1 Transition-Metal-Catalyzed Carbonylative Domino Reactions

Xiao-Feng Wu, Helfried Neumann, and Matthias Beller

1.1 Introduction

“Sustainable development” has become one of the hottest terms in the twenty-first century. Of particular relevance in organic chemistry are the reaction efficiency and the avoidance of waste generation. With regard to sustainability, methodologies based on domino reactions, including multicomponent reactions, are a highly efficient strategy to synthesize complicated organic compounds. Domino reactions are defined as processes of two or more bond-forming reactions under identical conditions, in which the subsequent transformations take place at the functionalities that are obtained in the previous bond-forming transformations. Using domino reactions, complicated compounds can be relatively easily prepared from simple substrates. No tedious preparation of intermediates and purification processes are needed, which are the most energy-consuming and waste-generating steps in organic synthesis [1]. One prominent example is the domino Knoevenagel/hetero-Diels–Alder reaction, in which dihydropyrans could be straightforwardly synthesized from readily available starting materials [2].

Transition-metal catalysts play an ever-increasing and important role in modern chemistry [3]. Numerous transition-metal-catalyzed coupling reactions have been developed and applied in the total synthesis of natural products, such as the Suzuki reaction, the Negishi reaction, the Heck reaction, and many others [4]. Interestingly, the power of transition-metal catalysts is even more visible in the area of domino reactions, where terms such as palladium walking show the value of transition metals in bond formations.

Carbonylation reactions are interesting and important with regard to both industrial and academic research [5]. In these reactions, carbon monoxide (CO) can be used as one of the cheapest C1 sources. By introducing one or even more CO units into the parent molecules, carbonyl-containing products are easily prepared, which can be further modified to yield important chemicals for organic synthesis. Following the definition of domino reactions, we realized to our surprise that all the carbonylative coupling reactions belong to domino reactions, in which at least two C–C bonds were formed under the same reaction conditions.
In order to assess the value of domino and carbonylation reactions, and also to
differentiate them from normal transition-metal-catalyzed carbonylation reactions,
in this chapter we will only describe the carbonylation reactions that produce at
least three bonds under the same conditions.

1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

Transition-metal-catalyzed carbonylation reactions have shown impressive progress
during past few decades; especially, the use of ruthenium, rhodium, and palladium
as catalysts is widespread. More recently, iron and copper catalysts have also
been attracting the attention of synthetic chemists because of their low cost and
environmentally benign properties.

1.2.1 Ruthenium-Catalyzed Carbonylative Domino Reactions

Compared with metathesis [6], the ability of ruthenium catalysts in carbonylation
is also impressive.

In 1998, the first ruthenium-catalyzed cyclocarbonylation of yne-aldehydes was
studied by the group of Murai [7]. Bicyclic α,β-unsaturated γ-butyrolactones were
synthesized in good to excellent yields (Scheme 1.1a), and two proposed reaction
mechanisms were discussed for this transformation. One involved a five-membered
metalacycle formed via a [2+2+1] cycloaddition, and the other proceeded through
a ruthenium acyl intermediate that was generated from the oxidative addition of an
aldehyde C–H bond to ruthenium. Later on, Kang and coworkers [8] developed a
ruthenium-catalyzed cyclocarbonylation of allenyl aldehydes and allenyl ketones to
synthesize various α-methylene-γ-butyrolactones in 48–85% yields (Scheme 1.1b).
More recently, Snapper and Finnegan prepared polycyclic lactones in moderate to
good yields through ruthenium catalysis, in which a ring-closing metathesis/hetero-
Pauson–Khand reaction mechanism was proposed (Scheme 1.1c) [9]. This strategy
was also adopted for the preparation of cyclopentenones [10].

Some intermolecular carbonylative cycloaddition reactions were developed as
well. In 1999, the group of Murai published a ruthenium-catalyzed intermolecular
cycocoupling of ketones, ethylene, and CO, producing lactones in good yields
(Scheme 1.2) [11a]. This reaction showed the catalytic synthesis of heterocycles
via an intermolecular carbonylative [2+2+1] cycloaddition for the first time. Many
different ketones, such as α-dicarbonyl compounds and N-heterocyclic ketones, are
used in this cycloaddition, and the addition of phosphines promotes the reactions of
α-dicarbonyl compounds. Among the tested phosphines, P(4-CF3C6H4)3 has proved
to be the ligand of choice. Beside ethylene cyclic olefins, unpolarized terminal olefins
and internal alkynes could also be employed successfully in the synthesis, yielding
highly functionalized lactones. An aromatic keto ester substituted with a CF3 group
accelerated the reaction of the keto ester with ethylene. On the other hand, by using
1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

Scheme 1.1 (a–c) Ruthenium-catalyzed hetero-Pauson–Khand reactions.

