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Critical Review

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# Carbon Monoxide as C1 Building Block in Fine Chemical Synthesis†

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## Keywords

Carbon monoxide | Fine chemicals | Carbonylation | Hydroformylation | C—H functionalization

## Comprehensive Summary


Carbon monoxide (CO) has become one of the most relevant and versatile renewable C1 building blocks for chemical synthesis, especially in the fine chemicals industry, due to the development of efficient and selective catalysts for its activation. In this review, we present a comprehensive critical analysis of the last 10 years literature on the use of CO as a renewable feedstock for fine chemicals production. The review is organized by type of catalytic reaction, namely alkene and alkyne carbonylation, hydroformylation, carbonylation of aryl halides, carbonylative cross-coupling and C—H carbonylation. Notable examples of the synthesis of relevant building blocks and/or known pharmaceuticals are highlighted. Emphasis is placed on examples of utilizing CO as the C1 building block in one or more catalytic steps. The catalyst used and the reaction conditions are consistently presented throughout all of the examples.

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† Dedicated to the Special Issue of C1 Chemistry.

**Left to Right:** Rui M. B. Carrilho, Mário J. F. Calvete, Mariette M. Pereira, László Kollár and Gábor Mikle

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**Mário J. F. Calvete** received his Industrial Chemistry diploma from University of Coimbra in 2000 and his PhD in Natural Sciences–Organic Chemistry in 2004, from Eberhard Karls University of Tuebingen, Germany, with Prof. Dr h. c. Michael Hanack. After a two-year stay at Tuebingen as a postdoctoral fellow in Industry/University, he returned to Portugal for a postdoctoral stay at University of Aveiro. In 2010 he was appointed as Auxiliary Researcher at University of Coimbra and since 2019, he is Assistant Professor at this university. His current research interests are tetrapyrrolic macrocycle design and other heterocyclic ligands and their uses in theranostics and homogeneous/heterogeneous (photo)catalysis, particularly in environmental remediation technologies. He has published *ca*. 100 peer-reviewed papers, 2 books and 15 book chapters.

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**Mariette M. Pereira** is currently a Full Professor of Organic and Medicinal Chemistry at University of Coimbra (Portugal). She obtained her PhD in Organic Chemistry in 1992 at University of Coimbra and worked as Fellow Assistant at Universities of Liverpool in 1993 and Autònoma de Barcelona in 1998. She was Director of the Chemistry Research Laboratory of pharmaceutical *spin-off* Luzitin SA, until 2015. Her research interests are focused on the synthesis of phosphorus ligands and their transition metal complexes for development of carbonylation catalysts and catalytic tandem reactions. Other research interests include the synthesis of tetrapyrrolic macrocycle-based photosensitizers for applications in photodynamic therapy of cancer and photo-inactivation of microorganisms. She published more than 200 peer-reviewed papers, 20 books/book chapters and she is inventor of 6 WO patents. She has won the *Prix Tremplin Mariano Gago* (2022) from the Portuguese and French Academies of Sciences, and received the award *Distinguished Guest Scientist* from the Hungarian Academy of Sciences (2023).

## Contents



## 1. Introduction

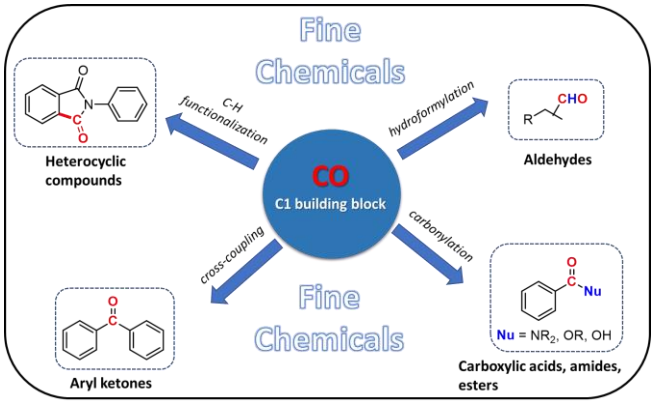
Carbon monoxide (CO) is a widely available feedstock in nature and, over the last decades, it has turned into one of the most relevant and versatile C1 building blocks in organic synthesis. CO can be produced from a variety of sources, including natural gas and biomass, making it a potentially sustainable alternative to traditional petrochemical feedstocks.[1-3] It is relatively inexpensive, hence, its utilization in carbonylative reactions is highly desired in industrial technologies as it has the ability and potential to produce a variety of multi-functionalized fine chemicals of key interest.[4-6] However, the use of carbon monoxide in organic synthesis also presents some significant challenges: for instance, it is highly toxic so it must be handled with precaution. Furthermore, it is a gas at room temperature and atmospheric pressure, which makes problematic its handling and storing. Therefore, research has been focused on developing new methods for using carbon monoxide in more sustainable and efficient ways, and on addressing the safety and handling challenges, by using CO surrogates.[7-12]

Carbon monoxide has been employed in industrial processes, such as in the carbonylation of methanol for the large scale production of acetic acid, a key chemical used in the manufacture of polymers, solvents and other products.[13] Over the last decades, CO has been widely used in several reactions and synthetic processes, namely in carbonylations of alkenes and alkynes, olefin hydroformylation, amino and alkoxycarbonylation of aryl halides, carbonylative cross-coupling reactions and C—H bond carbonylation (Scheme 1). Since then, CO has become one of the most relevant C1 building-blocks for the preparation of fine chemicals.

The term "*fine chemicals*" refer to high-value pure chemical substances that are produced in relatively small quantities, being typically produced through precise and specialized chemical processes, often involving complex synthetic routes. Fine chemicals require high purity, stringent quality control, and customization

**Scheme 1** General overview of carbonylation reactions for fine chemicals synthesis




according to specific requirements, providing tailored chemical solutions with high quality and performance characteristics. They can be used in a wide range of sectors such as in biotechnology, and in the synthesis of pharmaceuticals, agrochemicals, flavors, fragrances and specialty materials.[14,15]

Among the multiple approaches for the preparation of fine chemicals, catalytic carbonylation reactions can be considered as one of the most versatile and efficient strategies. By harnessing the reactivity of carbon monoxide, chemists can introduce carbon atoms, modify structures, and create complex molecules with desired functionalities.[16] Such reactions play a vital role in the synthesis of active pharmaceutical ingredients, modification of natural products, development of specialty chemicals, and advancement towards more sustainable chemical processes.

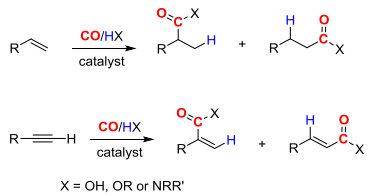
In this review, we discuss selected examples from the literature of the last ten years that demonstrate the relevance of the applications of CO as C1 building block in the sustainable synthesis of fine chemicals. It is organized by the reaction types depicted in Scheme 1. The carbonylative cyclization of unsaturated substrates under oxidative conditions using $PdI_2$/KI catalytic systems, for the synthesis of heterocycles, was recently reviewed,[17-18] so these examples are not covered in this review. Furthermore, the application of carbonylation reactions using $^{11}C$, $^{13}C$ and $^{14}C$ isotopes for preparation of C-labeled compounds are also not included, since this topic has been recently reviewed by other authors.[19-20]

## 2. Synthesis of Fine Chemicals Using CO

### 2.1. Carbonylation of alkenes and alkynes

Alkenes and alkynes may undergo catalytic hydrocarbonylation reactions in the presence of a HX reagent.[21-23] These include hydroalkoxycarbonylation or hydroaryloxycarbonylation (X = OR, R = alkyl or aryl), hydroaminocarbonylation (X = NRR') and hydrocarboxylation (X = OH) (Scheme 2).

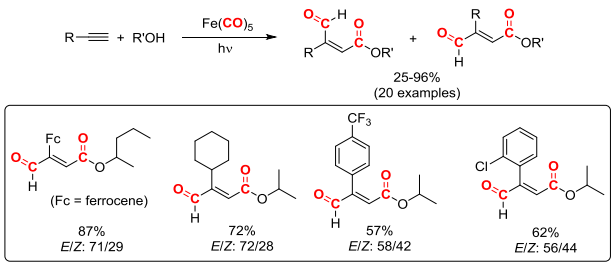
**Scheme 2** General scheme of the catalytic hydrocarbonylation of alkenes and alkynes




Carbonylation reactions of alkenes and alkynes have become important tools in fine chemical synthesis, due to their potential to selectively introduce functional groups into unsaturated compounds. The broad substrate scope and the possibility of using mild conditions turned these reactions into versatile strategies to afford a wide range of biologically relevant esters, amides and carboxylic acid derivatives.

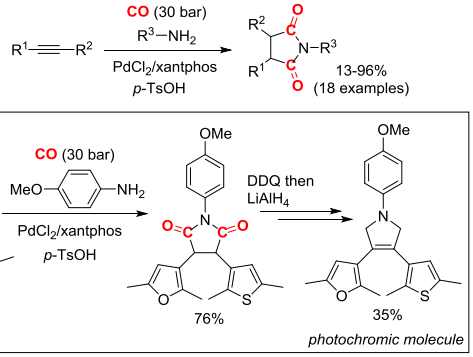
Joshi[24] developed an efficient iron-catalyzed regioselective carbonylative strategy for preparation of biologically relevant retinoid esters,[25] which may serve as key structural motifs in drug and pharmaceutical applications (Scheme 3). Twenty different 3-formyl-3-alkyl/aryl/ferrocenyl-2-propenoates have been successfully synthesized by photolysis of alcoholic solutions of terminal acetylenes and carbon monoxide, and the highest yields were achieved with tertiary and secondary alcohols. This method represents a feasible, economic and environmentally friendly synthetic approach for preparation of retinoid esters.

**Scheme 3** Synthesis of retinoid esters via iron-catalyzed carbonylation of terminal acetylenes with CO and alcohols




Succinimides are also useful building blocks for the synthesis of natural products and drugs.[26] In this regard, Liu and Dyson[27] described an efficient route to succinimide derivatives, through a Pd(xantphos)$Cl_2$-catalyzed aminocarbonylation of alkynes with aromatic or aliphatic amines in the presence of *p*-TsOH (Scheme 4). One of the succinimide compounds prepared was used as intermediate for the synthesis of a photochromic molecule (Scheme 4).

**Scheme 4** Synthesis of succinimides via Pd-catalyzed aminocarbonylation of alkynes



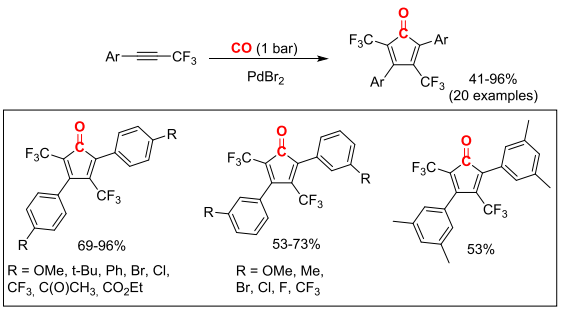

Cyclopentadienones are recognized as important compounds in various fields, namely as intermediates in organic synthesis as well as in biological and material sciences applications.[28] In this context, Kawatsura[29] reported the [2 + 2 + 1] cycloaddition reaction of carbon monoxide to aryl- and trifluoromethyl substituted internal alkynes catalyzed by $PdBr_2$ in the absence of copper salts. The reaction provided cyclopentadienone derivatives containing aryl- and trifluoromethyl groups in up to 96% yield (Scheme 5).

In recent years, α,β-unsaturated primary amides have found numerous applications as synthetic intermediates in drug development and in the preparation of organic polymeric materials. In this context, Huang[30] described an unprecedented palladium-catalyzed hydroaminocarbonylation of alkynes with $NH_4Cl$ as the

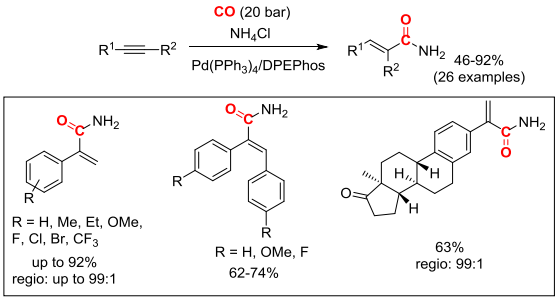
  

amine source, enabling a highly chemo- and regioselective process for preparation of α,β-unsaturated primary amides. This method turned the non-coordinating ability of ammonium salts into a strategic advantage, enabling the gram-scale synthesis of a diversity of alkynes, including aromatic and aliphatic, both terminal and internal alkynes, with excellent yields and selectivity (Scheme 6).

**Scheme 5** Synthesis of cyclopentadienone derivatives through Pd-catalyzed carbonylation of alkynes containing aryl- and trifluoromethyl groups

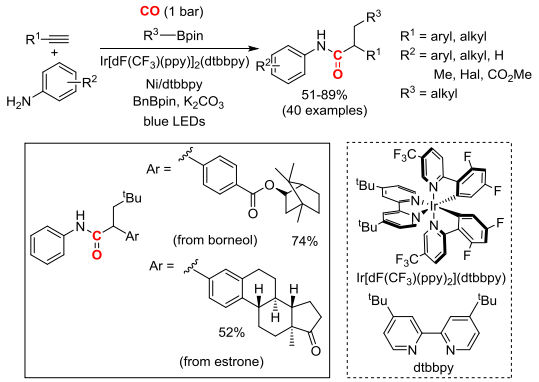



**Scheme 6** Synthesis of α,β-unsaturated primary amides via Pd-catalyzed regioselective hydroaminocarbonylation of alkynes



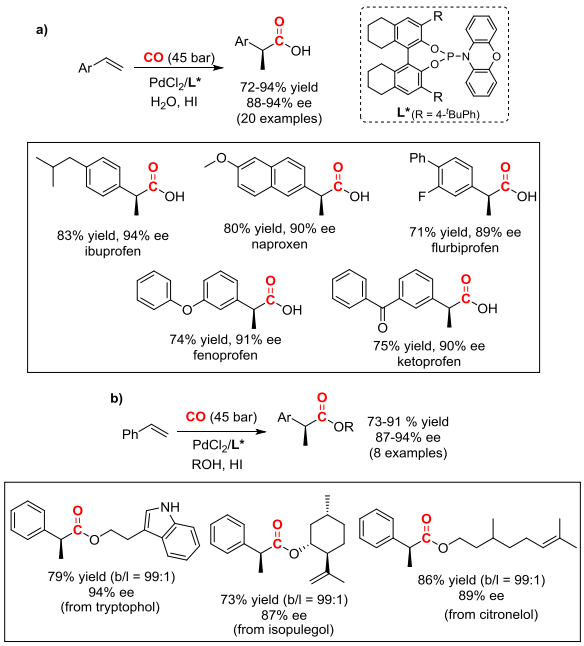

Chu[31] implemented a Ni/photoredox dual catalyzed sequential hydroaminocarbonylation/radical alkylation reaction of terminal alkynes with aryl amines as nucleophiles and alkyl boronates esters as alkylating agents under 1 bar CO pressure. The reaction was carried out using Ir[dF(CF$_3$)(ppy)$_2$](dtbbpy)PF$_6$ (ppy = 2-phenylpyridine and dtbbpy = di*tert*butylbipyridine) and NiCl$_2$·DME (DME = dimethoxyethane) as catalysts, K$_2$CO$_3$ as base and BnBpin (benzylboronic pinacol ester) as additive, under blue LED irradiation (Scheme 7). Among the many examples reported, the authors also used this elegant strategy to modify some natural products, successfully obtaining bomeol and estrone analogues.

