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Advances in Palladium-Catalyzed Cascade Cyclizations

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Abstract: The past decades in organic chemistry have witnessed significant improvements in synthetic efficiency as a result of considerable progress in cascade reactions, tandem reactions, and related one-pot processes. These methods are less time-consuming and produce less waste compared to the classical stepwise approach. However, cascade chemistry requires a more careful design and compatible reaction types for success. Palladium-catalyzed cross-coupling reactions, with their well understood multistep catalytic cycles, form a promising basis for the design of cascade reactions. Furthermore, they are compatible with a range of functional groups and can be combined with a range of secondary transformations. The resulting palladium-catalyzed cascade reactions have provided access to a plethora of complex small molecules of high medicinal relevance. This review provides an overview of the developments in palladium-catalyzed cascade reactions since 2011, classified according to the initiation, propagation, and termination steps comprising the palladium cascade reactions. This classification should assist the reader and may provide inspiration for the design of new cascade reactions.

Keywords: cascade reactions; catalysis; cyclization; domino reactions; palladium

1 Introduction

Historically, organic chemists have mainly used a classical stepwise approach for the synthesis of complex molecules. Usually, a single new bond is formed in the reaction and the product needs to be purified before continuing to the next step in the synthesis. However, this is a time-consuming process generating large amounts of waste, mostly resulting from the purification method. Nature takes a more subtle approach, providing molecules from subsequent reactions of *in situ* formed intermediates until the formation of the desired product.[1] More recently, scientists have exploited the use of these cascade reactions in the synthesis of high added-value compounds.[2–6]

Designing multistep reactions is a challenging process, because all individual steps need to be compatible. To increase the ease of designing compatible reactions and allow the creation of more complex cascade reactions, versatile intermediates and reactions are required.

Palladium is a transition metal capable of catalyzing numerous cross-coupling reactions between carbon fragments (Scheme 1). An interesting and well-known coupling is the Mizoroki–Heck reaction, which connects an unsaturated (pseudo)halide **1** and alkene **3** (Scheme 1A).[7,8] The oxidative insertion of Pd(0) into the C–X bond generates the organopalladium species **2**. Carbopalladation of the alkene forms the alkyl-Pd(II) complex **4**, and β-hydride elimination

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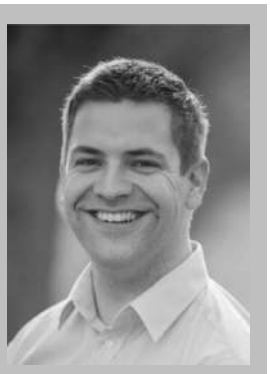
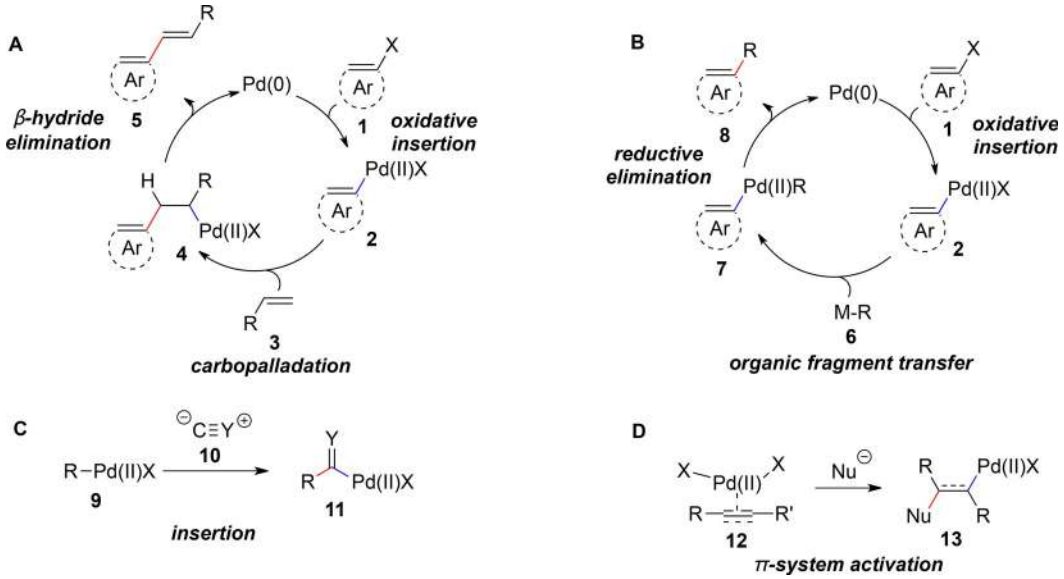


Eelco Ruijter obtained his PhD from the Vrije Universiteit Amsterdam and the Leibniz Institute of Plant Biochemistry (Halle/Saale, Germany) in 2005. After a postdoctoral stay at Utrecht University (2004–2006) with Profs. Liskamp and Heck, he was appointed assistant professor of organic chemistry at the Vrije Universiteit Amsterdam and received tenure in 2012. In 2018, he was promoted to associate professor. His research interests include the development of synthetic methods based on cascade reactions and homogeneous catalysis for the efficient and sustainable production of high added value molecules.

yields the 1,2-disubstituted alkene **5**. The organopalladium species can also undergo other cross-couplings, namely a Suzuki [Scheme 1B, M = $B(OH)_2$ or $B(OR)_2$],[9] Stille (Scheme 1B, M = SnR_3)[10] or Sonogashira (Scheme 1B, M–R = copper acetylide).[11] Another versatile reaction of organopalladium complexes is the insertion of either an isocyanide (Scheme 1C, Y = NR) or carbon monoxide (Scheme 1C, Y = O). These insertions provide a new, more electrophilic organopalladium complex and can be used in tandem with any of the cross-coupling reactions.

The oxidative insertion of Pd(0) into carbon-(pseudo)halide bonds is not the only method to generate organopalladium complexes. Coordination of Pd(II) to alkenes and alkynes in presence of a nucleophile also provides organopalladium species (Scheme 1D). The feasibility of many Pd-catalyzed processes, especially those involving Pd(0) catalysis, critically depends on the presence of an appropriate (phosphine) ligand (Scheme 2). These ligands not only stabilize the Pd center in the required oxidation states, but also increase the reactivity of the metal center. Especially in palladium-catalyzed cascade reactions, where



Scheme 1. Overview of the most common palladium-catalyzed processes. A: carbopalladation; B: organic fragment transfer (transmetallation); C: (migratory) insertion; D: π-system activation.

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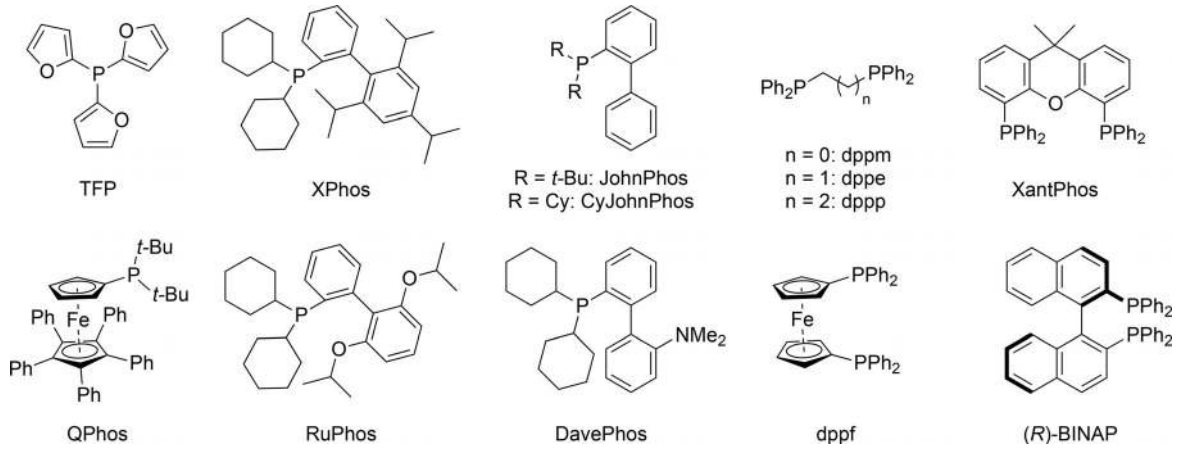

Scheme 2. Overview of phosphine ligands commonly employed in palladium-catalyzed reactions.

the ligands must provide assistance to different reaction types, optimization of the ligand is critical.

A closer look at palladium-catalyzed cascade reactions reveals several distinct common features. First, an organopalladium species needs to be formed, which can be referred to as the initiation step. This typically occurs either by oxidative insertion of Pd(0) into a C–X bond or by coordination of Pd(II) to a π-system with subsequent attack of a nucleophile. The propagation steps typically involve the insertion of two-carbon fragments (carbopalladation of alkenes and/or alkynes, benzyne insertions) or one-carbon fragments (carbon monoxide, isocyanide or carbene insertions). The final step is the coupling of the organopalladium complex with an organic fragment, which removes the palladium from the product (termination). An overview of the different initiation, propagation and termination pathways is presented in Table 1. This classification was also used by Düfert and Werz in their review of palladium-catalyzed cascade reactions of alkynes.[12]

We recently reviewed the advances in palladium-catalyzed cascade cyclization reactions until 2011.[13] Given the progress made in this area we now present an update on the topic covering the literature up to April 2017. This review will be limited to cascade reactions which include at least two distinct palladium-catalyzed reactions. However, subsequent reactions occurring in addition to the palladium-catalyzed reactions will be discussed when they happen during the cascade reaction. Rather than being exhaustive, we aim to give an overview of the various possibilities of palladium-catalyzed cascade reactions, focusing primarily on cyclization reactions, but including non-cyclization reactions whenever useful for generating a more complete overview. The sections of this review will follow the classifications of initiation, propagation and termination steps as presented in Table 1. Section 2 will present palladium-catalyzed cascade reactions initiated by the oxidative insertion of Pd(0) in carbon-(pseudo)halide bonds, while Section 3 will focus on cascade reactions initiated by the activation of π-systems by Pd(II). However, not all cascade reactions can be categorized in these two sections. Therefore, Section 4 will discuss specific building blocks or systems that are better discussed in a separate section. The final sections will highlight the use of palladium-catalyzed cascade reactions in total synthesis, comparing two syntheses of the same natural product by leading researchers in the field.

2 Palladium-Catalyzed Cascade Reactions *via* C–X Activation

As mentioned in the introductory section, the oxidative insertion of Pd(0) in carbon-(pseudo)halide

Table 1. The components from which most palladium-catalyzed cascade reactions are built.

Initiation	Propagation	Termination
- oxidative insertion in R–X bonds	- carbopalladation of alkenes	- Suzuki coupling
- π-system activation	- carbopalladation of alkynes	- Stille coupling
	- benzyne insertion	- Sonogashira reaction
	- CO insertion	- Buchwald–Hartwig coupling
	- isocyanide insertion	- Heck reaction
	- carbene insertion	- C–H activation
		- ion capture

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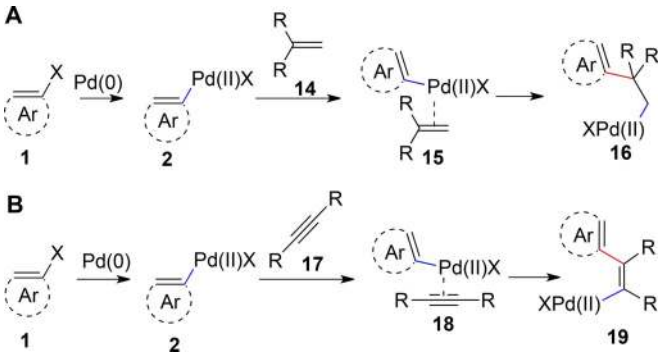
bonds is a well understood and versatile process. The resulting alkenyl-, aryl-, or benzyl-Pd(II) species can undergo a wide range of subsequent propagation and termination steps. Typically, initiation is followed by carbopalladation of an alkene or alkyne. Since the resulting organopalladium species should undergo a second reaction, Heck-type termination pathways need to be inhibited. The most straightforward approach is the formation of an organopalladium intermediate lacking β-hydrogens.

