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Palladium-catalyzed oxidative dehydrogenative carbonylation reactions using carbon monoxide and mechanistic overviews

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Carbon monoxide, which is an abundant and inexpensive carbonyl source, has been widely applied to synthesize carbonyl-containing compounds, for example ketones, esters, and amides. These types of compounds are ubiquitous in natural products, pharmaceuticals, as well as in functional materials. This review focuses on the palladium-catalyzed dehydrogenative C–H/X–H (X = C, N, O) carbonylation transformations under oxidative conditions. The related C–H bonds here include C(sp)³–H, C(sp²)–H, and C(sp³)–H bonds. From a step- and atom-economy perspective, transition metal-catalyzed oxidative dehydrogenative C–H/X–H carbonylation reactions with CO constitute one of the most efficient strategies for the construction of versatile carbonyl groups, without the requirement of pre-functionalized substrates.

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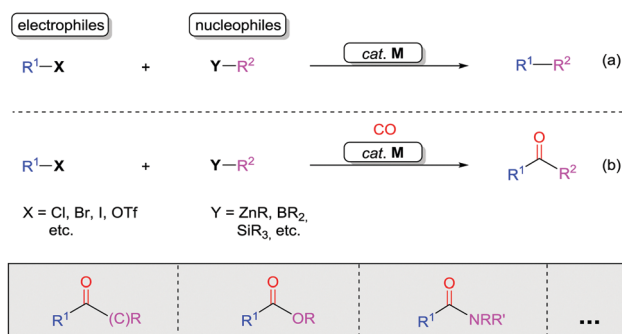
Key learning points

1. Palladium-catalyzed carbonylative coupling reactions using CO
2. Oxidative dehydrogenative coupling reactions
3. Four different means for the palladation of C–H bonds
4. Pathways of carbonylation step using CO with weak/strong nucleophiles
5. Oxidation of Pd(0) to Pd(II) by various oxidants

1. Introduction

The carbonyl group, a basic yet crucial functional group in organic chemistry, widely exists in natural products, pharmaceutical compounds, and functional materials. A carbonyl group can be easily transformed into many other functional groups, such as alcohols, imines, amines, amides, and olefins.¹

Classic transition metal-catalyzed cross-coupling reactions provide efficient pathways for construction of complex molecules from pre-functionalized electrophiles and nucleophiles (Scheme 1a).² In these cross-coupling reactions, palladium catalysts are highly efficient.³ Since the identification of carbon monoxide (CO) by William Cruikshank in 1800, exploration of the utility of this cheap and abundant C1 feedstock in organic chemistry has been at the core of organic synthesis.⁴ The bond-dissociation energy of CO is stronger than that of N₂



Scheme 1 (a) Transition metal-catalyzed coupling reactions. (b) Transition metal-catalyzed carbonylative coupling reactions. M = transition metal.

(1072 kJ mol⁻¹ vs. 942 kJ mol⁻¹) and represents the strongest chemical bond known, which makes CO relatively inert. It can be activated by various transition metals and here the identity of the metal is extremely important for imparting reactivity. In recent years, CO has become an attractive renewable building block in carbonylation reactions, in particular in those catalyzed by palladium. The reason why palladium is frequently used is that it can also participate in many other fundamental organometallic

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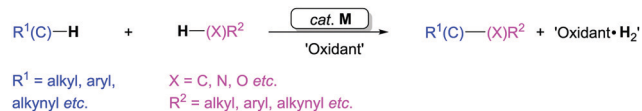
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reactions, such as oxidative addition, reductive elimination, migratory insertion, β -elimination, and nucleophilic attack on coordinated ligands as well as in oxidation reactions. In the presence of a transition metal catalyst, reactions of electrophiles, nucleophiles, and carbon monoxide result in carbonylative coupling reactions (Scheme 1b).^{5,6} This type of carbonylation reaction has been demonstrated as a direct strategy for the synthesis of various carbonyl-containing compounds and their derivatives. However, these reactions require pre-functionalized substrates, for example, aromatic halides or triflates as electrophiles, and boronic acids or zinc reagents as nucleophiles.

Oxidative dehydrogenative coupling reactions constitute a direct approach for the construction of C–X (X = C, N, or O) bonds by only using C–H/X–H bonds (Scheme 2).⁷ The related



Scheme 2 Transition metal-catalyzed oxidative dehydrogenative cross-coupling reactions.

C–H bonds here include $\text{C}(\text{sp})\text{--H}$, $\text{C}(\text{sp}^2)\text{--H}$, and $\text{C}(\text{sp}^3)\text{--H}$ bonds. These dehydrogenative coupling reactions do not require the preparation of pre-functionalized substrates, which can shorten synthetic routes. Oxidative dehydrogenative coupling reactions are therefore considered as one of the most efficient synthetic methods in the field of chemical synthesis.



Can Zhu

Can Zhu received his PhD degree under the supervision of Prof. Shengming Ma from Shanghai Institute of Organic Chemistry, China in 2014. After that, he started his postdoctoral studies in the group of Prof. Jan-E. Bäckvall at Stockholm University. In Sep. 2016, he was awarded Alexander von Humboldt Foundation Postdoctoral Fellowship to join Prof. Frank Glorius's research group, Westfälische Wilhelms-Universität Münster, working on non-noble metal catalysis. Since July 2018, he moved back to Stockholm University as a researcher. Currently, his interests focus on the development of green oxidation methodology via a biomimetic approach.



Jie Liu

Jie Liu was born in 1990 in Hunan, China. He studied at Wuhan University, China, where he obtained his BS and MSc degree in 2012 and 2014 under the supervision of Prof. Aiwen Lei. Then he joined Prof. Matthias Beller's group at the Leibniz Institute for Catalysis, Germany and received his PhD degree in 2017. He is currently a postdoctoral researcher in Prof. Jan-E. Bäckvall's research group at Stockholm University, Sweden. He is interested in the development of homogenous catalysts for oxidation chemistry.



Man-Bo Li

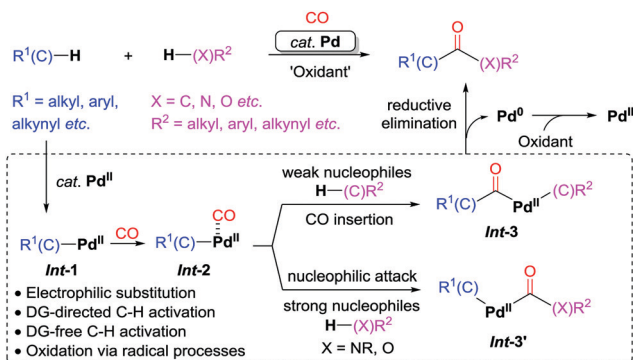
Man-Bo Li was born in 1986. He finished his bachelor studies and received his PhD degree at the University of Science and Technology of China in 2013 under the supervision of Prof. Shi-Kai Tian. After three years of research work on metal nano-clusters at the Chinese Academy of Sciences and a short stay at KAUST on heterogeneous catalysis, he joined Prof. Jan-E. Bäckvall's research group at Stockholm University to develop efficient heterogeneous Pd-catalyzed oxidations. In November of 2019, he finished his postdoctoral research in Sweden and was appointed professor at Anhui University, China.



Jan-E. Bäckvall

Jan-Erling Bäckvall was born in Malung, Sweden, in 1947. He received his PhD from the Royal Institute of Technology, Stockholm, in 1975 with Prof. B. Åkermark. After postdoctoral work (1975–1976) with Prof. K. B. Sharpless at Massachusetts Institute of Technology, he joined the faculty at Royal Institute of Technology. He was appointed Professor of Organic Chemistry at Uppsala University in 1986. In 1997, he moved to Stockholm University where he is currently Professor of Organic Chemistry. He is a member of the Royal Swedish Academy of Sciences, Finnish Academy of Science and Letters, and Academia Europaea. His current research interests include transition-metal-catalyzed organic transformations, biomimetic oxidations, and enzyme catalysis.





Scheme 3 Palladium-catalyzed oxidative dehydrogenative carbonylation reactions. DG = directing group.

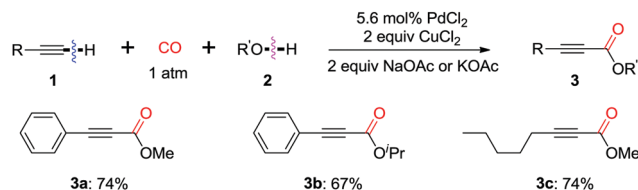
Oxidative dehydrogenative carbonylation reactions using carbon monoxide combine the concept of dehydrogenative coupling and carbon monoxide-based carbonylation. These reactions lead to significant increase of efficiency in the synthesis of carbonyl-containing compounds (Scheme 3). In the past decade, palladium catalysis has played a major role in oxidative dehydrogenative carbonylation.^{6,8,9} This review focuses on the research progress achieved in recent years within the area of palladium-catalyzed oxidative dehydrogenative carbonylation.

