yield (Scheme 1.110).



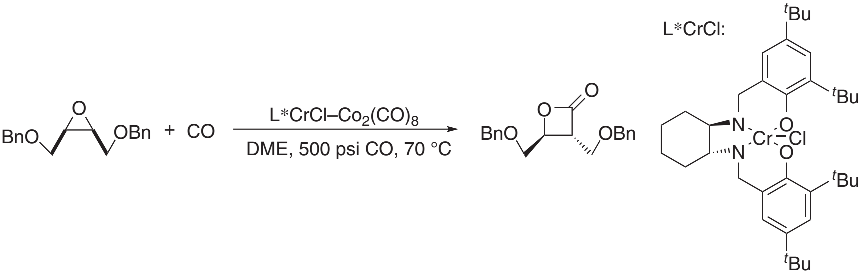
Scheme 1.110 $Co_2(CO)_8$-catalyzed ring-expansion carbonylation.

Alper et al. reported intramolecular cyclization results in the production of 2(5*H*)-furanone and the regeneration of the acylcobalt complex. Furthermore, triple carbonylation proceeded by employing 2-aryl-3-(hydroxymethyl)oxiranes as substrates and tris(3,6-dioxaheptyl)amine as a phase transfer catalyst (Scheme 1.111) [253].



Scheme 1.111 Production of 2(5*H*)-furanone. Source: Modified from Alper et al. [253].

In 2012, Ibrahim and coworker described the first asymmetric ring-expansion carbonylation of *meso*-epoxides by using L*CrCl–$Co_2(CO)_8$ (Scheme 1.112) [254]. Under 500 psi pressure of CO, the corresponding β-lactones in 47–94% yields with up to 56% ee can be obtained at 70 °C.

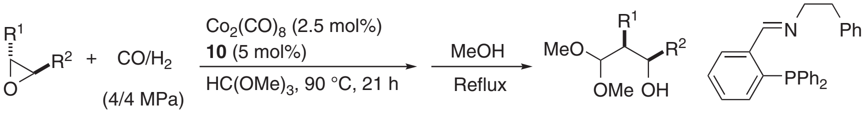


Scheme 1.112 L*CrCl−$Co_2(CO)_8$-catalyzed asymmetric ring-expansion carbonylation. Source: Ganji and Ibrahim [254].

1.6.2 Hydroformylation and Silylformylation of Epoxides

Hydroformylation of ethylene oxide is attractive in industry because hydrogenation of the product 3-hydroxypropanal gives 1,3-propane diol which is an intermediate in the production of polyester fibers and films. To achieve this reaction, many catalysts have been employed [255–257].

A successful example of protection of the resulting formyl group is the cobalt-catalyzed hydroformylation of epoxides in the presence of trimethyl orthoformate reported by Nozaki. The product β-hydroxyaldehydes were converted into its dimethyl acetal forms [258]. Under this catalyst system, hydroformylation–acetalization of epoxides in $HC(OMe)_3$ produces in 13–74% yield (Scheme 1.113).



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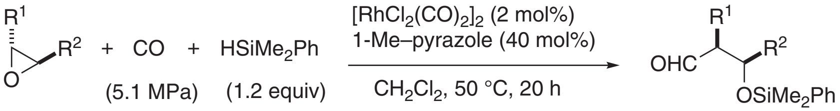
Scheme 1.113 Cobalt-catalyzed hydroformylation of epoxides.

Silylformylation is another successful catalytic formylation of epoxides involving the in situ protection of functional group. As a hydrosilane is deemed to behave much like molecular hydrogen, formylation of epoxides can be carried out using a hydrosilane in place of hydrogen to give β-siloxyaldehydes [259–262].

Murai and coworkers reported silylformylation of epoxides by using rhodium catalysts [261]. Under the optimized conditions ($[RhCl(CO)_2]_2$: 2 mol%, 1-methylpyrazole: 40 mol%, CO: 5.1 MPa, $HSiMe_2Ph$: 1.2 equiv, CH_2Cl_2, 50 °C, 20 h), a wide range of epoxides were formylated in good yields (Scheme 1.114).

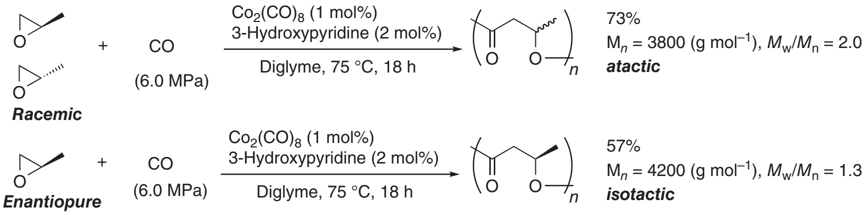


Scheme 1.114 Rhodium-catalyzed silylformylation of epoxides.

1.6.3 Alternating Copolymerization of Epoxides

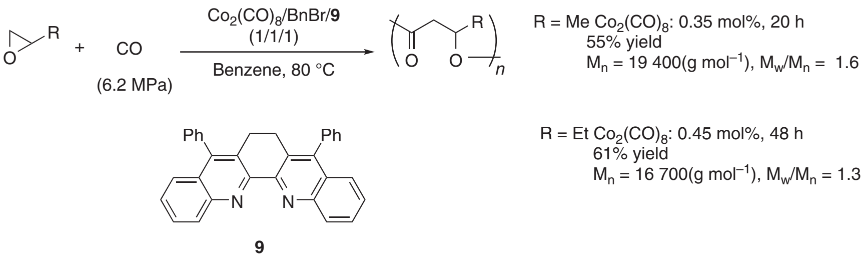
The alternating copolymerization of epoxides with CO, which was first reported by Furukawa et al. in 1965 [263], should be a more efficient and direct route to produce them.

Rieger and coworkers [264–266] and Osakada and coworkers [267] independently studied the alternating copolymerization of epoxides with CO by using $Co_2(CO)_8$/3-hydroxypyridine catalyst system, which was originally discovered by Drent and coworker [268]. The copolymerization of propylene oxide with CO proceeded with high regioselectivity to give poly(3-hydroxybutyrate). Racemic propylene oxide gave atactic polyester, while enantiomerically pure (*S*)-propylene oxide afforded isotactic polyester with retention of configuration (Scheme 1.115), indicating the ring-opening at the less hindered epoxide carbon through the back-side attack by the tetracarbonyl cobaltate.



Scheme 1.115 Copolymerization of epoxides with CO.

An equimolar mixture of $Co_2(CO)_8$, benzyl bromide (BnBr), and dihydro-1,10-phenanthroline **9**, which generated $BnCOCo(CO)_4$ under the reaction conditions, copolymerized propylene oxide or 1,2-epoxybutane with CO to give the corresponding atactic polyesters with high regioregularities, perfectly alternating structures, and high molecular weights (Scheme 1.116) [269].



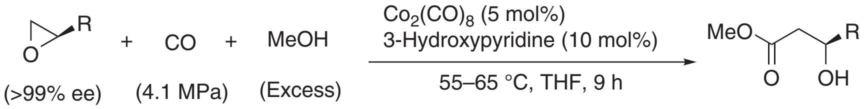
Scheme 1.116 Copolymerized propylene oxide or 1,2-epoxybutane with CO. Source: Modified from Lee and Alper [269].

1.6.4 Alkoxycarbonylation and Aminocarbonylation of Epoxides

Carbonylation of epoxides in the presence of an alcohol gives β-hydroxyesters has been known for a long time [270, 271]. In 1961, Howard prepared methyl/3-hydroxybutyrate by alkoxycarbonylation of propylene oxide with $Co_2(CO)_8$ catalyst. The catalyst system requires 3500 psi pressure, high temperature, and the methyl/3-hydroxybutyrate yields up to 40%.

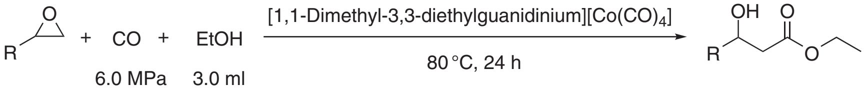
In 1999, Jacobsen and coworker demonstrated that methoxycarbonylation of epoxides proceeds effectively under relatively mild conditions (55–65 °C) by using $Co_2(CO)_8$/3-hydroxypyridine catalyst system in the presence of methanol (Scheme 1.117) [272]. The high yields in 86–91% and high enantioselectivities (ee > 99%) were obtained.

In 2017, Liu and coworkers reported [1,1-dimethyl-3,3-diethylguanidinium] [$Co(CO)_4$]-catalyzed alkoxycarbonylation of terminal epoxides to β-hydroxy esters



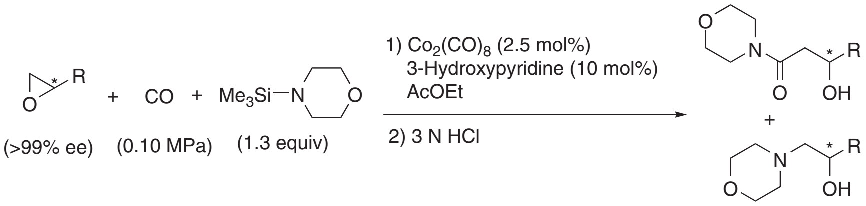
Scheme 1.117 Methoxycarbonylation of epoxides. Source: Modified from Hinterding and Jacobsen [272].

(Scheme 1.118) [273]. Under 6 MPa CO and at 80 °C for 24 h, the corresponding β-hydroxy esters with up to 92% isolated yield can be obtained. This catalyst can be reused for six times without loss of activity.



Scheme 1.118 Ethoxycarbonylation of terminal epoxides. Source: Modified from Zhang et al. [273].