In the case of alkyne insertion, the use of internal alkynes is key in making a stable alkenyl-Pd(II) moiety (Scheme 3B). Since carbopalladation usually proceeds *via syn* addition of the organopalladium complex, the resulting alkenyl-Pd(II) species **19** lacks β-hydrogens, preventing β-hydride elimination. Similarly, alkyl-Pd(II) intermediates **16** lacking β-hydrogens can be generated by the use of 1,1-disubstituted olefins. However, as carbopalladation preferably occurs at the least substituted position of the alkene in intermolecular processes, the desired regioselectivity is typically achieved by performing the reaction in an intramolecular fashion, the cyclization being governed by the Baldwin rules.



Scheme 3. A: Carbopalladation of a 1,1-disubstituted alkene, yielding a stable alkyl-Pd(II) intermediate. B: *syn*-Carbopalladation of an alkyne, resulting in a stable alkenyl-palladium intermediate.

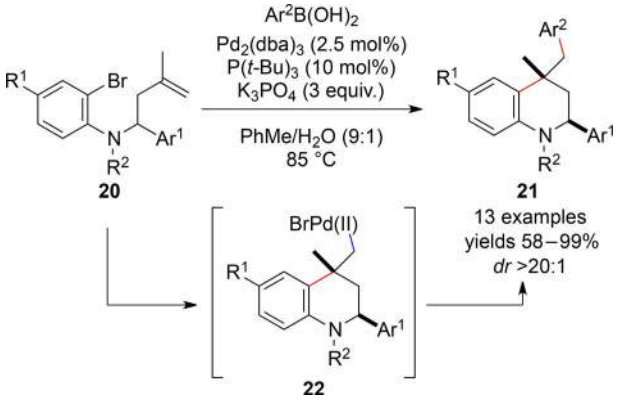
2.1 Direct Termination Approach

The following examples involve palladium-catalyzed cascade reactions in which the initial carbopalladation is followed by a second palladium-catalyzed step with no organopalladium complex at the end of the reaction. Therefore, this section will be limited to cascade reactions involving two palladium-catalyzed steps. However, subsequent non-palladium-catalyzed steps may occur and will be discussed when applicable.

2.1.1 Carbopalladation/Suzuki Coupling

The Suzuki cross-coupling reaction is a versatile and important reaction in contemporary organic synthesis.[9] The original reaction couples aryl or vinyl (pseudo)halides to boronic acids or esters. The reaction proceeds via the general mechanism as depicted in Scheme 2B. However, activation of the boronic acid or ester by hydroxide or an alkoxide is required before the organic fragment can be transferred to the Pd complex.

In 2012, Wilson reported a carbopalladation/Suzuki sequence in his efforts to synthesize 2,4,4,7-tetrasubstituted-tetrahydroquinolines **21** (Scheme 4).[14] The key intermediate of the reaction is alkyl-Pd(II) complex **22**, formed by a 6-*exo-trig* carbopalladation. The reaction proceeds diastereoselectively, with the cone angle of the ligand determining the selectivity. A variety of arylboronic acids was used, with the use of electron-rich boronic acids resulting in the direct Suzuki coupling between the aryl-Pd(II) complex and the boronic acid. Furthermore, R^1 and Ar^1 were only varied slightly.



Scheme 4. Carbopalladation/Suzuki sequence for tetrahydroquinolines.

Mårtensson et al. reported the synthesis of kinase inhibitor precursors (3-benzylidene-substituted cyclopenta[*b*]indole-2-ones) **24** *via* a 5-*exo-dig* carbopalladation/Suzuki cascade (Scheme 5).[15] The *E/Z* selectivity of the alkene formation is determined by the *syn* addition of the aryl-Pd(II) species to the alkyne. Various (hetero)aromatic boronic acids were used, showing high yields for systems with electron-donating and inductively electron-withdrawing substituents. Tolerance of the Ar substitution pattern was limited to *para* and *meta* substituents. The authors hypothesized the sterically encumbered Pd(II) complex to be unable to undergo organic fragment transfer of *ortho*-substituted arylboronic acids.

A similar strategy was employed a few years earlier by Arcadi et al. in the synthesis of 3-ylidene-dihydro-

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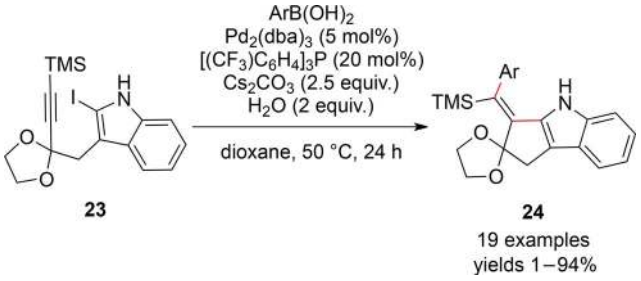
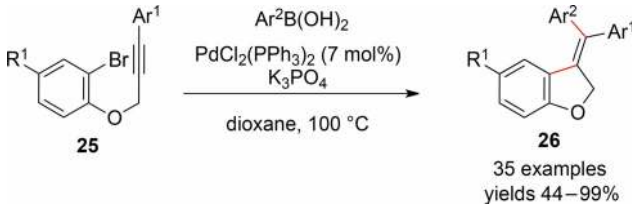


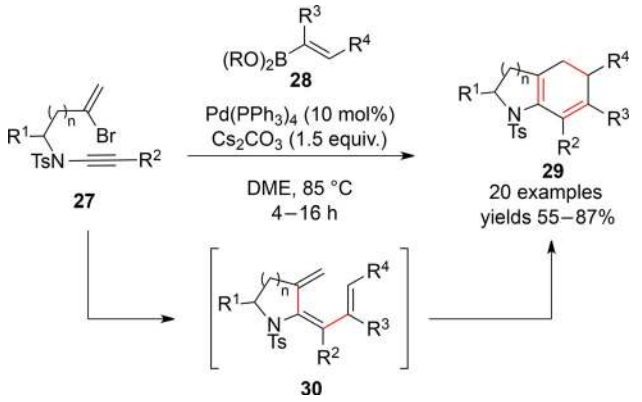
Scheme 5. Carbopalladation/Suzuki cascade reaction for the synthesis of kinase inhibitor precursors.

benzofurans **26** from 2-aryl propargyl ethers **25** (Scheme 6).[16] The authors propose a 5-*exo-dig* carbopalladation at the alkyne, followed by the Suzuki coupling of the arylboronic acid. Variation on R^1 was limited as was Ar^1, while both *para* and *meta* substituents on the arylboronic acid were tolerated. A very similar cascade was reported by Jana et al., who performed a subsequent iron-catalyzed cycloisomerization/aromatization on the products.[17]



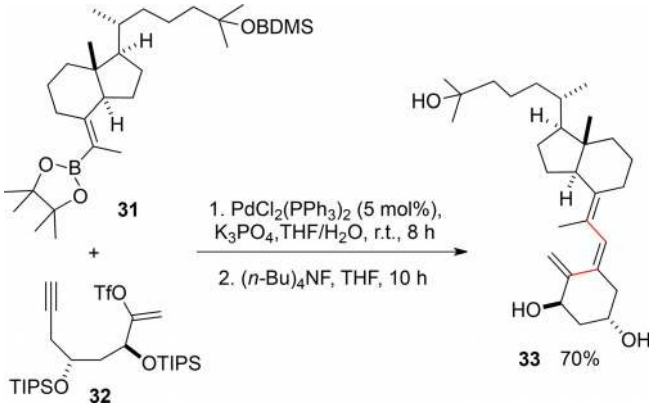
Scheme 6. Carbopalladation/Suzuki coupling strategy for 3-ylidene-dihydrobenzofurans.

Rational reactant design can lead to subsequent reactions, independent of the palladium-catalyzed steps. An example of this approach was reported by Anderson and co-workers in 2011.[18] The authors aimed to construct tetrahydroindoles, hexahydroquinolines and hexahydrobenzoazepines **29** by 6π-electrocyclization of conjugated trienes **30**. These trienes can be synthesized from bromoenynamides **27** *via* a (5–7)-*exo-dig* carbopalladation and subsequent Suzuki reaction with alkenylboronic esters **28** (Scheme 7). *In situ* oxidation of the system only occurs in specific cases and an additional oxidation step after the cascade reactions was typically required to obtain the aromatic compounds. The reaction tolerates various alkyl and aryl substituents at the R^1 and R^2 positions. Furthermore, the substitution pattern on the alkenylboronic ester did not drastically influence the yield and a range of different boronic esters could be used. However, electron-deficient boronic acids or electron-deficient alkynes resulted in the *in situ* oxidation of the cyclohexadiene ring to give fused benzene derivatives without the requirement of post-cascade oxidation.



Scheme 7. Carbopalladation/Suzuki cascade with subsequent 6π-electrocyclization.

The use of the carbopalladation/Suzuki sequence is not limited to the synthesis of compound libraries, but can also be implemented in natural product synthesis. Sicinski et al. reported the use of such a cascade in the total synthesis of vitamin D derivatives **33** (Scheme 8).[19] The reaction is proposed to proceed *via* a 6-*exo-dig* carbopalladation and Suzuki coupling. The good yield (70%) of the palladium-catalyzed cascade reaction and subsequent deprotection step shows the utility of palladium-catalyzed cascade reactions in total synthesis.



Scheme 8. Carbopalladation/Suzuki sequence in the synthesis of vitamin D derivatives. BDMS = $Bn(Me_2)Si$.

In 2012, Ishikura et al. reported the use of a palladium-catalyzed cascade reaction in their total synthesis of calothrixins A and B (Scheme 9).[20] The reactions proceeds *via* a 6-*exo-dig* cross-coupling between the alkene and alkyne in reactant **34**, producing the vinyl-Pd(II) complex with *syn* geometry. Subsequently, transfer of the indole moiety **35** to the vinyl-Pd(II) complex and reductive elimination form the desired product **36**.

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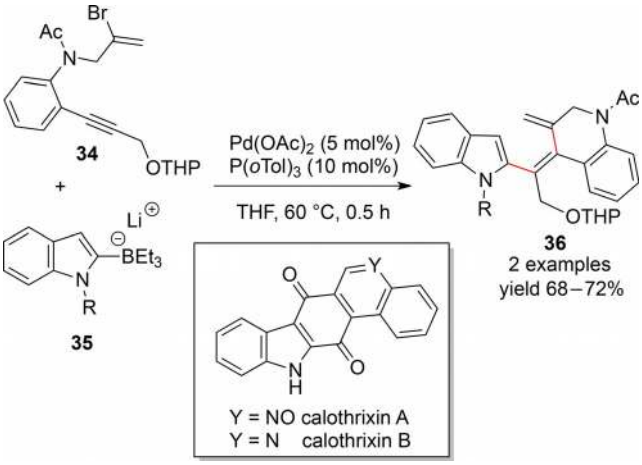


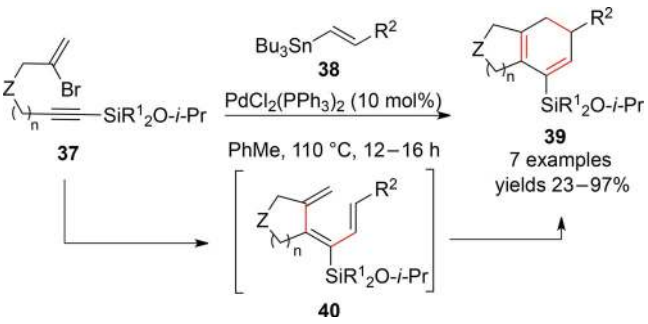
Scheme 9. Carbopalladation/indole transfer in the total synthesis of calothrixins A and B.