**Scheme 7** Ni/photoredox dual catalyzed sequential hydroaminocarbonylation/radical alkylation reaction of terminal alkynes with aryl amines




Asymmetric hydroxycarbonylation is one of the most attractive methods for the synthesis of chiral carboxylic acids, namely 2-arylpropionic acids, commonly used as non-steroidal anti-inflammatory drugs. In this regard, Guan[32] reported the development of a highly regioselective (Markovnikov) and enantioselective catalytic hydroxycarbonylation of vinylarenes, CO and water, using a palladium/phosphoramidite catalyst, which provided a facile and atom-economical synthetic approach to obtain a set of 2-arylpropionic acids (Scheme 8a). The same catalytic system was also applied in the asymmetric hydroalkoxycarbonylation of vinylarenes with CO and alcohols, which afforded the corresponding 2-arylpropanoates, including bioactive tryptophol, isopulegol and citronellol derivatives (Scheme 8b).

**Scheme 8** Synthesis of: a) 2-arylpropionic acids non-steroidal anti-inflammatory drugs; b) bioactive 2-arylpropionic esters

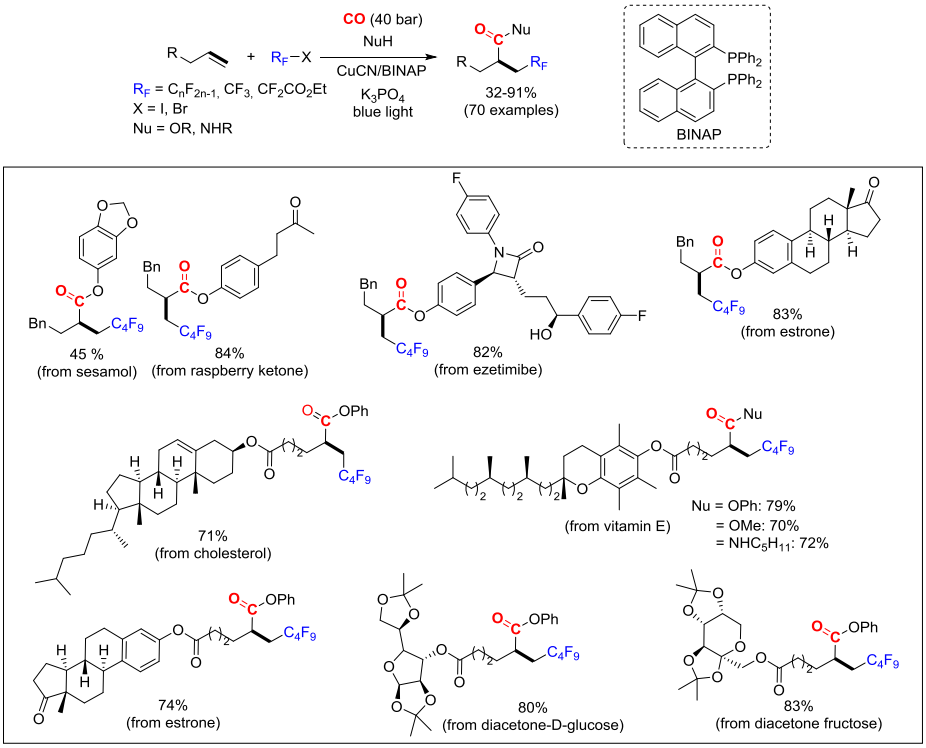



Fluorine is one of the most ubiquitous elements in pharmaceuticals and agrochemicals, as it can change the physical, chemical and biological properties of the parent molecules. Recently, Wu[33] reported the first photoinduced Cu/BINAP-catalyzed multicomponent perfluoroalkylation/carbonylation tandem sequence of non-activated alkenes with perfluoroalkyl halides, carbon monoxide and different nucleophiles (including phenols, alcohols, and amines). This strategy allowed the straightforward construction of a set of valuable β-perfluoroalkyl esters and amides (*ca*. 70 examples) from inexpensive and readily available starting materials in good to excellent yields, with broad functional group tolerance and excellent chemo- and regioselectivity. Furthermore, this method was applied to the perfluoroalkylative carbonylation of several pharmaceutical and bioactive molecules, providing the efficient synthesis of biologically relevant β-perfluoroalkyl carbonyl compounds (Scheme 9).

## 2.2. Hydroformylation-based reactions

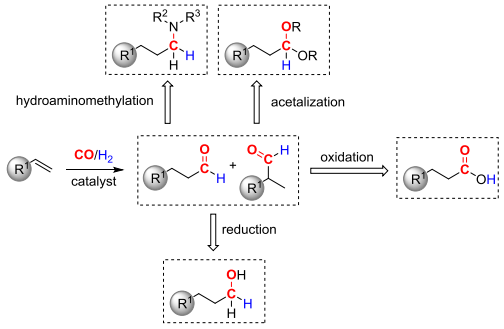
Catalytic hydroformylation is the formal addition of a hydrogen atom and a formyl group across the π system of a C=C double bond, in the presence of *syngas* (CO/H$_2$).[34] It is usually catalyzed by transition metal-based catalysts, yielding linear or branched aldehydes with an additional carbon atom relatively to the starting olefin.[35] The first industrial application of the catalytic hydroformylation was in the production of butyraldehyde from propylene.[36] Since then, hydroformylation has become one of the most important and widely used homogeneously catalyzed industrial

**Scheme 9** Synthesis of β-perfluoroalkyl carbonyl compounds *via* Cu/BINAP-catalyzed multicomponent perfluoroalkylation/carbonylation of non-activated olefins




processes,[37] particularly in polymer and detergent industries, with production capacities of more than nine million tons/year.[38] Hydroformylation reaction offers great potential for preparing aldehydes with biological relevance,[39] and it is currently used in the production of fragrances[40] and drug synthetic intermediates, since the produced aldehydes can be transformed, through sequential reactions, into different alcohols, amines, carboxylic acids and other functional groups, leading to the efficient preparation of fine chemicals (Scheme 10).[41-46]

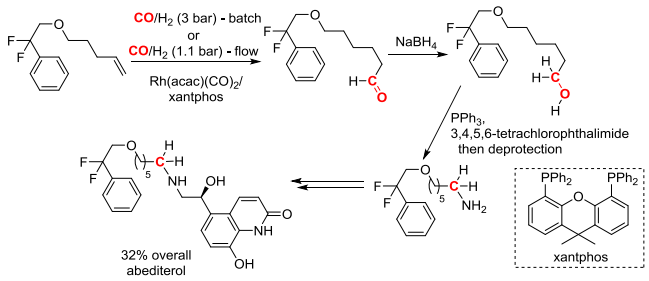
**Scheme 10** General scheme of catalytic olefin hydroformylation and sequential reactions




Noonan[47] reported a sustainable hydroformylation of a vinyl fluorinated compound using $Rh(acac)(CO)_2$/xantphos as catalyst and low $CO:H_2$ pressure (3 bar) as an alternative synthetic strategy to access the lipophilic amine portion of abediterol, a compound applied in the treatment of respiratory disease (Scheme 11).

The strategy started with the hydroformylation of the corresponding terminal alkene, selectively yielding the terminal aldehyde, followed by borohydride mediated reduction, amine formation *via* Mitsunobu reaction and deprotection to generate the free amine. Further steps would provide the desired drug. This methodology obtained a similar overall yield (30%) to the original abediterol synthesis[48] but advantageously avoids the use of hazardous materials and intermediate isolation. Later, Kappe[49] implemented a continuous-flow sequence for the synthesis of the same lipophilic amine synthon of this drug. The multistep flow process was successfully operated over 6 h, in which the hydroformylation step produced the desired linear aldehyde in a space-time yield of 2.5 g/h, using also $Rh(acac)(CO)_2$/xantphos as catalyst, 1.1 equiv. of $CO:H_2$, and anisole as green solvent. This multistep flow approach led to an improvement of the overall yield (38%).

**Scheme 11** Synthesis of the lipophilic amine fragment of abediterol via Rh-catalyzed hydroformylation

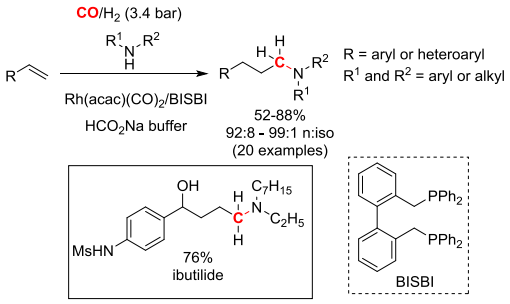



Hartwig[50] reported the hydroaminomethylation of a set of α-olefins with a wide range of alkyl, aryl, and heteroarylamines, using $Rh(acac)(CO)_2$/BISBI as catalyst, in presence of a $CO:H_2$ 1 : 1 (3.4 bar), and aqueous sodium formate as reducing agent (Scheme 12). Besides the large family of arylamines prepared using this single catalyst methodology, the authors managed to extend its applicability to the synthesis of ibutilide, a Class III antiarrhythmic agent that is indicated for acute cardioconversion of atrial fibrillation, in 76% yield.

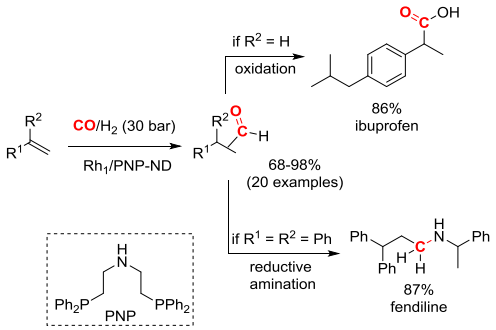
Liang and Chen[51] performed the hydroformylation of several aryl olefins, using a heterogeneous phosphorus coordinated Rh single-atom catalyst, through a PNP ligand, with nanodiamond (ND) as support, designating it as $Rh_1$/PNP-ND, in the presence of $CO/H_2$ 1 : 1 at 30 bar pressure (Scheme 13). Excellent activity and regioselectivity were obtained in hydroformylation of various arylethylenes, with high conversion (>99%) and regioselectivity

(>90%). The catalyst remained active during six consecutive reutilization cycles in styrene hydroformylation, demonstrating its high stability, which was attributed to the strong anchoring of the Rh single atoms over nanodiamonds through Rh—P bonds. In an extension of the wide applicability of this system, the authors further synthesized two pharmaceutical molecules, ibuprofen and fendiline, used as non-steroidal anti-inflammatory drug and anti-anginal agent for the treatment of coronary heart disease, respectively. The racemic forms of these drugs were efficiently prepared in high overall yields (86%—87%) after oxidation and reductive amination, respectively (Scheme 13).

**Scheme 12** Synthesis of arylamines via Rh-catalyzed hydroaminomethylation of α-olefins



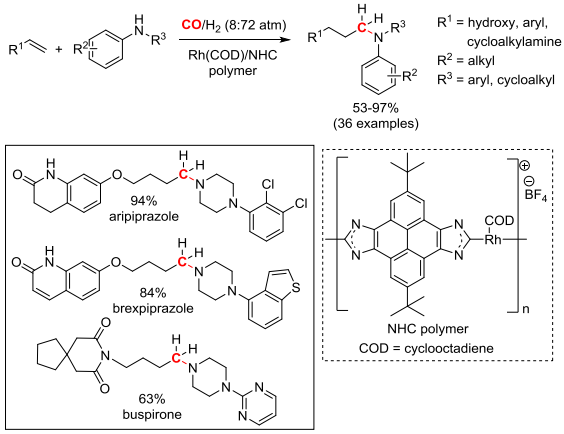

**Scheme 13** Synthesis of pharmaceutical drugs by heterogeneous hydroformylation reactions



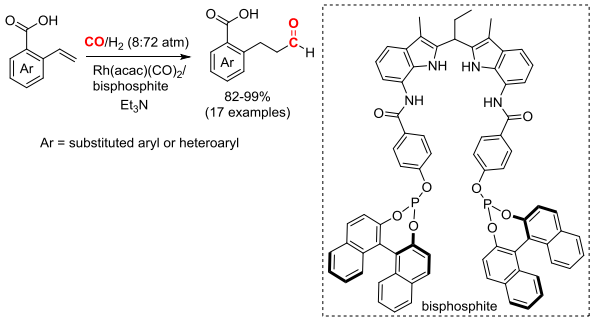

Tu[52] prepared solid NHC–rhodium(I) polymers formed by coordination assembly and used them as heterogeneous catalysts in the hydroaminomethylation of several olefins (Scheme 14). The reactions were carried out under syngas atmosphere ($CO/H_2$ 8 : 72 bar) in THF as solvent and the complexes, used in 1 mol%, were found to be highly efficient single-site catalysts, in terms of productivity (up to 98% yield) and linear to branched products selectivity (up to 99 : 1), which was ascribed to the constraints imposed by the extended coordination assembly structure of the solid catalysts. Along with a wide applicability, with high tolerance of sensitive functional groups, a turnover number of $2 \times 10^5$ was accomplished, and the solid catalyst was reused 18 times with negligible loss of activity and selectivity. The utility of this strategy was also demonstrated by the synthesis of several leading pharmaceuticals directly from allyl alcohols or heterocyclic amines, to provide aripiprazole, brexpiprazole and buspirone, the two first drugs used for treating the symptoms of schizophrenia and the last to treat generalized anxiety disorder.

Reek[53] implemented the synthesis of formylated arenecarboxylic acid derivatives, which are building blocks for the synthesis of several valuable active pharmaceutical ingredients (*e.g.*, anti-obesity[54] and Alzheimer's disease treatment[55] pharmaceuticals), by using a regioselective hydroformylation strategy on vinylarene-2-carboxylic acid derivative. The reactions proceeded using a $Rh(acac)(CO)_2$/bisphosphite complex as catalyst, in the presence of triethylamine using 20 bar $CO/H_2$ 1 : 1. This system led to 100% chemoselectivity and regioselectivity for linear aldehydes, which allowed to perform a multigram synthesis of the desired products in excellent yields (Scheme 15).