Scheme 1.2 Ruthenium-catalyzed intermolecular carbonylative cycloaddition reaction.
aromatic N-heterocyclic ketones, the rate of the reaction with ethylene slowed down when the phenyl ring contained a CF$_3$ and went up when CF$_3$ was replaced by a methoxy group [11b]. An increase in the pressure of ethylene or a lowering of the pressure of CO had a positive influence on the rate of the reaction in the case of the keto ester. Interestingly, a reversed behavior of the pressure rate was observed with N-heterocyclic ketones when using ethene.

In 2002, a novel and rapid ruthenium-catalyzed synthesis of pyranopyrandiones was developed by the group of Mitsudo [12]. Single cyclopropenones and cyclopropenones in combination with internal alkynes could be converted, in the presence of Ru$_3$(CO)$_{12}$ as catalyst, to pyranopyrandiones by cross-carbonylation of 2 equiv of CO in good yields (Scheme 1.3a,b). Interestingly, this reaction was successful when simple NEt$_3$ was used as an efficient ligand. In contrast to other amine ligands (NBu$_3$, N-methylpiperidine, pyridine, and N,N-diethylaniline), phosphorus ligands (PCy$_3$ and PBu$_3$) gave only moderate catalytic activity in this transformation. The right choice of the ruthenium precursor is very important, since the use of RuCl$_2$(PPh$_3$)$_3$, RuH$_2$(CO)(PPh$_3$)$_3$, and RuCl$_3$·3H$_2$O was ineffective even in the presence of NEt$_3$. In addition, Ryu and coworkers [13] developed a synthesis of α-pyrone based on a ruthenium-catalyzed intermolecular carbonylative cycloaddition of α,β-unsaturated ketones with silylacetylenes and CO. Moderate yields were achieved by this new transformation (Scheme 1.3c).

The group of Murai [14] could demonstrate that ruthenium-catalyzed cyclocarbonylation of yne-imines resulted in formation of lactams (Scheme 1.4a). Catalytic amounts of Ru$_3$(CO)$_{12}$ promote this cyclocarbonylation of 1,6- and 1,7-ynem-imines, giving bicyclic α,β-unsaturated lactams. Similar to the Pauson–Khand reaction, the
1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

![Scheme 1.4](image)

Scheme 1.4 (a, b) Ruthenium-catalyzed carbonylative synthesis of lactams.

Lactam is formed in a [2+2+1] cycloaddition in which the acetylene π-bond, the imine π-bond, and the carbon atom of CO are involved. The acetylenic terminal carbon has to consist of an alkyl, an aryl, or silyl groups in order to give bicyclic α,β-unsaturated lactams via cyclocarbonylation of yne-imines. If the acetylenic terminal carbon has no substituents instead of the corresponding lactam, a dihydropyridine derivative will be generated without the incorporation of CO. Later on, the authors also showed that the cyclocarbonylation of imines, alkenes, or alkynes and CO gives γ-butyrolactams in good yields (Scheme 1.4b) [15].

In 2000, a selective cycloaddition of cyclopropyl imines, derived from cyclopropyl phenyl ketone and tert-butylamine and CO (2 bar), was developed by the same group (Scheme 1.5) [16]. The reaction was allowed to proceed in toluene (3 ml) in presence of a catalytic amount of Ru$_3$(CO)$_{12}$ (0.02 mmol) at 160 °C for 60 h, giving the pyridinone derivative in 76% isolated yield.

![Scheme 1.5](image)

Scheme 1.5 Ruthenium-catalyzed carbonylative reaction of cyclopropyl imines.

Moreover, in 2008, a novel ruthenium-catalyzed cyclization based on a combination of isocyanates, alkynes, and CO was developed by the group of Kondo et al. [17]. Polysubstituted maleimides could be obtained in excellent yields under CO at atmospheric pressure with low catalyst loading (Scheme 1.6).

In 1997, Murai’s [18] group developed the first ruthenium-catalyzed Pauson–Khand reaction, which originally was carried out by a cobalt catalyst. They showed that good yields of cyclopentenones could be achieved in an intramolecular, ruthenium-catalyzed cyclocarbonylation of 1,6-enynes (Scheme 1.7a). Later on, the cyclocarbonylation was extended to an intermolecular version in which alkynes, CO, and alkenes were converted into many cyclopentenones with excellent regioselectivity (Scheme 1.7b) [19]. Different substituted alkynes could be employed, showing the tolerance of the reaction. Notably, when a 2-PyMe$_2$Si-substituted alkyne was
Ru$_3$(CO)$_{12}$ (1.1 mol%) in Mesitylene, 130°C and CO (1 bar) gives a reaction yield of 13 examples with 82–98%.