2.1.2 Carbopalladation/Stille Coupling

The Stille reaction couples organostannanes to aryl or vinyl (pseudo)halides, its historical importance being the high substrate scope of the reagents. However, the high toxicity of stannanes and recent developments in the scope of the Suzuki reaction have limited the use of Stille couplings. The mechanism of the Stille coupling is similar to that of the Suzuki coupling, but does not require activation of the stannane.

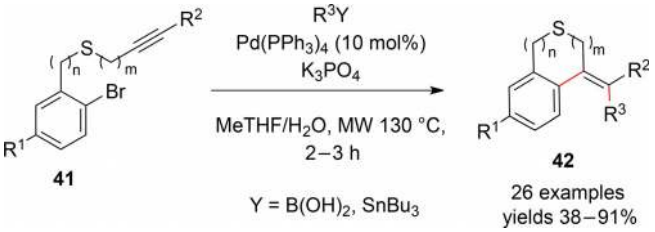
In 2014, Anderson and co-workers reported a carbopalladation/Stille coupling/6π-electrocyclization reaction similar to their earlier work (Scheme 7), by replacing boronic esters with stannanes (Scheme 10).[21] High yields were reported for the synthesis of dimethyl 1,3-dihydro-2*H*-indene-2,2-dicarboxylate derivatives [**39**, $Z=C(CO_2Me)_2$], while the scope could be extended to tosylated isoindolines and dihydroisobenzofurans. The yields of the reaction ranged from poor to excellent, with the dihydroisobenzofurans being responsible for the lower yields.

The thiophilicity of Pd has limited the utility of palladium catalysis in the synthesis of sulfur-containing molecules. However, the group of Suffert reported



Scheme 10. A carbopalladation/Stille cascade with subsequent 6π-electrocyclization.

the combination of a 5/6-*exo-dig* carbopalladation with a Stille or Suzuki coupling for the synthesis of dihydro[*b*]/[*c*]thiophenes and isothiochromanes **42** (Scheme 11).[22] The use of both boronic acids and stannanes yielded the desired products. The organic fragments R^3 were limited to (hetero)aryls and allyls with generally good yields.

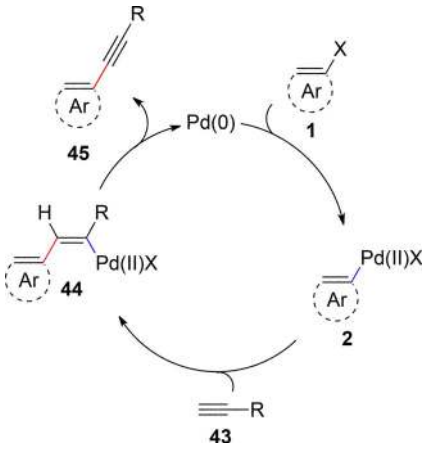


Scheme 11. A carbopalladation/Stille or Suzuki cascade reaction for the synthesis of sulfur-containing bicyclic ring systems.

2.1.3 Carbopalladation/Sonogashira Coupling

The Sonogashira reaction originally coupled terminal alkynes and aryl or vinyl (pseudo)halides using a combination of Pd and Cu catalysts. The Sonogashira cross-coupling proceeds *via* the general coupling mechanism (Scheme 1B). A second catalytic cycle generates a copper acetylide intermediate from a terminal alkyne and a Cu(I) salt. The alkynyl fragment is then transferred from copper to the palladium center.

Two groups reported a copper-free coupling between terminal alkynes and aryl or vinyl (pseudo)halides at about the same time as the Sonogashira reaction.[23,24] These couplings were an extension of the Heck reaction and follow the same mechanism (Scheme 12). The reaction is initiated by the oxidative insertion of Pd(0) into the C–X bond, followed by



Scheme 12. The mechanism of the copper-free Sonogashira reaction.

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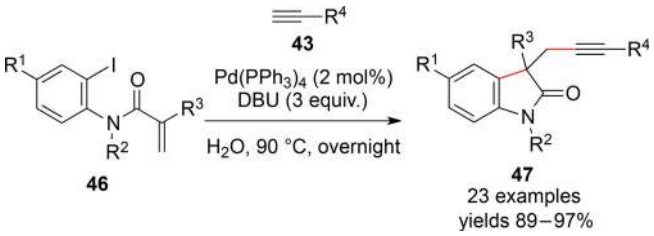
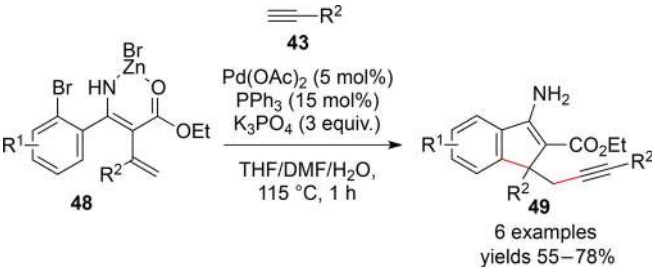
carbopalladation of alkyne **43**, forming alkenyl-Pd(II) complex **44**. The alkyne is then regenerated by β-hydride elimination; however, this process is slower than the transmetallation in the Sonogashira reaction. While the slower kinetics are undesired for most applications due to lower catalyst turnovers, they can suppress direct couplings during cascade reactions. Therefore, these copper-free Sonogashira reactions, as they are sometimes referred to, are used more frequently in palladium-catalyzed cascade reactions.

The use of a copper-free Sonogashira coupling in a palladium-catalyzed cascade reaction was reported by Guo et al. in 2016.[25] In their study, 3,3-substituted oxindoles **47** were synthesized from *N*-(2-iodoaryl)-acrylamides **46** and terminal alkynes **43** in excellent yields (Scheme 13). The reaction is proposed to proceed *via* a 5-*exo*-*trig* carbopalladation, followed by a copper-free Sonogashira reaction. Protection of the amide nitrogen is required, but the use of Boc as a protecting group was not tolerated. Furthermore, electron-withdrawing and electron-donating groups on the aromatic system did not influence the yield. Various alkynes were tolerated, with the exception of ethynyltrimethylsilane and propiolates.



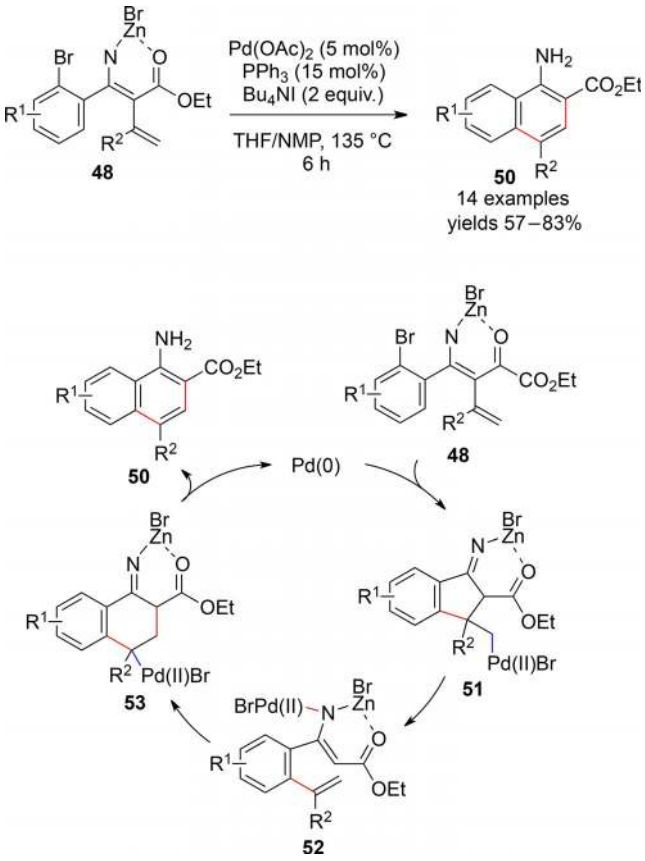
Scheme 13. Synthesis of 3,3-substituted oxindoles *via* a carbopalladation/Sonogashira cascade.

In 2014, Lee et al. reported five different palladium-catalyzed cascade reactions starting from a single starting material (**48**, Scheme 14).[26] One of the cascade reactions involves a 5-*exo*-*trig* carbopalladation and subsequent Sonogashira coupling. The authors employed $Pd(OAc)_2$ as the catalyst precursor, with triphenylphosphine as a ligand and potassium phosphate as the base. The reaction tolerated (hetero)aryl alkyne substituents, while a lower yield was observed when 1-ethynylcyclohexene was employed. Furthermore, small variations of the aromatic system were tolerated, as well as both aryl and alkenyl substituents at the α-position.



Scheme 14. Carbopalladation/copper-free Sonogashira cascade.

While this section is devoted to the carbopalladation/Sonogashira cascade, Lee et al. reported in the same paper a cascade with a remarkable proposed mechanism (Scheme 15). The same starting material **48** undergoes a 5-*exo*-*trig* carbopalladation, yielding the alkyl-Pd(II) species **51**. This complex then undergoes a β-carbon cleavage to give intermediate **52**, in the absence of β-hydride and coupling partners. Subsequently, the new alkyl-Pd(II) species undergoes a 6-*endo*-*trig* cyclization to afford the alkyl-Pd(II) species **53**, β-hydride elimination and aromatization then occur to produce 1-aminonapthalene-2-carboxylic esters **50**. The cascade reaction tolerates various aromatic and aliphatic substituents at R^2, together with small variations at the aromatic ring (R^1). The remarkable outcome of this reaction likely originates from the facile β-carbon cleavage in this system. Plau-



Scheme 15. Carbopalladation/β-carbon cleavage type sequence.