**Scheme 14** Synthesis of pharmaceuticals via hydroaminomethylation of alkenes catalyzed by heterogeneous Rh(I)/NHC polymer

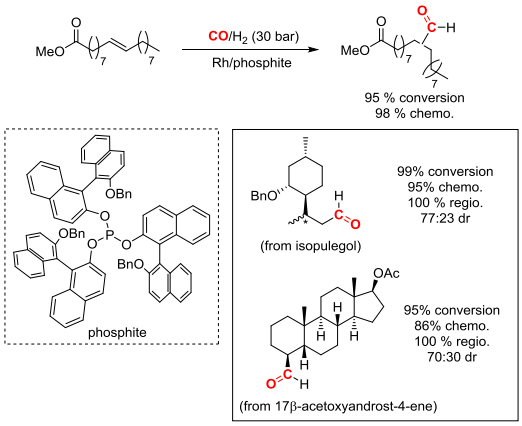



**Scheme 15** Synthesis of formylated arylcarboxylic acid derivatives via Rh-catalyzed hydroformylation




Natural oils are attractive bio-source derived fine chemical compounds, used as excipients in pharmaceuticals and as an emulsifying or solubilizing agent in aerosol products. In this regard, Pereira[56] reported Rh-catalyzed hydroformylation of methyl oleate (Scheme 16), obtained after transesterification of natural oils extracted from *Calophyllum inophyllum* seeds. A highly active rhodium/tris-BINOL monophosphite catalytic system led to complete conversions and 98% chemoselectivity for aldehydes with conventional heating. When performed under microwave irradiation, the reactions provided up to 30% chemoselectivity for

**Scheme 16** Rh-catalyzed hydroformylation of natural oils, terpene and steroid using rhodium/tris-Binol monophosphite catalyst

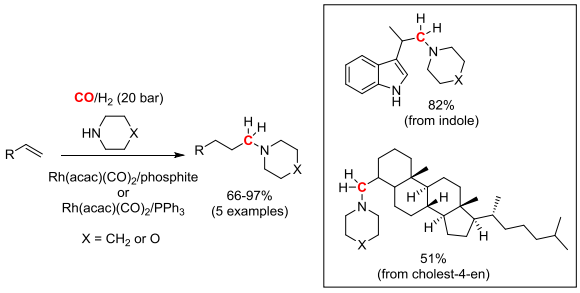


aldehydes. The same authors further prepared the corresponding aldehydes from isopulegol and 17β-acetoxyandrost-4-ene using the same strategy (Scheme 16).[57]

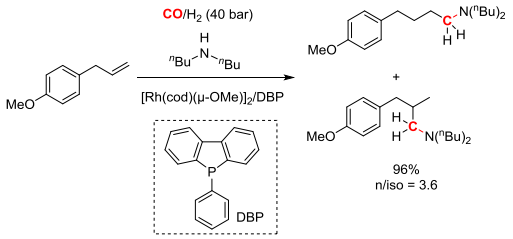
Pereira[58] also reported the hydroaminomethylation reaction of 3-vinyl-1*H*-indole and cholest-4-ene, using $Rh(acac)(CO)_2/PPh_3$ as catalyst in the first case to promote the production of the branched aldehyde, and $Rh(acac)(CO)_2$/tris-Binol monophosphite catalyst in the latter case, to promote the hydroformylation of sterically hindered double bond (Scheme 17). In both cases, *syngas* ($CO/H_2$ 1 : 1) was used under 20 bar pressure, in THF as solvent, in the presence of piperidine or morpholine as amine nucleophiles.

**Scheme 17** Synthesis of biologically relevant tertiary amines via hydroaminomethylation of 3-vinyl-1*H*-indole and cholest-4-ene, using Rh catalysts




Dos Santos[59] described the hydroaminomethylation reaction of estragole, a bio-renewable starting material, using di-*n*-butylamine as nucleophile. This sequential process consisted of the hydroformylation of the biosubstrate, catalyzed by $[Rh(cod)(\mu\text{-OMe})]_2$/DBP (DBP = 1-phenyldibenzophosphole) at 40 bar ($CO : H_2$ = 1 : 3), followed by nucleophilic addition of the di-*n*-butylamine (Scheme 18).

**Scheme 18** Rh-catalyzed hydroaminomethylation of estragole

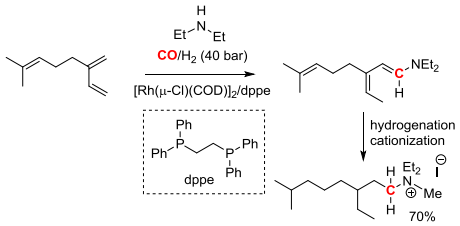



Vorholt[60] used myrcene as a bio-sourced material, aiming at the synthesis of renewable surfactants. It was selectively and exclusively functionalized on the disubstituted double bond of the 1,3-diene moiety by the $[Rh_2(\mu\text{-Cl})_2(COD)_2]$/dppe (dppe = 1,2-bis(diphenylphosphino)ethane) catalytic system in the presence of $HNEt_2$, resulting in the 3-ethyl enamine as product. Attempts to obtain directly the fully saturated product were unsuccessful, so the authors used Pd/C as catalyst to that end, followed by cationization with methyl iodide to produce the corresponding quaternary ammonium salt (Scheme 19).

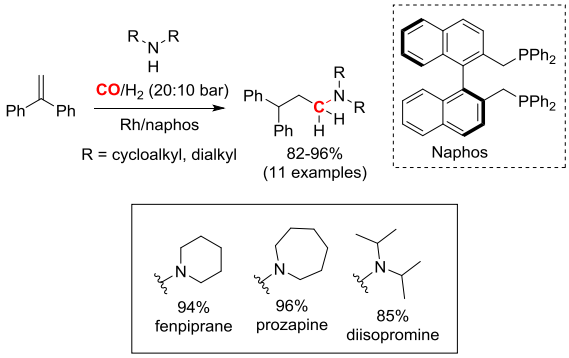
Zhang[61] reported the hydroaminomethylation reaction of 1,1-diphenylethene with *syngas* [$CO/H_2$ (20/10 bar)], catalyzed by a Rh/Naphos system in the presence of amines as nucleophiles, yielding several 3,3-diphenylpropylamines of pharmaceutical interest, including fenpiprane, prozapine and diisopromine (all used in the treatment of functional gastrointestinal disorders) (Scheme 20). The Rh/Naphos catalyst was shown to favor the regioselectivity to linear aldehydes and corresponding amines due to the steric hindrance of the two aryl substituents.

Aiming at the preparation of potential fragrances, Carrilho and Pereira,[62] reported the sequential catalytic hydroformylation/acetalization of eugenol acetate. The synthesis operated through a multi-stage continuous flow system, consisting of a tubular reactor for the homogenous $Rh(acac)(CO)_2$/xantphos catalyzed hydroformylation, coupled in series with a K10 resin packed bed reactor for the aldehyde acetalization step (Scheme 21). This pioneering strategy allowed obtaining 94% chemoselectivity for acetal formation and 96% regioselectivity for the linear product, resulting in a process productivity of 10 g/per day.

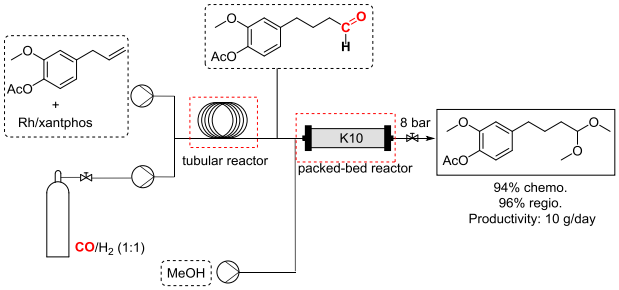
**Scheme 19** Synthesis of myrcene derived quaternary ammonium salt via Rh-catalyzed hydroformylation/reductive amination/cationization sequence




**Scheme 20** Hydroaminomethylation of 1,1-diphenylethene with secondary amines as nucleophiles




**Scheme 21** Synthesis of potential fragrances via sequential catalytic hydroformylation/acetalization of eugenol derivatives in continuous-flow

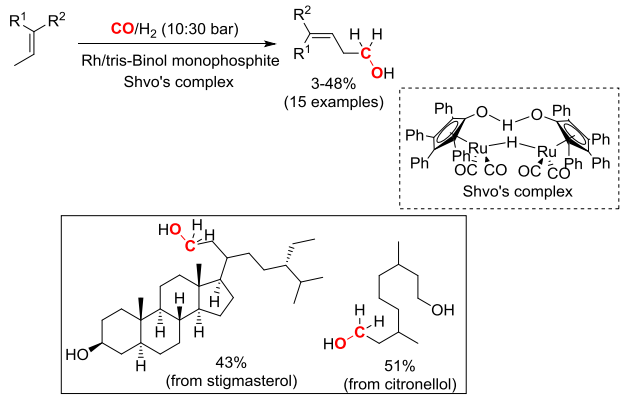



Pereira and Beller[63] described the synthesis of alcohols with interest for fine chemistry, mediated by a selective dual catalytic system to promote the domino hydroformylation–reduction reaction of di- and trisubstituted olefins (Scheme 22). The authors used a combination of Rh complexes with bulky tris-Binol monophosphite ligand and the Ru-based Shvo's complex in the presence of syngas in a $CO/H_2$ ratio of 10 : 30 bar. This highly useful strategy was further applied to the synthesis of bioactive alcohols derived from stigmasterol and citronellol.

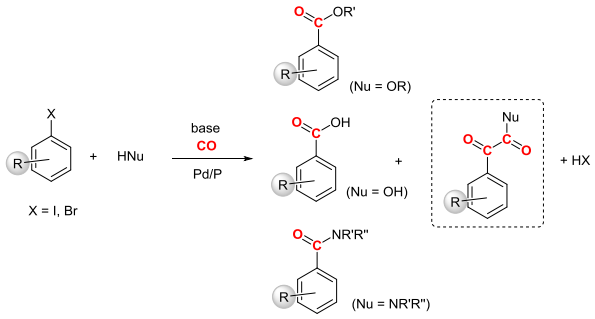
## 2.3. Carbonylation of aryl and alkenyl halides

Carbonylation of aryl, benzyl and alkenyl halides (or *pseudo-halide*) involves the incorporation of a carbonyl group into a substrate by the reaction with CO, generally catalyzed by palladium complexes, in the presence of a base and nucleophile (Scheme 23).

**Scheme 22** Synthesis of alcohols via hydroformylation–reduction of di- and trisubstituted olefins, catalyzed by a dual Rh-Ru system




**Scheme 23** Carbonylation of aryl halides, with different possible nucleophiles




The reactions yield coupled products, forming esters from alcohols (alkoxycarbonylation), phenols (phenoxycarbonylation), carboxylic acids from water (hydroxycarbonylation) or amides in the presence of amine nucleophiles (aminocarbonylation).[1,64-65]

Carbonylation reactions often compete with double carbonylation,[66-68] which is usually consequence of higher CO pressures, with occurrence of CO insertion into the Pd—Nu bond before reductive elimination occurs. The reaction's selectivity is affected by several factors, such as CO pressure, reaction temperature, the choice of the base used as hydrogen halide scavenger, electronic and steric properties of the amine nucleophile and properties/functional groups of the iodoarenes themselves.

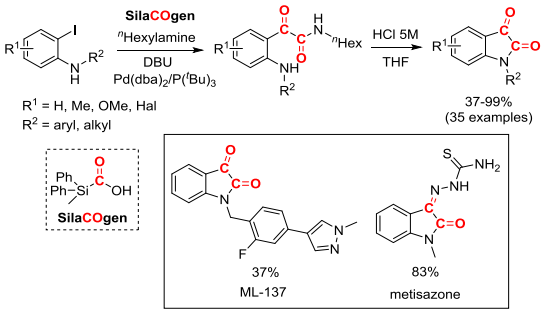
Overall, palladium-catalyzed carbonylation reactions of aryl or alkenyl halides have become a valuable tool for organic synthesis, being extensively applied to generate a range of carbonyl compounds, including various carboxylic acid, amide and ester derivatives with high synthetic relevance for fine chemicals synthesis.

### 2.3.1. Aminocarbonylation

Catalytic aminocarbonylation reactions, in which the nucleophile is an amine, have received significant attention, since it has become an easy and practical method for the synthesis of carboxamides and 2-ketoamides with biological relevance.[69]

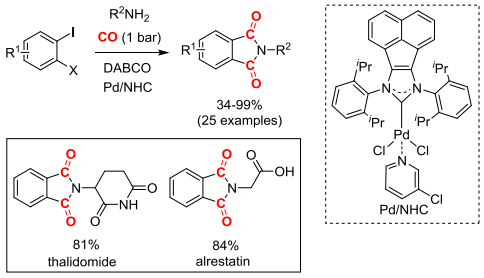
For instance, isatins (1*H*-indole-2,3-diones) are important synthons of biologically relevant molecules. Lindhardt and Skrydstrup[70] reported a one-pot synthesis of isatin heterocycles by carbonylation of 2-iodoanilines but using methyldiphenylsilanecarboxylic acid (SilaCOgen) as CO surrogate, followed by acid-promoted cyclization (Scheme 24). The reaction was catalyzed by $Pd(dba)_2$/$P(^tBu)_3$ in the presence of *n*-hexylamine and DBU as base, followed by acid-catalyzed cyclization to yield the desired isatin derivatives. This protocol was further applied to synthesis of antiviral drug metisazone and the antischizophrenia experimental drug ML-137.

**Scheme 24** Synthesis of isatin derivatives via Pd-catalyzed aminocarbonylation using SilaCOgen as CO surrogate



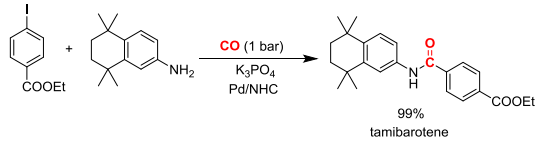

Tu[71] reported the use of palladium/*N*-heterocyclic carbene complex bearing a robust acenaphthoimidazolylidene ligand, as an efficient catalyst in double aminocarbonylations under 1 bar CO pressure at extremely low loading of the Pd/NHC catalyst, in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as base (Scheme 25). In this way, various *N*-substituted phthalimide products were synthesized, including thalidomide, a drug used to treat nausea and the ester analogue of alrestatin, used in the treatment of diabetes.

**Scheme 25** Synthesis of *N*-substituted phthalimides *via* catalytic aminocarbonylation reaction




The same group[72] applied the same catalytic palladium-NHC complex in the aminocarbonylation of various (hetero)aryl iodides under 1 bar CO pressure. Due to the high functional group tolerance, a wide range of carboxamides of practical importance were prepared, namely the anticancer drug tamibarotene (Scheme 26).