Scheme 1.6 Ruthenium-catalyzed carbonylative synthesis of maleimides.

used, the leaving group could be cleaved after the reaction. In 2000, Mitsudo and coworkers [20] reported another synthesis of cyclopentenones, which relied on a combination of allylic carbonates, alkenes, and CO. Here, the cyclocarbonylation was performed with either [RuCl$_2$(CO)$_3$]$_2$/NEt$_3$ or ($\eta^3$-C$_3$H$_5$)RuBr(CO)$_3$/NEt$_3$, which constitutes a highly effective catalyst system (Scheme 1.7c).

Scheme 1.7 (a–c) Ruthenium-catalyzed carbonylative synthesis of cyclopentenones.

Starting from the same substrates, even hydroquinones can be prepared by insertion of two molecules of CO. In 1998, Mitsudo and coworkers [21a] demonstrated that hydroquinones could be achieved in a ruthenium-catalyzed cyclocarbonylation by using alkynes and 2-norbornenes. Unsymmetrically substituted hydroquinones were obtained in high yields by this novel ruthenium-catalyzed transformation. For the preparation of higher substituted hydroquinones, functionalized alkenes could
also be employed as starting material. Here, \([\text{Cp}^*\text{RuCl}_2]_2\) was used as the catalyst (Scheme 1.8) [21b].

![Scheme 1.8](image)

**Scheme 1.8** Ruthenium-catalyzed carbynylation synthesis of hydroquinones.

### 1.2.2 Rhodium-Catalyzed Carbonylative Domino Reactions

In 2006, the group of Artok showed that 5-aryl-2(5H)-furanones could be prepared in moderate to good yields by a rhodium-catalyzed carbynylation arylation of internal alkynes with aryl boronic acids (Scheme 1.9a) [22]. \(\alpha,\beta\)-Unsaturated ketones (chalone derivatives) were formed as the major product when some TFA (trifluoroacetic acid) was added under the same reaction conditions [23a]. By varying the catalytic system, indanones could be produced as the main product [23b]. The chemical behavior of terminal alkynes is different, and either \(\alpha,\beta\)-unsaturated ketones or furans starting from propargylic alcohols can be achieved (Scheme 1.9b) [24, 25]. In the case of vinyl ketones, 1,4-diketones were obtained by rhodium-catalyzed coupling of arylboronic acids in the presence of 20–40 bar of CO [26]. In 2007, Chatani demonstrated that indenones could be accessed by a carbynylation rhodium-catalyzed cyclization of alkynes with 2-bromophenylboronic acids (Scheme 1.9c) [27]. Here, the key intermediate is a vinylrhodium(I) species that is formed by transmetallation of RhCl with 2-bromophenylboronic acid followed by insertion of

![Scheme 1.9](image)

**Scheme 1.9** (a–c) Rhodium-catalyzed carbynylation of alkynes and boronic acids.
an alkyne. Next, the C–Br bonds on the adjacent phenyl ring were oxidatively added to provide a benzonorhodacyclopentene species. After CO insertion and reductive elimination, the desired indenone was obtained. With regard to the regioselectivity, an alkyne substituted with a bulky and electron-withdrawing group favors the α-position of indenones. The highest regioselectivity was achieved in the case of silyl- or ester-substituted alkynes in the order SiMe₃ > COOR ≫ aryl ≫ alkyl. Similarly, also indanone derivatives could be obtained when 2-bromophenylboronic acid was reacted with norbornene under 1 bar of CO. On conducting the reaction without CO, two molecules of alkynes were incorporated during the reaction sequence with 2-bromophenylboronic acid to give naphthalene derivatives. With the aid of carbonylative rhodium-catalyzed cyclization of 1-(2-bromophenyl)-hept-2-yn-1-one and PhB(OH)₂, indan-1,3-dione derivatives were obtained.

In 2001, a novel rhodium-catalyzed cyclohydrocarbonylation of imino alkynes was developed by Alper and Van den Hoven [28]. The reaction was catalyzed by a zwitterionic rhodium complex and P(OPh)₃, giving aldehyde-substituted pyrrolinones in 67–82% yield (Scheme 1.10a). Imino alkynes with alkyl, alkoxyl, vinyl, and aryl substituents can be used in this unique transformation. This synthetic approach is a convenient way for the synthesis of highly functionalized pyrrolinones, which constitute often biologically active compounds. In 2001, the group of Saito reported on the intramolecular carbonylation of alkyne-carbodiimides, giving 4,5-dihydro-1H-pyrrolo[2,3-b]pyrrolin-2-ones and 1H-pyrrolo[2,3-b]indol-2-ones in reasonably good yields (Scheme 1.10b) [29]. Later on, they could apply their methodology on N-[2-(2-alkyn-1-yl)phenyl]carbodiimides to synthesize 2,3-dihydro-1H-pyrrolo[2,3-b]quinolin-2-ones in good yields (Scheme 1.10c) [30].