As the initial step in Scheme 3, C-H palladation would produce the active species **Int-1** via mechanistically different pathways depending on the interaction of the substrates and the palladium catalyst, including electrophilic substitution, DG (DG = directing group)-directed C-H activation, DG-free C-H activation, or oxidation via radical processes.¹⁰ Coordination of CO to palladium leads to **Int-2**, which would undergo a subsequent CO insertion followed by reaction with a weak nucleophile to give **Int-3**. Reductive elimination from **Int-3** would furnish the product. When N- or O-containing strong nucleophiles are employed, nucleophilic attack on the coordinated CO may occur to give **Int-3'**, which would undergo reductive elimination forming the carbonyl products. The released Pd(0) is reoxidized to Pd(II) with a suitable oxidant, which closes the catalytic cycle. We believe that this strategy will have a positive impact on the development of organic synthesis.

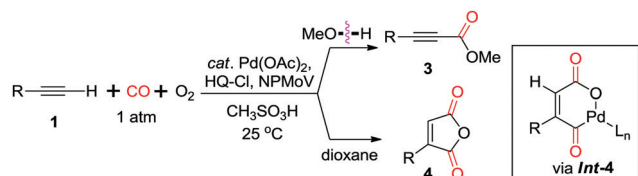
2. Palladium-catalyzed oxidative dehydrogenative carbonylation reactions

2.1 C(sp)-H/(X)-H oxidative dehydrogenative carbonylation

In 1980, Tsuji *et al.* reported the first example on a palladium-catalyzed oxidative dehydrogenative carbonylation reaction of terminal alkynes with alcohols in the presence of CO (Scheme 4).^{11a} Stoichiometric amounts of CuCl₂ were employed to reoxidize the palladium catalyst. Terminal acetylenes were successfully converted to acetylenecarboxylates in high yields under an atmospheric pressure of carbon monoxide at room temperature. This oxidative coupling approach, using readily available alkynes and alcohols, provided a direct and efficient access to acetylenecarboxylates, which are usually prepared



Scheme 4 Palladium-catalyzed oxidative carbonylation of terminal acetylenes.



Scheme 5 Palladium-catalyzed aerobic oxidative carbonylation of terminal acetylenes. HQ-Cl = chlorohydroquinone.

from the oxidation of the corresponding propargylic alcohols, or the corresponding olefinic acids.

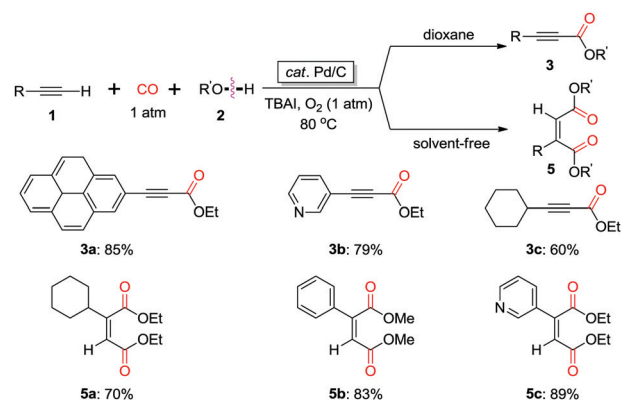
In 1999, Ishii and co-workers modified the catalytic system, by using molybdovanadophosphate (NPMoV) as the oxidation catalyst together with oxygen as the terminal oxidant (Scheme 5).^{11b} It was observed that the reaction gave the acetylenecarboxylate product in MeOH, while a double insertion of CO was observed in dioxane to afford the corresponding maleic anhydride **4** via cyclopalladium(II) intermediate **Int-4**.

In 2013, the group of Bhanage found that a heterogeneous catalyst, palladium-on-carbon (Pd/C) was efficient for promoting the oxidative carbonylation using CO as the C1 source (Scheme 6).^{11c} Interestingly, the reaction in dioxane gave acetylenecarboxylate product **3**, while the reaction under solvent-free conditions afforded *cis*-diester product **5**. Moreover, the heterogeneous catalyst, Pd/C showed remarkable recyclability, being used in up to six consecutive cycles without significant loss of activity or selectivity.

2.2 C(sp²)-H/(X)-H oxidative dehydrogenative carbonylation

2.2.1 C(sp²)-H/(O)-H dehydrogenative carbonylation.

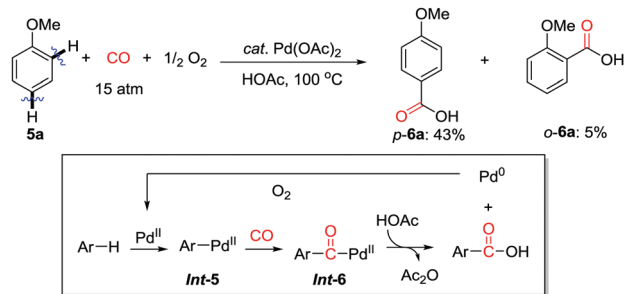
Palladium(II)-catalyzed C(sp²)-H carbonylation of aromatic



Scheme 6 Synthesis of α,β -alkynyl esters and unsymmetrical maleate esters catalyzed by heterogeneous catalyst Pd/C.



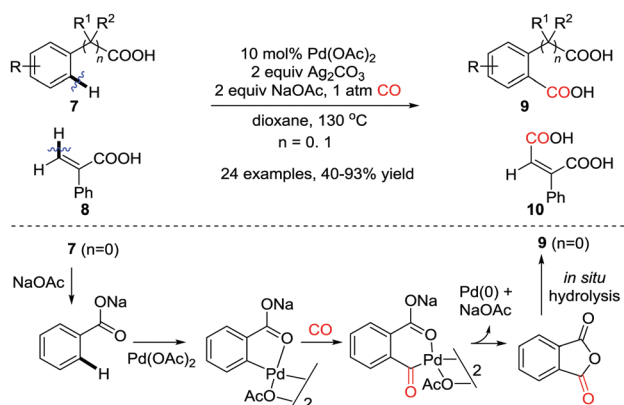
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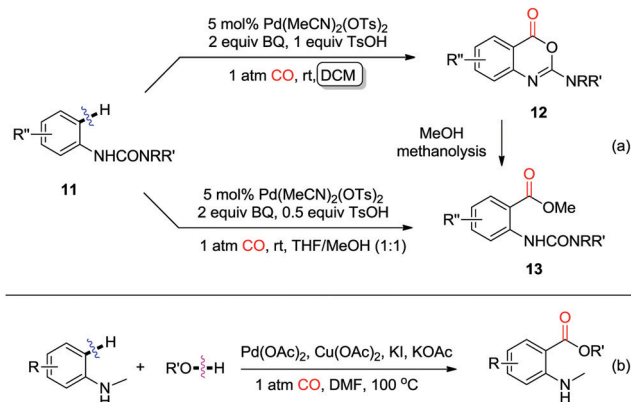
Scheme 7 Carboxylation of anisole derivatives with CO and O₂ catalyzed by Pd(OAc)₂.

compounds with the use of CO has been considered as an efficient pathway for the synthesis of aromatic carboxylic acids and their esters. As early as in 1980, Fujiwara *et al.* originally disclosed a Pd-catalyzed direct carboxylation of arene derivatives using CO and O₂ (Scheme 7) to give regioisomeric mixtures of aromatic carboxylic acids.¹² Although only a limited number of electron-rich arenes can be employed, the presented approach was the first synthetic protocol for preparation of benzoic acids *via* direct C(sp²)-H palladation/carboxylation. Direct C(sp²)-H palladation *via* the electrophilic substitution of aromatic C-H bonds by Pd(II) generates an arylpalladium species **Int-5**, which undergoes insertion of CO and acid-quenching leading to the final carboxylic acid. The released Pd(0) is reoxidized to Pd(II) by O₂.

In 2008 the first example of regioselective Pd(II)-catalyzed carbonylation of unactivated aryl and vinyl C(sp²)-H bonds was reported by the Yu group (Scheme 8).¹³ A carboxylic acid group was used as the directing group for the C(sp²)-H activation forming a C-Pd bond, therefore dicarboxylic acid derivatives were produced from benzoic and phenylacetic acids. In an analogous manner *cis*-1,2-dicarboxylic acids were successfully obtained when an α,β -unsaturated carboxylic acid was employed. Treatment of benzoic acid with sodium acetate produces sodium carboxylate, in which the carboxylate group functions as the directing group for the Pd-catalyzed C-H carbonylation. Subsequent intramolecular cyclization of the carboxylate directing group leads to the formation of phthalic



Scheme 8 Pd(II)-Catalyzed carboxylation of aryl and vinyl C-H bonds.