Aminocarbonylation can also be carried out by use of CO and a silyl amide. Watanabe and coworkers reported the cobalt-catalyzed aminocarbonylation of epoxides [274]. Some silyl amides such as $PhCH_2NHSiMe_3$ and Et_2NSiMe_3 were applicable to the reaction to give the β-siloxyamide in 30–80% yields, whereas high reaction temperature (100–160 °C) was required. The use of 4-(trimethylsilyl) morpholine was found to be crucial for a milder (25–50 °C) and more efficient carboamination (56–85%): the reaction proceeded at ambient temperature under 0.1 MPa of CO (Scheme 1.119) [275].



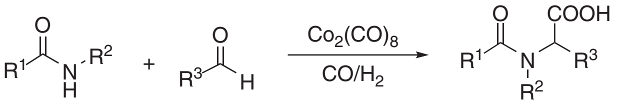
Scheme 1.119 Cobalt-catalyzed aminocarbonylation of epoxides. Source: Modified from Goodman and Jacobsen [275].

1.7 Carbonylation of Aldehydes

Carbonylations of aldehydes incorporate an inexpensive source of carbon, CO, and can convert ubiquitously available aldehydes into various synthetically useful functionalities.

1.7.1 Amidocarbonylations of Aldehydes

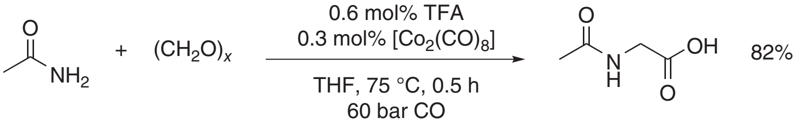
As early as in 1971, Wakamatsu et al. described amidocarbonylation reaction of aldehydes and amides in the presence of CO for the synthesis of *N*-acyl-α-amino acids



Scheme 1.120 Amidocarbonylation of aldehydes. Source: Wakamatsu et al. [276]; Wakamatsu et al. [277].

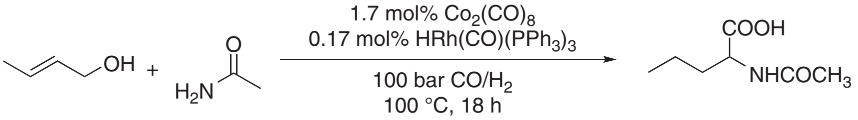
(Scheme 1.120) [276, 277]. Under $Co_2(CO)_8$ catalyst system, the products yielded in 26–80% at 110–150 °C.

Lin and coworkers reported the catalytic performance of various cobalt/ligand systems in the synthesis of *N*-acetylglycine. Basic phosphines, such as PBu_3, were shown to allow low-pressure conditions (55 bar). The addition of Ph_2SO or succinonitrile resulted in improved selectivity and facilitated the catalyst recovery [278, 279]. The addition of acid cocatalysts ($pK_a < 3$, e.g., trifluoroacetic acid [TFA]) allowed for low-temperature conditions and absence of hydrogen [280] (Scheme 1.121).



Scheme 1.121 Acid cocatalyst obviates the need for H_2.

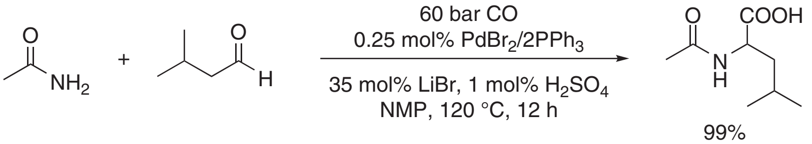
The in situ generation of the aldehyde can be achieved by a preceding rearrangement of epoxides and allyl alcohols. Ojima et al. demonstrated the use of styrene oxide and propene oxide in the presence of $[Ti(O\textit{i}Pr)_4]$ or $[Al(O\textit{i}Pr)_3]$ as cocatalysts [281]. The transition metal-mediated isomerization of allylic alcohols ($HRh(CO)(PPh_3)_3$, $Fe_2(CO)_9$, $RuCl_2(PPh_3)_3$, $PdCl_2(PPh_3)_2$) was also shown compatible with amidocarbonylation conditions (Scheme 1.122) [282].



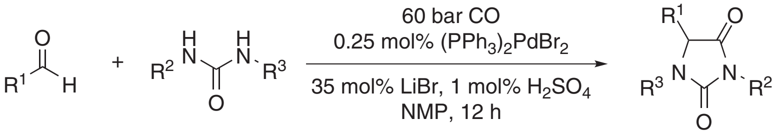
Scheme 1.122 Domino isomerization–amidocarbonylation of allylic alcohols. Source: Modified from Hirai et al. [282].

In 1997, Beller's group found that $PdBr_2/2PPh_3$ is a capable catalysts for the amidocarbonylation of aldehydes. This reaction was typically run at 80–120 °C and 30–60 bar CO. Under optimized conditions, the desired *N*-acyl-α-amino acids could be afforded with TON up to 60 000 (Scheme 1.123) [283, 284].

Later, Beller et al. developed the ureidocarbonylation reaction that provides access to hydantoins containing diverse substituents in the 1-, 3-, and 5-positions (Scheme 1.124) [285]. Under 60 bar CO and 80–130 °C, the isolated products can be obtained in 39–93% yields with TON up to 356.

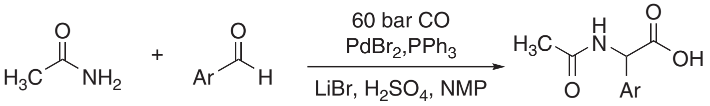


Scheme 1.123 Palladium-catalyzed amidocarbonylation of isovaleraldehyde. Source: Beller et al. [283]; Beller et al. [284].



Scheme 1.124 Palladium-catalyzed ureidocarbonylation.

The one-pot amidocarbonylation of commercially more attractive nitriles can be performed via preceding nitrile hydrolysis in HCl/HCO_2H [286, 287]. Systematic studies have shown that amidocarbonylation of benzaldehydes in the presence of palladium catalysts allows for the synthesis of functionalized, racemic *N*-acetyl-α-arylglycines (Scheme 1.125) [288].



Scheme 1.125 Palladium-catalyzed amidocarbonylation of benzaldehydes. Source: Modified from Beller et al. [285].

1.7.2 Hydroformylation and Silylformylation of Aldehydes

Chan found rhodium/phosphine catalysts and the presence of catalytic amounts of an amine to enhance the catalyst activity most effectively [289]. The nature of the employed ligand (e.g., PPh_3, $(p\text{-}CF_3C_6H_4)_3P$) and base (e.g., NEt_3, py) must be carefully balanced in order to facilitate deprotonation of the hydridorhodium species and prevent base-promoted aldol condensation of glycolaldehyde. Pyridines as solvents greatly enhanced the activity and selectivity of the catalyst, and with pyridines immiscible with water (4-pentylpyridine), 99% of the desired glycolaldehyde could be extracted into the aqueous phase (Scheme 1.126) [290].

$$CH_2O \xrightarrow[\text{90 bar CO/H}_2\text{ (1/2), 70 °C, 6 h}]{\text{0.25 mol\% RhCl(CO)(PPh}_3)_2,\ \gamma\text{-picoline}} \underset{95\%}{HOCH_2CHO}$$

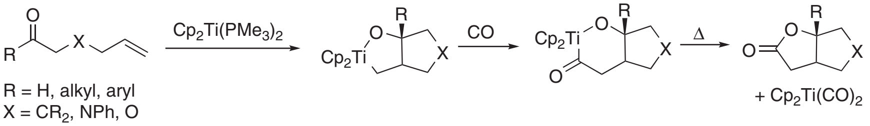
Scheme 1.126 Hydroformylation of formaldehyde. Source: Modified from Okano et al. [290].

Murai et al. reported the direct silylformylation of aliphatic aldehydes (threefold excess) with diethylmethylsilane and CO in the presence of catalytic $Co_2(CO)_8/PPh_3$

to afford α-siloxyaldehydes in moderate yields (100 °C, benzene) [291]. Wright and coworker demonstrated the superior selectivity of a rhodium-catalyzed variant [292]. With 0.5 mol% $[(cod)RhCl]_2$ and Me_2PhSiH, the silylformylation of aliphatic and aromatic aldehydes affords high yields of the α-siloxyaldehydes. The mild reaction conditions (17 bar CO, room temperature) permit discrimination of the starting aldehyde from the newly formed and bulkier siloxyaldehyde.

1.7.3 Hetero Pauson–Khand Reactions of Aldehydes

Hetero PKRs with an aldehyde or ketone component have been shown to afford synthetically versatile γ-butyrolactones. Buchwald and coworkers [293] and Crowe and coworker [294] independently showed that aliphatic enones and enals react with CO under $Cp_2Ti(PMe_3)_2$ mediation (Scheme 1.127). CO insertion and thermal (or oxidative) decomposition gave diastereomerically pure bicyclic γ-butyrolactones and stable $Cp_2Ti(CO)_2$. Imines did not react under the reaction conditions.