In 2004, the synthesis of indazolo[2,1-a]indazole-6,12-diones was carried out by a rhodium-catalyzed cyclocarbonylation of azobenzenes by the group of
Takahashi [31]. To get good yields, nitrobenzene was added as a hydrogen acceptor (Scheme 1.11a). But on running the carbonylation of azobenzene via cobalt catalysis, quinazoline was obtained as the terminal product. Furthermore, Chatani and coworkers described a rhodium-catalyzed synthesis of maleimides starting from a combination of alkynes and pyridine-2-ylmethylamine in the presence of CO (Scheme 1.11b) [53].

Lautens and coworkers investigated an asymmetrical ring-opening reaction in which meso-diazabicycles were opened by acyl anion nucleophiles in a catalytic manner to give functionalized trans-1,2-hydrazinoacyl cyclopentenes stereoselectively [32]. Under very mild conditions, an acyl anion is generated \textit{in situ}, starting from readily available organoboron precursors (Scheme 1.12).

In 2007, a series of 3-methylcyclopent-2-enones were synthesized by a rhodium-catalyzed carbonylation of spiropentanes [33]. Here, two different types of carbon–carbon bond cleavage processes were involved to get the product in good yield (Scheme 1.13).
1.2.3 Palladium-Catalyzed Carbonylative Domino Reactions

The outstanding ability of palladium catalysts was demonstrated in the area of carbonylative coupling reactions mainly with activated arenes. Nevertheless, palladium catalysts can also be used in oxidative cyclization chemistry. The group of Gabriele succeeded in producing substituted furans from the corresponding alkynols under oxidative conditions (Scheme 1.14a) [34]. Here, in the presence of catalytic amounts of $[\text{PdI}_4]^{2-}$ in conjunction with an excess of KI, 4-yn-1-ols containing a terminal triple bond undergo oxidative cyclization/alkoxy-carbonylation in methanol at 70°C and 100 bar of a 9:1 mixture of CO and air to give 2E-[(methoxycarbonyl)methylene]tetrahydrofurans in good yield. A side reaction, producing 2-methoxy-2-methyltetrahydrofurans via a cycloisomerization/hydromethoxylation sequence, could be easily prevented by increasing the KI excess. Without KI excess and in the absence of carbon monoxide, the latter product can be formed from 4-yn-1-ols and methanol in high yields using the same catalytic system. Another system that needs no KI and high pressure leading to different products was developed by Akita and coworkers [35] (Scheme 1.14b). Following this procedure, they were able to perform the reaction in an asymmetric manner by applying chiral bisoxazolines as ligands.

![Scheme 1.14](image)

Gabriele and coworkers [36] showed that, besides lactones, furans could also be prepared by a similar process starting from different substrates. Here, a variety of (Z)-2-en-4-yn-1-ols have been carbonylated under oxidative conditions to give substituted furan-2-acetic esters in good yields (Scheme 1.15a). The cyclization/alkoxycarbonylation sequence was carried out in alcoholic media at 50–70°C under 100 bar pressure of a 9:1 mixture of CO and air. As catalyst system, PdI$_2$ in combination with KI was used. The proposed reaction pathway involves the in situ isomerization of the initially formed (E)-2-[(alkoxycarbonyl)methylene]-2,5-dihydrofuran species, which in some cases have been isolated and proved to be the intermediates. Under similar reaction conditions, 3-yn-1,2-diols were transformed into the corresponding furan-3-carboxylic esters in good yield (Scheme 1.15b).
1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

The palladium-catalyzed carbonylation of alkynols resulted in the formation of synthetically interesting lactones and furans. In 1994, Sakamoto and coworkers showed that the palladium-catalyzed carbonylation reaction of 2-alkynylanilines and 2-alkynylphenols in methanol could give the corresponding indoles and benzofurans in moderate yields. Starting from 2-alkynylbenzamides, 3-alkylidenisoindoles were obtained (Scheme 1.16) [37a]. A similar methodology was applied by Scammells for the synthesis of XH-14 and its derivatives, which contain a benzofuran as the main skeleton [37b].

Costa and coworkers [38] used an oxidative Pd-catalyzed cyclization/alkoxycarbonylation sequence for the synthesis of 1-(alkoxycarbonylmethylene-1,3-dihydroisobenzofurans and 4-(alkoxycarbonyl)benzo[c]-pyrans starting from 2-alkynylbenzyl alcohols and 2-alkynylbenzaldehydes or 2-alkynylphenyl ketones. The reactions were run in ROH or CH₃CN/ROH (R = Me, i-Pr) mixtures as solvent at 70–105 °C in the presence of catalytic amounts of PdI₂ in combination with KI under a CO/air mixture in the ratio 4 : 1 or 3 : 1 (20 or 32 bar total pressure at 25 °C). The reaction proceeds via an intramolecular attack of nucleophilic oxygen atom (either already present in the starting material or generated in situ by ROH attack on carbonyl group) directed to the triple bond which is coordinated to
Pd(II). The reaction sequence is closed by a subsequent alkoxy carbonylation. The presence of substituents at the alkyne terminal position and at the carbon atom \( \alpha \) to the hydroxy group control the selectivity of the process by forming a five- or six-membered ring (Scheme 1.17). Alternatively, the reaction of alkynyl oxiranes could also lead to 1,3-dihydroisobenzofurans and tetrahydrofurans. Moderate to good yields of the products were obtained under similar reaction conditions (PdI\(_2\)/KI/CO/O\(_2\)).