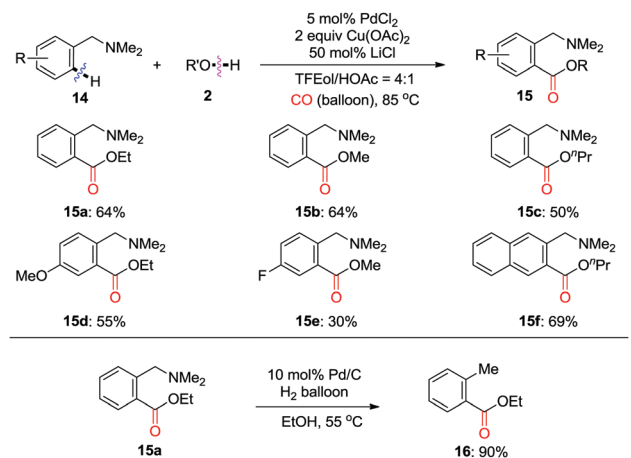
Scheme 9 Palladium-catalyzed C-H activation/carboxylation of aniline derivatives.

anhydride derivatives, which are *in situ* hydrolyzed to give dicarboxylic acid derivatives.

Shortly thereafter, in 2009, the Booker-Milburn group developed a room-temperature palladium-catalyzed C-H activation/carboxylation/alcohol-quenching of anilines for the synthesis of *o*-aminobenzoic acid esters (Scheme 9a).¹⁴ Ureas were efficient directing groups for the *ortho*-C-H activation. The reaction leads to imidates **12** in DCM, while methyl anthranilates **13** are selectively produced in a mixed solvent of THF/MeOH *via* methanolysis of imidates **12**. Later, an amine was also employed as the directing group to promote the C-H activation/carboxylation/alcohol-quenching for the synthesis of *o*-aminobenzoates (Scheme 9b).¹⁵

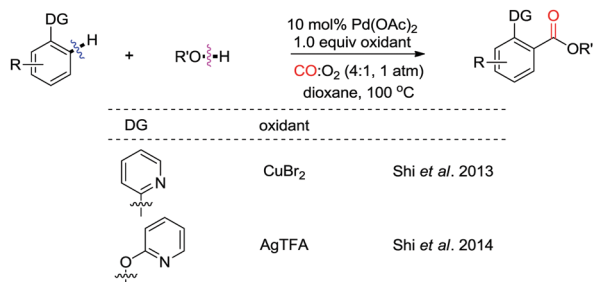
In 2010, the Shi group extensively developed a Pd(II)-catalyzed directed *ortho*-carbonylation of *N,N*-dimethylbenzylamines **14** to give **15** using CO (Scheme 10).¹⁶ It was demonstrated that LiCl is crucial for enhancing the product yield. It is worth mentioning that the directing group can be efficiently removed under catalytic hydrogenation conditions, as shown by the formation of **16** in 90% yield from **15a**.

Other nitrogen-containing groups were also reported to be useful directing groups for *ortho*-C-H activation/carboxylation.



Scheme 10 Pd(II)-Catalyzed directed *ortho*-carbonylation of *N,N*-dimethylbenzylamines using CO.

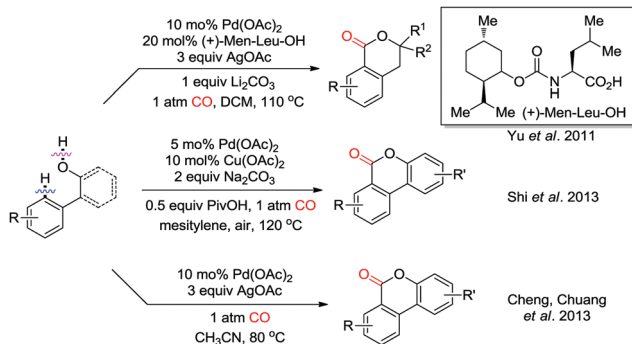




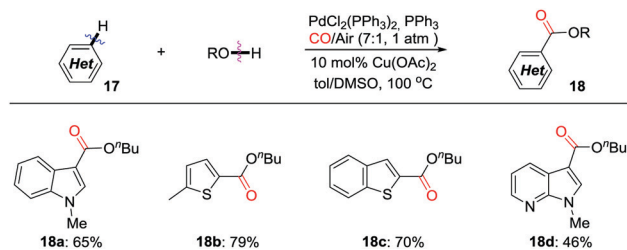
Scheme 11 Palladium(II)-catalyzed direct alkoxy carbonylation of arenes with CO and alcohols.

Shi and co-workers observed that, when the DG is a 2-pyridyl group, CuBr₂ is the best oxidant for the esterification (Scheme 11).¹⁷ However, AgTFA performs much better than CuBr₂ for phenol substrates.¹⁸ Therefore, with these methods, a variety of benzoic acid esters were obtained with high efficiency, avoiding the use of pre-functionalized substrates, such as aryl halides. Moreover, it is interesting to note that, in both cases, atmospheric pressure of CO/O₂ (4:1) was employed. A lower yield was obtained in the absence of O₂, indicating that oxygen participates as a co-oxidant in the reactions.

Weak coordination of a hydroxyl group to the palladium catalyst was demonstrated to trigger the *ortho*-carbonylation in the presence of CO (Scheme 12). Intramolecular nucleophilic attack on *Int-2* to give *Int-3'* (see Scheme 3) and subsequent reductive elimination would generate the corresponding lactones as the products. In 2011, the Yu group reported a Pd(II)-catalyzed *ortho*-C–H carbonylation reaction with phenethyl alcohol derivatives for the synthesis of benzoic acid esters (Scheme 12).¹⁹ A mono-*N*-protected amino acid was employed as an efficient ligand to ensure the C–H carbonylation transformation. Subsequently, Shi *et al.* successfully applied an *ortho*-C–H carbonylation strategy for the synthesis of dibenzopyranones from 2-phenylphenol derivatives (Scheme 12).²⁰ Air was used as the terminal oxidant together with Cu(OAc)₂ as catalytic oxidant/electron transfer mediator. At the same time, the group of Chuang independently developed a similar approach with stoichiometric amounts of AgOAc as the oxidant (Scheme 12).²¹



Scheme 12 Hydroxyl group-directed Pd(II)-catalyzed *ortho*-C–H carbonylation reactions.

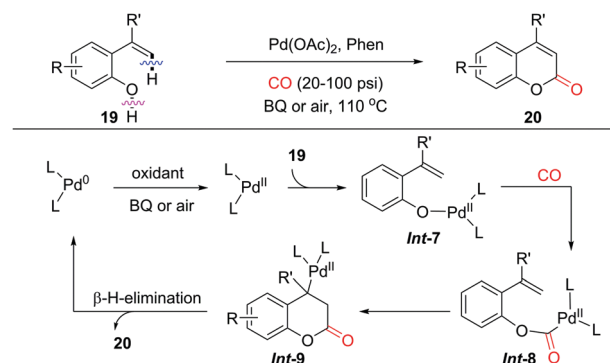


Scheme 13 Palladium-catalyzed regioselective aerobic oxidative C–H/O–H carbonylation of heteroarenes.

In 2011, the Lei group developed an efficient protocol for aerobic oxidative C–H carbonylation of heteroarenes for the synthesis of various heterocyclic esters in the presence of CO (Scheme 13).²² An electrophilic palladation mechanism was proposed to explain the regioselective carbonylation reaction. Air was used as the terminal oxidant, with catalytic amounts of Cu(II) as electron transfer mediator. The carbonylation approach can be extended to other heteroarene systems, including thiophene, benzo[*b*]thiophene, and pyrrolo[2,3-*b*]pyridine.

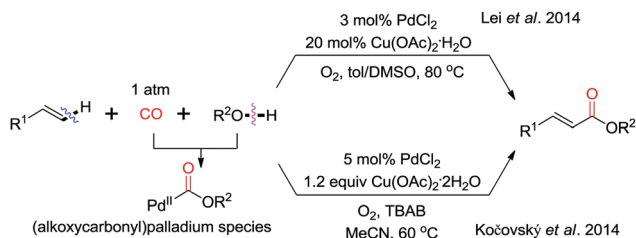
Intramolecular alkenyl C(sp²)–H/(O)–H cyclocarbonylation was demonstrated as a convenient approach for the synthesis of α,β -unsaturated lactones by the group of Alper in 2012 (Scheme 14).²³ 2-Vinylphenols as substrates afforded the corresponding coumarins as products with a variety of functional groups tolerated. Instead of the initial C(sp²)–H palladation pathway, the reaction of Pd(II) with 2-vinylphenol generates a palladium phenoxide species *Int-7* via ligand exchange. Subsequent CO insertion and intramolecular olefin insertions would give *Int-9*, which undergoes β -H-elimination to furnish coumarin as the final product. The released Pd(0) is reoxidized to Pd(II) by BQ (BQ = benzoquinone) or air, which closes the catalytic cycle.