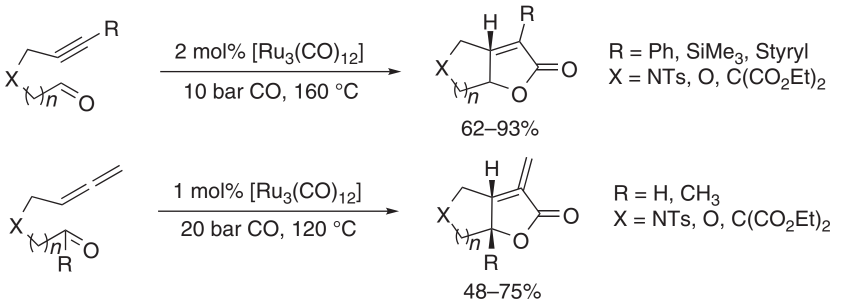
Scheme 1.127 Titanium-mediated hetero Pauson–Khand reaction.

o-Allyl acetophenones have been found capable of displacing CO on $Cp_2Ti(CO)_2$ via electron transfer processes and thus allowing catalytic reactions [295]. While the strong Ti–O bond renders a catalytic reaction difficult in most cases, the use of a late transition metal facilitates the realization of catalytic protocols. Murai reported on the cyclocarbonylation of ynals with CO to give bicyclic lactones in the presence of 2 mol% $Ru_3(CO)_{12}$. Two alternative mechanisms have been discussed, one commencing with oxidative addition of the aldehyde–CH bond to Ru, while the other involves the intermediacy of a metallacycle [296]. Kang et al. developed a related reaction with allenyl aldehydes with CO to afford α-methyl-γ-butyrolactones in good yields (Scheme 1.128) [297].

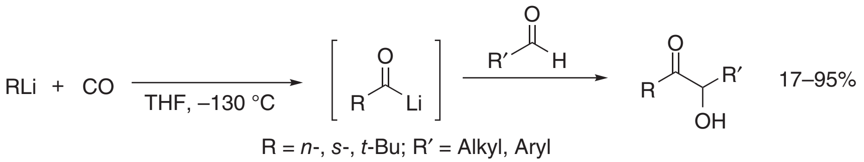
1.7.4 Reactions of Aldehydes with Acylanions

While various CO-free Umpolung approaches utilize the intermediacy of masked acylanion equivalents, alkyllithium species have been shown to undergo selective carbonylation at low temperatures (<−110 °C) to form acylanions. Such in situ prepared acyllithium species have been demonstrated as versatile reagents for the direct nucleophilic acylation of aldehydes [298, 299]. The resultant acyloins were obtained in good yields from reactions of *s*- and *t*-BuLi with aliphatic and aromatic aldehydes (<95%, Scheme 1.129).

Stable acylzirconocene chloride has been utilized by Hanzawa and coworkers [300] for the synthesis of α-hydroxy ketones. Consecutive hydrozirconation of

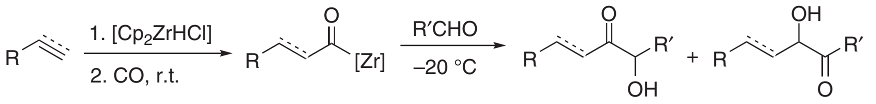


Scheme 1.128 Ruthenium-catalyzed hetero Pauson–Khand reactions with alkynes and allenes. Source: Modified from Kang et al. [297].



Scheme 1.129 Acyllithium addition to aldehydes.

terminal alkenes or alkynes with Schwartz's reagent and in situ carbonylation with gaseous CO at room temperature afford acylzirconocene chloride. The yields of addition reactions to aldehydes were strongly dependent on the presence of a Lewis acid. Interestingly, the isomeric α-ketol was obtained in some reactions with alkenes when $BF_3 \cdot OEt_2$ was used (Scheme 1.130).



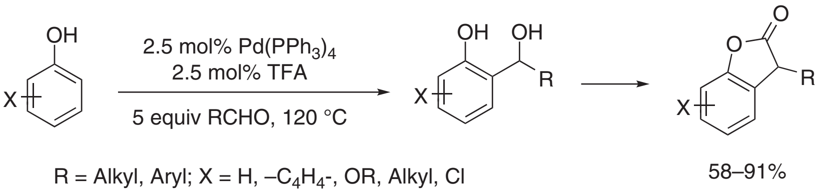
Scheme 1.130 Acylzirconocene addition to aldehydes.

1.7.5 Miscellaneous of Aldehydes

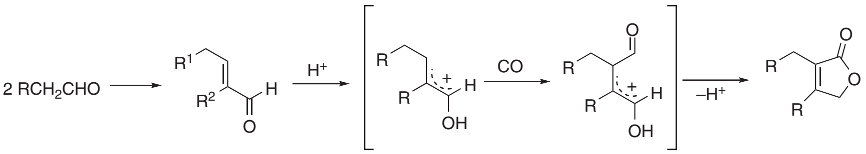
The three-component synthesis of benzo and naphthofuran-2(3*H*)-ones from the corresponding aromatic alcohol (phenols or naphthols) with aldehydes and CO (5 bar) can be performed under palladium catalysis (Scheme 1.131) [301, 302].

Woo showed that α,β-unsaturated aldehydes can be carbonylated in conc. H_2SO_4 to give 3,4-dialkyl-2(5*H*)-furanones (70 bar CO, 50 °C) [303]. Although carbonylation occurs in conjugate fashion, secondary intramolecular carbonylation of the aldehydeoxygen results in the formation of the furanone ring. Simple aldehydes can be converted to α,β-unsaturated aldehydes by rapid aldol condensation under the acidic reaction conditions and give only slightly lower yields (Scheme 1.132).

Toniolo and coworker reported the carbonylation of aromatic aldehydes containing electron-donating substituents with a Pd/PPh_3 catalyst system in the presence of HCl to give phenylacetic acid derivatives [304]. No activity was observed in the



Scheme 1.131 Cyclocarbonylation to furanones. Source: Satoh et al. [301]; Satoh et al. [302].



Scheme 1.132 Acid-mediated conjugate carbonylation.

absence of PPh_3 or HCl, and high yields could be achieved with alkanols as a solvent (e.g., EtOH). After decarboxylation of the resultant phenylmalonate, the desired phenylacetic acid derivative in 70–75% yield can be obtained.

1.8 Oxidative Carbonylation Reaction

Oxidative carbonylations have acquired a growing importance during the last few years, owing to the development of new and selective catalytic systems, mainly based on palladium, which are able to promote ordered sequences of transformations under mild conditions with formation of highly functionalized carbonyl compounds in one step starting from simple building blocks [305–307].

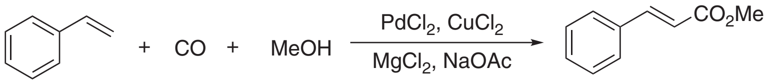
1.8.1 Oxidative Carbonylation of Alkenes

In 1963, Tsuji et al. reported the reaction of olefin–palladium chloride complexes with CO and alcohols to produce β-chloroacyl chlorides for the first time [308, 309]. Using internal and terminal aliphatic olefins under 4–10 MPa CO pressure, the corresponding chloroesters in 5–41% yields were transformed.

In 1969, Yukawa and Tsutsumi reported the reaction of a styrene–palladium complex with CO in alcohols [310]. Various cinnamates and phenylsuccinates were synthesized with up to 41% yield.

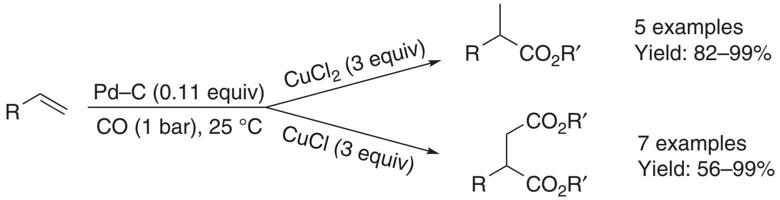
In 1979, Cometti and Chiusoli published their results on the synthesis of methyl cinnamates from styrene [311]. Using a mixture of $PdCl_2$, $CuCl_2$, $MgCl_2$, and NaOAc, the reaction was run in methanol at room temperature under atmospheric pressure of CO to produce methyl cinnamate with up to 80% selectivity together with dimethyl phenylsuccinate as products (Scheme 1.133).

In 1990, Inomata et al. reported the Pd/C-catalyzed oxidative carbonylation of terminal olefins [312]. The reaction proceeded selectively to mono- or diesters under



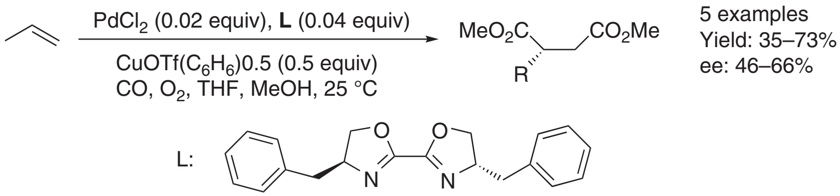
Scheme 1.133 Palladium-catalyzed synthesis of methyl cinnamate.

1 bar of CO at room temperature in good yields in the presence of $CuCl_2$ or CuCl as an additive. Interestingly, mainly monoesters were observed in 82–99% yields if $CuCl_2$ was applied as an oxidant, whereas diesters were formed in 56–99% yields by using CuCl as the oxidizing reagent (Scheme 1.134).



Scheme 1.134 Pd/C-catalyzed oxidative carbonylation of alkenes.

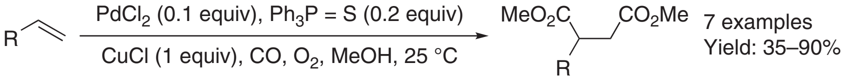
Later, an asymmetric version for the synthesis of diesters was published by Inomata and coworkers [313]. By using a chiral bisoxazoline ligand in the presence of Cu^I triflate at room temperature, terminal olefins were carbonylated to enantiomerically enriched diesters in 35–73% yields with up to 66% ee (Scheme 1.135).