Because of the interesting biological properties of 3(2\(H\))-furanone derivatives, many methodologies have been developed for their syntheses [39a]. In 1988, Inoue and coworkers described the coupling of \( \alpha \)-ethynyl tertiary alcohols and acyl chlorides to give 3(2\(H\))-furanones in the presence of a palladium catalyst and CO\(_2\). Next, they started with the same reaction conditions with CO and CO\(_2\) under pressure but using aryl halides instead of acyl chlorides [39b]. They showed that acetylenic ketone was formed as an intermediate by a combination of acetylenic alcohol, CO, and the aryl halides. Subsequent reaction with CO\(_2\) resulted in the formation of a cyclic carbonate, which was decarboxylated to 3(2\(H\))-furanones with the release of CO\(_2\) (Scheme 1.18a). Alternatively, Kiji and coworkers [39c] showed that, in the absence of CO\(_2\), 3-isopropylidene-5-phenyl-2(2\(H\))-furanone could be achieved as the main product. Carbonylative coupling of iodobenzene and 2-methyl-3-butyn-2-ol in aqueous biphasic NaOH/benzene system was carried out by using Pd(OAc)\(_2\)/PPh\(_3\)/Bu\(_4\)PBr as catalyst. This biphasic solvent system gave, in sharp contrast to a homogeneous Et\(_3\)N solution, 3-isopropylidene-5-phenyl-2(2\(H\))-furanone in moderate yield accompanied by 2,2-dimethyl-5-phenyl-3(2\(H\))-furanone and benzoic acid as side products. The formation of the main product was explained by a carbonylative coupling of iodobenzene with 2-methyl-3-butyn-2-ol, forming 4-hydroxy-4-methyl-1-phenyl-2-pentyn-1-one, which underwent hydrogenolysis to yield 4-methyl-1-phenyl-2,3-pentadien-1-one. Subsequent cyclocarbonylation yielded 3-isopropylidene-5-phenyl-2(2\(H\))-furanone as the final product (Scheme 1.18b). Concerning the formation of 3-alkylidenefuran-2-ones, the group of Alper [39d] established a palladium catalyst system for the carbonylative coupling of aryl
1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

\[
\text{Ar} \equiv \text{OH} + \text{CO} + \text{ArX} \xrightarrow{[\text{Pd}]} \text{Ar} \equiv \text{CO}_2
\]

(a)

\[
\begin{align*}
\text{Ar} & \equiv \text{Ph} \\
\text{Ph} & \equiv \text{OH} + \text{CO} \xrightarrow{\text{Pd(OAc)}_2/\text{PPh}_3/\text{Bu}_4\text{PBr}} \text{Ph} \equiv \text{CO}_2 \\
\text{Ph} & \equiv \text{OH} + \text{CO} + \text{Ph}_2 \xrightarrow{\text{aq NaOH/C}_6\text{H}_6, \text{CO (20 bar), 100 °C} \xrightarrow{16\%} \text{Ph} \equiv \text{CO}_2 \\
\text{Ph} & \equiv \text{OH} + \text{CO} + \text{Ph}_2 \xrightarrow{\text{[(cinnamyl)PdCl]_2, Xantphos, CO}} \text{NEt}_3, \text{toluene} 110 °C, 20 h \xrightarrow{65\%} \text{BE-23372M}
\end{align*}
\]

(b)(c)

Scheme 1.18 (a–c) Palladium-catalyzed carbonylative synthesis of furanones.

iodides with benzyl acetylenes. More recently, our group developed a general and efficient method for the synthesis of furanones starting from aryl bromides and aryl triflates [39e]. After double carbonylation with benzyl acetylenes, furanones were produced in good yields. Methylated BE-23372M, a kinase inhibitor, was also produced in a one-pot sequence with 65% yield (Scheme 1.18c).