In 2014, the groups of Lei and Kočovský independently reported the intermolecular alkenyl C(sp²)–H/(O)–H cyclocarbonylation for the synthesis of acrylate derivatives (Scheme 15).^{24,25} In both cases, Cu(OAc)₂ and molecular oxygen were used as the oxidation system. The reaction of alcohol with Pd(II) in the presence of CO generates an (alkoxycarbonyl)palladium species, which undergoes olefin insertion and β -H-elimination to give acrylate derivatives.



Scheme 14 Synthesis of coumarins via Pd-catalyzed oxidative cyclocarbonylation of 2-vinylphenols.



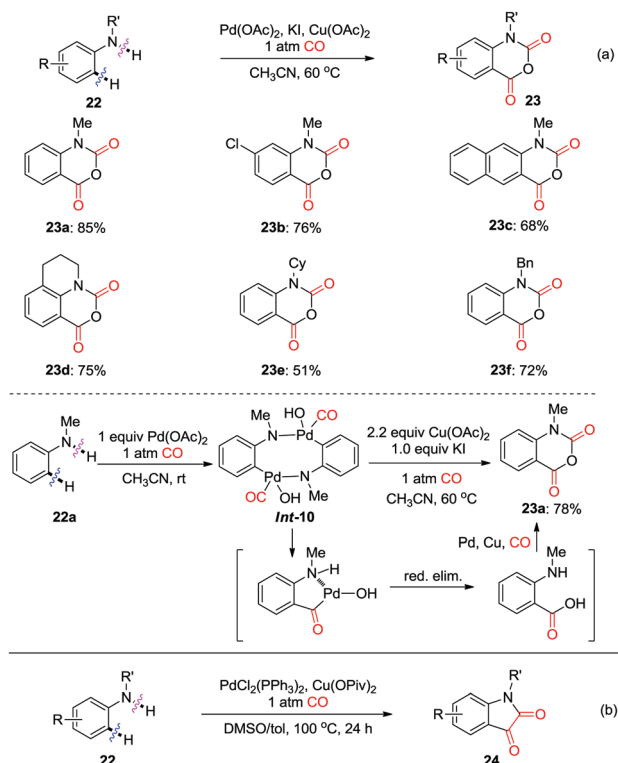


Scheme 15 Synthesis of acrylate derivatives via Pd-catalyzed oxidative intermolecular vinyl C(sp²)-H/(O)-H cyclocarbonylation.

2.2.2 C(sp²)-H/(N)-H dehydrogenative carbonylation.

In 2004, Orito *et al.* developed the chelation-assisted Pd-catalyzed C-H carbonylation in an atmosphere of CO gas containing air for the synthesis of benzolactams **21** (Scheme 16a).^{26a} A variety of five- and six-membered benzolactams **21** were obtained from secondary ω -phenylalkylamines **14**. When a secondary amine **14d** was used, in which there were two different *N*-benzyl groups, an isomeric mixture of benzolactams (**21d** and **21d'**) was obtained in 86% yield in a ratio of 2.5:1 (Scheme 16b). In 2011, the group of Garcia and Granell developed an unprecedented NH₂-directed Pd(II)-catalytic carbonylation of quaternary aromatic α -amino esters to yield 6-membered benzolactams (Scheme 16c).^{26b} The reaction shows a strong bias to 6-membered lactams over 5-membered ones, as shown by the selective formation of 6-membered lactam **21e** in 87% yield from **14e**.

In 2012, the Guan group reported on the palladium-catalyzed regioselective carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides in the presence of CO (Scheme 17a).^{26c} Various isatoic anhydrides were produced from *N*-alkyl anilines under mild conditions. The key intermediate, **Int-10** was isolated from the reaction of *N*-methyl aniline with stoichiometric amounts of Pd(OAc)₂ under CO atmosphere (1 atm). The transformation of cyclic organopalladium intermediate **Int-10** to product **23a** was achieved *via* double CO



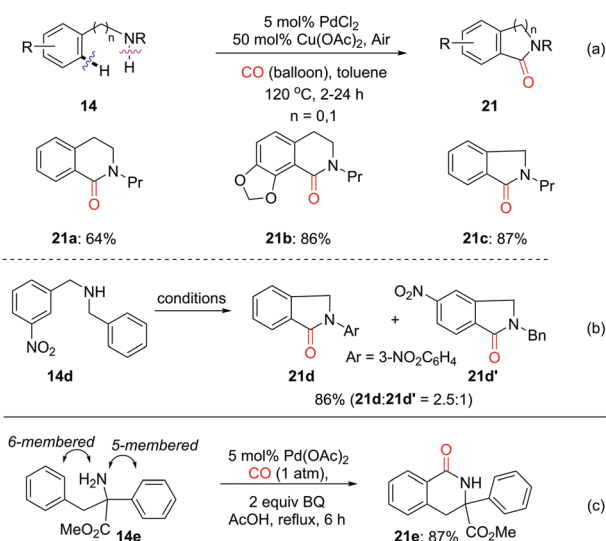
Scheme 17 Palladium-catalyzed regioselective carbonylation of *N*-alkyl anilines for the synthesis of isatoic anhydrides (a) and isatins (b) in the presence of CO.

insertion with Cu(OAc)₂ as the oxidant. Pd-catalyzed oxidative dehydrogenative double carbonylation was described by the Lei group (Scheme 17b).^{26d} Various isatins **24** were prepared by using the same substrate **22**.

In 2013, the Lei group reported an aerobic palladium/copper-catalyzed oxidative C-H alkenylation/*N*-dealkylative carbonylation of tertiary anilines **25**, which afforded 3-methyl-eneindolin-2-ones derivatives **26** (Scheme 18).^{26e} Intermolecular Heck-type reaction of dimethylaniline **25** with the terminal olefin gives olefination intermediate **27**, which undergoes C-N bond cleavage in the presence of copper and O₂ to afford **Int-11**. Subsequent transmetalation, carbonylation and intramolecular Heck reaction furnish the final product **26** *via* **Int-12**.

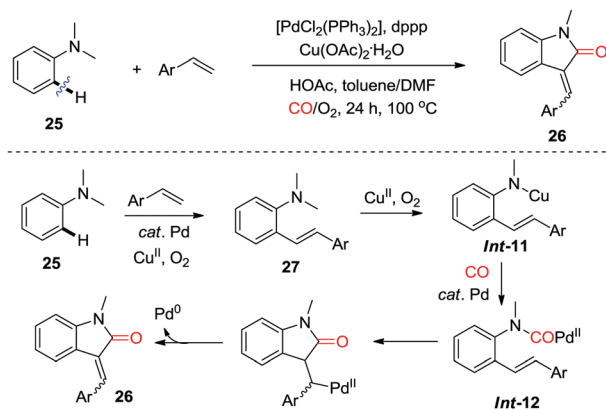
Later, Zhu *et al.* developed an efficient palladium-catalyzed C(sp²)-H pyridocarbonylation of *N*-aryl-2-aminopyridines (Scheme 19).²⁷ A 2-pyridyl group was used as the directing group to trigger C(sp²)-H activation forming a C-Pd bond, followed by insertion of CO. Intramolecular nucleophilic attack and subsequent reductive elimination give fused tricycles **28** selectively. K₂S₂O₈ was found to be the best oxidant for the overall transformations.

At the same time, Jiang and co-workers reported a palladium-catalyzed oxidative carbonylation for the synthesis of polycyclic aromatic compounds, 6*H*-isochromeno[4,3-*c*]quinolin-6-ones (Scheme 20).²⁸ The reaction proceeds *via* Pd-catalyzed oxidative carbonylation, and intramolecular reductive elimination with high atom-efficiency. However, when a 1,8-naphthyridine

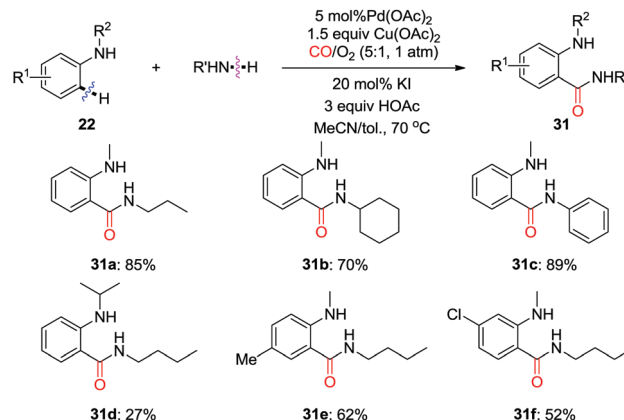


Scheme 16 Palladium-catalyzed C-H carbonylation with CO for the synthesis of benzolactams.