**Scheme 26** Synthesis of tamibarotene ester derivative *via* catalytic aminocarbonylation reaction

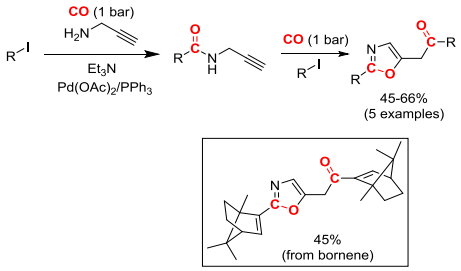



Kollár[73] described the aminocarbonylation of several iodoalkenes, using propargylamine and its derivatives as *N*-nucleophiles, $Pd(OAc)_2$/$PPh_3$ as catalyst and $Et_3N$ as base, under 1 bar CO pressure. The subsequent carbonylative Sonogashira coupling reaction of the resulting *N*-propargylcarboxamides with the iodoalkene substrate, followed by cyclization allowed to prepare a range of oxazol and oxazoline derivatives known as biologically relevant synthetic building blocks (Scheme 27).

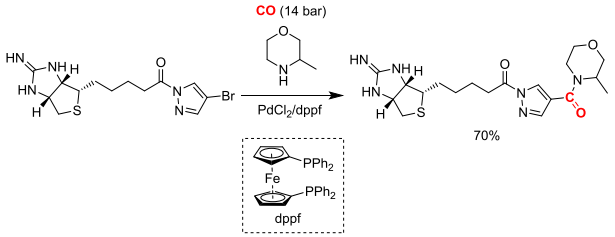
Soni[74] reported the synthesis of modified biotin derivatives (biotin-pyrazole conjugates), considered as potential anticancer agents, particularly for brain cancer, *via* palladium catalyzed aminocarbonylation of brominated pyrazole-biotin $PdCl_2$/dppf as catalyst [dppf = ferrocenediyl-bis(diphenylphosphine)] and 14 bar CO (Scheme 28).

**Scheme 27** Synthesis of oxazol derivatives via aminocarbonylation followed by carbonylative Sonogashira coupling and cyclization

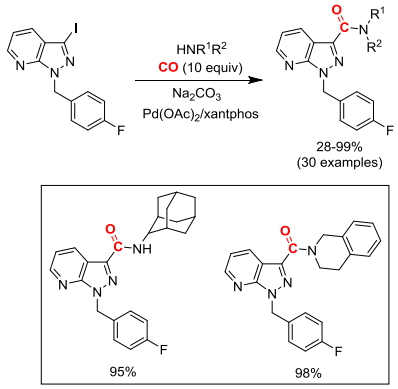



**Scheme 28** Synthesis of biotin-pyrazole carboxamides via Pd-catalyzed aminocarbonylation




Keating[75] described the synthesis of pharmacologically relevant 1,3-disubstituted pyrazolo[3,4-*b*]pyridine-3-carboxamide derivatives, by aminocarbonylation (Scheme 29), using [$Pd(OAc)_2$/xantphos)] as catalyst in the presence of $Na_2CO_3$ as base, and employing *ex situ* generated CO gas using a two-chamber reactor. This strategy allowed to prepare a range of diversely substituted C-3 carboxamide pyrazolo[3,4-*b*]pyridines in moderate to excellent yields (28%-99%).

**Scheme 29** Synthesis of pharmacologically relevant pyrazolo[3,4-*b*]pyridine-carboxamides via aminocarbonylation

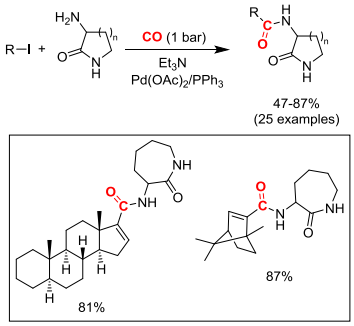



Kollár[76] used 3-aminolactams as *N*-nucleophiles in the aminocarbonylation of iodoalkenes and iodoarenes using $Pd(OAc)_2$/$PPh_3$ as catalyst in the presence of $Et_3N$ under 1 bar CO pressure. The application of 3-aminoazepan-2-one led to compounds of direct pharmacological interest (Scheme 30).

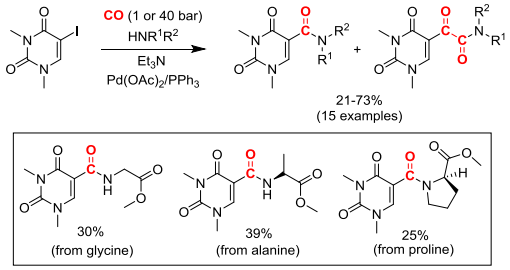
Functionalized *N*-substituted 5-iodouracils, with well-known antimicrobial and anticancer properties,[77] were prepared through aminocarbonylation of 5-iodouracil in the presence of primary and secondary amines, using $Pd(OAc)_2/PPh_3$ as catalyst.[78] Depending on the reaction conditions, both carboxamides and 2-ketocarboxamides were synthesized through mono or double carbon monoxide insertion, respectively (Scheme 31).

Nortropinone and nortropine which are 8-azabicyclo[3.2.1]octane derivatives with useful application as opioid receptor modulators,[79] were used as secondary amines in aminocarbonylation resulting in the formation of a variety of tertiary carboxamides (*N*-acylated tropane derivatives).[80] Using iodoalkenyl compounds as substrates and $Pd(OAc)_2/PPh_3$ as catalyst, carboxamides could be synthesized under 1 bar CO pressure (Scheme 32).

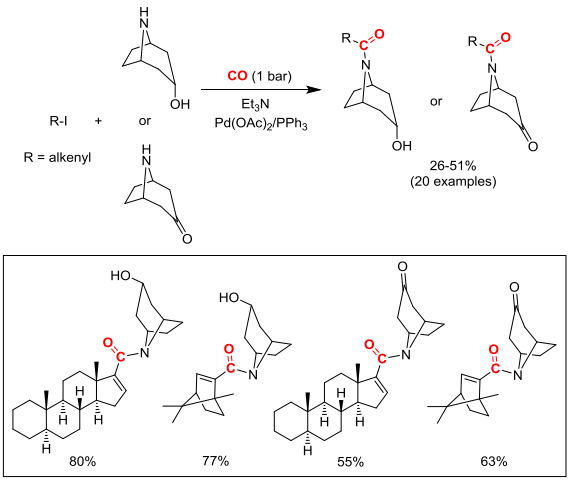
**Scheme 30** Synthesis of biologically active 3-aminoazepan-2-ones via Pd-catalyzed aminocarbonylation




**Scheme 31** Synthesis of *N*-substituted 5-carboxamide uracils via Pd-catalyzed aminocarbonylation




**Scheme 32** Synthesis of nortropinone and nortropine carboxamide derivatives via Pd-catalyzed aminocarbonylation

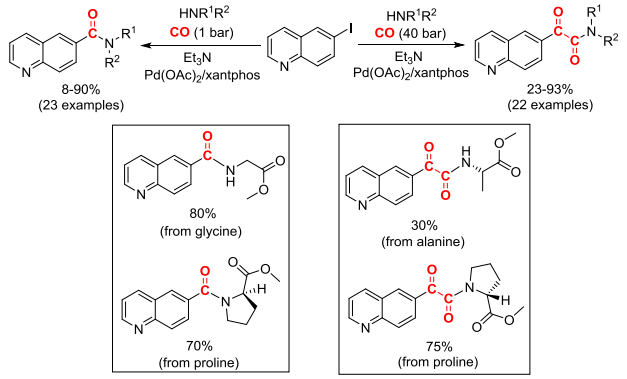



It is well documented that 6-quinoline derivatives are important synthons for the preparation of central nervous system and anti-asthmatic drugs.[81] In this regard, palladium-catalyzed aminocarbonylation of 6-iodoquinoline, recently described by Kollár,[82] is another paradigmatic example of the application of this reaction in the preparation of carboxamide and ketocarboxamide quinoline derivatives, catalyzed by $Pd(OAc)_2$/xantphos (using 1 bar CO) or $Pd(OAc)_2$/triphenylphosphine (using 40 bar CO pressure), respectively (Scheme 33).

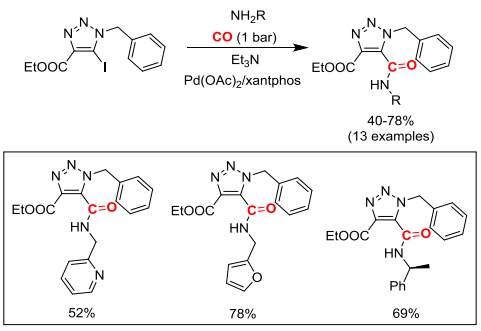
Aiming at the synthesis of carboxamidotriazoles, which are known to act as calcium channel blockers with anti-cancer activity,[83] Kollár described the aminocarbonylation of iodo-substituted 1,2,3-triazoles,[84] previously prepared from the corresponding

acetylene derivatives.[84-85] These compounds underwent palladium-catalyzed aminocarbonylation using $Pd(OAc)_2$/xantphos as catalysts and 1 bar CO, in presence of triethylamine as base (Scheme 34), yielding 1,4- or 1,5-substituted carboxamidotriazols in moderate to high yields (40%—78%).

**Scheme 33** Synthesis of quinoline derivatives via Pd-catalyzed aminocarbonylation

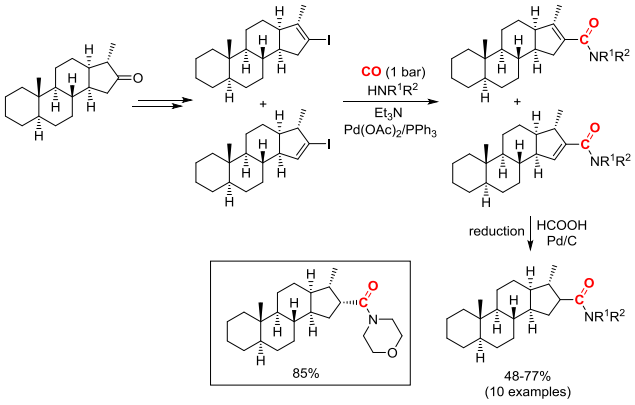



**Scheme 34** Synthesis of bioactive 1,5-substituted carboxamidotriazoles via Pd-catalyzed aminocarbonylation



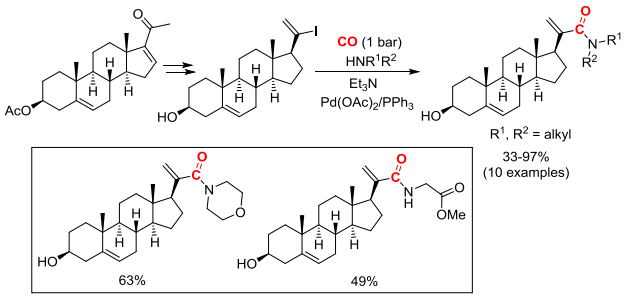

Kollár and Skoda-Földes described a palladium-catalyzed aminocarbonylation strategy for the functionalization of steroidal skeleton with $Pd(OAc)_2/PPh_3$ as catalysts and 1 bar CO, in the presence of triethylamine as base (Scheme 35).[86] Several 13α-18-nor-16-carboxamides were synthesized from the 16-iodo-16-ene and 16-iodo-15-ene substrates, prepared from the 16-keto derivative by Barton's method. The mixture was then subjected to the aminocarbonylation reaction, after which, when morpholine was used as nucleophile, the resulting mixture of ene-carboxamides could be reduced by formic acid catalyzed by Pd/C, yielding the desired carboxamide selectively.

**Scheme 35** Synthesis of 13α-18-nor-16-carboxamide steroid derivatives via Pd-catalyzed aminocarbonylation



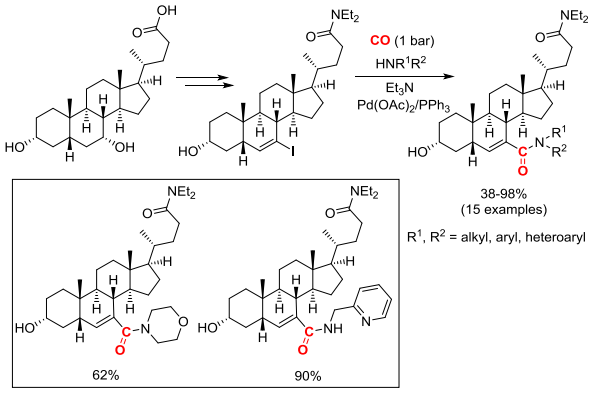

The same authors reported the aminocarbonylation of steroidal substrate pregna-20-iodo-20-ene,[87] prepared also from its corresponding 3α-acetoxy-pregna-5,16-dien-20-one by Barton's method (Scheme 36). The iodoalkene functionality was aminocarbonylated with several primary and secondary amines as *N*-nucleophiles, using $Pd(OAc)_2/PPh_3$ as catalyst and 1 bar CO, in the presence of triethylamine as base.

**Scheme 36** Synthesis of pregna-20-carboxamide-20-ene derivatives via Pd-catalyzed aminocarbonylation




One of the most hindered positions of the steroidal skeleton is position 7. Nevertheless, Kollár reported the conversion of the 7-keto functionality of chenodesoxycholic acid into 7-iodo-6-ene via Barton's method.[88] The resulting product was then used as substrate in palladium-catalyzed aminocarbonylation reaction, with $Pd(OAc)_2/PPh_3$ as catalyst, to give the biologically relevant 7-carboxamides, using triethylamine as base and 1 bar CO (Scheme 37).

**Scheme 37** Synthesis of chenodesoxycholic acid 7-carboxamide derivatives *via* Pd-catalyzed aminocarbonylation




Steroid dimers are recognized synthons for a diversity of pharmaceutical applications.[89] In this regard, Pereira and Kollár[90,91] described the synthesis of a set of steroid-based dicarboxamides, through palladium-catalyzed aminocarbonylation of iodo-steroids, using several alkyl- and aryldiamines as *N*-nucleophiles, and $Pd(OAc)_2/PPh_3$ as catalysts, in the presence of 30 bar CO. The delivered steroid dimeric dicarboxamides are depicted in Scheme 38, bearing the diaminobutyl fragment as bridge demonstrating quite promising results against human lung carcinoma A549 cells.[91]

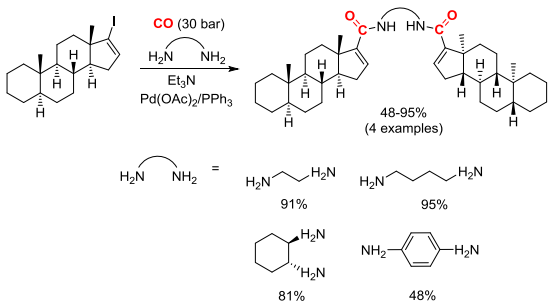
Picolylamines are important building blocks in pharmaceutically relevant compounds. There, they have been applied as nucleophiles in the aminocarbonylation of iodoaromatics and iodoalkenes,[92] including chiral substrates,[93] to prepare biologically relevant families of picolyl-carboxamides, using $Pd(OAc)_2/PPh_3$ as catalyst, in the presence of 1 bar CO (Scheme 39).