In 2005, Chatani and coworkers [40a] reported on the carbonylation of yne esters giving lactones in good yields under 1 bar of CO (Scheme 1.19a). It turned out that the 2-pyridinyloxy moiety was a good leaving group among the groups tested. Similarly, the cyclocarbonylation of 2-propynyl-1,3-dicarbonyls with organo halides or triflates gave rise to the formation of furans in good yields (Scheme 1.19b) [40b]. Kato and coworkers [40c] developed a palladium-mediated oxidative cyclocarbonylation of 2-alkyl-2-proparglycyclohexane-1,3-diones, generating bicyclic-β-alkoxyacrylates in 51–74% yield with 72–82% ee (Scheme 1.19c). The authors were able to extend their palladium-catalyzed cyclocarbonylation to propargylic esters, propargylic acetates, 4-yn-1-ones, and allenyl ketones. Mukai and coworkers [40d] were able to apply this methodology in the total synthesis of naturally occurring diacetylenic spiroacetal enol ethers. A related mechanistic study supported by both experiment and DFT (density functional theory) study was carried out by Carfagna and coworkers [40e]. They proposed that, under the carbonylative conditions of Gabriele et al., the concatenation occurs between a Pd(0)-promoted deallylation and
a Pd(II)-promoted heterocyclization catalytic cycle to convert 1-(2-allyloxyphenyl)-2-yn-1-ols to 2-benzofuran-2-ylacetic esters and \( \beta,\gamma \)-unsaturated esters in high yields. This reaction sequence is named \emph{sequential homobimetallic catalysis} [40f]. Owing to the theoretical and synthetic importance of the process, a closer look at the mechanism and scope of the reaction revealed that the experimental results fit to the sequential homobimetallic mechanism. In place of the esters, under the same conditions, amides could also be produced in the presence of amines [40g]. The methodology could be extended to the synthesis of coumarins by using similar reaction conditions [40h]. Here, 3-[[methoxycarbonyl]-methyl]coumarins were prepared starting from readily available 2-(1-hydroxyprop-2-ynyl)phenols. In the presence of catalytic amounts of \( \text{PdI}_2 \) and an excess of \( \text{KI} \) in \( \text{MeOH} \) at room temperature and under 90 bar of \( \text{CO} \), the product was obtained in good to high isolated yields (62–87%).

Moreover, Shim and coworkers [41a] studied the cyclocarbonylation of 2-(2-bromophenyl)-2-oxazolines to the corresponding isoindolinones. By using a palladium–nickel catalyst under 3 bar of \( \text{CO} \), the products were produced in high yields (Scheme 1.20a). Later on, isoindolinones could also be achieved by coupling 2-iodobenzoyl chloride with imines in moderate yields using \( \text{NET}_3 \) and \( \text{Pd(PPh}_3)_2\text{Cl}_2/\text{PPh}_3 \) (Scheme 1.20b) [41b]. The same group could synthesize even more complex isoindolinones through a palladium-catalyzed carbonylative coupling of 2-bromobenzaldehydes with aminoalcohols or diamines [41c]. At lower temperature
1.2 Transition-Metal-Catalyzed Carbonylative Domino Reactions

Scheme 1.20  (a–d) Palladium-catalyzed carbonylative synthesis of isoindolin-1-ones.

and lower catalyst loading, the corresponding isoindolinonones were achieved in good isolated yields (Scheme 1.20c). Interestingly, when primary amines were used for the palladium-catalyzed coupling of 2-bromobenzaldehydes or 2-bromocyclohex-1-enecarbaldehydes, no base was needed (Scheme 1.20d) [41d]. The mechanism is believed to start with the condensation of the aldehyde and the primary amine, forming an imine. After the oxidative addition of the carbon–bromide bond of the imine to the active palladium(0) catalyst and subsequent CO insertion, an aroylpalladium(II) intermediate is formed. Next, an intramolecular acylpalladation to the imine gives the alkylpalladium(II) intermediate, which is decomposed to isoindolin-1-one by hydrogenolysis with molecular hydrogen. It is assumed that hydrogen is produced by the water-gas shift reaction of CO and H₂O which comes from the initial condensation stage.

The group of Arndtsen developed a number of elegant multicomponent reactions that introduce one or two CO groups into the parent molecules [42]. A combination of alkynes, imines, acid chlorides, and CO gives pyrroles as the terminal products in the presence of a palladium catalyst (Scheme 1.21a). By using α-amidoesters and alkynes, the reaction proceeds to give the same products (Scheme 1.21b). Even imidazoles could be formed when the reaction was carried out with imines and acid chlorides. Interestingly, by simply changing the reaction sequence of adding the substrates, imidazolium salts or imidazolines could be produced. In general, these methods offer convenient pathways for the production of heterocycles from easily available substrates.
Recently, Alper and coworkers [43] reported on novel processes for the synthesis of carbonylated indole derivatives via a palladium-catalyzed N–C coupling/carbonylation sequence. 2-Carboxyindoles with a variety of functional groups were achieved in good yields (Scheme 1.22a). Similarly, 2-aroylindoles could also be obtained from the same substrates in moderate yields (Scheme 1.22b). In 2011, Alper and Zeng [43c] published a facile and selective palladium-catalyzed domino synthesis of carbonylated benzothiophenes. By a carbonylative intramolecular C–S coupling/intermolecular cascade sequence, 2-carbonylbenzo[b]thiophene derivatives were produced from 2-gem-dihalovinylthiophenols in 24–73% yield (Scheme 1.22c). This protocol allows access to various highly functionalized benzo[b]thiophenes.