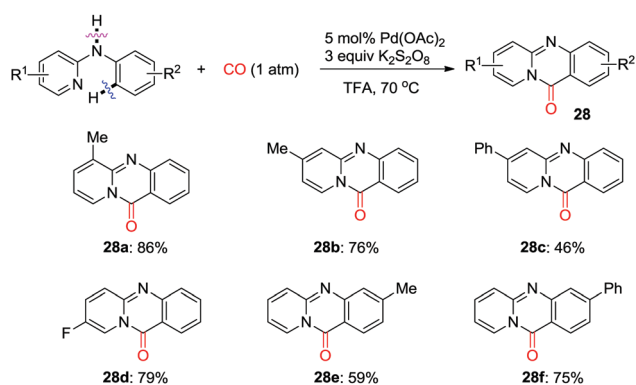




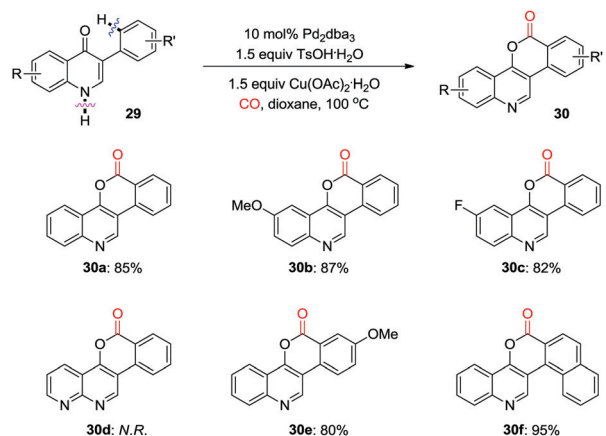
Scheme 18 Palladium/copper-catalyzed oxidative C–H alkenylation/N-dealkylative carbonylation of tertiary anilines.



Scheme 21 Palladium-catalyzed $C(sp^2)$ –H carbonylation of anilines with CO and primary amines for the synthesis of *o*-aminobenzamides.



Scheme 19 Palladium-catalyzed $C(sp^2)$ –H pyridocarbonylation of *N*-aryl-2-aminopyridines.



Scheme 20 Palladium-catalyzed oxidative carbonylation for the synthesis of polycyclic aromatic cycles.

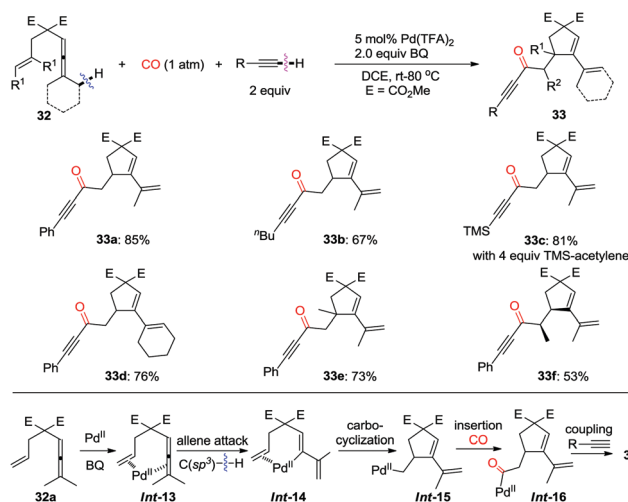
derivative was used as the substrate, none of the corresponding product (**30d**) could be detected under the optimized reaction conditions.

In 2016, the group of Zhang reported a practical intermolecular aminocarbonylation of anilines for the construction of *o*-aminobenzamides (Scheme 21).²⁹ The employment of C–H

activation for aminocarbonylation with CO as C1 source is an elegant solution for the synthesis of amides. In this work, both aromatic and aliphatic primary amines were utilized as the coupling partners. However, secondary amines, as well as bulky primary amines, were not tolerated under the reaction conditions.

2.3 $C(sp^3)$ –H/(X)–H oxidative dehydrogenative carbonylation

2.3.1 $C(sp^3)$ –H/(C)–H dehydrogenative carbonylation. In 2014, the Bäckvall group developed the first example of $C(sp^3)$ –H/(C)–H oxidative dehydrogenative carbonylation reaction, which is a palladium-catalyzed oxidative carbonylative Sonogashira coupling of enallenes with terminal alkynes (Scheme 22).³⁰ In this way, the corresponding ynones **33** were synthesized from enallenes. The reaction proceeds at room temperature under 1 atm of CO, and products were obtained in good to excellent yields by using various aliphatic, aromatic, as well as silyl-protected terminal alkynes. The mechanism involves bidentate coordination of **32a** to palladium to form complex **Int-13**, which undergoes allene



Scheme 22 Oxidative coupling reaction of enallenes with terminal alkynes via $C(sp^3)$ –H cleavage in the presence of carbon monoxide.



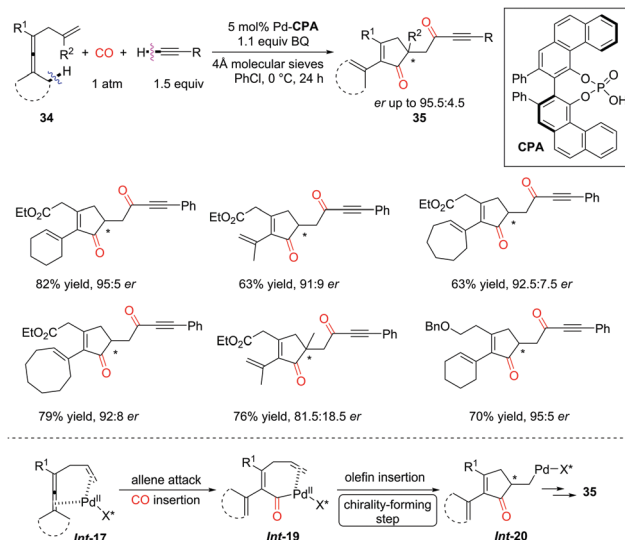
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attack *via* an allenic C(sp³)-H bond cleavage affording **Int-14**. Carbocyclization of **Int-14** gives **Int-15**, and the corresponding product is generated *via* a subsequent carbonylative Sonogashira coupling. Overall, three C-C bonds are formed during the transformations.

In 2015, a one-pot palladium-catalyzed oxidative cascade reaction of enallenes *via* carbonylation-carbocyclization-carbonylation-alkynylation was reported by the same group (Scheme 23).³¹ The insertion cascade is highly efficient and gives products **35** with exclusive chemoselectivity, which proceeds *via* sequential CO-olefin-CO insertion, involving overall formation of four C-C bonds.

The pending olefin was demonstrated to be indispensable for triggering the initial allene attack.³² This olefin acts as the directing/assisting group in **Int-17** to give **Int-18** *via* C(sp³)-H bond cleavage, which is the rate-limiting step during the overall transformations as confirmed by kinetic isotope effect studies (Scheme 24). The insertion cascade proceeds *via* sequential CO-olefin-CO insertion to generate **Int-21** from **Int-18**. Final products **35** were produced from the oxidative coupling reaction of **Int-21** with terminal alkynes. Four C-C bonds were formed in the overall cascade reaction.

Moreover, the Bäckvall group found that, under the catalysis of Pd^{II} and VAPOL phosphoric acid (CPA), the asymmetric version of the dehydrogenative carbonylation-carbocyclization reaction was realized to afford ketones bearing α -chirality from enallenes (Scheme 25).³³ Vaulted biaryl-type chiral phosphoric acids served as useful co-catalysts for this asymmetric transformation, therefore ketone products were generated in good

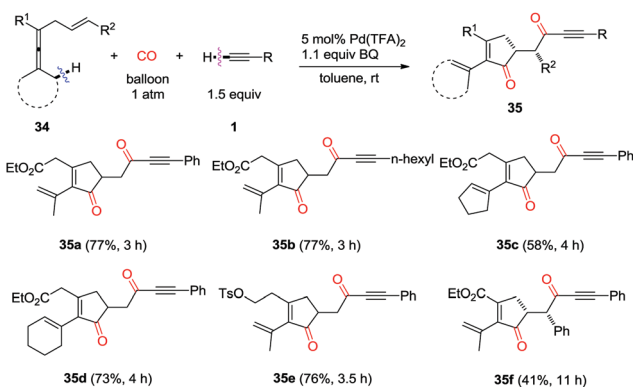


Scheme 25 Asymmetric version of the dehydrogenative carbonylation-carbocyclization reaction.