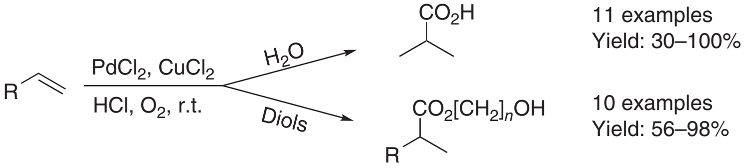
Scheme 1.135 Palladium-catalyzed oxidative carbonylation of olefins. Tf = trifluoromethanesulfonate.

In 1998, Saigo and coworkers reported the use of phosphine sulfides as ligands for the oxidative carbonylation of olefins [314]. Diesters were produced in 35–90% yields starting from the corresponding alkenes at room temperature (Scheme 1.136). Enantioselectivity can be obtained by applying chiral biphosphine sulfides as ligands. Notably, their model system gave rise to 36% and 60% yield in the absence of a ligand and with triphenylphosphine oxide, respectively. However, no reaction occurred in the presence of PPh_3.

Alper and coworkers reported another protocol for the hydroxycarbonylation of alkenes [41]. When $PdCl_2$ and $CuCl_2$ were applied as the catalytic system, alkenes were transformed into branched propionic acids in 30–100% yields in the presence of water, oxygen, and HCl. Later, they extended their protocol to the



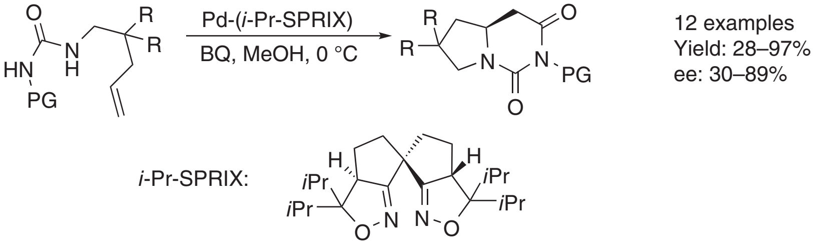
Scheme 1.136 Palladium-catalyzed oxidative carbonylation of olefins using triphenylphosphine sulfide as a ligand.



Scheme 1.137 Palladium-catalyzed oxidative carbonylation of alkenes to branched products.

monohydroesterification of diols [315]. Under 1 bar of CO and at room temperature, the products could be yielded in 56–98% (Scheme 1.137).

Sasai and coworkers published the enantioselective oxidative carbonylation of alkenylureas. By using the PE-spiro bis(isoxazoline) system, the desired products were produced in 28–97% yields and with 30–89% ee (Scheme 1.138) [316].

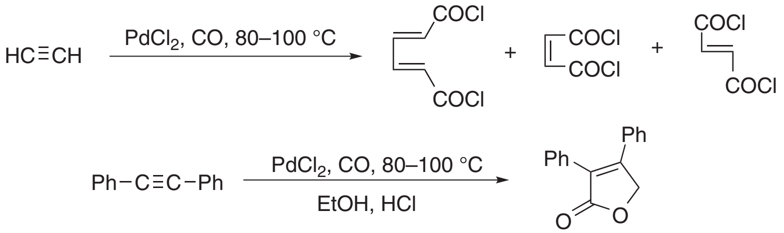


Scheme 1.138 Palladium-catalyzed oxidative carbonylation of alkenylureas. PG = protecting group. Source: Modified from Jamison et al. [116].

The oxidative carbonylation of alkenes has been used in many applications in total synthesis [317–320], but most of the work has focused on ligands and catalyst systems. In general, large amounts of excess copper salts or other organic oxidants are still required. This has an impact on the environment, and the separation of products is difficult. Therefore, the important goal in the future is to utilize air, oxygen, or hydrogen peroxide as "green oxidants" under mild conditions.

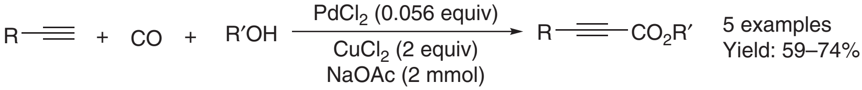
1.8.2 Oxidative Carbonylation of Alkynes

The first example of oxidative carbonylations of alkynes was reported in 1964. Tsuji et al. demonstrated the palladium-mediated transformation of acetylene into muconyl, fumaryl, and maleic acid chloride (Scheme 1.139) [321]. Later, they used diphenylacetylene as a substrate for the synthesis of lactones in the presence of alcohol and HCl [322].



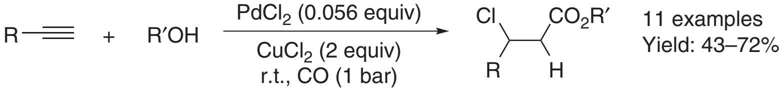
Scheme 1.139 Palladium-mediated oxidative carbonylation of alkynes. Source: Modified from Tsuji et al. [321].

Tsuji et al. further developed the palladium-catalyzed oxidative carbonylation of terminal acetylenes. For example, acetylenecarboxylates were produced in 59–74% yields at room temperature under atmospheric pressure of CO, but stoichiometric amounts of $CuCl_2$ were needed to reoxidize Pd^0 (Scheme 1.140) [69].



Scheme 1.140 Palladium-catalyzed oxidative carbonylation of acetylenes to acetylenecarboxylates. Source: Modified from Tsuji et al. [69].

Jiang and coworkers described the synthesis of 3-chloroacrylate esters [323]. The reaction proceeded under 1 bar of CO at room temperature yielding 30–72% of the desired products in a highly regio- and stereoselective manner (Scheme 1.141).

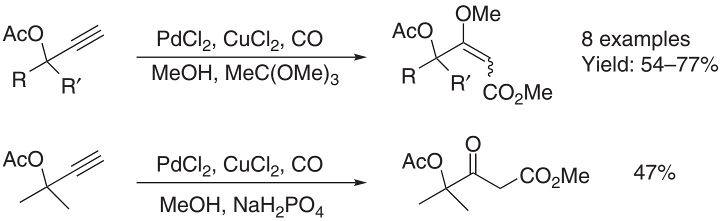


Scheme 1.141 Palladium-catalyzed oxidative carbonylation of acetylenes to chloroacrylates.

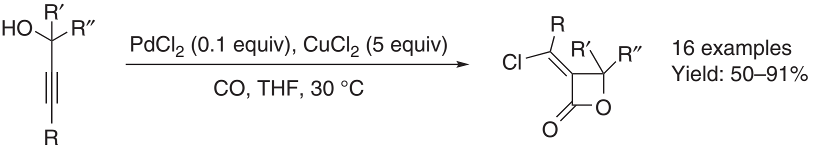
The oxidative carbonylation of 1,1-disubstituted propargyl acetates to unsaturated esters was developed by Okumoto et al. in 1999 [324]. Stoichiometric amounts of $CuCl_2$ were used as the oxidant, and the reaction had to be conducted at 0 °C (Scheme 1.142).

A mild and efficient methodology for the palladium-catalyzed carbonylative synthesis of four-membered β-lactones has been published by Ma et al. [325]. In the presence of $PdCl_2$ and $CuCl_2$, β-lactones were produced from 2-alkynols in good yields (Scheme 1.143). Using readily available optically active propargylic alcohols, the corresponding b-lactones were generated with high ee.

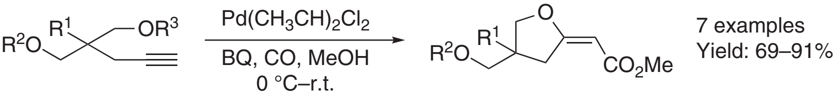
Moreover, an improved method for the oxidative carbonylation of hydroxyalkynes was developed by Kato et al. [326]. Applying $Pd(MeCN)_2Cl_2$ (0.05 equiv) and 1.1 equiv of BQ in methanol at 0 °C under 1 bar of CO, the desired products were



Scheme 1.142 Palladium-catalyzed oxidative carbonylation of propargylic acetates.



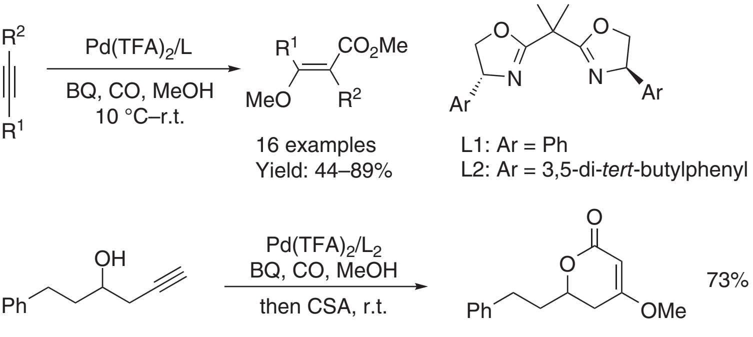
Scheme 1.143 Palladium-catalyzed oxidative carbonylation of alkynes to β-lactones.



Scheme 1.144 Palladium-catalyzed oxidative carbonylation of alkynes to furans.

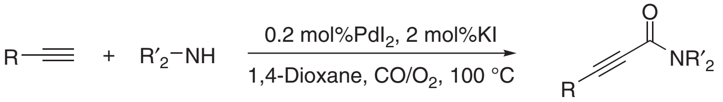
obtained from the corresponding cyclic- and acyclic-4-yn-1-ols in 69–91% yields (Scheme 1.144).

In 2009, Kato et al. applied their Pd^{II} bis(oxazoline) complexes in the intermolecular methoxycarbonylation of terminal alkynes. Terminal alkynes were transformed into β-methoxyacrylates in good yields (Scheme 1.145) [327]. In addition, this methodology was applied in the total synthesis of annularin G and annularin H [328].