Aminocarbasugar compounds are well-known useful synthons for the synthesis of pharmaceuticals.[94] In this context, Kollár and Pereira[95] described the synthesis of conduritol based carbox-

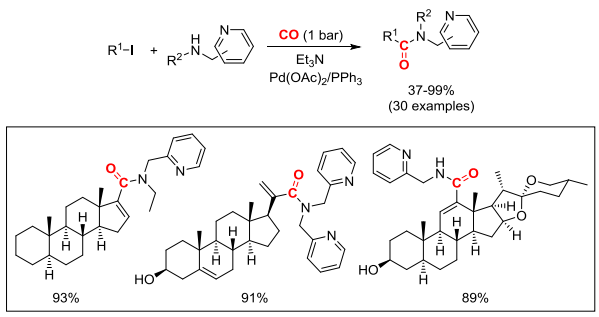
  

amides bearing aminoacid groups, *via* palladium-catalyzed aminocarbonylation of bromo or iodocyclohexenetetraols, using $Pd(OAc)_2/PPh_3$ as catalyst and 30 bar CO pressure. Two aminoacid derivatives were used as nucleophiles, namely (*L*)-alanine and (*L*)-valine methyl esters, providing the corresponding biologically relevant carboxamides in 85% and 66% yields, respectively (Scheme 40).

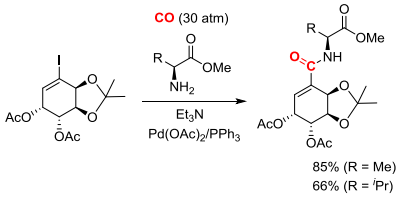
**Scheme 38** Synthesis of steroid dimers with a dicarboxamide linkage via Pd-catalyzed aminocarbonylation




**Scheme 39** Synthesis of picolyl-carboxamides *via* Pd-catalyzed aminocarbonylation



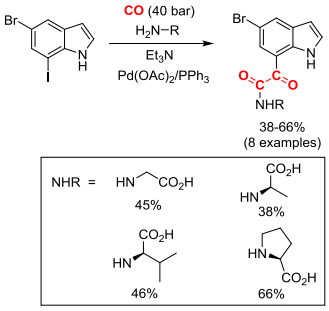

**Scheme 40** Synthesis of conduritol-based carboxamides via Pd-catalyzed aminocarbonylation of iodo-cyclohexenetetraol derivatives



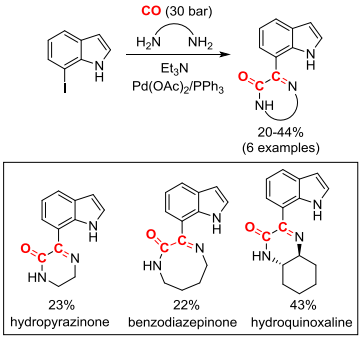

The same authors[96] reported the selective functionalization of 5-bromo-7-iodo-indole through palladium-catalyzed double carbonylation, using $Pd(OAc)_2/PPh_3$ as catalyst and 40 bar CO pressure. Among the many primary and secondary amines used as nucleophiles, we highlight the use of amino acid methyl esters, namely those from glycine, alanine, valine and proline, providing the corresponding 7-ketocarboxamide-indole derivatives in moderate yields (Scheme 41).

More recently, a Pd-catalyzed sequential aminocarbonylation/cyclization approach[97] was described for the synthesis of *N*-heterocycles containing the indole motif also using diamines as *N*-nucleophiles, yielding several biologically relevant indole-based *N*-heterocyclic derivatives such as hydropyrazinones, benzodiazepinones and hydroquinoxalines (Scheme 42). The authors observed an influence of the structure of the diamine nucleophile on reaction's selectivity, with the best yield for the cyclic products being obtained in the presence of (*1S*,*2S*)-(+)-cyclohexane-1,2-diamine as the nucleophile (43 % yield).

**Scheme 41** Synthesis of indole-based carboxamides via Pd-catalyzed aminocarbonylation of 5-bromo-7-iodo-indole derivatives

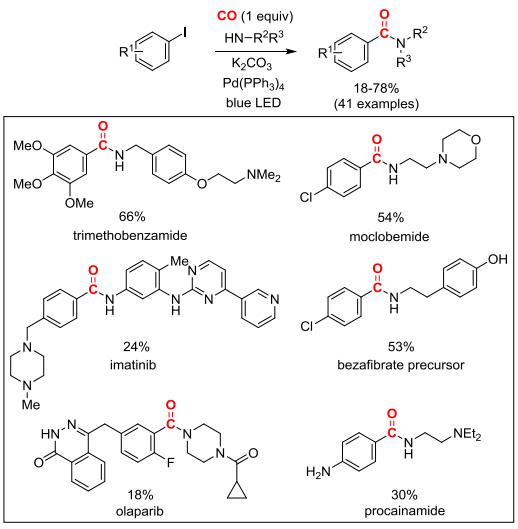



**Scheme 42** Synthesis of hydropyrazinones, benzodiazepinones and hydroquinoxalines via Pd-catalyzed double aminocarbonylation/cyclization approach




The efficiency of palladium-catalyzed aminocarbonylation of iodoarenes was substantially increased by blue LED visible light irradiation using $Pd(PPh_3)_4$ as catalyst precursor and potassium carbonate as base (Scheme 43).[98] The mild reaction conditions, the stoichiometric amounts of carbon monoxide and the use of wide range of aryl substrates and amine nucleophiles yielded a range of carboxamide pharmaceutical products in moderate to good yields (18%—78%), namely trimethobenzamide, an antiemetic drug, moclobenzamide, for the treatment of depression, bezafibrate precursor, a drug against hyperlipidaemia, procainamide, to treat cardiac atthythmias, imatinib and anticancer drug and olaparib, a PARP (poly (ADP-ribose) polymerase) inhibiting drug.

**Scheme 43** Synthesis of carboxamide-based drugs via blue LED activated Pd-catalyzed aminocarbonylation



As one of the most promising ways to produce carbon monoxide, the photocatalytic $CO_2$ reduction ($CO_2RR$) was developed and efficiently implemented in the value-added synthesis of fine chemicals (Figure 1).[99] This system was used for the aminocarbonylation reaction of 2-chloro-3-iodopyridine with 4'-chloro-[1,1'-biphenyl]-2-amine, catalyzed by $Pd(PPh_3)_4$ as catalyst in the presence of triethylamine as base, yielding boscalid, an active broad range fungicide agent (Scheme 44).

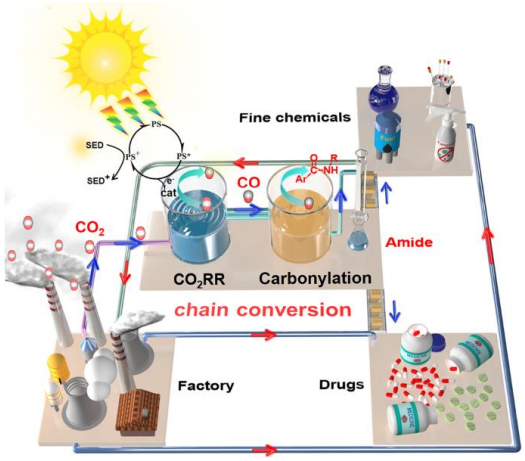
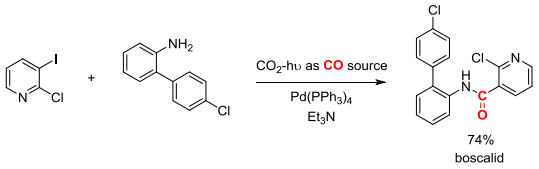



**Figure 1** Tandem coupling of photocatalytic reduction ($CO_2RR$) and aminocarbonylation reaction for the synthesis of carboxamide fine chemicals. Reproduced with permission. Copyright 2022 Springer Nature & The Authors.

**Scheme 44** Synthesis of boscalid through Pd-catalyzed aminocarbonylation reaction using $CO_2$ as CO surrogate (via photoreduction)

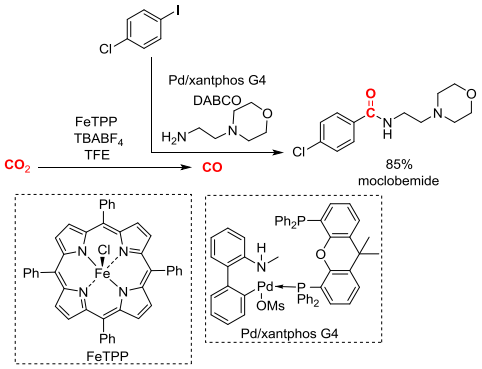



Another strategy to obtain CO from $CO_2$ is by electrochemical reduction. This strategy was employed in both Pd-catalyzed amino- and alkoxycarbonylation reactions. A selected example of the relevant pharmaceutical compounds prepared through this strategy is moclobemide, a drug used for treatment of depressive disorder (Scheme 45).[100] Using a two-chamber reactor, $CO_2$ was first reduced to CO by means of electroreduction, using iron(III) tetraphenyl porphyrin (FeTPP) as electrocatalyst, in the presence of tetrabutylammonium tetrafluoroborate ($TBABF_4$) as electrolyte and trifluoroethanol (TFE) as proton source. The generated CO was then transferred to the second chamber and used in the aminocarbonylation of 1-chloro-4-iodobenzene with the corresponding amine, in the presence of Pd/xantphos G4 as catalyst and DABCO as base.

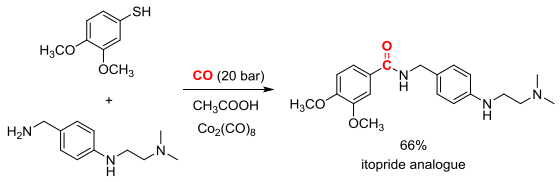
Pérez-Castells[101] reported a methodology for obtaining amides using thiols and amines as substrates, through a carbonylative coupling, using $Co_2(CO)_8$ as catalyst under 20 bar CO pressure, in the presence of acetic acid. Among several amides, the synthesis of an itopride analogue was transposed to continuous-flow conditions, which allowed its scale-up, leading to a 66% yield (Scheme 46).

Solvents constitute the largest component for many chemical processes and in the pharmaceutical industry, the substitution of conventional (non-renewable) organic solvents is of upmost importance. Thus, palladium-catalyzed aminocarbonylation reactions were successfully carried out using renewable solvents, such as 2-methyltetrahydrofuran, limonene and dimethyl carbonate (DMC), as well as biomass-derived 1,1-diethoxyethane, isosorbide dimethyl ether, eucalyptol, rose oxide, γ-terpinene, and α-pinene.[102] As an example, the use of DMC as alternative solvent allowed for the synthesis of trimetozine (a sedative) and an itopride analogue (used for the treatment of gastrointestinal symptoms) in excellent yields (95%—96%). The authors used Pd/xantphos G3 as catalyst and a CO surrogate (COgen – 9-methyl-9*H*-fluorene-9-carbonyl chloride) in DMC as alternative solvent (Scheme 47).

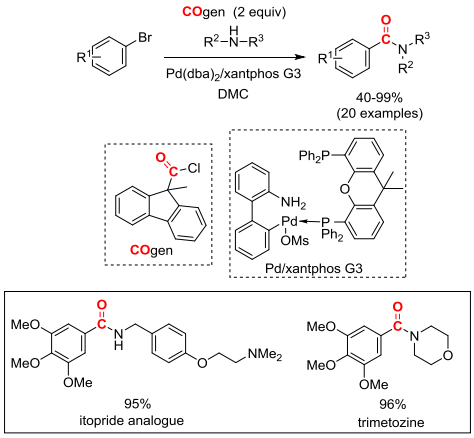
**Scheme 45** Synthesis of moclobemide through Pd-catalyzed aminocarbonylation using $CO_2$ as CO surrogate (via electroreduction)




**Scheme 46** Synthesis of an itopride analogue via Co-catalyzed aminocarbonylation of 3,4-dimethoxybenzenethiol



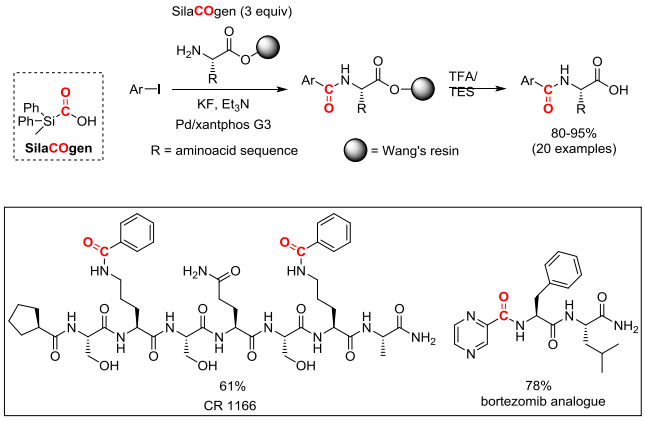

**Scheme 47** Drugs synthesis *via* Pd-catalyzed aminocarbonylation using DMC as green solvent




The same group[103] introduced N-capping terminal groups onto peptides via aminocarbonylation of aryl halides, also catalyzed by Pd/xantphos G3 palladacycle, using Wang type polystyrene resin immobilized peptides as nucleophiles, in the presence of potassium fluoride and triethylamine as base. In this strategy, SilaCOgen was used as '*in situ*' carbon monoxide-releasing compound, followed by peptide cleavage from the resin using 95% trifluoroacetic acid (TFA) in triethylsilane (TES) (Scheme 48). Using this procedure, the authors managed to prepare a large set of carboxamide compounds, including CR 1166, an anticancer agent, and a bortezomib analogue, an antineoplastic drug to treat multiple myeloma.

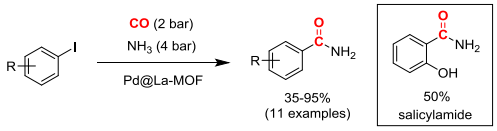
  

**Scheme 48** Drugs synthesis *via* Pd-catalyzed aminocarbonylation of aryl iodides with solid phase-bound peptide amino acid as nucleophiles



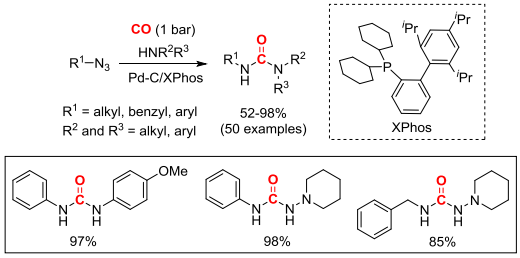

Islam and Bordoloi[104] reported the synthesis of carboxamide derivatives such as salicylamide, an analgesic and antipyretic drug, through aminocarbonylation reaction between aryl halides (including substituted iodo-benzene, iodo-thiophene and iodo-pyridine substrates), carbon monoxide (2 bar) and 4 bar gaseous ammonia, using an immobilized palladium catalyst (Pd@La-MOF) (Scheme 49). The catalyst was prepared by incorporation of Pd(0) clusters into the metal organic framework (MOF), stabilized by organic linkers, which prevent Pd clusters from leaching during the reaction. The catalyst could be recycled and reused up to four times, with a negligible loss of activity.