In 2000, a palladium-catalyzed decarboxylative carbonylation of 5-vinylxazolidin-2-ones was studied by Knight and coworkers [44]. By a palladium-catalyzed decarboxylative carbonylation process, 5-vinylxazolidin-2-ones, which are prepared
from amino acids, reacted to form 3,6-dihydro-1H-pyridin-2-ones in good yields (Scheme 1.23).

![Scheme 1.23 Palladium-catalyzed carbonylative synthesis of pyridinones.](image)

Alper and Xiao [45] synthesized thiochromanones by palladium-catalyzed carbonylative ring-forming reactions of 2-iodothiophenol derivatives, allenes, and CO. The thiochroman-4-ones were achieved in good to excellent isolated yields with high regioselectivity, which was probably caused by electronic effects (Scheme 1.24). This catalytic heteroannulation comprises the regioselective addition of the sulfur moiety on the more electrophilic carbon center of the allene, arylpalladium formation, CO insertion, subsequent intramolecular cyclization, and, finally, the reductive elimination.

![Scheme 1.24 Palladium-catalyzed carbonylative synthesis of thiochromanones.](image)

Recently, an efficient method for the synthesis of 1,4-benzo- and pyrido-oxazepinones was also disclosed [46]. This reaction proceeds via a domino process through one-pot ring-opening/carboxamidation reaction sequences of N-tosylaziridines with 2-halophenols/pyridinol under phase-transfer conditions (benzyltriethylammonium chloride, TEBA). A variety of 1,4-benzo- and pyrido-oxazepinones
could be easily synthesized by using a range of \( N \)-tosylaziridines and 2-halo-phenols/pyridinol (Scheme 1.25a). Analogously, when 2-iodothiophenols were employed, 1,4-benzothiazepin-5-ones were obtained in good yields (Scheme 1.25b).

\[
\begin{align*}
\text{NTs} & \quad R^' \quad R'' \\
\text{I} \quad \text{OH} \\
\text{PdCl}_2(\text{PPh}_3)_2 (1.5 \text{ mol\%}) \\
\text{K}_2\text{CO}_3 (3 \text{ equiv}), \text{THF}, 80^{\circ}\text{C} \\
\text{CO} (14–28 \text{ bar}) 
\end{align*}
\]

\[
\begin{align*}
\text{NTs} & \quad R^' \quad R'' \\
\text{I} \quad \text{SH} \\
\text{Pd(OAc)}_2 (4 \text{ mol\%}) \\
\text{NEt}_3 (3 \text{ equiv}), \text{THF} \\
100^{\circ}\text{C}, \text{CO} (35 \text{ bar}) 
\end{align*}
\]

\textbf{Scheme 1.25} (a,b) Palladium-catalyzed carbonylation of \( N \)-tosyl aziridines.

\textbf{1.2.4} Iron-, Copper-, Nickel-, and Cobalt-Catalyzed Carbonylative Domino Reactions

Compared to palladium, rhodium, and ruthenium, iron and copper are less developed in carbonylation reactions. But the advantages of iron and copper are attracting more and more chemists to work in this area. \( \text{Fe(CO)}_5 \) as a more easily available iron–carbonyl complex has found an important place in the stoichiometric and catalytic carbonylation reactions [47]. The group of Periasamy applied \( \text{Fe(CO)}_5 \) as precursor for the \textit{in situ} generation of NaHFe(CO)$_4$ for double carbonylation of alkynes to cyclobutenediones. In their procedures, CuCl$_2$ was needed as the oxidant reagent. The active species was \([\text{Fe(CO)}_4]\), which could be generated from various reagents, such as MeI, NaBH$_4$, amines, Me$_3$NO, and NaH. Additionally, using these methods, \( \alpha,\beta \)-unsaturated acids, benzoquinones, and cyclic anhydrides could also be produced as unexpected products (Scheme 1.26). In the mentioned reactions, stoichiometric amount of iron salts were still needed.

Notably, Beller’s group developed a series of iron-catalyzed aminocarbonylation of alkynes in 2009 [48a–d]. Starting from alkynes and amines, succinimidines were prepared in good yields in the presence of carbon monoxide (Scheme 1.27). This methodology was also applied for the synthesis of himanimides A and B. Under the same conditions, cinnamides were also synthesized by adding 1,4-diazabutadiene as ligand or by using microwave irradiation. NEt$_3$ was the ligand of choice [48e]. A combination of \( \text{Fe(CO)}_5 \) and irradiation was also used for producing vinylesters and lactones from alkynes at 0° C [48f].