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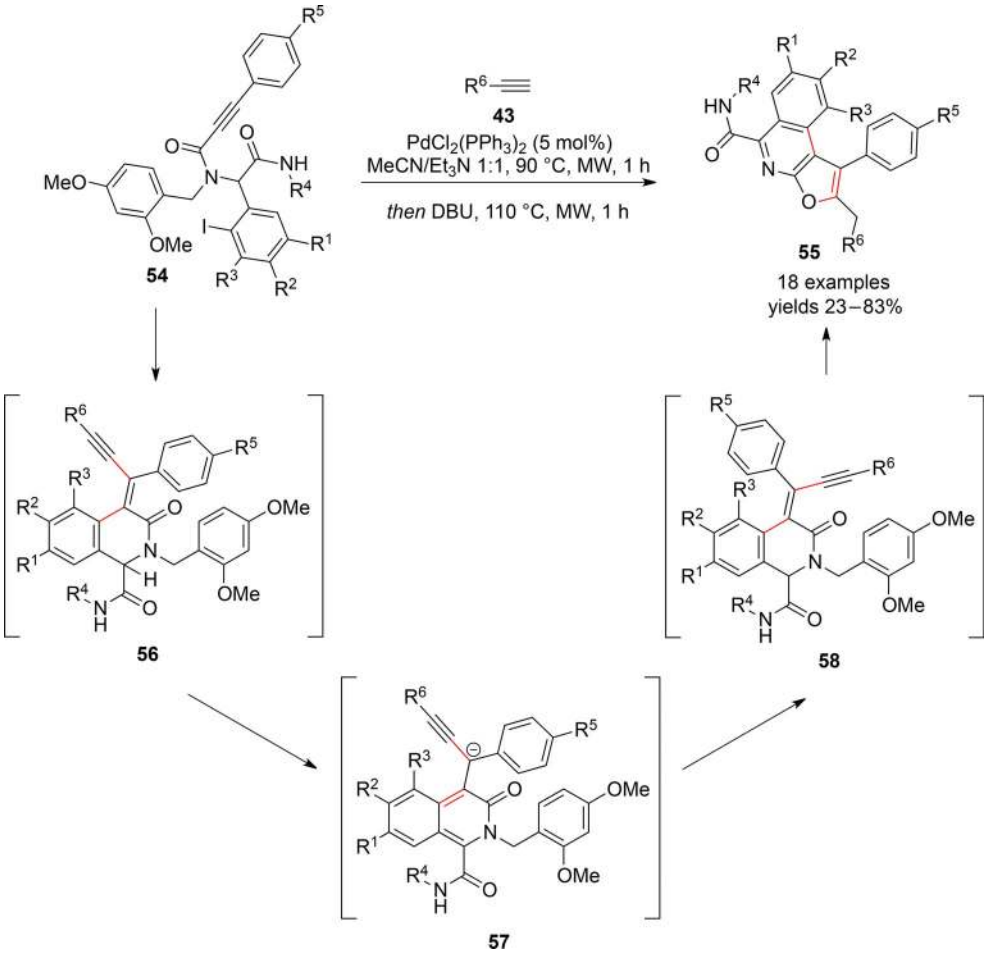


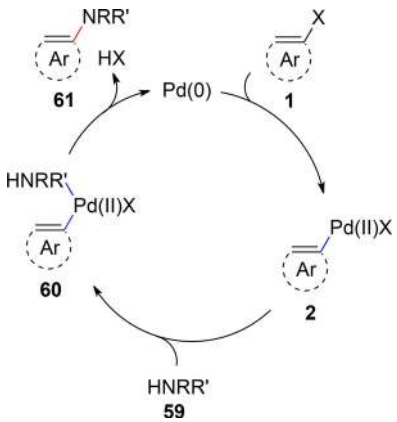
Scheme 16. Carbopalladation/copper-free Sonogashira/cycloaromatization cascade.

sibly, intermediates **51** and **53** are in equilibrium under the reaction conditions *via* 5-*exo-trig* and 6-*endo-trig* cyclizations of **52**, respectively. Although typically 5-*exo-trig* cyclization is expected to predominate, only **53** can undergo aromatization, leading to **50** as the thermodynamic product.

Riva et al. reported a palladium-catalyzed cascade reaction of Ugi products **54** for the formation of furo[2,3-*c*]isoquinolines **55** (Scheme 16).[27] The authors propose an initiation by a 6-*exo-dig* carbopalladation followed by a copper-free Sonogashira coupling to alkyne **56**. Isomerization of the alkene *via* the deprotonated intermediate **57** yields *cis*-isomer **58** with suitable geometry for a second cyclization and further aromatization. The resulting furo[2,3-*c*]isoquinolines **55** were also studied for their photophysical properties, showing a blue fluorescence that is highly dependent on the electron-donating/electron-accepting abilities of the substituents.

2.1.4 Carbopalladation/Buchwald–Hartwig Coupling

The Buchwald–Hartwig reaction couples aryl or vinyl (pseudo)halides to primary or secondary amines (Scheme 17).[28,29] The catalytic cycle is initiated by the oxidative insertion of Pd(0) into the aryl or vinyl



Scheme 17. The mechanism for the Buchwald–Hartwig amination.

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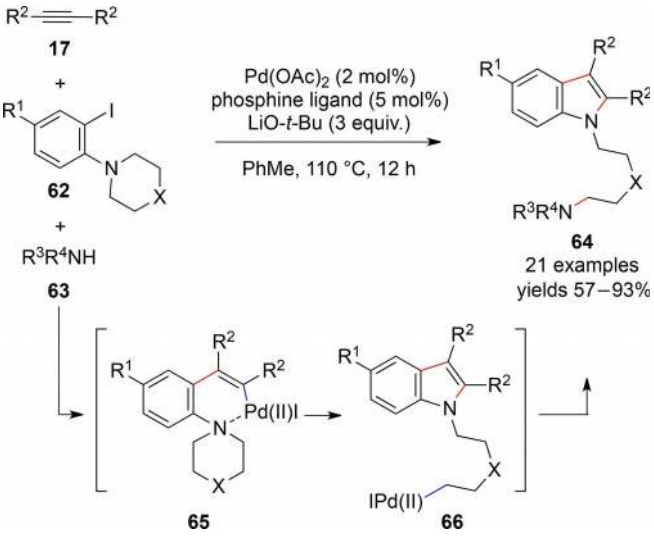
(pseudo)halide bond. Subsequently, association of the amine, ligand exchange, and loss of HX produce the Pd(II) complex containing both the organyl fragment and the amine. Reductive elimination of Pd then yields the product. While the Buchwald–Hartwig reaction refers to nitrogen couplings, similar reactions have been reported by Buchwald and Hartwig for etherification.[30]

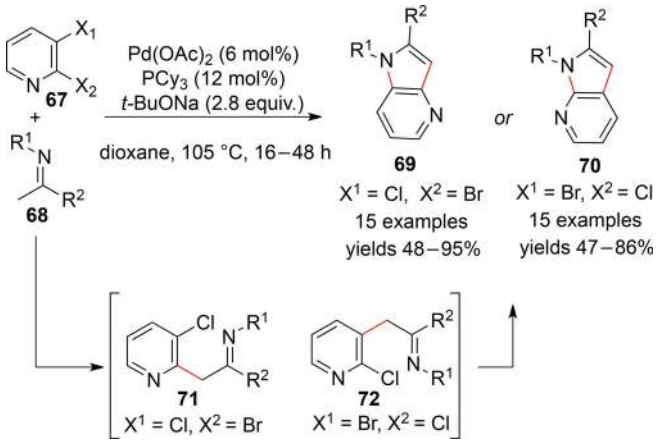
The use of a carbopalladation/Buchwald–Hartwig amination cascade reaction was reported by Xi et al. for the synthesis of indoles **64** (Scheme 18).[31] The authors propose a carbopalladation connecting alkyne **17** to aromatic system **62** and a subsequent Buchwald–Hartwig amination with concomitant C–N bond cleavage which forms alkyl-Pd(II) species **66**. Finally, Buchwald–Hartwig coupling with external amine **63** generates the product. However, the formation of the iminium by the first Buchwald–Hartwig amination and ring opening by nucleophilic attack of the external amine could not be excluded.



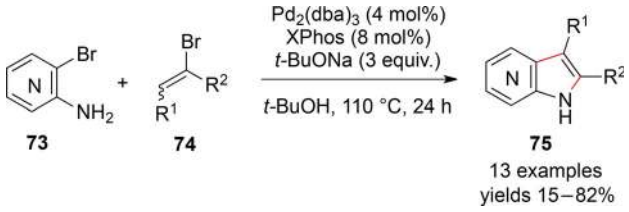
Scheme 18. Carbopalladation/Buchwald–Hartwig amination cascade with cleavage of a C–N bond.

Langer et al. reported a selective synthesis of 4- and 7-azaindoles **69** and **70** *via* the combination of a Heck reaction and a Buchwald–Hartwig amination (Scheme 19).[32] The regioselectivity is determined by the substitution pattern at the pyridine ring of **67**, as oxidative insertion of Pd(0) is significantly faster for C–Br bonds than for C–Cl bonds. The authors elegantly used this preferred insertion to control the formation of the initial aryl-Pd(II) species. A Heck-type addition between the brominated position and enamine **68** produces intermediate **71** or **72**, after which the chlorine-substituted carbon is coupled to the imine nitrogen by a Buchwald–Hartwig-type amination.

A more diverse synthesis of azaindoles **75** was reported by Marques et al., starting from aminobromopyridines **73** and vinylic bromides **74** (Scheme 20).[33] The authors suggest an initial Buchwald–Hartwig amination of the vinylic bromide followed by a 5-*endo*-*trig* Heck-type reaction. While this method can be used to generate various 2,3-substituted azaindoles, the yields are generally only modest.

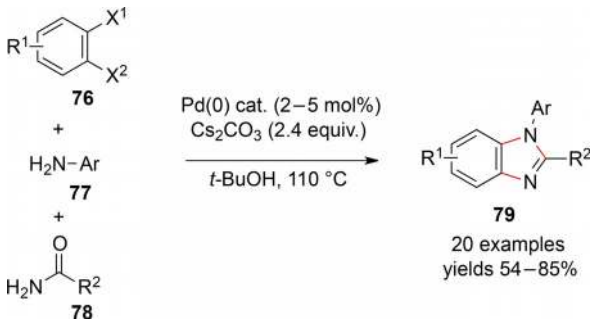


Scheme 19. Selective synthesis of 4- and 7-azaindoles *via* a carbopalladation/Buchwald–Hartwig cascade.



Scheme 20. Synthesis of azaindoles *via* a Buchwald–Hartwig/Heck-type cascade reaction.

In 2013, Buchwald and Jui reported the synthesis of *N*-arylbenzimidazoles **79** from aryl di(pseudo)halides **76**, arylamines **77** and amides **78** (Scheme 21).[34] The regioselectivity of the products was determined by the initial chemoselective oxidative addition of Pd(0), similar to the work of Pham (Scheme 19). The first oxidative addition is followed by a Buchwald–Hartwig



Scheme 21. Regioselectivity control in the synthesis of *N*-arylbenzimidazoles.

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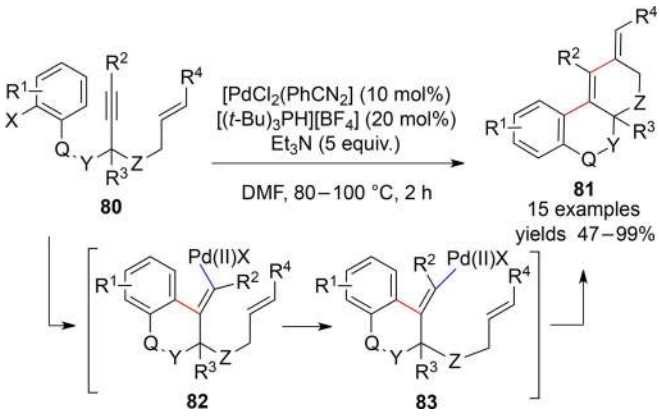
amination with arylamine **77**, while a second oxidative addition couples amide **78**. Condensation of the amide and amine functionalities then forms the imidazole ring. Electron-withdrawing R^1 substituents lower the overall good yields of the reaction.

2.1.5 Carbopalladation/Heck Reaction

Another termination option for palladium-catalyzed casade reactions is the Heck reaction. Carbopalladation/Heck-derived cascade reactions are common and their regioselectivity is typically governed by the Baldwin rules.