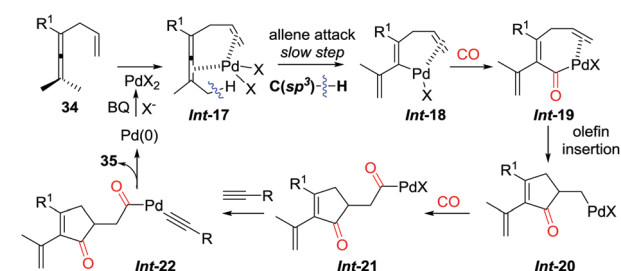
yields with up to 95.5:4.5 e.r. In the catalytic cycle, enantioselective migratory insertion of the olefin into the C-Pd bond produces the carbocyclic intermediate **Int-20**, introducing the chirality at the α -position of the ketone. However, a racemization pathway in **Int-20** probably lowered the e.r. of the ketone products **35** *via* reversible β -hydride elimination-hydropalladation.

Spirocarbocyclic scaffolds bearing a quaternary carbon center, have attracted an increasing interest recently, because they occur as structural elements in a range of natural products, pharmaceutical ingredients, and chiral ligands. By introducing an additional distal olefin unit, spiro[3.4]octenes **37** and spiro[4.4]nonene **38** derivatives were obtained chemoselectively by controlling the reaction conditions (Scheme 26).³⁴ Lower temperature in DCE favored double insertion of CO into C-Pd bond to provide compounds **38**, while spirocyclobutene derivatives **37** were generated as single diastereoisomers at a higher temperature in MeCN.

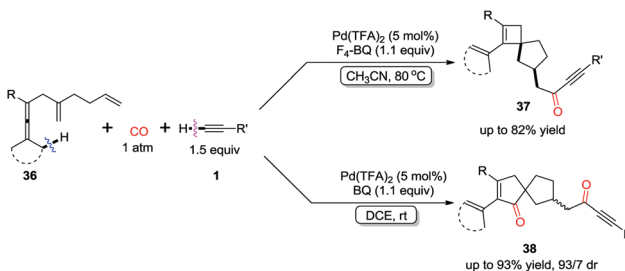
The coordination of dienallene to Pd^{II} generates the chelate **Int-23**, in which the pending olefin is an indispensable element for the subsequent allene attack to afford vinylpalladium intermediate **Int-24** (Scheme 27).^{32,34} Direct insertion of the pending olefin into the C-Pd bond gives **Int-25**, which proceeds *via* sequential olefin-CO insertion to produce carbonyl-palladium intermediate **Int-26**. Spirocyclobutene derivatives



Scheme 23 Insertion cascade forming cyclopentenones.

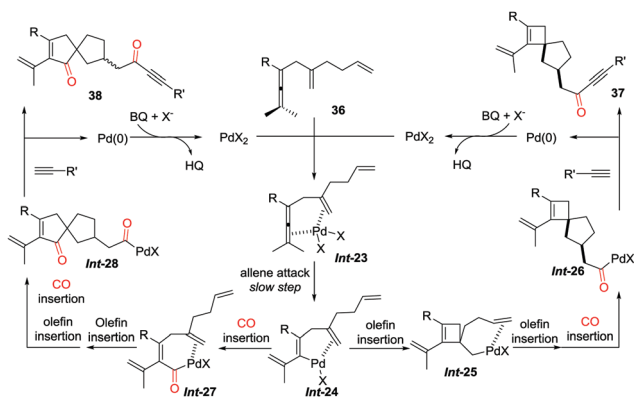


Scheme 24 Proposed mechanism for the insertion cascade reactions.



Scheme 26 Selective formation of spirocarbocyclic scaffolds.





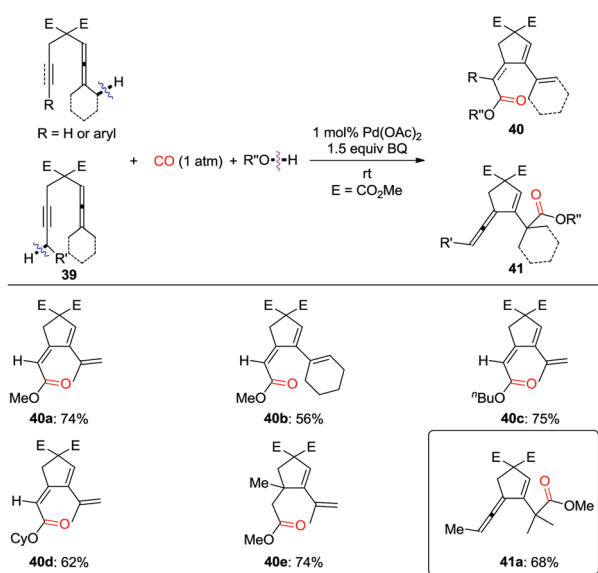
Scheme 27 Proposed mechanism for the selective formation of spiro-carbocyclic scaffolds.

37 is subsequently obtained from the coupling reaction of **Int-26** with a terminal alkyne. However, by using DCE as the solvent at lower temperature, sequential insertions of CO–olefin–olefin–CO give spiro[4.4]nonene derivatives **38** in high selectivity.

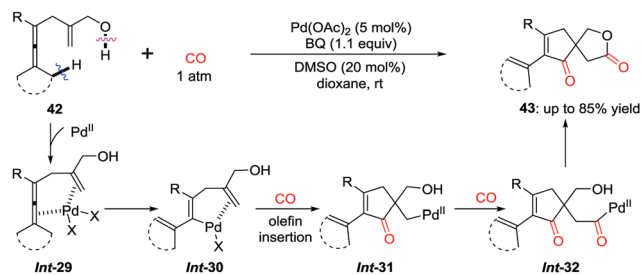
2.3.2 C(sp³)–H/(O)–H dehydrogenative carbonylation.

In 2014, the Bäckvall group reported the Pd-catalyzed oxidative domino carbocyclization–carbonylation reaction of enallenes and allenynes (Scheme 28).³⁵ For the enallene substrates, an allenic C(sp³)–H bond cleavage was observed, and the corresponding cyclopentene derivatives **40** bearing the ester functionality were obtained. For allenynes, when R is H or an aryl group, the reaction underwent allenic C(sp³)–H bond cleavage leading to product **40**. Interestingly, when R is an alkyl group bearing a propargylic C–H bond, the selective formation of allene product **41** was detected via propargylic C(sp³)–H bond cleavage.

The cascade insertion can be extended to synthesize spirolactones. By using an internal hydroxyl group as an



Scheme 28 Oxidative palladium-catalyzed carbocyclization–carbonylation of allenynes and enallenes.



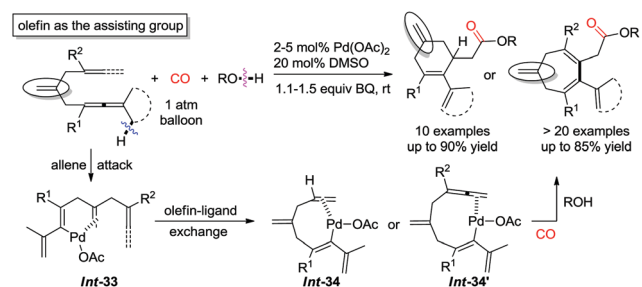
Scheme 29 Oxidative cascade carbonylative spirolactonization of enallenols.

intramolecular quencher, cascade carbonylative spirolactonization of enallenols was realized to afford spirolactones **43**.³⁶ After the sequential insertion of CO–olefin–CO into the C–Pd bond in **Int-29** (Scheme 29), the internal hydroxyl group quenching of the carbonyl–palladium intermediate **Int-32** leads to the selective formation of spirolactones **43**, bearing an all-carbon quaternary center.

Recently, a pending olefin was successfully employed as the assisting group for the carbocyclization–alkoxycarbonylation of dienallenes or bisallenenes, and in this manner six- or seven-membered carbocycles were generated selectively and efficiently (Scheme 30).^{37,38} The olefin–ligand exchange from the pending olefin in **Int-33** to the remote olefin/allene forming **Int-34** or **Int-34'** was found to be the key step for the overall transformations.