Additionally, the reactions with alkynes and iron catalyst were also applied to the carbonylative homocoupling of aryl iodides to give benzophenones [49]. As catalyst system, \( \text{Fe(CO)}_5\cdot\text{Co}_2(\text{CO})_8 \) was used under phase-transfer conditions to give carbonylate aryl iodides in moderate yields.
Scheme 1.26 Double carbonylation of alkynes.

Scheme 1.27 Iron-catalyzed carbonylative synthesis of amides and esters.

In 2008, Bhanage and coworkers [50a] reported on a copper-catalyzed carbonylative Sonogashira reaction of aryl iodides. In this procedure, copper bis(2,2,6,6-tetramethyl-3,5-heptanedionate) [Cu(TMHD)$_2$] was used as the catalyst for this transformation and NEt$_3$ as base. Alkynones were produced in good yields. Recently, Xia and coworkers [50b] described a general and efficient copper-catalyzed
double aminocarbonylation of aryl iodides (Scheme 1.28). Aryl iodides were double-
carbonylated with amines in good yields by using the NHC–Cu catalyst (72–93%).

Scheme 1.28 Copper-catalyzed double carbonylation of aryl iodides.

Skoda-Földes and coworkers [51] investigated the domino reaction of ethyl
diazoacetate, CO, and ferrocenylimines in the presence of \( \text{Co}_2(\text{CO})_8 \) as catalyst (Scheme 1.29). In most cases, the main products were 2-(1-ferrocenylnmethylidene) malonates formed by an N(1)–C(4) cleavage of the primarily derived \( \beta \)-lactams. The latter compounds could only be isolated when the reaction was carried out at relatively low CO pressure, using an excess of ethyl diazoacetate. Among these compounds, \textit{trans}-\textit{N}(\text{-}(-\text{tert}-\text{butyl})\text{-}3\text{-}\text{ethoxycarbonyl}\text{-}4\text{-}\text{ferrocenyl}\text{-}\beta\text{-}lactam\text{ proved to be the most stable one and could be isolated in 55\% yield.} \textit{N-Alkyl} \beta\text{-}lactams\text{ were shown to undergo an acidic cleavage, leading to the } (E)\text{-isomers of 2-(1-ferrocenylnmethylidene)malonates as the main products. The structures of the two new compounds, namely } (E)-2\text{-}\text{ethoxycarbonyl}\text{-}3\text{-}\text{ferrocenyl}\text{-}}\textit{N}(-((\text{R})\text{-1-phenylethyl})\text{-}\text{2-propenamide and } \textit{trans}-\textit{N}(\text{-}(-\text{tert}-\text{butyl})\text{-}3\text{-}\text{ethoxycarbonyl}\text{-}4\text{-}\text{ferrocenyl}\text{-}\beta\text{-lactam, were confirmed by X-ray crystallography. The relative thermodynamic stability of the products as well as the energetics of the acid-mediated cleavage of the } \beta\text{-lactam ring was elucidated with DFT calculations.}\n
Scheme 1.29 Cobalt-catalyzed carboxylative synthesis of malonic acid derivatives.

Even though \( \text{Ni}(\text{CO})_4 \) is called \textit{liquid death}, this nickel catalyst has been applied in carboxylation reactions [52]. The group of Ricart reported a nickel-catalyzed carboxylative cycloaddition of alkynes and allyl halides to cyclopentanes. The desired products were obtained in high yields and with controlled stereoselectivity. Iron was used as a reductant. An extension of the reaction to new substrates led to the conclusion that, although the steric and electronic effects of the alkyne substituents are generally irrelevant in relation to the adducts and their yields, those of the allylic counterpart may have a significant influence on the outcome of the reaction. However, the presence of the amine moiety in the alkyne completely inhibited the reaction. The feasibility of a multicentered reaction was verified with a triacetylene, in which up to 12 bonds were created simultaneously and in good yield (Scheme 1.30).
Scheme 1.30  Nickel-catalyzed carbynylative synthesis of cyclopentanes.

1.3  Outlook

In summary, we have summarized representative examples of transition-metal-catalyzed carbynylative domino reactions. In the area of carbynylations, palladium, rhodium, and cobalt are still the main actors. The ability of palladium catalysts in carbynylative cross-coupling, rhodium catalysts in carbynylative C–H activation, and cobalt catalyst in carbynylative reactions with unsaturated bonds is impressive.

In the future, cheap catalysts such as iron and copper are expected to be explored and applied. In the case of noble metals, their reaction efficiency and selectivity should be improved. The use of nickel catalysts in carbynylation is potentially accompanied with the formation of Ni(CO)₄, which is highly dangerous for the operators. Therefore, methods for stabilizing Ni must be developed before Ni can be used in catalytic reactions.

With regard to oxidative carbynylations, green oxidants, such as air or oxygen, are much more interesting than equal amounts of Cu(OAc)₂ or BQ.

In conclusion, the main direction for methodology development in the future is looking at “sustainable development.”

References


3. For selected reviews on transition metal-catalyzed coupling reactions, see:


References