**Scheme 49** Synthesis of salicylamide via heterogeneous aminocarbonylation



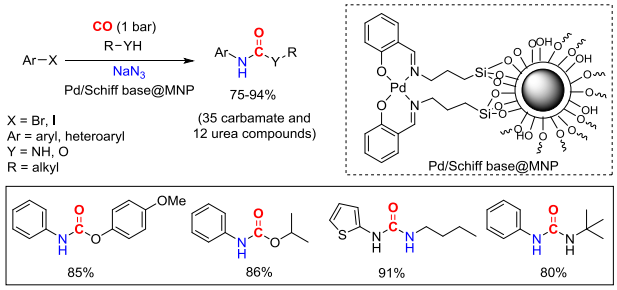

Ureas are relevant bioactive functional groups,[105] particularly alkyl/benzyl unsymmetrical ureas are widely found in a wide range of pharmaceuticals and agrochemicals. In this regard, Zhang[106] reported an efficient protocol that involved a palladium-catalyzed carbonylative amination of alkyl or aryl azides as substrates, using Pd-C/XPhos as catalyst and 1 bar CO (Scheme 50). Through this strategy, more than 50 examples of non-symmetric, biologically active urea derivatives were synthesized in good to excellent yields (52%—98%).

**Scheme 50** Synthesis of biologically relevant ureas *via* catalytic carbonylation of azides



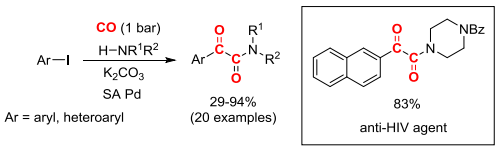

Inaloo[107] reported a convenient one-pot domino methodology for the preparation of carbamates and ureas, which can serve as synthons in the pharmaceutical, cosmetics and agriculture industries. The authors used a Pd/Schiff base complex immobilized onto magnetic nanoparticles (MNP) as catalyst, under 1 bar CO pressure, to promote the reaction between the suitable aryl halides (bromides and iodides) with sodium azide in the presence of the corresponding amine (for ureas) or alcohols (for carbamates) (Scheme 51). Excellent yields (75%—94%) and a broad substrate scope with high functional group tolerance were achieved. In addition, this catalyst was magnetically recovered and reused in seven cycles without significant decrease in the catalytic activity.

**Scheme 51** Synthesis of biologically relevant ureas and carbamates via Pd-catalyzed aminocarbonylation of azides



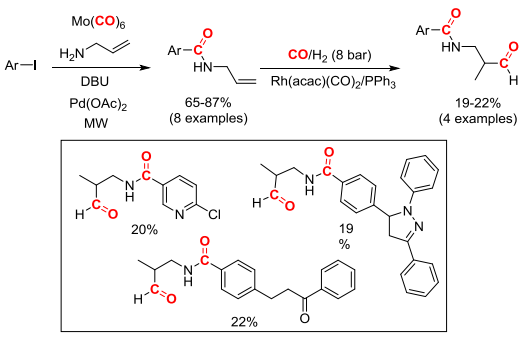

Sato[108] used sulfur-modified Au-supported palladium nanoparticles (SA Pd) as catalysts for preparing α-ketoamides, under 1 bar CO pressure and $K_2CO_3$ as base, without any additional additives or ligands (Scheme 52). This ligand-free catalyst was shown to favor the CO coordination to the surface of Pd nanoparticles and, consequently, the double insertion of CO onto the intermediate before the nucleophilic attack of amines occurred. Remarkably, this method was applied to the synthesis of an anti-HIV drug with 83% selectivity.

**Scheme 52** Synthesis of α-ketoamides via double carbonylation reaction using palladium nanoparticles as catalyst




Carrilho and Pereira[109] developed an innovative methodology for the synthesis of highly functionalized formylcarboxamide derivatives with biological relevance, prepared by a sequential aminocarbonylation/hydroformylation approach. The first step involved a palladium-catalyzed aminocarbonylation of iodoaromatic substrates with $Pd(OAc)_2$ as catalyst precursor using allylamine as nucleophile, DBU as base and $Mo(CO)_6$ as alternative CO source under microwave irradiation, yielding a set of *N*-heterocyclic-based allylcarboxamides (Scheme 53). Subsequent rhodium catalyzed hydroformylation of the allylcarboxamide derivatives using

**Scheme 53** Synthesis of formylcarboxamide derivatives with biological relevance via sequential aminocarbonylation/hydroformylation

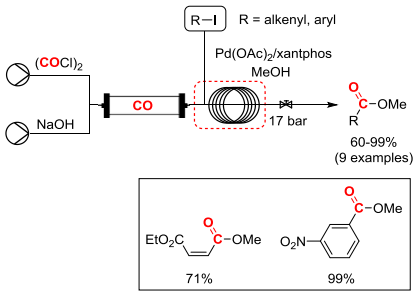


$Rh(acac)(CO)_2/PPh_3$ and 8 bar $CO/H_2$ (1 : 1) produced the corresponding indole, pyridine and pyrazoline derivatives encompassing both carboxamide and formyl moieties.

### 2.3.2. Alkoxy, phenoxy and hydroxycarbonylation

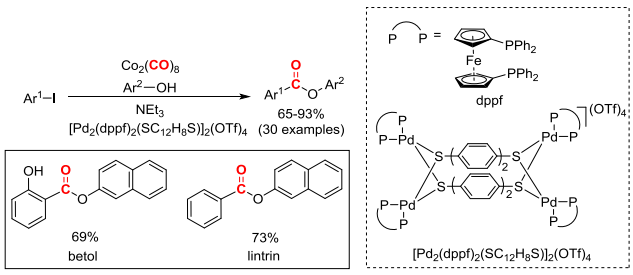
Although most alkoxycarbonylations are carried out using polarizable iodoarenes, the alkoxycarbonylation of various *N*-heteroaryl chlorides has been successfully performed by using appropriate ligands in palladium-based catalytic systems. For instance, Ulven and Ley[110] applied a flow chemistry alkoxycarbonylation using oxalyl chloride to provide a controlled generation of CO in flow (Scheme 54). By using a tube-in-tube reactor, oxalyl chloride could be conveniently and safely hydrolyzed using a NaOH solution to generate CO in the outer stream, which then passed through a semi-permeable inner tubing to enrich a reaction stream where it was consumed. The reactions were carried out under mild reaction conditions, using $Pd(OAc)_2$/xantphos as catalyst and methanol as alkoxylating agent. This approach allowed the transformation of terminal iodoalkenes and iodoheteroarenes into the corresponding biologically relevant esters.

**Scheme 54** Synthesis of esters using a continuous-flow controlled CO generation and sequential use in Pd-catalyzed alkoxycarbonylation reactions



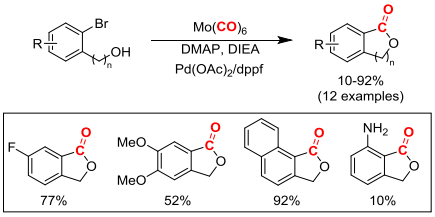

Dey and Bhanage[111] reported the use of a tetranuclear palladium/dppf dithiolate complex (dppf = 1,1'-bis(diphenylphosphino)ferrocene) as catalyst in the phenoxycarbonylation reaction, to synthesize various aryl/alkyl benzoates, including aryl salicylates. Using $Co_2(CO)_8$ as less toxic carbon monoxide source, several drug molecules were synthesized, such as betol, a muscle relaxer, and lintrin, commonly used in the treatment of community acquired pneumonia (Scheme 55).

**Scheme 55** Synthesis of drugs by co-catalyzed phenoxycarbonylation of aryl iodides



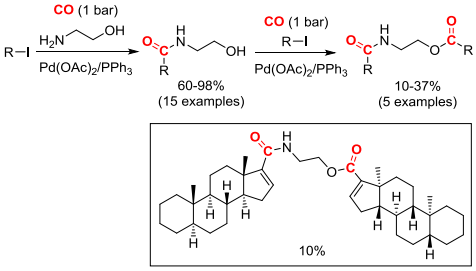

Phthalides are a class of natural compounds known mainly as bioactive constituents of different plant species, and widely used for medicinal purposes.[112] In this regard, Alterman[113] reported the synthesis of biologically relevant phthalides from the corresponding aryl bromides, using an intramolecular alkoxycarbonylation strategy, using $Pd(OAc)_2$/dppf as catalyst. Carbon monoxide was generated *in situ* from DMF and $Mo(CO)_6$ under microwave irradiation, which enabled the carbonylation–lactone formation under mild reaction conditions (Scheme 56).

**Scheme 56** Synthesis of biologically relevant phthalides by intramolecular alkoxycarbonylation



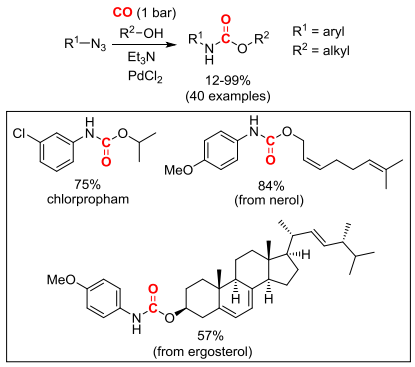

Kollár[114] described an efficient carbonylation strategy, using *N*,*O*-nucleophiles, for the synthesis of unprecedented bifunctional amide-ester compounds. The aminocarbonylation of 2-iodobornene and steroids with iodoalkene functionality was followed by alkoxycarbonylation, both catalyzed by $Pd(OAc)_2/PPh_3$, in the presence of 1 bar CO, resulting in several amide-ester products, including biologically relevant steroid dimers (Scheme 57).

**Scheme 57** Synthesis of bifunctional amide-ester compounds, including biologically relevant steroid dimers, via Pd-catalyzed carbonylation using *N*,*O*-nucleophiles




Jiao[115] described the synthesis of a large set of biologically relevant carbamates by $PdCl_2$-catalyzed carbonylative alkoxylation of aryl azides with suitable alcohols, in the presence of 1 bar CO. Among the several products, several bioactive compounds were obtained, including the drug chlorpropham, used as plant growth regulator and herbicide, as well as terpene and steroid derivatives (Scheme 58).

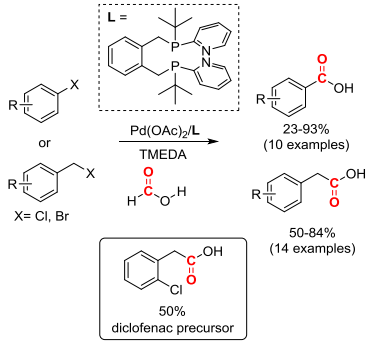
**Scheme 58** Synthesis of bioactive carbamates via $PdCl_2$-catalyzed carbonylative alkoxylation of aryl azides




A highly active *in situ* generated Pd catalyst, obtained from palladium(II) acetate and 1,2-bis((*tert*-butyl(2-pyridinyl)phosphinyl)methyl)benzene, was developed by Beller[116] to promote the carboxylative synthesis of arylacetic and benzoic acids, using formic acid as CO surrogate and tetramethylethylenediamine (TMEDA) as base. Carboxylic acids, including non-steroidal anti-inflammatory drugs (NSAIDs), such as a diclofenac precursor, were synthesized under mild conditions in good yields (Scheme 59).

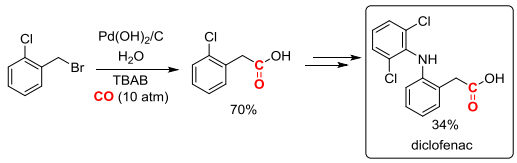
  

**Scheme 59** Pd-catalyzed carbonylative synthesis of arylacetic and benzoic acids using formic acid as CO surrogate



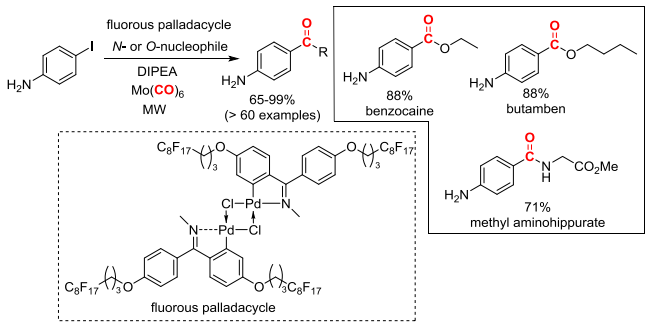

Echeverria and Evano[117] reported the carboxylation of benzylic bromides using CO as a tool to prepare benzylic acids. The reaction was performed using $Pd(OH)_2/C$ as catalyst and tetrabutylammonium bromide (TBAB) as catalyst stabilizer, in the presence of 4 equiv. $H_2O$ and 10 bar CO, smoothly obtaining an array of aryl acetic acids after simple extraction and acid-base wash. This reaction was found to be broadly applicable, and was successfully extended to the synthesis of the nonsteroidal-inflammatory drug diclofenac (Scheme 60).

**Scheme 60** Hydroxycarbonylation of benzylic bromides for the synthesis of benzylic acids, including diclofenac precursor




Lam[118] developed a Pd-catalyzed carbonylation strategy for aryl halides coupling with nucleophiles such as alcohols and amines, using microwave radiation. A fluorinated palladacycle catalyst was used, in the presence of $Mo(CO)_6$ as CO source and DIPEA (*N*,*N*-diisopropylethylamine) as base. Among several products, pharmaceutically important compounds were prepared in good to excellent yields (65%—99%), such as benzocaine and butamben as anesthetics, and methyl aminohippurate, a diagnostic agent. The oxime-based palladacycle fluorinated catalyst demonstrated high recoverability by fluorous solid-phase extraction and reusability for 5 cycles with minor catalytic activity loss (Scheme 61).

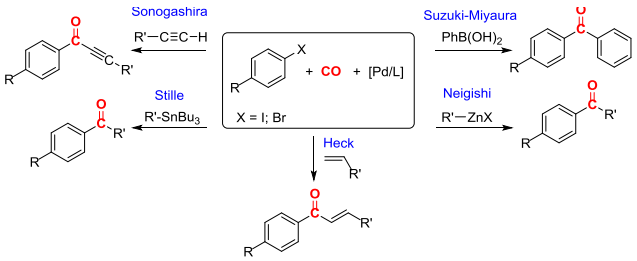
**Scheme 61** Synthesis of pharmaceutically relevant ester and amide derivatives via Pd-catalyzed carbonylation of aryl halides using $Mo(CO)_6$ as CO source




## 2.4. Carbonylative cross-coupling reactions

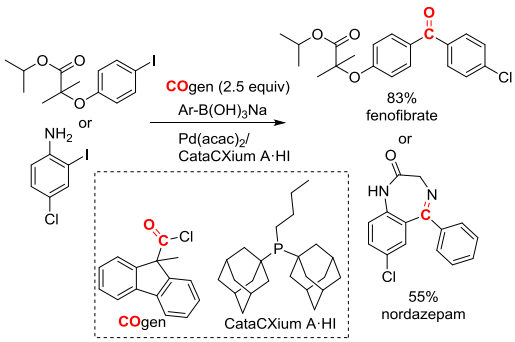
Carbonylative coupling reactions are a class of organic reactions that involve the formation of a new carbon-carbon bond through the reaction of an organic halide and a *C*-nucleophile, in the presence of CO or its surrogates.[119-121] The reaction typically occurs in the presence of a transition metal catalyst, often palladium and is characterized by the incorporation of carbon monoxide into the products. These reactions have been extensively studied and developed over the past few decades due to their synthetic utility and ability to generate complex organic structures in a single step.[122] Depending on the type of C-nucleophile, catalyst and reaction conditions, used in the fine chemicals synthesis and herein covered, there are several different types of carbonylative coupling reactions (Scheme 62). Carbonylative coupling reactions are powerful tools for the synthesis of complex organic molecules and have broad applications in organic synthesis, turning possible the preparation of a wide range of synthetically versatile fine chemicals.