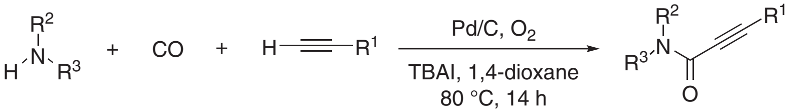
Scheme 1.145 Palladium/BQ-catalyzed oxidative carbonylation of alkynes. CSA = (+)-10-camphorsulfonic acid. Source: Modified from Kato et al. [327].

In 2001, Gabriele and Salerno reported the first catalytic aminocarbonylation of alk-1-ynes [329]. Using a 4 : 1 CO : air mixture (20 atm total pressure), both alkyl- and arylacetylenes could be converted to the corresponding 2-ynamides in 42–80% yields successfully and the latter were more reactive substrates (Scheme 1.146).



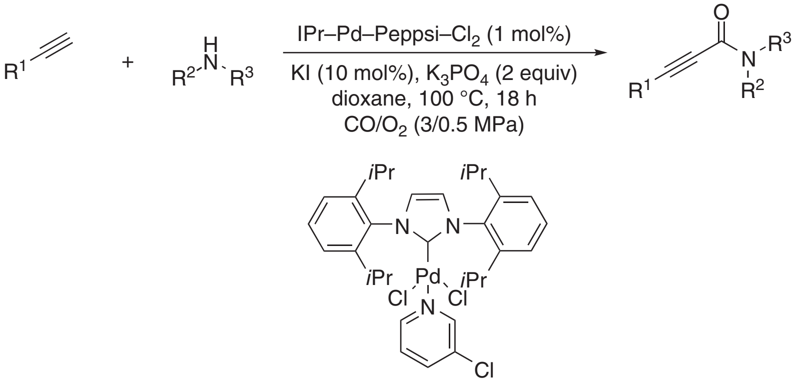
Scheme 1.146 Palladium-catalyzed oxidative aminocarbonylation of alk-1-ynes.

In 2012, Bhanage and coworkers presented Pd/C-catalyzed oxidative aminocarbonylations of alk-1-ynes that is applicable for the synthesis of a wide range of biologically active alk-2-ynamide derivatives (Scheme 1.147). Under the mild conditions, secondary amines provide the corresponding alk-2-ynamides in 55–94% yields [330]. The catalyst can reuse for up to four consecutive cycles.



Scheme 1.147 Pd/C-catalyzed oxidative aminocarbonylation of alk-1-ynes.

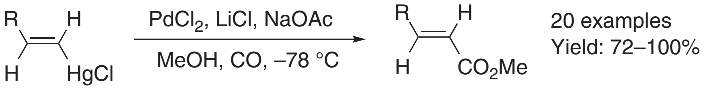
In 2015, Xia and Liu described palladium–NHC catalytic system that allows the direct formation of a range of 2-ynamides from commercially available alkynes via oxidative aminocarbonylation (Scheme 1.148) [331]. Under 3 MPa CO, 0.5 MPa O_2 and at 100 °C, the corresponding products in 50–95% yields can be obtained. They also prove that amido-Pd could be transformed into amido-Pd-alkynyl in this efficient process.



Scheme 1.148 Palladium–NHC-catalyzed oxidative aminocarbonylation of alkynes. Source: Zhang et al. [331].

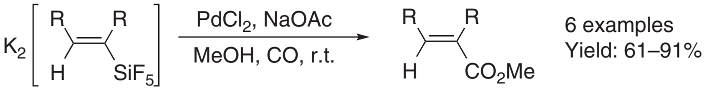
1.8.3 Oxidative Carbonylation of Organometallic Reagents

In 1974, Stille and Wong published the first oxidative carbonylation based on organomercury compounds [332]. Using stoichiometric amounts of $PdCl_2$, LiCl, and NaOAc, stereoselective carbonylation occurred at room temperature. However, the desired products were obtained only in low yield. Larock improved the methodology by conducting the reaction at −78 °C [333]. Unsaturated carboxylic acids and esters were formed in 72–100% yields starting from the corresponding vinylmercurials. Although stoichiometric amounts of palladium were still necessary, a catalytic version was realized by addition of a large excess of $CuCl_2$ (Scheme 1.149).



Scheme 1.149 Palladium-promoted carbonylation of organomercuries.

In 1979, Tamao et al. published concerning the oxidative carbonylation of organosilanes [334]. The reaction was carried out at room temperature and under 1 bar of CO, but stoichiometric amounts of $PdCl_2$ were required to form 61–91% of the corresponding vinyl esters (Scheme 1.150).



Scheme 1.150 Palladium-promoted carbonylation of organosilanes.

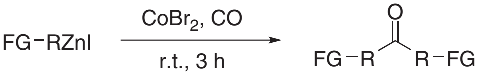
Lei and coworkers developed the first example of palladium-catalyzed oxidative carbonylation of organoindium reagents to produce different esters with desyl chloride as an oxidant [335]. Primary and secondary alkyl indium reagents as well as aryl indium reagents were carbonylated at 60 °C in the presence of catalytic amounts of palladium as a catalyst. The corresponding esters were formed in 60–96% yields, and the methodology showed broad functional group tolerance (Scheme 1.151).

$$Ar_2InCl \xrightarrow[\text{Desyl chloride, NEt}_3 \text{ EtOH, CO, 60 °C}]{PdCl_2(dppf)\ (5\ mol\%)} ArCO_2Et$$

21 examples
Yield: 60–96%

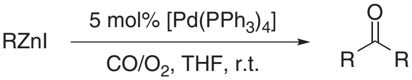
Scheme 1.151 Palladium-catalyzed carbonylation of organoindiums. DPPF = 1,1′-bis(diphenylphosphino)ferrocene.

In 1995, Knochel and coworker reported the oxidative carbonylation of organozinc reagents to produce symmetric ketones in the presence of stoichiometric cobalt bromide (Scheme 1.152) [336].A series of alkyl and aromatic symmetric ketones were prepared in 56–80% yields at room temperature.



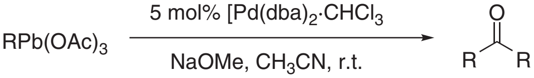
Scheme 1.152 Stoichiometric $CoBr_2$-mediated oxidative carbonylation of organozinc reagents. FG = functional group. Source: Modified from Devasagayaraj and Knochel [336].

Then, Jackson and coworkers reported the palladium-catalyzed oxidative carbonylation of organozinc reagents using O_2 as the oxidant (Scheme 1.153) [208]. Under 1 atm pressure of CO, the corresponding symmetric ketones with up to 84% yield can be obtained at room temperature.



Scheme 1.153 Palladium-catalyzed oxidative carbonylation of organozinc reagents. Source: Modified from Jackson et al. [208].

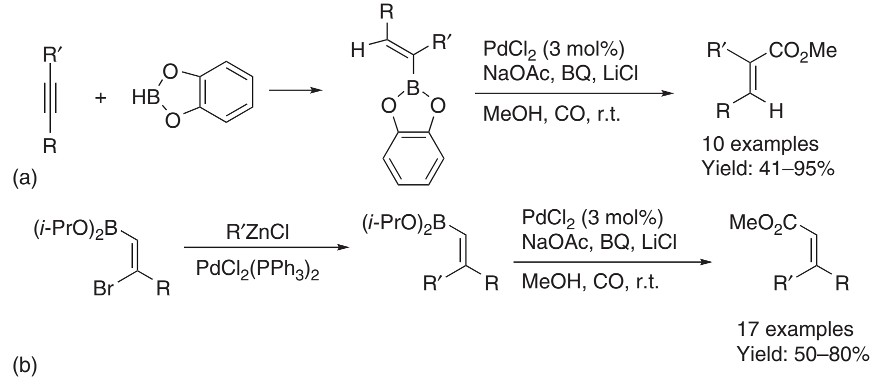
Kang and coworkers found oxidative carbonylation of organolead reagents was also employed to produce symmetric ketones (Scheme 1.154) [337]. In the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%) and NaOMe (5 equiv) in CH_3CN under atmospheric pressure of CO at room temperature, organolead acetates can be carbonylated to afford symmetrical ketones with wide range of functional groups including heterocycles in 69–85% yields. Notably, the organolead compounds acted as both nucleophiles and oxidants, and the authors proposed that $RPb(OMe)_3$ was formed as a key intermediate.



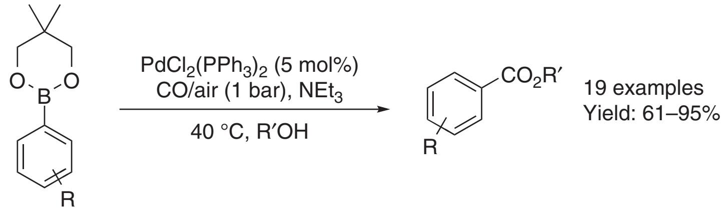
Scheme 1.154 Palladium-catalyzed oxidative carbonylation of organolead reagents. dba=dibenzylideneacetone. Source: Modified from Kang et al. [337].

Suzuki and coworker reported the palladium-catalyzed oxidative carbonylation of alkenylboranes as early as 1981. They prepared 1-alkenylboranes through hydroboration of alkynes, and subsequent oxidative carbonylation mediated by catalytic amounts of $PdCl_2$ in the presence of NaOAc and BQ in methanol provided unsaturated esters in good yields (Scheme 1.155a) [338]. Later, a stereoselective synthesis of β-mono and β,β-disubstituted α,β-unsaturated esters was established through a stepwise cross-coupling alkylation followed by an oxidative carbonylation of 2-bromo-1-alkenylboranes (Scheme 1.155b) [339]. Good yield and excellent stereoselectivity were achieved.