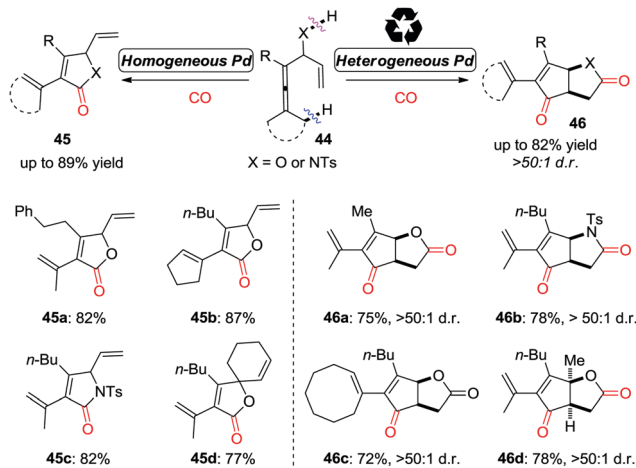
More recently, this group developed a palladium-catalyzed oxidative carbonylation reaction of enallenols for the chemodivergent synthesis of γ -lactone and γ -lactam derivatives (Scheme 31).³⁹ Interestingly, the catalyst-controlled chemodivergent carbonylation forming products **45** and **46**, respectively, was achieved by switching between homogeneous and heterogeneous catalysts.

Allylic oxidation followed by subsequent nucleophilic attack presents a highly efficient approach for the synthesis of functionalized olefins. In 2011, the group of Jiang found that, in the presence of CO, allylic oxidation for the formation of linear β,γ -unsaturated ester **48** was realized using alcohol as the quencher (Scheme 32).⁴⁰ Mechanistic studies on the kinetic isotope effects indicated that the initial cleavage of the allylic C(sp³)–H bond is involved in the rate-determining step. This allylic C(sp³)–H oxidation/carbonylation approach provides a new route for accessing more synthetically useful β -enoic acid esters with high regioselectivity.

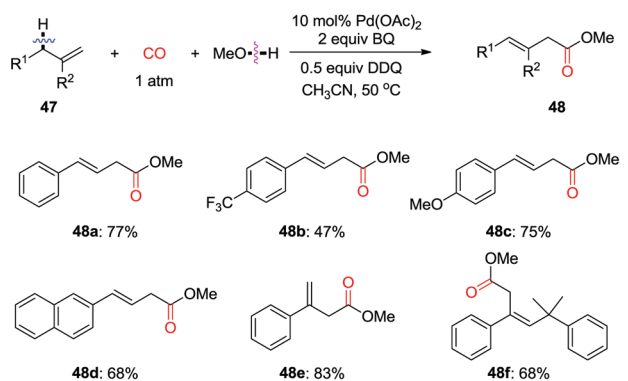


Scheme 30 Oxidative carbocyclization–alkoxycarbonylation of dienallenes or bisallenenes.





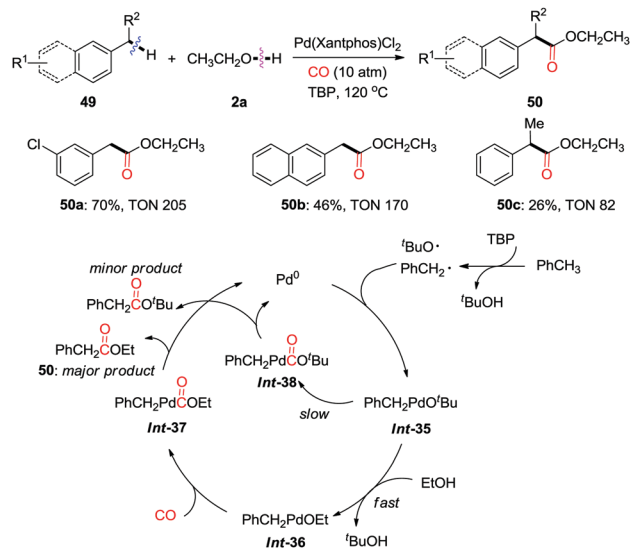
Scheme 31 Oxidative tandem reaction of enallenols for the chemo-divergent and diastereoselective synthesis of γ -lactone and γ -lactam derivatives.



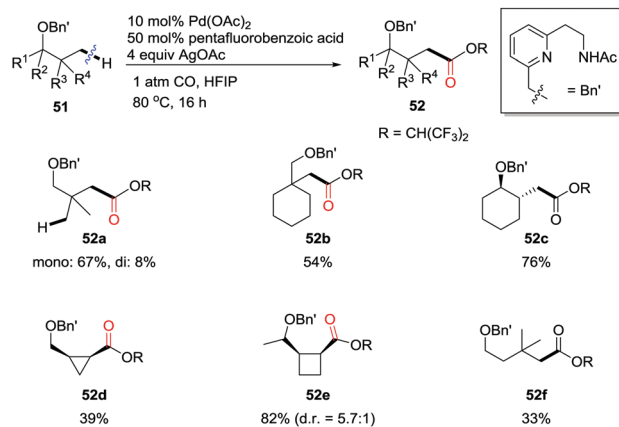
Scheme 32 Regioselective palladium-catalysed oxidative allylic C-H carbonylation of alkenes.

In 2012, Huang *et al.* reported a palladium-catalyzed oxidative carbonylation of benzylic $C(sp^3)$ -H bonds to benzylic esters in the presence of a high pressure of CO (10 atm) (Scheme 33).^{41a} In this study, they developed a new strategy for generating reactive benzylpalladium species from toluenes *via* nondirected $C(sp^3)$ -H activation using TBP (di-*tert*-butyl peroxide) as the oxidant. High TONs (turnover numbers) were observed for almost all of the substrates. This approach produces ethyl esters *via* transmetalation/reductive elimination as the major products. However, the corresponding *tert*-butyl ester was also detected as a minor product due to the reductive elimination from *Int-38*.

Very recently, Yu and colleagues reported the design of a hemilabile directing group, which exploited the chelation of a readily removable benzyl ether moiety to direct γ - or δ - $C(sp^3)$ -H carbonylation of alcohols (Scheme 34).^{41b} Under an atmospheric pressure of carbon monoxide, the remote methyl C-H



Scheme 33 Palladium-catalyzed oxidative carbonylation of benzylic C-H bonds to benzylic esters in the presence of CO.



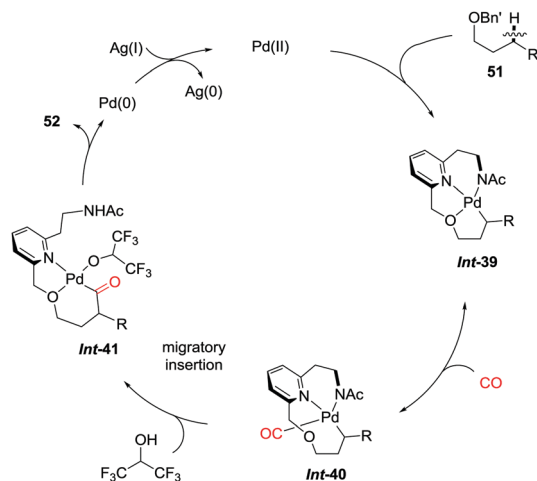
Scheme 34 Palladium-catalyzed $C(sp^3)$ -H carbonylation of alcohols.

bonds, as well as the methylene C-H bonds in cyclopropane and cyclobutane substrates were successfully converted to ester functionalities in the products under the catalysis of Pd(II). δ - $C(sp^3)$ -H carbonylation of alcohols through remote palladation was also realized as shown by the formation of **52f** in 33% yield.

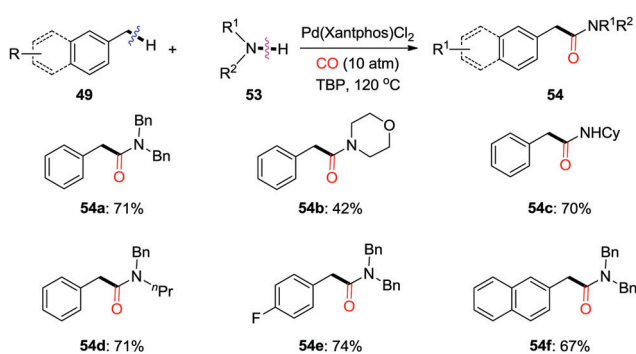
The directing group coordinated to Pd(II) triggers the cyclo-palladation of the C-H bond to give *Int-39*, which is accelerated by participation of the NHAc motif (Scheme 35). The dissociation of the hemilabile ether from the palladium center allows the binding of carbon monoxide to furnish *Int-40*. Subsequent migratory insertion and oxidative coupling with the solvent give the final product **52** *via* *Int-41*. The authors concluded that both the acceleration caused by the internal ligand and the lability of the ether to dissociate during the catalytic cycle were crucial for the reaction to occur.

2.3.3 $C(sp^3)$ -H(N)-H dehydrogenative carbonylation. In 2013, the Huang group extended the Pd(II)-catalytic system^{41a} to the aminocarbonylation reaction by using primary or secondary





Scheme 35 Proposed catalytic cycle for the palladium-catalyzed $C(sp^3)$ -H carbonylation of alcohols.