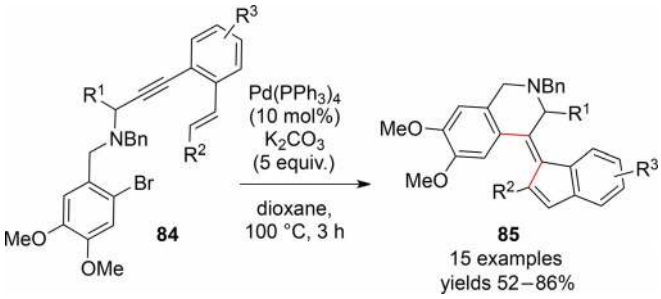
In 2015, Werz et al. reported a carbopalladation/Heck cascade reaction for the formation of tricyclic ring systems **81** (Scheme 22).[35] The reaction is proposed to proceed *via* a 6-*exo*-*dig* and 6-*exo*-*trig* sequence with a final β-hydride elimination. However, the *syn* addition intermediate resulting from the first carbopalladation is unable to undergo the second carbopalladation (**82**). An *E*/*Z* isomerization (to **83**), found during an earlier study, correctly positions the alkenyl-Pd(II) complex with respect to the alkene for the Heck reaction. The reaction is compatible with various tethers (Z), generating the tricyclic ring systems in fair to excellent yields.



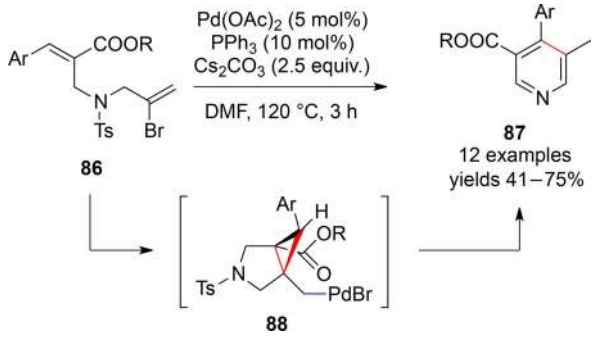
Scheme 22. Formation of a tricyclic ring system by a carbopalladation/Heck process.

Perumal et al. reported the synthesis of indenylidene tetrahydroisoquinolines **85** from bromoenynes **84** (Scheme 23).[36] The proposed mechanism comprises a 6-*exo*-*dig* carbopalladation with a subsequent 5-*exo*-*trig* Heck reaction and *anti* β-hydride elimination. The reaction tolerates various aromatic systems at both R^1 and R^2, and provides the products in moderate to excellent yields.

In 2013, Kim et al. reported the synthesis of 3,4,5-trisubstituted pyridines **87** from *N*-allyl-2-bromoprop-2-en-1-amine derivatives **86** (Scheme 24).[37] The reaction proceeds *via* an interesting ring expansion mechanism, which is initiated by a 5-*exo*-*trig* carbopalladation followed by a 3-*exo*-*trig* carbopalladation, generating 3-azabicyclo[3.1.0]hexanes **88**. The alkyl-Pd(II) intermediate undergoes β-carbon cleavage because of the lack of β-hydrogens. The now six-membered ring aromatizes by loss of HPd(II)Br and TsH.



Scheme 23. Carbopalladation/Heck cascade.



Scheme 24. Ring expansion *via* a double carbopalladation reaction and β-carbon cleavage.

2.1.6 Carbopalladation/C–H Activation

The previously discussed examples used a second coupling partner to couple the stable organopalladium complex. However, the Pd(II) complex may also undergo cross-coupling with a neighboring group in of the absence of suitable classical cross-coupling partners (boronates, stannanes, etc.). These couplings are typically observed when an organopalladium intermediate is in close proximity to an aryl-hydrogen bond. Activation of the C–H bond and loss of HX yields a palladacycle with a typical ring size of six to seven atoms. Reductive elimination subsequently leads to five- or six-membered rings. However, the C–H activation process is not limited to intermolecular arylic hydrogens.

In 2011, Gong et al. reported the formation of 3-methylene-3*H*-indolenines **90** *via* a carbopalladation/C(sp^2)–H activation from *N*-aryl-propargylimines **89** (Scheme 25).[38] Although a Pd(II) species is added as a palladium source in the absence of a phosphine

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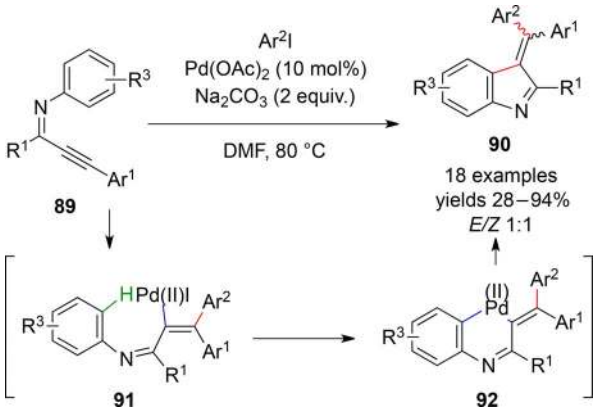


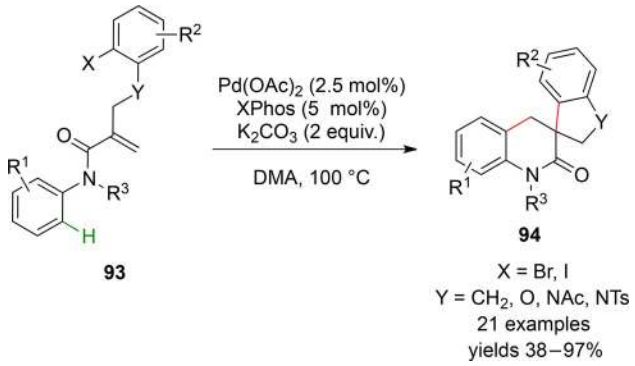
Scheme 25. Carbopalladation/C(sp^2)–H activation cascade reaction for 3-methylene-3*H*-indoles.

ligand or another reducing agent, the authors suggest that a Pd(0) species is the active catalyst. They propose a mechanism starting with the intramolecular carbopalladation of the aryl-Pd(II) and the alkyne. The proximity of the vinyl-Pd(II) species **91** to the arene ring leads to C(sp^2)–H activation, forming the six-membered palladacycle intermediates **92**. Subsequently, reductive elimination produces the 3-methylene-3*H*-indoles **90**.

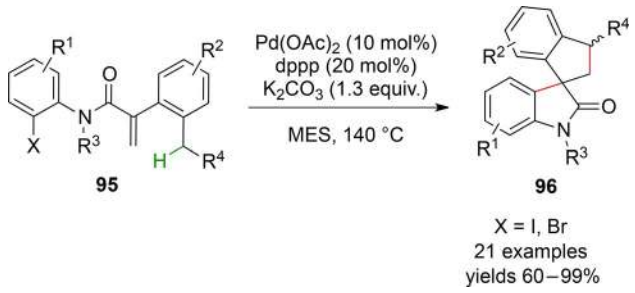
Different substituents at the arene ring were tolerated, with *ortho* and *para* substituents logically leading to single products. In the case of *meta* substituents, only modest regioselectivity was observed. Substituents at R^1 were limited to fluorinated alkanes and a single example of an alkyl substituent, giving a somewhat lower yield. The most interesting result was observed when the arenes on the alkyne and aryl iodide were different. No *E/Z* selectivity was observed, while the *syn* geometry of the carbopalladation should dictate the product geometry. While the authors did not elaborate on this issue, a possible explanation is the isomerization of the vinyl-Pd(II) species to the corresponding allenylamine (or its Pd complex).

In a similar fashion, Zhu and co-workers reported a 5-*exo-trig* carbopalladation/C(sp^2)–H activation cascade for the formation of dihydroquinolinones spiro-fused to dihydrobenzofurans, indolines and indanyls **94** (Scheme 26).[39] Remarkably, the conditions did not vary significantly between ether, alkane or amine (Y) tethered systems, and the variation did not impact the yields of the cascade. Electron-withdrawing and electron-donating groups at R^1 were tolerated, as were also various R^2 substituents.

Zhu and co-workers continued their research towards the synthesis of spiro-fused ring systems **96** from *N*-(2-bromoaryl)-acrylamides **95** (Scheme 27).[40] In this case, a bidentate ligand (dppp) was used. Attempts to render the reaction enantioselective did not lead to significant chiral induction. The mechanism proceeds *via* a 5-*exo-trig* carbopalladation followed by



Scheme 26. Carbopalladation/C(sp^2)–H activation sequence.



Scheme 27. Carbopalladation/benzylic C(sp^3)–H activation cascade.

activation of the benzylic C(sp^3)–H bond. Substitution of the amide is required, while the reaction tolerated different substituents at R^1. However, substituents at the *ortho* position of the halide decreased the yield significantly. Furthermore, different R^2 substituents did not decrease the yield of the reaction, making the reaction very robust with high yields. A single example was reported where $R^4 \neq H$, producing **96** as a 2:1 mixture of diastereomers.

In 2013, Senadi and co-workers reported the synthesis of triazolo[1,5-*a*]isoindoles **98** and **99** *via* an intermolecular carbopalladation/C(sp^2)–H functionalization (Scheme 28).[41] A noteworthy aspect of this study was the observed *anti* carbopalladation of the aryl-Pd(II) moiety on the alkyne. When the substituent on the alkyne was an aryl group, *syn* addition was favored. However, when the alkyne substituents was an alkyl, *anti* addition was favored. The experimental outcomes are supported by simulations showing energetic minima in both cases.

A remarkable version of a carbopalladation/C(sp^2)–H activation cascade was reported by Doucet et al. who described the formation of substituted *N*-sulfonyltetrahydroquinolines **101** from *N*-allylaniline sulfonamides **100** (Scheme 29).[42] Various aromatic sulfonyl chlorides were tolerated as were different substitution patterns at the *N*-aryl group.

The mechanism proposed by the authors starts with the oxidative insertion of the palladium in the S–Cl

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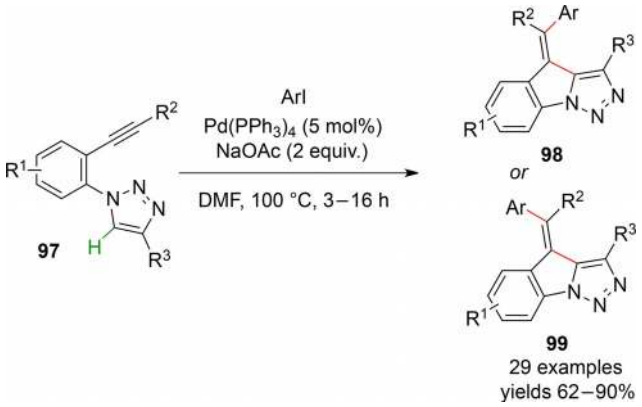
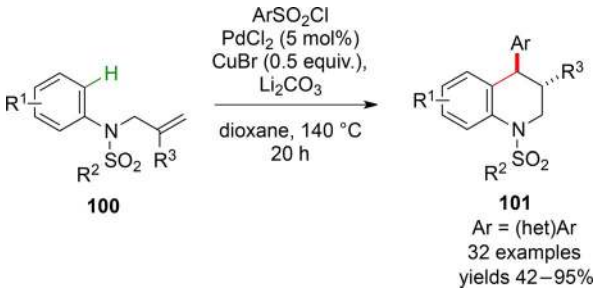


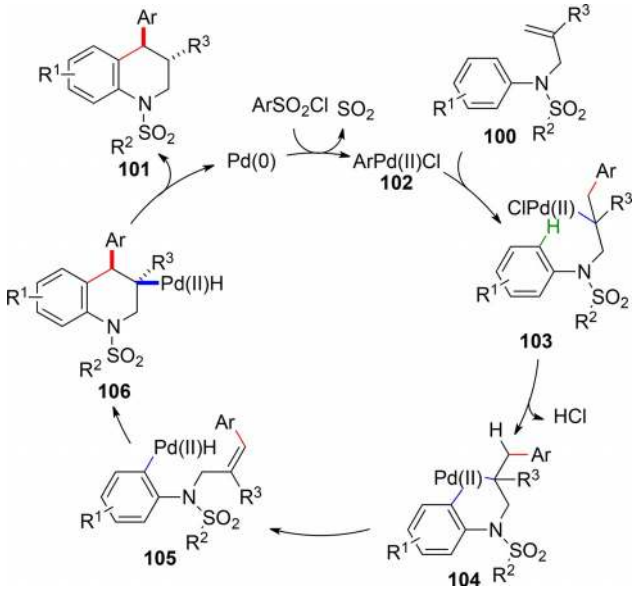
Scheme 28. Carbopalladation/tetrazole C(sp^2)–H activation cascade.