Lei and coworkers discovered a new protocol making use of air as an oxidant at low temperature [340]. Using a balloon pressure of a CO/air mixture, arylboronates were converted into the corresponding esters in 61–95% yields (Scheme 1.156). This was the first example of simply applying air in the oxidative carbonylation of organoboron compounds with alcohols.



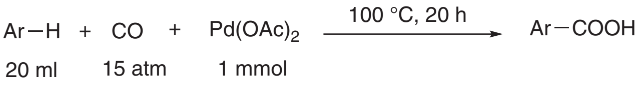
Scheme 1.155 Palladium-catalyzed oxidative carbonylation of alkenylboranes. Source: Modified from Miyaura and Suzuki [338]; Modified from Yamashina et al. [339].



Scheme 1.156 Palladium-catalyzed oxidative carbonylation of arylboronates using air.

1.8.4 Oxidative Carbonylation of Arenes

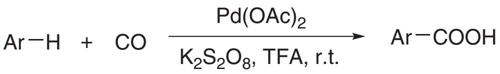
In 1980, Fujiwara et al. reported for the first time a palladium-mediated oxidative carbonylation of arenes to benzoic acids (Scheme 1.157) [341]. The direct carbonylation of benzene, toluene, anisole, chlorobenzene, furan, and thiophene was performed under CO and in the presence of $Pd(OAc)_2$. 2–43% of the corresponding benzoic acids were formed as the terminal products.



$$\underset{20\ \text{ml}}{\text{Ar–H}} + \underset{15\ \text{atm}}{\text{CO}} + \underset{1\ \text{mmol}}{\text{Pd(OAc)}_2} \xrightarrow{100\ ^\circ\text{C, 20 h}} \text{Ar–COOH}$$

Scheme 1.157 Stoichiometric amounts of $Pd(OAc)_2$ for mediation of the oxidative carbonylation of simple arenes. Source: Modified from Fujiwara et al. [341].

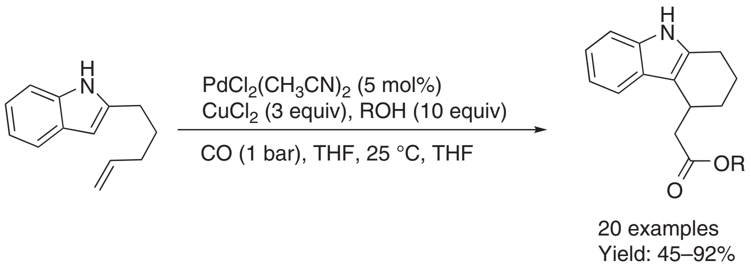
Later, Fujiwara and coworkers developed a more powerful catalytic system (Scheme 1.158) [342, 343]. A series of simple arenes such as benzene, toluene, chlorobenzene, anisole, and naphthalene were oxidatively carboxylated by $Pd(OAc)_2$ in the presence of potassium peroxodisulfate as the oxidant in TFA at room temperature under an atmosphere of CO. The aromatic carboxylic acids were formed in good yields.



$$\mathrm{Ar{-}H} + \mathrm{CO} \xrightarrow[\mathrm{K_2S_2O_8,\ TFA,\ r.t.}]{\mathrm{Pd(OAc)_2}} \mathrm{Ar{-}COOH}$$

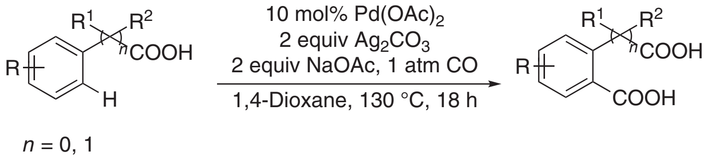
Scheme 1.158 $Pd(OAc)_2$/TFA-catalyzed oxidative carbonylation of simple arenes. Source: Lu et al. [342]. Taniguchi et al. [343].

Widenhoefer and Liu succeeded in palladium-catalyzed oxidative carbonylations for the synthesis of tetrahydrocarbazoles [344, 345]. Starting from alkenyl indoles in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%) and $CuCl_2$ (3 equiv) under 1 bar of CO in THF, the corresponding products were obtained in 45–92% yields with high regioselectivity (Scheme 1.159).



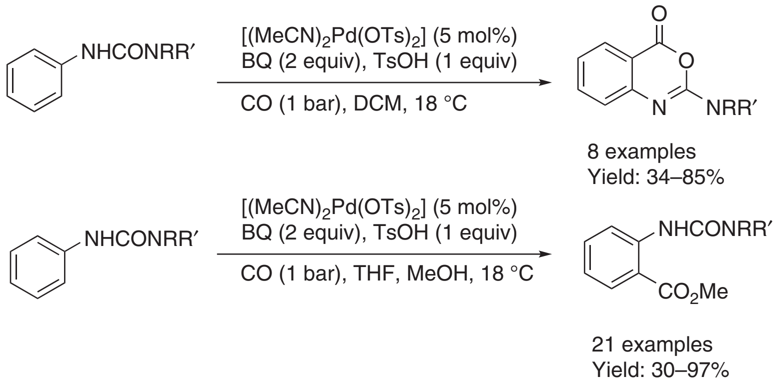
Scheme 1.159 Palladium-catalyzed cyclization/alkoxycarbonylation of alkenyl indoles.

In 2008, Yu and coworker subsequently reported the Pd^{II}-catalyzed direct carboxylation of benzoic and phenylacetic acid derivatives to form dicarboxylic acids (Scheme 1.160) [346]. In the presence of Ag_2CO_3 as an oxidant, 40–93% yields of dicarboxylic acids can be obtained at 130 °C with 1 atm CO. They also characterized the first cyclometalation complex formed from carboxylic acids by X-ray crystallography.



Scheme 1.160 $Pd(OAc)_2$-catalyzed oxidative carbonylation of benzoic and phenylacetic acid. Source: Giri and Yu [346].

Booker-Milburn and Lloyd-Jones published an interesting oxidative carbonylation of aniline derivatives [347]. The reaction proceeded under 1 bar of CO at room temperature with 5 mol% of $[Pd(OTs)_2(MeCN)_2]$ as a precatalyst. Cyclic imidates in 34–85% yields and methyl anthranilates in 30–97% yields can be obtained (Scheme 1.161). Notably, different products can be achieved by simply changing the reaction conditions, such as solvents.



Scheme 1.161 Palladium-catalyzed oxidative carbonylation of aniline derivatives.

1.8.5 Oxidative Carbonylation of Amines

The palladium-catalyzed oxidative carbonylations of amines to ureas were described for the first time by Tsuji and Iwamoto in 1966 [348]. With *n*-decylamine (7.9 g) and palladium chloride (0.5 g) in benzene (30 ml) at 180 °C for 20 hours with shaking, *N*,*N′*-didecyloxamide (3.8 g) and l,3-didecylurea (2.2 g) were obtained.

In 2001, Deng and Shi reported the first gold(I) complex-catalyzed oxidative carbonylation of amines for the syntheses of carbamates (Scheme 1.162) [349]. At 200 °C and 5 MPa of initial total pressure, 34–100% conversions and 35–93% selectivities can be obtained. Then, they prepared polymer-immobilized gold catalysts ($HAuCl_4{\cdot}4H_2O$) for the oxidative carbonylation of aniline and its derivatives [350]. Carbamates and symmetric ureas with up to 99% selectivity can be obtained at 175 °C with 5.0 MPa mixed gases (CO of 99.99% purity at 4.0 MPa and O_2 of 99.99% purity at 1.0 MPa).

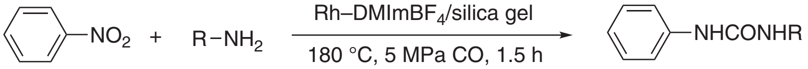
$$\mathrm{R(NH_2)}_n + \mathrm{CO} + \mathrm{O_2} + \mathrm{R'OH} \xrightarrow[\text{200 °C, 3 h}]{[\mathrm{Au(PPh_3)}_x]_y\mathrm{Z},\ \mathrm{PPh_3}} \mathrm{R(NHCO_2R')}_n + \mathrm{H_2O}$$

R = Ph, alkyl
$R' = CH_3, CH_3CH_2$
n = 1 or 2; x,y = 1 or 2
Z = Cl, NO_3, S

Scheme 1.162 Gold(I) complex-catalyzed oxidative carbonylation of amines. Source: Shi and Deng [349].

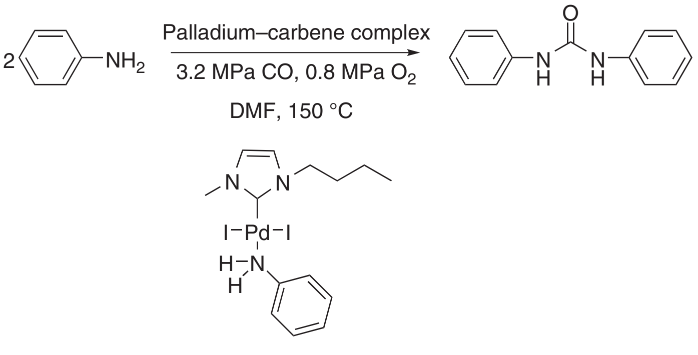
In 2001, Deng and Shi also found a novel $PdCl_2/ZrO_2–SO_4^{2-}$ catalyst for the synthesis of carbamates by oxidative carbonylation of amines [351]. For example, under O_2/CO (MPa) = 0.7/3.3 and at 170 °C, β-naphthylamine was oxidatively carbonylated, almost 100% conversion and 95% selectivity could be achieved as the reaction proceeded in only 15 min. Then, they developed palladium complex–IL catalyst system for the carbonylation of amines to give carbamate or urea [352]. When using $BMImBF_4$ as IL, under 4.0 MPa CO and 1.0 MPa O_2 at 175 °C, 99% conversion of aniline and 98% selectivity of methyl phenylcarbamate with 4540 h^{-1} TOF can be observed. In addition, IL-containing $Pd(phen)Cl_2$ could also be recovered and reused.