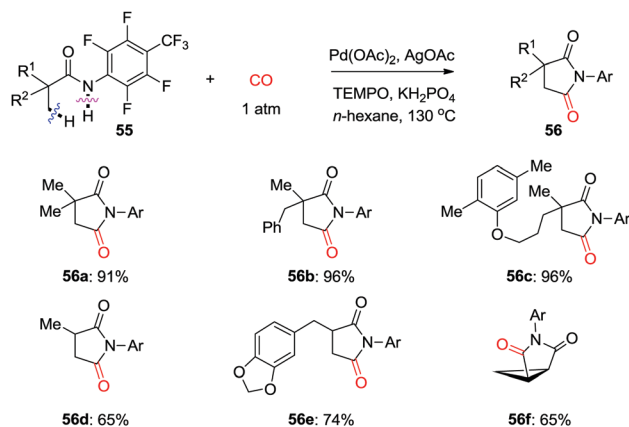


Scheme 36 Palladium-catalyzed oxidative aminocarbonylation of benzylic C-H bonds to amides in the presence of CO.

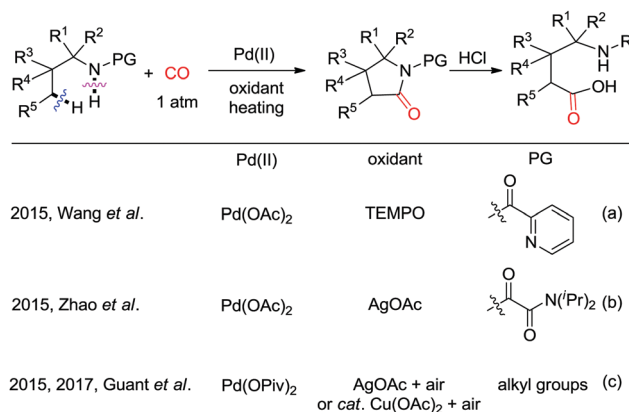
amines as the quenchers (Scheme 36).⁴² The palladium-catalyzed oxidative aminocarbonylation afforded the corresponding amides *via* C-H activation, generally in good yields.

As early as 2010, the Yu group found that, when an amide was used as the directing group, $C(sp^3)$ -H carbonylation catalyzed by Pd(II) was achieved under atmospheric pressure of CO (Scheme 37).⁴³ Following amide-directed $C(sp^3)$ -H cleavage and insertion of CO into the formed C-Pd bond, intramolecular C-N reductive elimination provides the corresponding succinimides. These products could be readily converted to acyclic 1,4-dicarbonyl compounds under basic conditions. This method can be also extended to cyclopropane substrates.

In 2015, the groups of Wang and Zhao independently reported Pd-catalyzed $C(sp^3)$ -H carbonylation of aliphatic amine substrates for the synthesis of γ -lactams and γ -amino acids (Scheme 38a and b).^{44,45} When the 2-pyridyl group was used as the directing group, TEMPO was found to be an efficient oxidant for the carbonylation transformations (Scheme 38a). However, in case of substrates having oxalyl amide as bidentate directing group, AgOAc performed better (Scheme 38b). Therefore, γ -lactams were obtained from γ -carbonylation reactions, and γ -amino acids were formed after subsequent hydrolysis in the presence of HCl.



Scheme 37 Pd(II)-Catalyzed carbonylation of $C(sp^3)$ -H bonds to 1,4-dicarbonyl compounds.



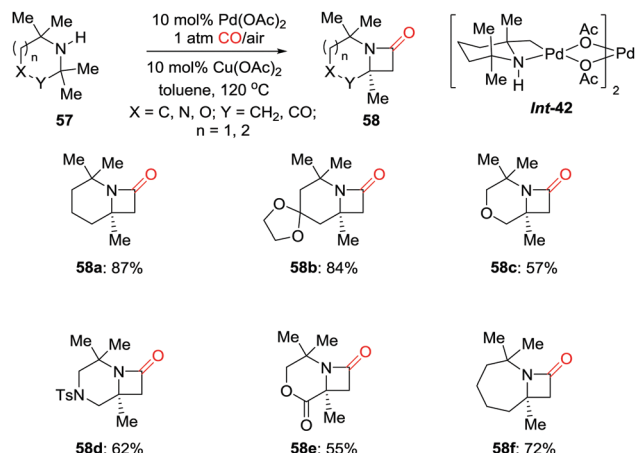
Scheme 38 Amine-directed Pd(II)-catalyzed carbonylation of $C(sp^3)$ -H bonds to γ -lactams.

Gaunt *et al.* used *N*-alkyl amines as the substrates and developed diastereoselective C-H carbonylative annulation of aliphatic amines (Scheme 38c).^{46,47} Here, Cu(OAc)₂ was employed as the co-catalyst with air as the terminal oxidant.

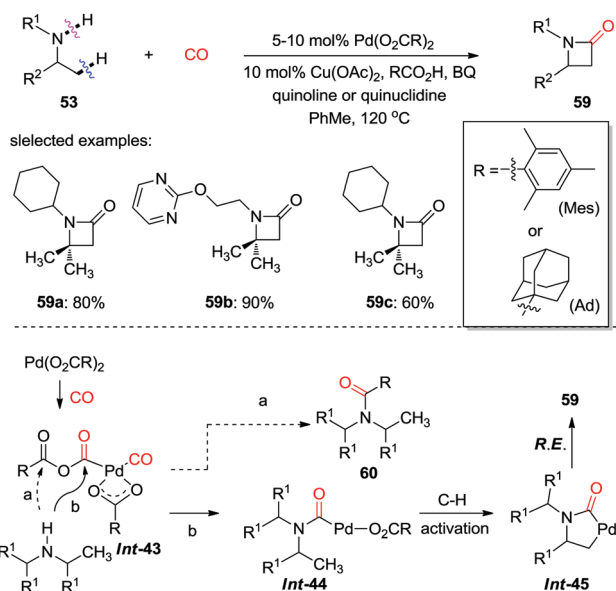
In 2014, the Gaunt group developed a palladium-catalyzed $C(sp^3)$ -H activation of hindered aliphatic amines for the synthesis of strained nitrogen heterocycles **58** (Scheme 39).⁴⁸ Mixing 2,2,6,6-tetramethylpiperidine (TMP) with stoichiometric Pd(OAc)₂ gave rise to a four-membered ring palladacycle (**Int-42**), which was directly characterized by X-ray diffraction. When this complex was treated with carbon monoxide, fused β -lactam **58a** was obtained in high yield. A number of β -lactams were prepared using the catalytic method. This methodology should find further application as this structural motif is considered important in the design of pharmaceutical agents.

Subsequently, the same group presented more general reaction conditions for the synthesis of diverse β -lactams from readily available aliphatic amines (Scheme 40).⁴⁹ In contrast to acetate as the anion in the palladium complex, a sterically hindered carboxylate ligand orchestrated an amine attack on the proximal carbonyl in a palladium anhydride **Int-43** more efficiently, therefore transformed aliphatic amines into β -lactams





Scheme 39 Palladium-catalyzed C–H activation of aliphatic amines for the synthesis of strained nitrogen heterocycles.



Scheme 40 A general catalytic β -C–H carbonylation of aliphatic amines to β -lactams.

59 via C–H activation and subsequent reductive elimination (path b). Under optimal reaction conditions, a wide range of secondary amines were successfully employed as substrates, and the corresponding β -lactams were produced in good to high yield.

3. Conclusions and perspectives

In conclusion, the main achievements of palladium-catalyzed oxidative dehydrogenative carbonylations have been summarized and discussed. This strategy has proven to be a powerful tool for the construction of carbonyl-containing compounds, including ketones, esters, and amides. However, there are still many disadvantages of this chemistry, and these drawbacks have to be overcome. First of all, although many groups have reported

aerobic oxidations with air or molecular oxygen as the terminal oxidant, there are many limitations associated with these processes. In most cases, stoichiometric amounts of a non-benign oxidant are still used to reoxidize Pd(0) to Pd(II). Therefore, environmentally benign oxidants are highly desirable in this field. For example, using biomimetic oxidations with the assistance of electron-transfer mediators (ETMs) will allow the use of benign terminal oxidant such as O₂ or H₂O₂.⁵⁰ Secondly, similar to Pd-catalyzed C–H functionalization reactions, the majority of the reported carbonylation examples use high catalyst loadings (5–10 mol%), therefore systems with higher catalytic activity has to be developed. Moreover, due to the presence of π back-bonding, CO is a strong field ligand to transition metals. The occupation of orbitals of palladium by carbon monoxide prevents the coordination of various nucleophiles to palladium, which results in the limited number of C–H carbonylation reactions compared to other C–H functionalization reactions. Above all, the oxidative dehydrogenative carbonylation reactions have been demonstrated as a powerful tool for the synthesis of carbonyl compounds, and it will remain as a hot topic in the future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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