**Scheme 62** General overview of carbonylative cross-coupling reactions




For instance, Skrydstrup and Molander[123] reported a carbonylative Suzuki–Miyaura reaction between aryl bromides and arylboronates, using an excess of carbon monoxide (2.5 equiv.), generated *ex situ* from the stable solid CO surrogate COgen (9-methyl-9*H*-fluorene-9-carbonyl chloride). The most promising results were obtained when the reaction was catalyzed by a palladium complex, *in situ* generated from Pd(II) salt and CataCXium A·HI® ligand (CataCXium A·HI® = di(1-adamantyl)-*n*-butylphosphine) (Scheme 63). Black palladium precipitation and competitive diaryl formation were minimized by using sodium aryl trihydroxy borates, under base-free conditions. The reaction's versatility was demonstrated by the efficient synthesis of a large set of non-symmetric diaryl ketones in moderate to good yields, including fenofibrate (83%), a triglyceride and cholesterol regulator drug, and the benzodiazepine drug nordazepam (55%).[124]

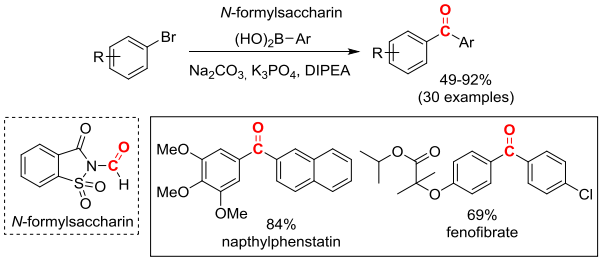
**Scheme 63** Synthesis of drugs via carbonylative Suzuki–Miyaura reaction between aryl bromides and arylboronates




Han's group[125] developed a sustainable transition-metal-free carbonylative Suzuki-Miyaura reaction, in which *N*-formylsaccharin was used as CO precursor (Scheme 64). Through this strategy, an array of aryl iodides and boronic acids were reacted, in the presence of sodium carbonate, tripotassium phosphate and DIPEA,

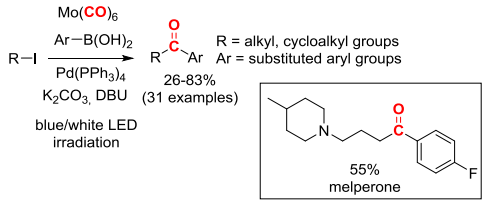
leading to the synthesis of a large range of aryl ketones in good to excellent yields (42%—92%). The developed protocol was successfully applied to the synthesis of fenofibrate (69%), and naphthylphenstatin (84%), a tubulin polymerization inhibitor and anticancer agent.

**Scheme 64** Drug synthesis via transition-metal-free carbonylative Suzuki-Miyaura reaction



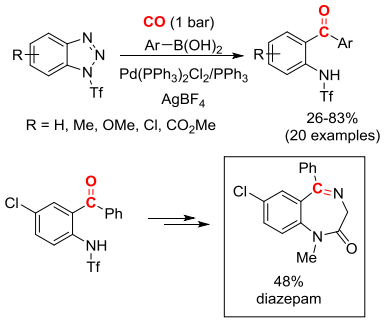

Odell[126] reported a method for visible light-mediated Pd-catalyzed carbonylative coupling using a double chamber system. Several aryl boronic acids and alkyl iodides were employed as coupling partners and $Mo(CO)_6$ (2.5 equiv.) was used as CO source, in the presence of $Pd(PPh_3)_4$ as catalyst, $K_2CO_3$ and DBU as bases (Scheme 65). Among the several ketone compounds (31 examples), prepared in modest to good yields (26%—83%), the method was transposed to the synthesis of the antipsychotic drug melperone.

**Scheme 65** Synthesis of ketones via visible light-mediated Pd-catalyzed carbonylative coupling




Tang[127] implemented a Pd-catalyzed Suzuki-Miyaura coupling reaction using 1 bar CO pressure, but introducing benzotriazoles as coupling partners along with boronic acids. The reaction was carried out using $Pd(PPh_3)_2Cl_2/PPh_3$ as catalyst, in the presence of $AgBF_4$ (Scheme 66). Computational studies allowed to attest that the benzotriazole's N1-substitution bearing a highly electron withdrawing group such as triflate (Tf) proved beneficial for the ring opening. It was concluded that the benzotriazole ring-opening was thermodynamically unfavorable; however, $AgBF_4$ was shown to play a crucial role by stabilizing *in-situ* formed diazonium zwitterionic intermediates. Besides the many products provided, the synthetic versatility of the method was demonstrated by the preparation of various drug molecules in moderate to good yields (26%—83%), including diazepam.

**Scheme 66** Pd-catalyzed Suzuki-Miyaura carbonylative coupling reaction between benzotriazoles

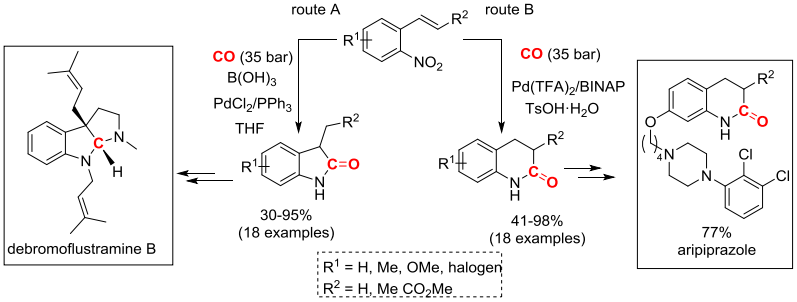



Indolin-2-one and dihydroquinolin-2-one derivatives are important synthons in pharmaceutical and medicinal chemistry. Li[128] developed different strategies for the synthesis of these types of heterocyclic building blocks, starting from *o*-nitrostyrene derivatives, using 35 bar CO pressure in both cases (Scheme 67). Using $PdCl_2/PPh_3$ in the presence of $B(OH)_3$ (Scheme 67, route A), olefin hydrocarboxylation was initially carried out, followed by partial reduction of the $NO_2$ moiety and cyclization reaction to give the *N*-hydroxyl indolin-2-ones, which were further catalytically reduced by CO to afford the indolin-2-one derivatives in up to 95% yield. When the reaction was performed using $Pd(TFA)_2$/BINAP (TFA = trifluoroacetate), in the presence of $TsOH{\cdot}H_2O$ (Scheme 67, route B), complete deoxygenation and carbonylation of the $NO_2$ group occurred first, yielding the corresponding isocyanate, which underwent internal hydrocyclization to generate 3,4-dihydroquinolin-2-one derivatives in up to 98% yield. Notably, the methodology could be successfully used to synthesize debromoflustramine B, a selective butyrylcholinesterase inhibitor, and aripiprazole, a worldwide top 3 sold pharmaceutical, mainly used for treatment of schizophrenia and bipolar disorder.

Das[129] also developed a carbonylative Suzuki coupling reaction, by reacting aryl iodides and aryl boronic acids, catalyzed by a Pd-NHC complex, in the presence of potassium carbonate as base and molybdenum hexacarbonyl as CO surrogate (Scheme 68). A wide range of diaryl ketones was prepared using this strategy, and was particularly effective for the synthesis of biologically active 3-aroylquinolin-4(*1H*)-one derivatives (62%—73% yields), as well as acridones (68%—78% yields), obtained after consecutive coupling and intramolecular cyclization, in the presence of a strong base potassium *tert*-butoxide.

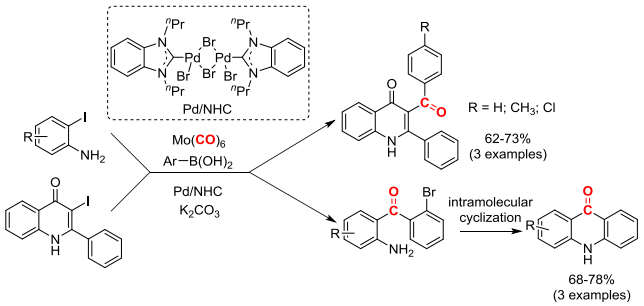
Kobayashi[130] reported another methodology for the preparation of diaryl ketone synthons through carbonylative Suzuki–Miyaura coupling reaction of aryl iodides with aryl boronic acids, using 1 bar CO pressure, in the presence of ligand-free palladium nanoparticles as catalyst, along with potassium carbonate base (Scheme 69). Several examples obtained in high yields (up to 97%) and selectivity were achieved even with low catalyst loading. Furthermore, the ligand-free immobilized palladium nanoparticles were able to be recovered by simple filtration and the catalytic activity was kept for up to 5 runs.

**Scheme 67** Synthesis of indolin-2-one and dihydroquinolin-2-one derivatives by carbonylative Suzuki-Miyaura reaction

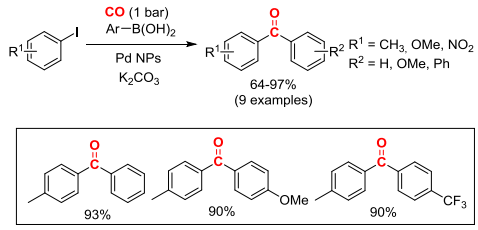


**Scheme 68** Synthesis of diaryl ketones via carbonylative Suzuki coupling reaction using molybdenum hexacarbonyl $Mo(CO)_6$ as CO surrogate

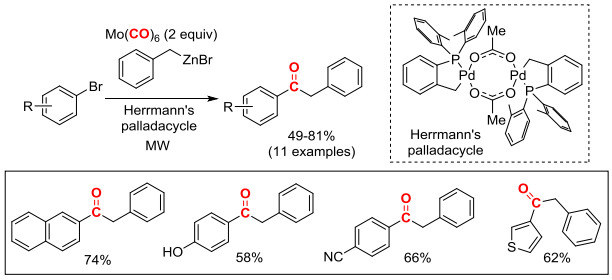



**Scheme 69** Synthesis of diaryl ketone synthons by ligand-free Pd-catalyzed Suzuki–Miyaura carbonylative coupling



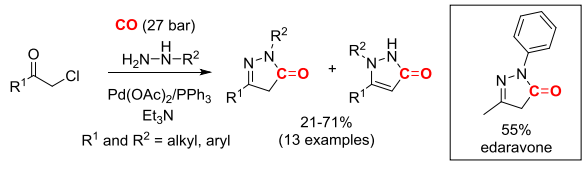

Larhed[131] described the carbonylative Negishi cross-coupling reaction of a set of aryl bromides with benzyl zinc bromide, using a palladium/phosphine catalyst (Herrmann' palladacycle) and $Mo(CO)_6$ (2 equiv.) as CO surrogate, under microwave (MW) irradiation (Scheme 70). Using this strategy, several biologically relevant benzyl aryl ketone synthons (diaryl ethanones) were synthesized in moderate to good yields (49%—81%).

**Scheme 70** Synthesis of diaryl ethanones via Pd-catalyzed Negishi carbonylative coupling




Perrone and Salomone[132] reported the synthesis of pyrazolone derivatives, through palladium-catalyzed carbonylative coupling of α-chloroketones with hydrazines. The reaction was performed using $Pd(OAc)_2/PPh_3$ as catalyst, using 27 bar CO pressure and $Et_3N$ as base (Scheme 71). When sterically demanding substrates were employed, the pyrazolone products having the substituents more distant from each other were obtained as major products. This methodology was successfully applied to the synthesis of edaravone, a drug used for treatment of brain and myocardial ischemia.

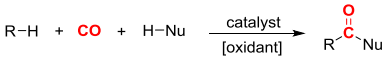
**Scheme 71** Synthesis of pyrazolones by Pd-catalyzed carbonylative coupling of α-chloroketones with hydrazines




## 2.5. C—H carbonylation

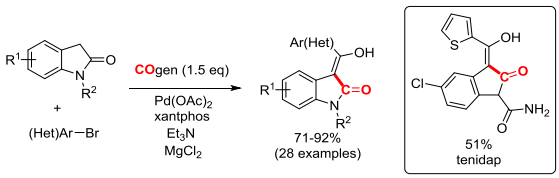
C—H carbonylation reactions, involving CO as starting material, have allowed the construction of more complex molecules, thus providing efficient, selective, and sustainable synthetic methodologies.[133-135] These oxidative carbonylation reactions usually involve a substrate with an activated C—H bond, CO, a nucleophile and an oxidant to regenerate the metal catalyst (Scheme 72).

**Scheme 72** General scheme of C—H carbonylation reactions

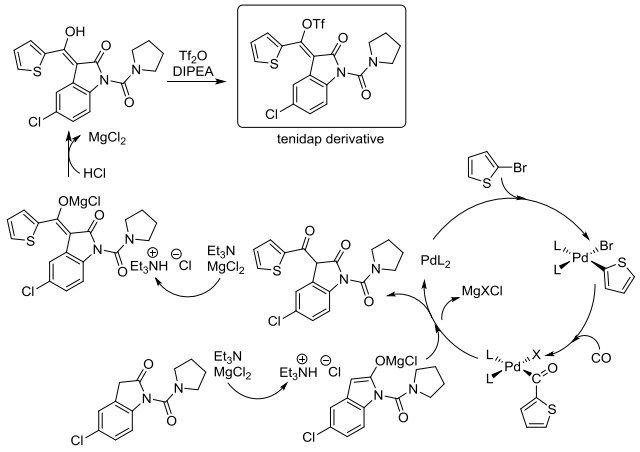



C—H carbonylation reactions have the potential to simplify synthetic routes, improve atom economy and reduce environmental impact, which make them key tools for the preparation of highly functionalized molecules, including heterocycles with great relevance for development of fine chemicals. For instance, oxindoles are relevant structures found in numerous fine chemicals. Particularly, 3-acyl-2-oxindoles are featured in a number of natural products and biologically active molecules, including several drugs such as tenidap, a potent cyclooxygenase inhibitor. In this regard, Skrydstrup[136] developed an efficient palladium-catalyzed C—H carbonylative α-arylation of 2-oxindoles with heteroaromatic bromides using COgen as CO surrogate, catalyzed by Pd/xantphos in the presence of $MgCl_2$ and using triethylamine as base (Scheme 73). Through this one-step synthetic strategy, several 3-acyl-2-oxindoles were prepared in good to excellent yields (71%—92%), including tenidap triflate derivative, which was easily purified and isolated. The proposed mechanism of the reaction is depicted in Scheme 74.