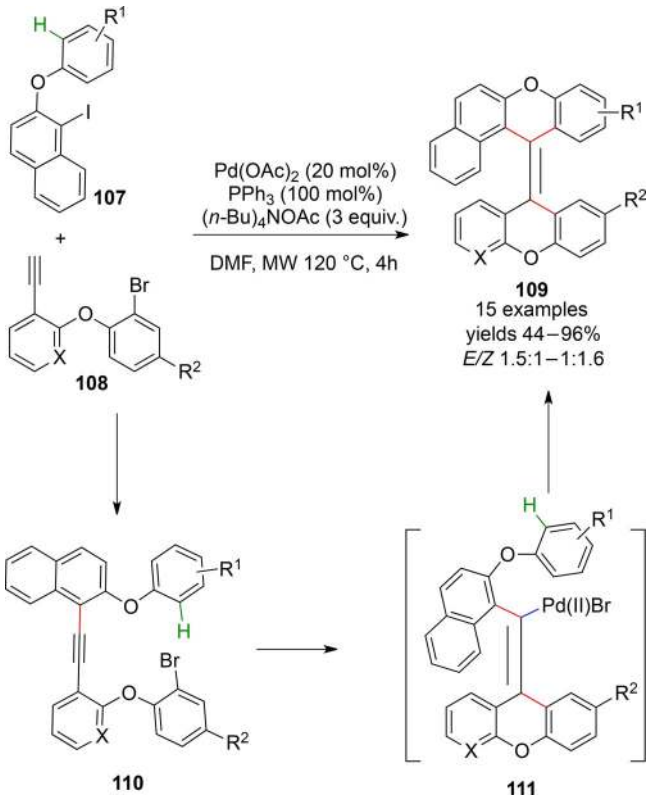
Scheme 29. Synthesis of *N*-sulfonyltetrahydroquinolines *via* a palladium-catalyzed cascade reaction.

bond (Scheme 30). Elimination of SO_2 results in the formation of an aryl-Pd(II) species **102** which regioselectively adds to the alkene forming alkyl-Pd(II) intermediates **103**. Activation of the C(sp^2)–H bond ensues as a result of the close proximity of the Pd(II) center, resulting in six-membered palladacycles **103**. However, instead of reductive elimination and formation of the indoline, β-hydride elimination occurs to form aryl-Pd(II)H complex **105**. An unusual 6-*endo-trig* carbopalladation of the aryl-Pd(II) species to the newly formed alkene generates alkyl-Pd(II)H species **106**, and reductive elimination finally produces tetrahydroquinolines **101**. The authors do not provide any rationalization as to why intermediate **105** undergoes an uncommon 6-*endo-trig* rather than the typical 5-*exo-trig* cyclization.

In 2013, Tietze and co-workers reported a cascade comprising a copper-free Sonogashira reaction, followed by coupling of aryl iodides **107** and alkynes **108** to give the primary product **110** (Scheme 31).[43] Formation of the aryl-Pd(II) complex from the aryl bromide then initiates a 6-*exo-dig* carbopalladation to alkenyl-Pd(II) species **115** followed by C(sp^2)–H activation and C–C bond formation to product **109**. The *E*/*Z* selectivity of the reaction is rather modest. The molecules produced in this process have interesting properties for use as molecular switches.[44] Similar strategies were reported by Tietze et al. over the following years.[45–47]



Scheme 30. Mechanism of *N*-sulfonyltetrahydroquinoline formation involving C(sp^2)–H activation and β-hydride elimination.



Scheme 31. Cascade reaction comprising a Sonogashira coupling and a carbopalladation/C(sp^2)–H activation.

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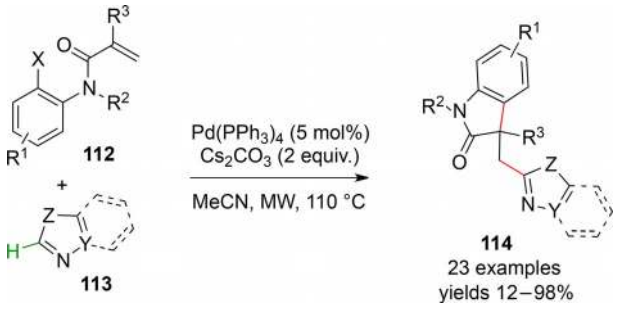
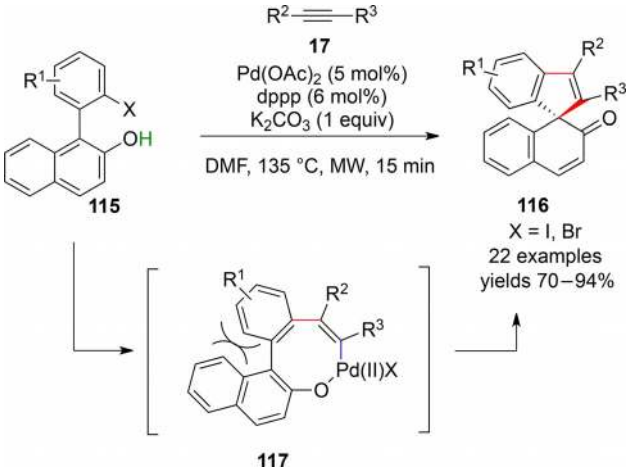
The use of an intermolecular C–H activation was reported by van der Eycken and co-workers, who reported a palladium-catalyzed cascade reaction of *N*-(2-haloaryl)acrylamides **112** and heteroaryls **113** for the formation of oxindoles **114** (Scheme 32).[48] The



Scheme 32. Carbopalladation/intermolecular C(sp^2)–H cascade.

alkyl-Pd(II) intermediate is generated by a 5-*exo-trig* cyclization, followed by coupling of a heteroarene ring *via* C(sp^2)–H activation. In the same paper, the authors also reported the synthesis of similar compounds from propiolamides *via* a similar mechanism. Both reactions tolerated various substitution patterns and generated the products in generally good to excellent yields.

A carbopalladation/semi C–H activation was reported by Luan and co-workers for the construction of spirocarbocycles **116** (Scheme 33).[49] The authors propose initiation by carbopalladation of the alkyne and coordination of the phenoxide to the alkenyl-Pd(II) complex, forming palladacycle **117**. While a Buchwald–Hartwig-type coupling seems straightforward, the steric clash of the two aromatic systems favors a ring contraction to afford the spiro compound in generally good yields.

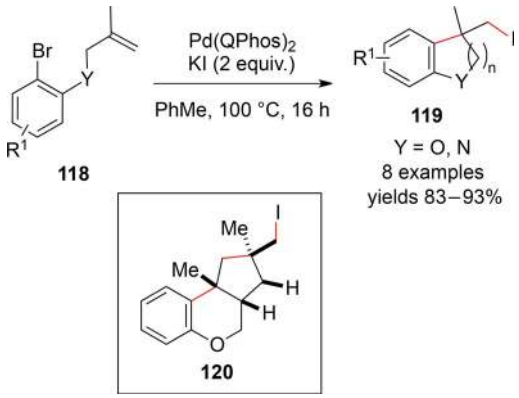


Scheme 33. Synthesis of spirocarbocycles by carbopalladation/semi C–H activation.

2.1.7 Carbopalladation/Ion Capture Sequence

The previous section touched on the subject of C–H activation when no suitable coupling partner is available. This section will discuss an alternative outcome of the reaction in the absence of coupling partners. When an intermediate organopalladium complex can undergo neither cross-coupling nor C–H activation, the last resort is the coupling of the organic fragment and an ion present in the solution. The Pd(II) complex can even undergo reductive elimination to give a C–X bond with the (pseudo)halide liberated during the initial oxidative insertion.

Lautens and co-workers reported the synthesis of 3,3-disubstituted benzohydrofurans and indolines **119** *via* a carbopalladation/carbohalogenation process (Scheme 34).[50] Pd(QPHOS)$_2$ was used as a catalyst



Scheme 34. A carbopalladation/ion capture cascade for the synthesis of benzodihydrofurans and dihydroindoles.

in toluene at 100 °C with potassium iodide as the halide source. Several substituents on the aromatic ring were successfully tolerated as was expansion of the ring system to isochromane. Preliminary studies showed the possibility of rendering the carbopalladation asymmetric by using Josiphos or Walphos as a chiral ligand. Furthermore, extending the cascade to include an additional carbopalladation reaction (carbopalladation/carbopalladation/carbohalogenation) is possible, producing more complex molecules such as **120**.

The mechanism involves a 5-*exo-trig* carbopalladation, forming an alkyl-Pd(II) intermediate. Since β-hydride elimination is not possible, the organic fragment is coupled to an iodide ion. Direct halogenation using the bromide liberated during the reaction was not observed. This problem was solved by adding stoichiometric potassium iodide to afford the alkyl iodide products.

Continuing this line of research, Lautens et al. reported a diastereoselective 6-*exo-trig* carbopalladation/halogenation using Pd(QPhos)$_2$ as a catalyst

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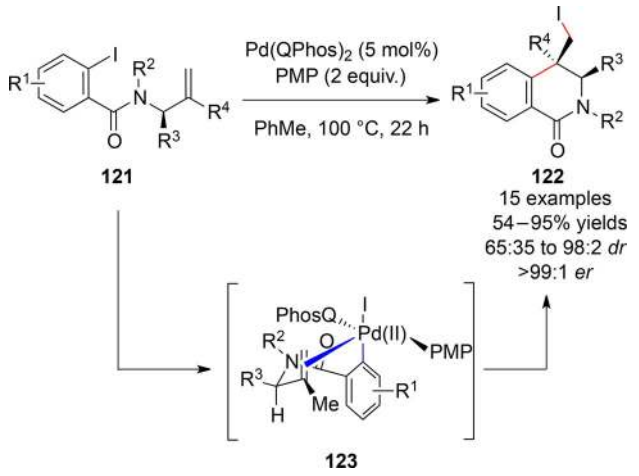
(Scheme 35).[51] Starting from optically pure *N*-allylcarboxamides **121**, 6-*exo-trig* carbopalladation and reductive elimination form the 3,4,4-substituted dihydroisoquinolinones **122**.