In 2005, Deng and Shi prepared silica gel confined IL containing a metal complex ($HRu(PPh_3)_2Cl_2$, $Rh(PPh_3)_3Cl$, $Pd(PPh_3)_2Cl_2$, and $Co(PPh_3)_3Cl_2$) as heterogenized catalysts for the carbonylation of amines and nitrobenzene without molecular oxygen to afford the corresponding ureas (Scheme 1.163) [353]. For example, when using Rh–$DMImBF_4$/silica gel as a catalyst, 92% conversion of aniline and 98% selectivity of disubstituted ureas with 11 548 h^{-1} TOF can be observed.



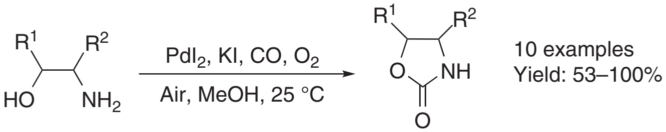
Scheme 1.163 Rh–$DMImBF_4$/silica gel-catalyzed oxidative carbonylation of amines. Source: Modified from Shi et al. [353].

In 2007, Xia and coworkers demonstrated that oxidative carbonylations of amines to ureas are also catalyzed by supported N-heterocyclic carbine (NHC)–palladium complexes (Scheme 1.164) [354, 355]. They showed that the palladium–carbene complex containing both an aniline and an NHC ligand was the active species for this oxidative carbonylation of amines. Without any promoter, various ureas were produced in 46–99% yields. Other immobilized palladium nanoparticles and water-soluble palladium catalysts were also presented [356, 357].



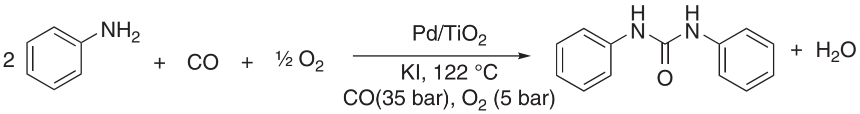
Scheme 1.164 One example of palladium–carbene-catalyzed oxidative carbonylation of amines. Source: Zheng et al. [354]; Zheng et al. [355].

In 2010, Giannoccaro et al. reported $L_nPdCl_2/NEt_3{\cdot}HI$ (L = 2,2′-dipyridine (dipy), 2-(β-diphenylphosphine)ethylpyridine (PN), PPh_3, CH_3CN)-catalyzed oxidative carbonylation of amino alcohols to *N*,*N*′-bis(hydroxyalkyl)ureas under mild conditions (30–60 °C, $P(CO/O_2) = 0.1$ MPa) using molecular oxygen as the oxidant [358]. 74–96% substrate conversions and 67–90% urea isolated yields can be obtained. The catalytic system can be easily recovered and recycled at least six times. Interestingly, the related catalytic carbonylation of amino alcohols to 2-oxazolidinones was also published previously [359]. 53–100% yields of the corresponding products were obtained through direct PdI_2/KI-catalyzed oxidative carbonylation of readily available 2-amino-1-alkanols (Scheme 1.165).



Scheme 1.165 Palladium-catalyzed oxidative carbonylation of 2-amino-alcohols.

In 2019, Shi's group reported Pd/TiO_2 catalyst system for the oxidative carbonylation of amines to ureas with ultra-low Pd content under organic ligand- and solvent-free conditions (Scheme 1.166) [360]. Under 35 bar CO and 5 bar O_2, the corresponding ureas can be obtained in 30–88% yields with up to 250 000 h^{-1} catalytic TOFs (moles of amines converted per mole of Pd per hour) at 122 °C. This is the reported highest TOF numbers so far. In addition, Pd/TiO_2 catalyst can be recycled at least 10 runs without loss in catalytic activity.

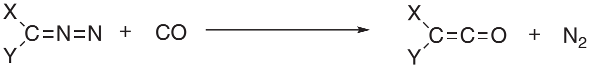


Scheme 1.166 One example of Pd/TiO_2-catalyzed oxidative carbonylation of amines. Source: Modified from Liu et al. [360].

Some other metal-catalyzed oxidative carbonylation of amines with homogeneous transition metal/organic ligand complexes [361–367] and heterogeneous catalysts [368–370] were also studied.

1.9 Other Reactions

To explore other ways to use CO, the replacement of the diazo group in diazoalkanes by CO to afford the corresponding ketenes (Scheme 1.167) might be a synthetically useful reaction since ketenes are versatile intermediates in organic synthesis [371, 372].

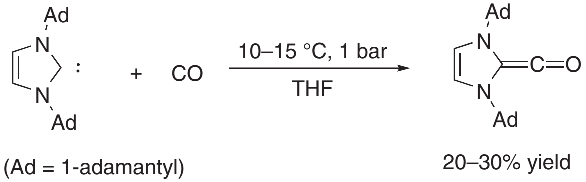


(X, Y = H, alkyl, aryl, alkylthio, acyl, alkoxycarbonyl, alkylamino, F, Cl, trialkylsilyl, etc.)

Scheme 1.167 Replacement of the diazo group in diazoalkanes by carbon monoxide.

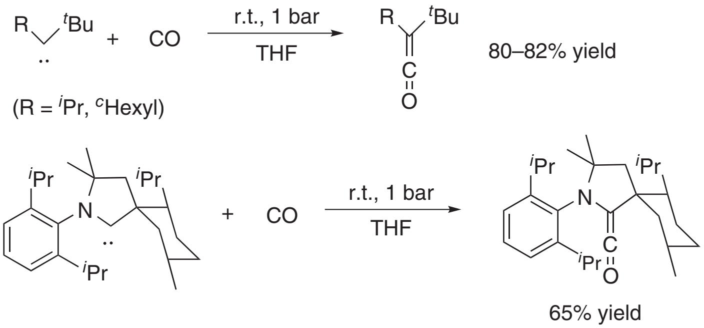
1.9.1 Reactions of Diazoalkanes with Carbon Monoxide

In 1994, Lyashchuk et al. reported the reactivity of stable imidazol-2-ylidenes toward CO. Under atmospheric pressure of CO, the synthesis of 1,3-di-1-adamantylimidazol-2-carbonyl from 1,3-di-1-adamantylimidazol-2-ylidene in 20–30% yield at 10–15 °C in THF solutions (Scheme 1.168) [373].



Scheme 1.168 Synthesis of 1,3-di-1-adamantylimidazol-2-carbonyl. Source: Modified from Lyashchuk and Skrypnik [373].

In 2006, Bertrand and coworkers described a smooth addition of CO at 1 bar pressure to the stable amino-substituted acyclic carbenes and a cyclic carbene at room temperature in THF, which resulted in the corresponding stable ketenes in 80–82% and 65% yields, respectively (Scheme 1.169) [374].

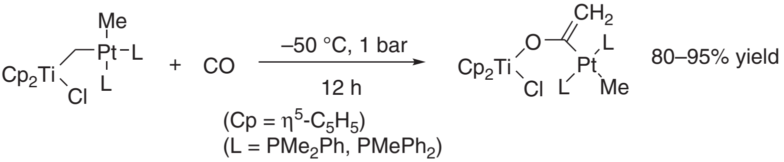


Scheme 1.169 Reactions of amino-substituted acyclic carbenes and a cyclic carbene. Source: Modified from Lavallo et al. [374].

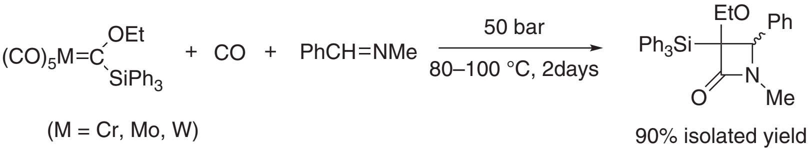
In 1989, Grubbs and coworkers found heterobinuclear complexes with *m*-methylene ligands $Cp_2Ti(Cl)CH_2Pt(CH_3)L_2$ (L = $P(CH_3)_2Ph$, PCH_3Ph_2) to react with CO at atmospheric pressure rapidly to give *m*-(C,O)-ketene species $Cp_2Ti(Cl){-}OC({=}CH_2){-}Pt(CH_3)L_2$ in 80–95% yields (Scheme 1.170) [375].

Kron et al. reported ketene $Ph_3Si(EtO)C{=}C{=}O$ prepared in situ from the carbene complexes $(CO)_5M{=}C(OEt)SiPh_3$ (M = Cr, Mo, W) with 50 bar CO to react at 80–100 °C, among others, with *N*-methylbenzimine to give the corresponding β-lactam in 90% isolated yield (Scheme 1.171) [376].

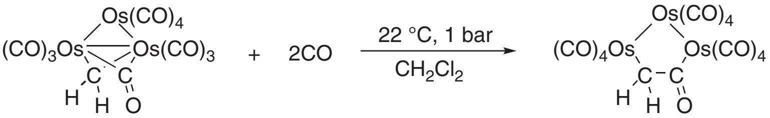
Geoffroy and coworkers reported the interconversion of methylene and ketene ligands on a triosmium cluster. It was found that a triosmium methylene complex in



Scheme 1.170 Heterobinuclear complexes with *m*-methylene ligands. Source: Modified from Ozawa et al. [375].