**Scheme 73** C—H carbonylative α-arylation of 2-oxindoles for the synthesis of 3-acyl-2-oxindoles

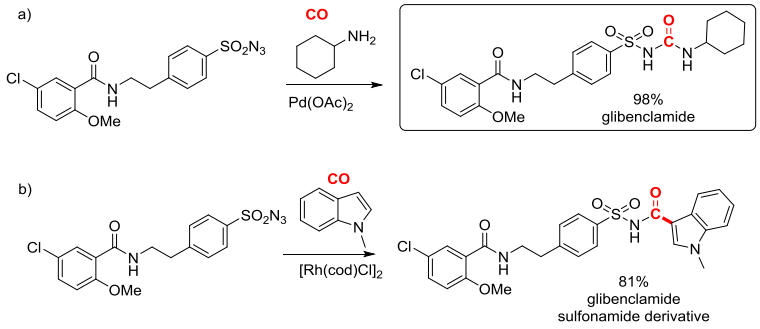



**Scheme 74** Proposed mechanism of C—H carbonylative α-arylation of 2-oxindoles for the preparation of tenidap derivative




Sulfonamide and sulfonylurea derivatives are also common structural motifs in pharmaceuticals. Zhang[137] reported the gram-scale synthesis of highly prescribed antidiabetic drug glibenclamide in 98% yield, by a direct aminocarbonylation reaction

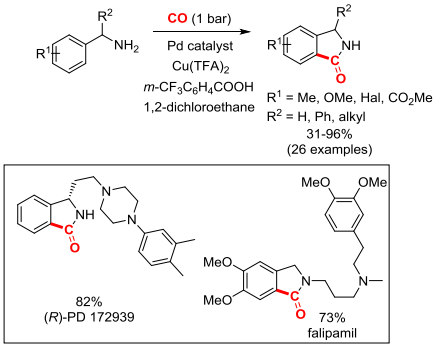
**Scheme 75** Synthesis of: a) glibenclamide via Pd-catalysed aminocarbonylation and; b) glibenclamide sulfonamide derivative via C—H carbonylation




between a sulfonylazide intermediate and cyclohexylamine, catalyzed by $Pd(OAc)_2$, using 1 bar CO pressure (Scheme 75 a). Using another approach, Xia[138] described the synthesis of a glibenclamide sulfonamide analogue in 81% yield, through an unprecedented rhodium catalyzed three-component C—H activation reaction of (hetero)arenes in the presence of carbon monoxide (1 bar) and the nitrene intermediate (Scheme 75 b). Remarkably, this reaction proceeded without either any directing groups nor additives, through an intermolecular fashion with $N_2$ being formed as the only by-product.

The development of effective methods to prepare fine chemicals containing a benzolactam core has been as well of great significance. In this regard, Li[139] developed a palladium-catalyzed $NH_2$ *ortho*-directed C($sp^2$)–H bond carbonylation of benzylamines as an efficient synthetic strategy to prepare a set of *N*-unprotected benzolactams (Scheme 76). The reactions were carried out under an atmospheric pressure of CO, and catalyzed by $Pd(OAc)_2$, using $Cu(TFA)_2$ to reoxidize Pd(0) to Pd(II). More than 25 examples were reported, including Falipamil, a calcium channel blocker with anti-ischemic properties and (*R*)-PD172939, a dopamine D4 antagonist. It should be highlighted that the use of an acidic additive, such as *m*-$CF_3C_6H_4COOH$, was required to achieve best yields, since it increases the coordination ability of the $NH_2$ groups.

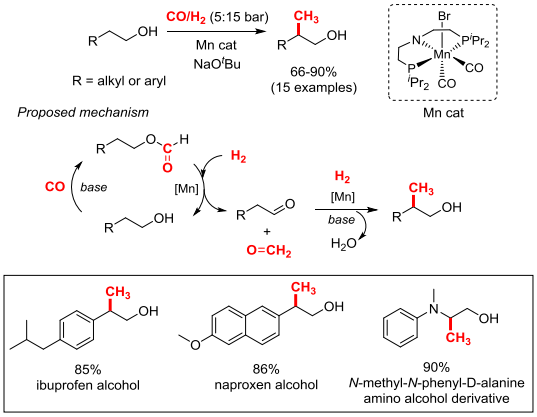
**Scheme 76** Pd-catalyzed *ortho*-directed C($sp^2$)–H bond carbonylation of benzylamines for the synthesis of *N*-unprotected benzolactams



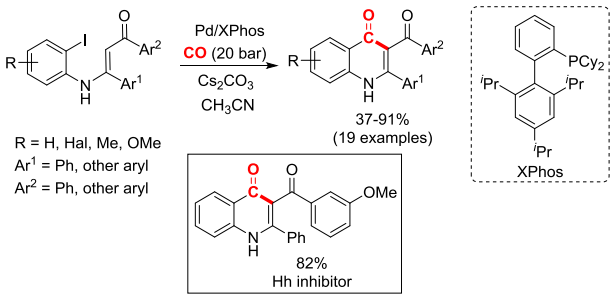

Leitner[140] developed and discussed the mechanism of an unprecedented catalytic β-methylation of alcohols using 20 bar *syngas* ($CO/H_2$ 1 : 3), and a Mn(I)/aminodiphosphine complex as catalyst, in the presence of sodium *tert*-butoxide as base, for the preparation of useful organic synthons (Scheme 77). Using this strategy, several important pharmaceutical drugs were prepared in good to excellent yields (66%—90%), such as the ibuprofen and naproxen alcohol derivatives as well as *N*-methyl-*N*-phenyl-*D*-alanine amino alcohol derivative.

Goggiamani[141] reported a palladium-catalyzed carbonylative process to promote the cyclization of *N*-(2-iodoaryl)enaminones (Scheme 78). The reactions were performed using $Pd_2(dba)_3$/XPhos as catalyst, using 20 bar CO and cesium carbonate as inorganic base. This process yielded several 2-substituted 3-aroylquinolin-4(1*H*)-ones in moderate to good yields (37%—91%). Some of them were tested as drugs and showed a remarkable activity for inhibiting the Hedgehog signaling (Hh inhibition), a crucial pathway in tumorigenesis process.

**Scheme 77** Mn-catalyzed methylation using *syngas* for the synthesis of ibuprofen, naproxen alcohols and an amino alcohol derivative




**Scheme 78** Pd-catalyzed C—H carbonylative cyclization of *N*-(2-iodoaryl)enaminones to prepare 2-substituted 3-aroylquinolin-4(1*H*)-ones, including a Hedgehog signaling inhibitor



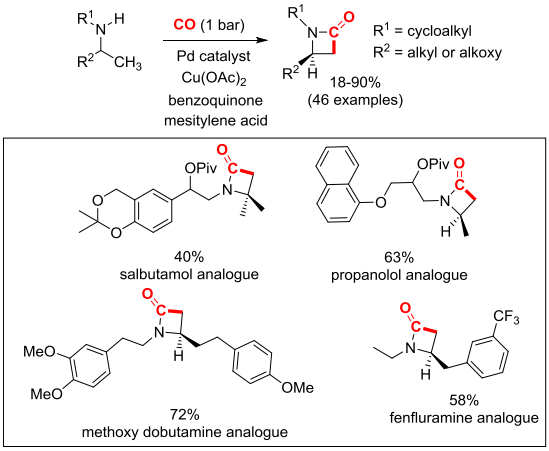

Willcox and Chappell[142] described and discussed the mechanism of a C—H carbonylative cyclization process of secondary aliphatic amines to yield β-lactams, using $Pd(OAc)_2$ as catalysts, $Cu(OAc)_2$ as oxidant and mesitylene acid/benzoquinone as additives, under 1 bar CO pressure (Scheme 79).

This synthetic strategy was successfully extended to the preparation of several pharmaceuticals in modest to excellent yields (18%—90%), namely salbutamol, propranolol, methoxy dobutamine and fenfluramine analogues, widely known drugs for treating asthma, heart failure, obesity and as β2-adregenic receptor agonist, respectively.

Pyrido[1,2-*a*]pyrimidin-4-ones are ubiquitous structural motifs of bioactive compounds. In this regard, Ackermann[143] developed

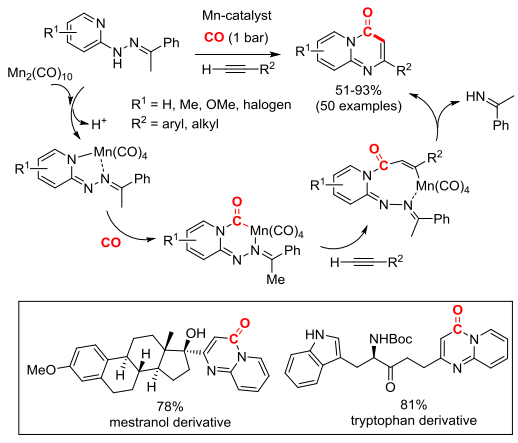
  

**Scheme 79** Pd-catalyzed C—H carbonylative cyclization of secondary amines to prepare β-lactams, including several pharmaceutical drug analogues



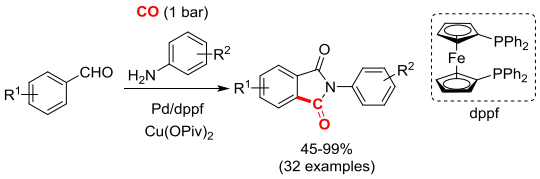

a manganese-catalyzed redox neutral carbonylative annulation between alkynes and (*E*)-2-(2-(1-phenylethylidene)hydrazineyl)pyridines, using 1 bar CO pressure, to yield pyridopyrimidinone derivatives in good to excellent yield (51%—93%), including the pharmaceutically relevant mestranol and tryptophan derivatives (Scheme 80). It is worth mentioning the use of inexpensive and highly abundant transition metal manganese as catalyst and the large scope, which included drugs and natural products such as mestranol and tryptophan analogues. The authors proposed a catalytic cycle starting with coordination of the manganese catalyst with the hydrazine moiety, followed by CO insertion, and migratory insertion of the alkyne, which produces an eight-membered metallacycle. Finally, the C—N bond formation occurs by imine elimination and demetallation, regenerating the catalytically active manganese complex (Scheme 80).

**Scheme 80** Mn-catalyzed carbonylative annulation of alkynes and (*E*)-2-(2-(1-phenylethylidene)hydrazineyl)pyridines for the synthesis of pyrido[1,2-*a*]pyrimidin-4-one derivatives



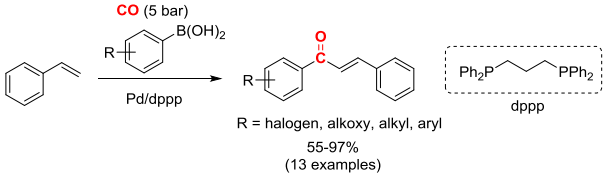

Phthalimide derivatives are promising pharmacologically active compounds, commonly used as analgesic, antimicrobial, anti-inflammatory, antitumor, and anticonvulsant drugs.[144] In this context, Lei[145] reported a palladium-catalyzed oxidative C—H carbonylation of aryl aldehydes, under 1 bar CO pressure, using aniline derivatives as nucleophiles, a Pd(II)/dppf as catalyst and $Cu(OPiv)_2$ (Piv = pivaloyl) as oxidant (Scheme 81). With this protocol, the authors managed to prepare a large family of biologically relevant phthalimide compounds, in moderate to good yields (45%—99%), compatible with diverse functional groups.

**Scheme 81** Synthesis of phthalimide compounds via Pd-catalyzed oxidative C—H aminocarbonylation



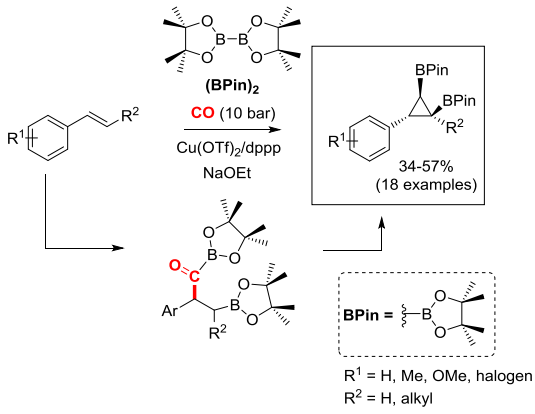

Chalcones are relevant fine chemical compounds, commonly applied as useful building blocks in the preparation of biologically active compounds.[146] In this regard, Beller[147] reported a general C—H oxidative-carbonylative coupling of arylboronic acids with styrene catalyzed by palladium/dppp (dppp = 1,3-bis(diphenylphosphino)propane) using 5 bar of CO, without the use of any additives (Scheme 82). This versatile methodology allowed preparing a set of potentially bioactive chalcones (13 examples) in moderate to excellent yields (55%—97%).

**Scheme 82** Synthesis of chalcones via Pd-catalyzed oxidative C—H oxidative-carbonylative coupling of arylboronic acids with vinylarenes




Conveniently substituted cyclopropanes are commonly found in many pharmaceuticals, and may act as intermediates in organic synthesis.[148] In this regard, Wu[149] reported an innovative synthesis of diborylated cyclopropanes via a copper-catalyzed carbonylation process using copper(II) triflate/dppp as catalyst, followed by cyclopropanation (Scheme 83). This reaction was effectively carried out using both internal or terminal aryl olefins, which allowed to prepare in moderate yields (34%—57%), a family of cyclopropyl bis(boronates) (18 examples), with a completely defined stereochemistry.

**Scheme 83** Synthesis of diborylated cyclopropanes via Cu-catalyzed carbonylation-cyclopropanation




## 3. Conclusions and Perspectives

In this critical literature review, covering the last 10 years, the relevance of developing active and selective catalysts for CO activation, enabling its use in fine chemical synthesis, such as pharmaceuticals, fragrances, agrochemicals and bioactive natural products, has been clearly demonstrated. Despite the restrictions

related with CO manipulation, due to toxicity issues and high-pressure, its activation under safe conditions will undoubtedly enlarge its use as one of the most promising C1 building blocks for the fine chemicals industry. Increased research on the application of CO surrogates, with particular relevance of $CO_2$ reduction to CO, is a key factor that can contribute to its broader applicability in the future. Another major challenge is the transposition of carbonylation from traditional batch reactions to more efficient and sustainable flow chemical synthetic methods, which will certainly allow their translation to large-scale industrial chemicals processes.

## Acknowledgement

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