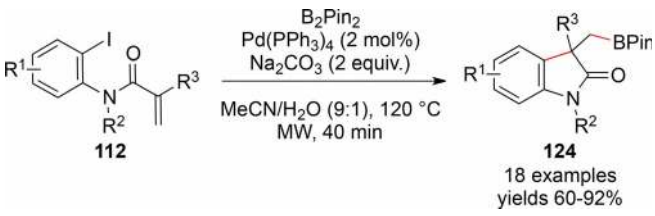


Scheme 35. Diastereoselective carbopalladation/ion capture cascade. PMP = 1,2,2,6,6-pentamethylpiperidine.

This reaction addresses several issues regarding the ligands, in particular the duality of bulky phosphine ligands: ligands inducing the best diastereoselectivity in the carbopalladation inhibited the subsequent reductive elimination. To overcome this problem, 1,2,2,6,6-pentamethylpiperidine (PMP) was employed as a weakly binding auxiliary ligand, increasing the *dr* significantly by forming aryl-Pd(II) complex **123**. Different R^1 and R^4 substituents were tolerated without greatly influencing the *dr*, however, bulky R^2 substituents decreased the *dr* significantly.

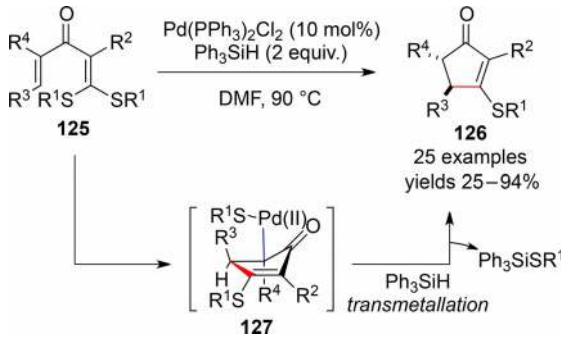
In the same year Lautens reported the cyanide ion capture of similar substrates.[52] Other systems tackled by Lautens included the diastereoselective transformation of indoles to isoindoloindolones.[53]

In 2015, van der Eycken et al. reported a carbopalladation/borylation cascade of acrylamides **112** for the formation of substituted oxindoles **124** (Scheme 36).[54] A 5-*exo-trig* carbopalladation reaction forms the oxindole, after which the alkyl-Pd(II) species captures pinacol boronate to form the final product. Water is required during the reaction, which is thought to promote transmetallation and reductive elimination. The reaction proceeds in good yields and tolerates various R^1 substituents and different aryl substituents at R^3. Substituents on the amide are required, but electron-withdrawing N-substituents proved to be incompatible with the reaction. A related carbopalladation/borylation cascade was reported by Yang and Song.[55]



Scheme 36. Carbopalladation/borylation cascade reaction for the synthesis of oxoindoles.

A reductive carbopalladation for the synthesis of polysubstituted 2-cyclopentenones **126** from the corresponding β-alkylthiodienones **125** was reported by Wang et al. in 2013 (Scheme 37).[56] The reaction is initiated by C–S activation of the ketene thioacetal by palladium, generating a vinyl-Pd(II) complex. Subsequently, the carbopalladation leads to cyclopentenone ring closure, generating alkyl-Pd(II) species **127**. This species always has the alkyl and palladium substituents *syn*-coplanar. The lack of *syn*-hydrogens in the alkyl-Pd(II) complex prevents β-hydride elimination, opening the possibility for hydrogenolysis. Transfer of a hydride from triphenylsilane to Pd forms the alkyl-Pd(II) hydride species, generating the final product by reductive elimination. Various aryl and alkyl substituents are tolerated as both R^2 and R^3, and the reaction proved diastereoselective for $R^4 \neq H$.



Scheme 37. Carbopalladation/hydride transfer cascade for the synthesis of cyclopentenones.

Wang and co-workers reported the production of benzofurans **129** from (*o*-alkynylphenoxy)methyl ketones **128** (Scheme 38).[57] The regioselective intermolecular carbopalladation between the aryl iodide and the alkyne forms vinyl-Pd(II) species **130** with a *syn* arrangement of palladium and the Ar^2 moiety. The authors propose deprotonation of the ketone α-position by sodium acetate, followed by coordination of the enolate to the Pd(II) complex. Reductive elimination then forms the ylidene-dihydrobenzofurans **131**, producing the benzofuran by tautomerization.

The scope of the substrates was limited to the use of aromatic ketones, while varieties of alkyl, cycloalkyl and aryl R^2 substituents were used. Furthermore, different aryl iodides were tolerated, as were different

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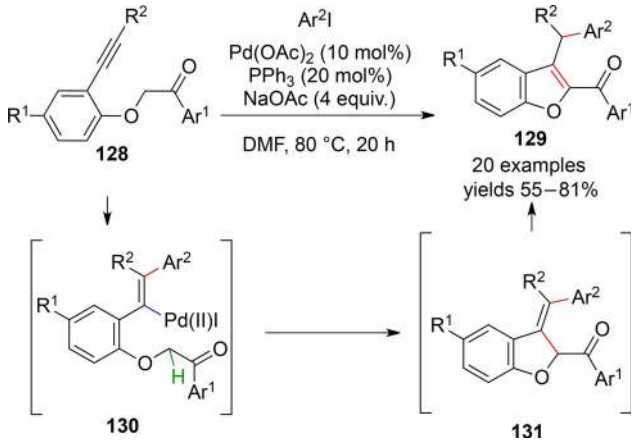
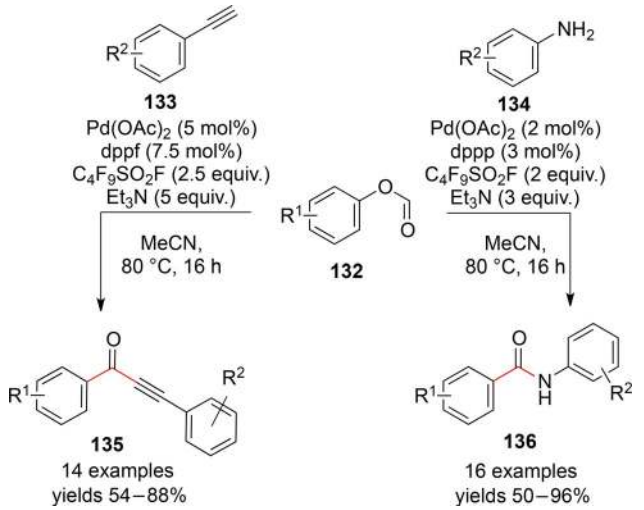


Scheme 38. Carbopalladation/enol capture cascade.



Scheme 39. Use of aryl formates as CO source combined with *in situ* aryl (pseudo)halide formation.

R^1 substituents. Although the termination step can also be regarded as a C–H activation, the explicit involvement of the enolate capture proposed by the authors led us to include it in the ion capture section.

2.2 Other Propagation Steps

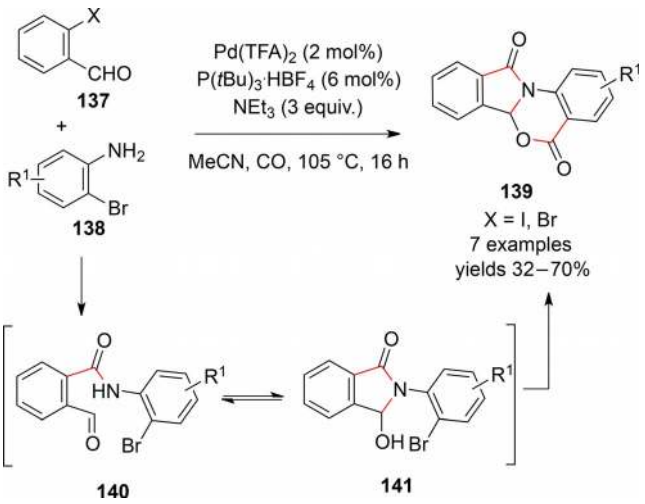
The previous section discussed cascade reactions initiated by R–X activation and carbopalladation as the first propagation step. However, other propagation methods are possible. Three main types of palladium-catalyzed C_1 insertions have been reported in the literature, i.e., insertion of carbon monoxide, isocyanides, and carbenes. All three contain a nucleophilic carbon center and extend the carbon chain by one atom.

2.2.1 Palladium-Catalyzed CO Insertion

The insertion of carbon monoxide in organopalladium species is a versatile method to generate carbonyl-containing compounds. The reaction proceeds *via* the coordination of CO to the Pd center and migratory insertion in the organopalladium bond. However, CO will function as a ligand in solution and will therefore always be bound to the catalyst. The high binding affinity potentially complicates cascade reactions involving CO insertion and carbopalladation, where CO insertion can occur in different stages of the reaction. Therefore the use of CO in extended palladium-catalyzed cascade reactions is limited. However, simple CO insertion reactions are numerous and only a few selected examples will be included in this review.[58,59]

In 2014, Beller and co-workers reported the synthesis of *N*-aryl-arylamides **136** and alkynones **135** *via* a carbonylative amination with anilines **134** and copper-free carbonylative Sonogashira with alkynes **133**, respectively (Scheme 39).[60] While both are possible using aryl halides under a CO atmosphere, Beller focused on the use of aryl formates **132**. The ingenious use of aryl formates as starting materials shows the diversity of suitable starting materials for palladium-catalyzed reactions. Under basic conditions and palladium catalysis, the aryl formates decompose into CO and aryl alcohols, providing CO for the carbonylation reaction. Furthermore, including nonafluorobutanesulfonyl fluoride in the reaction mixture converted the aryl alcohols to the corresponding nonafluorobutanesulfonates *in situ*. The catalytic cycle starts with the insertion of the Pd(0) into the aryl-pseudohalide bond, after which CO insertion and cross-coupling with either the alkyne or aniline forms the desired product.

Another report by Beller included an aminocarbonylation/hemiaminal formation/carbonylative esterification cascade (Scheme 40).[61] Using 2-halobenzalde-



Scheme 40. A double CO insertion cascade.

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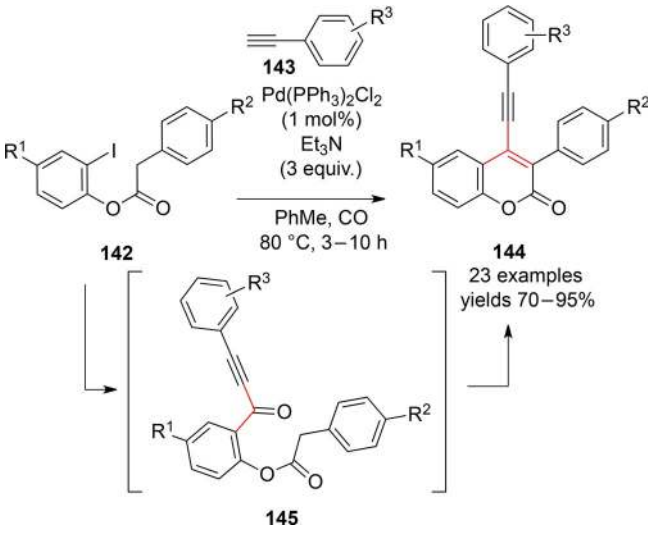
hyde **137** and 2-bromoanilines **138**, the sequence forms tetracyclic products **139** in reasonable to good yields. The reaction is proposed to involve two catalytic cycles, the first of which starts with the carbonylation of the more electron-deficient 2-halobenzaldehyde. Subsequently, the acyl-Pd(II) species is coupled to the amine of the bromoaniline, forming 2-formyl-*N*-(2-bromoaryl)-benzamides **140**. The benzamide reversible forms hemiaminal **141**, which is the substrate of the second catalytic cycle. Herein, oxidative insertion of Pd(0) into the bromoaniline moiety forms an aryl-Pd(II) complex, which undergoes CO insertion and esterification with the hemiaminal OH to form the desired product.