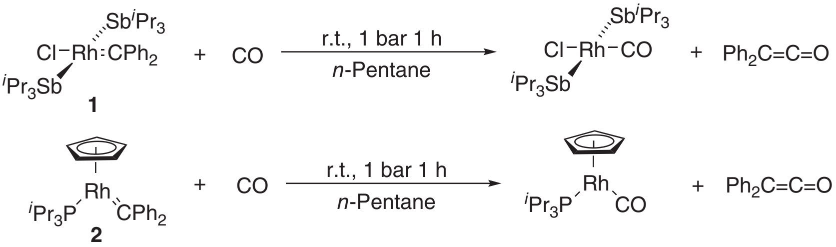
Scheme 1.171 Preparation of $Ph_3Si(EtO)C=C=O$. Source: Based on Kron and Schubert [376].



Scheme 1.172 Interconversion of methylene and ketene ligands. Source: Morrison et al. [377]; Morrison et al. [378].

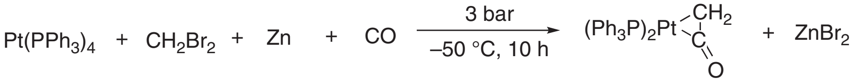
CH_2Cl_2 solution readily adds two moles of CO at 22 °C to yield 16–20% the ketene derivative (Scheme 1.172) [377, 378].

In 2000, Werner et al. reported carbonylation of the rhodium diphenylcarbene complexes **1** and **2** resulted in the formation of diphenylketene in 83–89% yields (Scheme 1.173). It was assumed that the diphenylketene is formed by carbon–carbon coupling in the coordination sphere of rhodium [379].



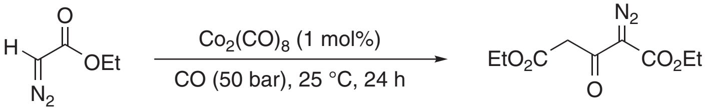
Scheme 1.173 Carbonylation of the rhodium diphenylcarbene complexes.

Miyashita et al. found the η^2-(C,C)-ketene complex of platinum could be isolated in 23% yield from the reaction of $Pt(PPh_3)_4$ and CH_2Br_2 in the presence of zinc powder under 3 bar CO pressure (Scheme 1.174) [380].



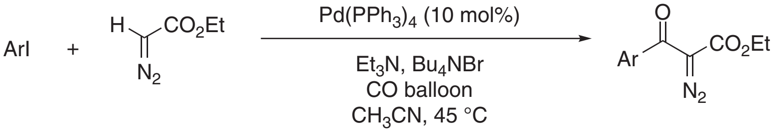
Scheme 1.174 Synthesis of the η^2-(C,C)-ketene complex of platinum. Source: Modified from Miyashita et al. [380].

Since 2003, Ungváry and coworkers have carried out systematic studies on $CO_2(CO)_8$-catalyzed carbonylation of ethyl diazoacetate [381, 382]. In the presence of 1 mol% $CO_2(CO)_8$ and under 50 bar pressure of CO at room temperature, ethyl diazoacetate (EDA) was converted to diethyl 2-diazo-3-oxoglutarate in 91% yield (Scheme 1.175).



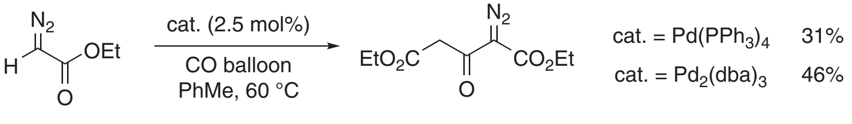
Scheme 1.175 $Co_2(CO)_8$-catalyzed carbonylation of ethyl diazoacetate.

In 2007, Wang and coworkers reported $Pd(PPh_3)_4$-catalyzed cross-coupling of aryl iodides with EDA [237]. Under atmospheric CO pressure, the carbonylation occurred to afford β-keto α-diazocarbonyl compounds in 43–66% yields at 45 °C (Scheme 1.176).



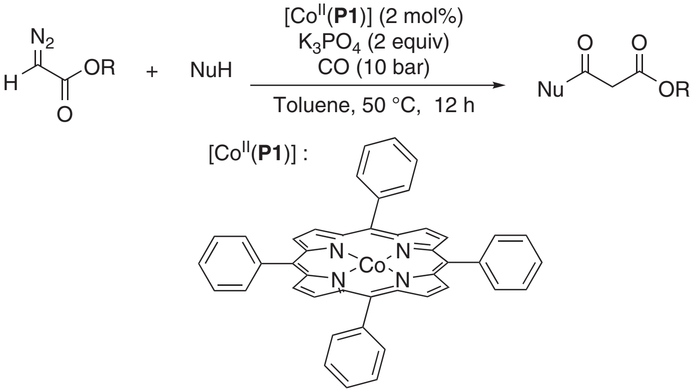
Scheme 1.176 $Pd(PPh_3)_4$-catalyzed cross-coupling of aryl iodides with EDA.

Later, Wang and Li found a comprehensive study of $Pd_2(dba)_3$-catalyzed carbonylation of diazo compounds [383]. In the initial study with EDA, similar results as in the $CO_2(CO)_8$-catalyzed system were observed with Pd(0) catalyst under atmospheric CO pressure (Scheme 1.177).



Scheme 1.177 $Pd_2(dba)_3$-catalyzed carbonylation of diazo compounds.

In 2013, de Bruin and coworkers reported cobalt(II)-porphyrin-catalyzed carbene carbonylation reactions (Scheme 1.178) [384]. Under 10 bar CO and at 50 °C, the β-ketoester products can be obtained in 53–75% yields when using CO, a-diazocarbonyl compounds and different nucleophiles.

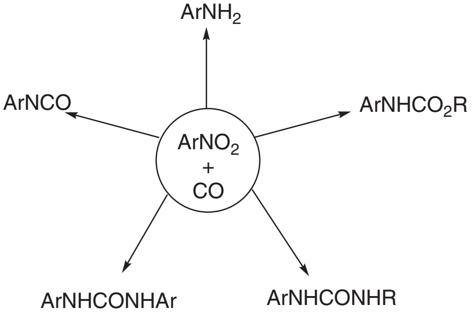


Scheme 1.178 [Co^{II}(Por)]-catalyzed β-ketoester synthesis. Source: Paul et al. [384].

In 2017, Sivasankar and Ramakrishna described that octacarbonyldicobalt as a nongaseous CO source catalyzed carbonylation of diazo compounds for the synthesis of amido esters and amido phosphonates [385]. When using 0.5 equiv $Co_2(CO)_8$ at room temperature, amido esters in 67–95% yields and amido phosphonates in 65–83% yields can be obtained.

1.9.2 Reaction of C–NO$_2$ with CO

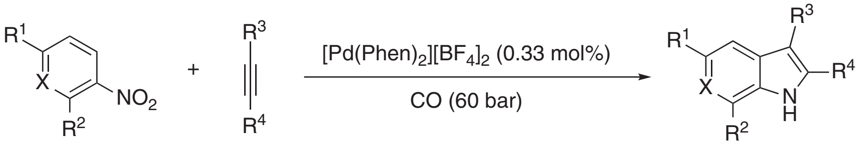
The catalytic carbonylation of nitro compounds is a field of great interest, as a number of important industrial products can be produced (Scheme 1.179) [386–388], such as the synthesis of isocyanates, carbamates, ureas, etc., which normally needed toxic phosgene as the reaction reagent and can be replaced by cheap CO.



Scheme 1.179 Carbonylation of nitro compounds. Source: Paul [386]; Tafesh and Weiguny [387].

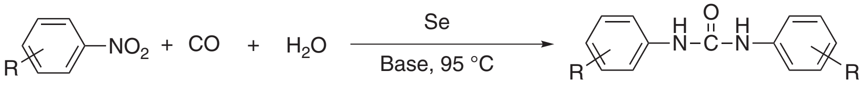
In 1990, the first isolation and characterization of a metallacyclic complex were performed [389, 390]. By combining $Pd(OAc)_2$, 1,10-phenanthroline (3 equiv), and $PhNO_2$ (40 equiv) and heating it in ethanol under CO (30 bar) at 80 °C, a yellow complex was precipitated, with 80% yield. PhNCO, $(PhNH)_2CO$, $(PhNHCO)_2NPh$, and CO_2 were produced by heating the complex in 1,2-dichlorobenzene under CO

(20 bar) at 170 °C. The addition of 2,4,6-trimethylbenzoic acid can increase the production of PhNCO. Finally, a mixture of the complex, $PhNO_2$, EtOH, under CO atmosphere, together with 2,4,6-trimethylbenzoic acid heated at 135 °C, 100% of the $PhNO_2$ was converted into $PhNHCO_2Et$ in 91% selectivity. Based on these studies, a reaction mechanism was given that was modified afterward for different product syntheses (Scheme 1.180).



Scheme 1.180 Reaction mechanism for Pd-catalyzed carbonylation of RNO_2.

Yu, Lu, and colleagues found that selenium can catalyze the carbonylation of nitroarenes to symmetrical 1,3-diarylureas under atmospheric pressure of CO [391]. In the presence of KOH or NaOAc as base, various ureas were produced with up to 94% yield in DMF at 95 °C (Scheme 1.181). They also reported a selenium-catalyzed reaction of nitroarenes and amides in the presence CO to *N*-arylamides [392]. Under the assistant of mixed organic bases NEt_3 and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), *N*-arylamides were produced in 41–88% yields by a selenium catalyst. Other catalytic carbonylation of organic nitro compounds can be found in reviews [386–388, 393].



Scheme 1.181 Selenium-catalyzed amide synthesis.