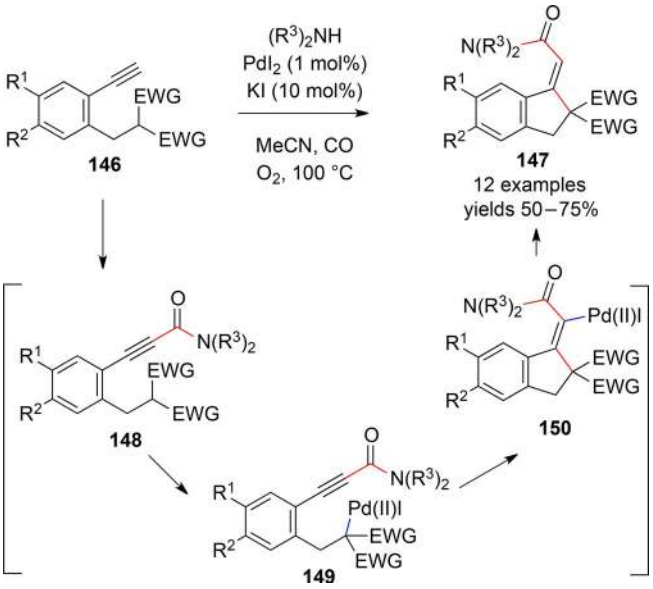
The study on the scope of the reaction was somewhat limited, showing only seven examples. The authors did show that the use of 2-iodobenzaldehydes increased the yields of the reaction significantly. Furthermore, substitution of the 2-bromoaniline was tolerated without a significant decrease in yield.

A carbonylative copper-free Sonogashira cascade to afford ketone **145** with a subsequent aldol condensation for the synthesis of 3-aryl-4-(arylethynyl)-coumarins **144** was reported by Sankararaman et al. (Scheme 41).[62] The reaction proceeds in good to excellent yields for a select range of substituents.



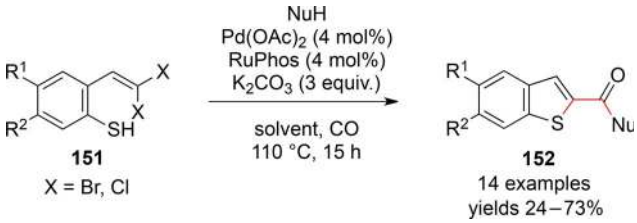
Scheme 41. Carbonylative copper-free Sonogashira cascade reaction with subsequent aldol condensation.

The carboxamidation of alkynes was employed by Gabriele and co-workers in the synthesis of dihydro-1*H*-inden-1-ylidene acetamides **147** (Scheme 42).[63] The authors propose the formation of an alkyl-Pd(II) iodide intermediate **149** after carboxamidation and deprotonation of the resulting amide **148**. A 5-*exo-dig* carbopalladation closes the ring, resulting in alkenyl-Pd(II) species **150**, which then yields the product after protonolysis.



Scheme 42. Sonogashira-type carboxamidation and carbocyclization sequence.

Alper and co-workers reported the synthesis of 2-carboxy- and 2-carboxamidobenzo[*b*]thiophenes **152** *via* carbonylative coupling and thioetherification (Scheme 43).[64] The reaction tolerates a variety of amines and alcohols as NuH, with a decrease in yield as the chain length of the nucleophile substituent increases. Furthermore, minor variations on the aromatic ring were shown to be compatible with the reaction.



Scheme 43. Palladium-catalyzed formation of a C–S bond and esterification/amidation.

A synthesis of phthalimides **155** *via* double carbonylation of dibromoarenes **153** in the presence of water and DBU or DBN **154** was reported by Wu and coworkers in 2015 (Scheme 44).[65] The reaction proceeds *via* initial carbonylation of an aryl-Pd(II) intermediate and amide formation with DBU or DBN, producing an acylamidinium intermediate. Attack of water yields the amidine hydrate **156**. A second carbonylation and amide formation opens the DBU or DBN ring, yielding the phthalimide-substituted lactams **155**.

The synthesis of quinazolin-4(3*H*)-ones **158** was also tackled by the group of Beller employing carbox-

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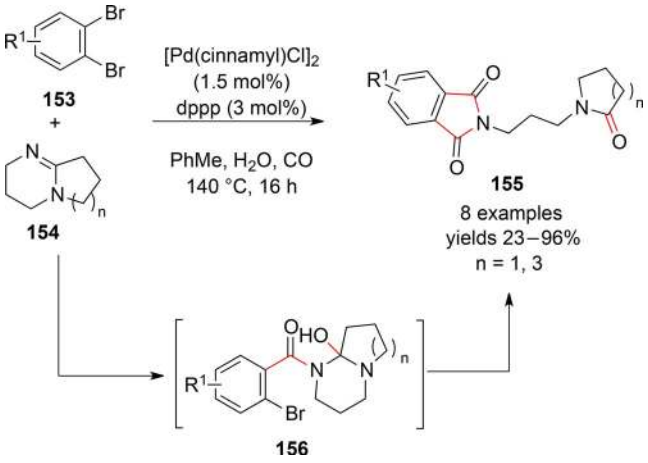
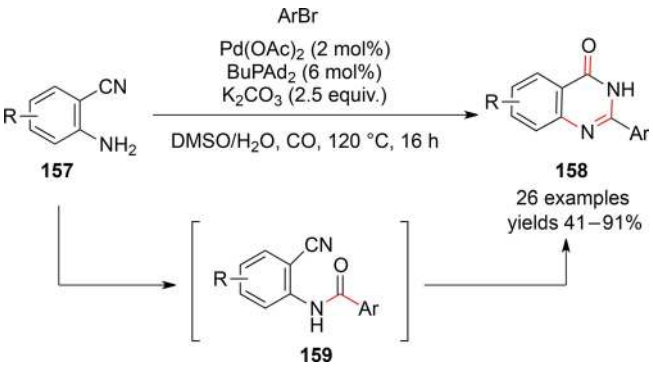


Scheme 44. Ring opening of DBU and DBN *via* double carbonylation and hydrolysis.

amidation of bromoarenes with 2-aminobenzonitriles **157** (Scheme 45).[66] After the formation of the *N*-(2-cyanoaryl)-arylamide **159**, hydrolysis of the nitrile forms a second amide functionality. Intramolecular condensation and tautomerization generates the products in fair to excellent yields.

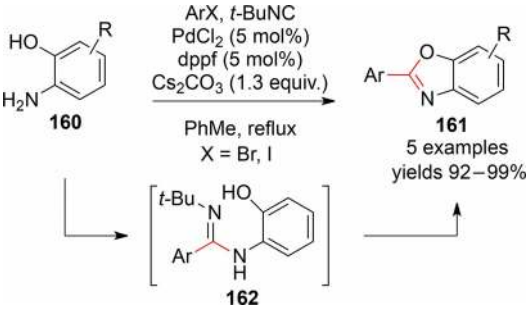


Scheme 45. The synthesis of quinazolin-4(3*H*)-ones by carboxamidation/cyclocondensation.

2.2.2 Palladium-Catalyzed Isocyanide Insertion

Isocyanides can be inserted *via* palladium catalysis in a similar fashion as carbon monoxide. However, isocyanides are more nucleophilic compared to CO, and therefore tend to be more reactive. A common problem connected to this higher reactivity is the double insertion of isocyanides. This side reaction is typically suppressed by the use of a strong or intramolecular nucleophile or specific ligands on Pd.

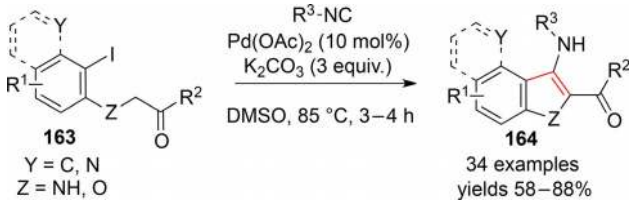
In 2013, Lang et al. reported the synthesis of benzoxazoles **161** *via* a palladium-catalyzed three-component reaction (Scheme 46).[67] The authors propose a pathway involving formation of the aryl-Pd(II) species followed by isocyanide insertion and coupling



Scheme 46. Synthesis of benzoxazoles *via* an isocyanide insertion.

with the aminophenol to give amidines **162**. Cyclization with loss of *t*-BuNH$_2$ then yields the products. The authors reported a limited scope for the substrate with excellent yields.

Isocyanide insertions were also employed in the synthesis of 2-acyl-3-aminobenzofurans and -indoles **164**, as reported by Wang et al. in 2015 (Scheme 47).[68] The catalytic cycle is initiated by the insertion of the isocyanide, followed by C(sp^3)–H functionalization and tautomerization to furnish the product. The reaction is compatible with aliphatic and aromatic isocyanides and afforded the products in good to excellent yields for various substitution patterns at R^1 and R^2 as well as different (hetero)arene systems.



Scheme 47. Isocyanide insertion/C(sp^3)–H functionalization cascade.

Wang et al. reported the use of isocyanide insertion for the synthesis of 4-aminoquinoline derivatives **166** from enaminones **165** in 2014 (Scheme 48).[69] The authors propose a palladium-catalyzed isocyanide insertion at the aryl iodide, followed by a reductive elimination forming arylimidoyl iodide **167**. Nucleophillic substitution of the imidoyl iodide by the enamine generates the six-membered ring, which after a [1,5] H-shift yields the product. However, direct coupling between the imidoyl-Pd(II) species and the α-carbon of the carbonyl cannot be ruled out. The reaction is compatible with aliphatic isocyanides and generates the 4-aminoquinoline derivatives in modest to excellent yields.

In 2014, Ruijter et al. reported the synthesis of pyridopyrimidines **169** *via* isocyanide insertion on hetero-

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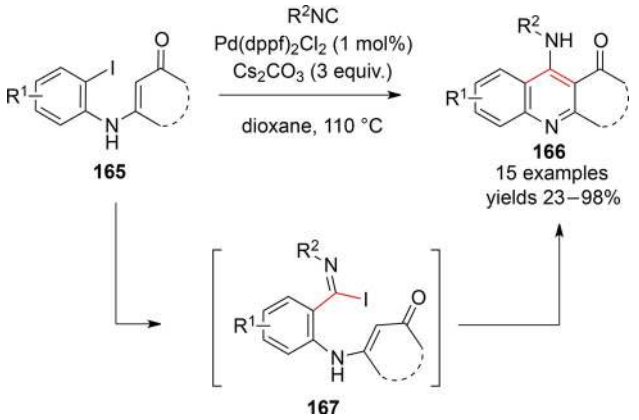
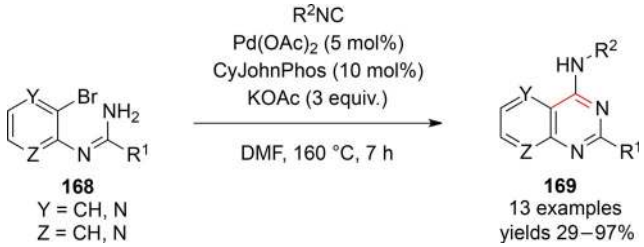


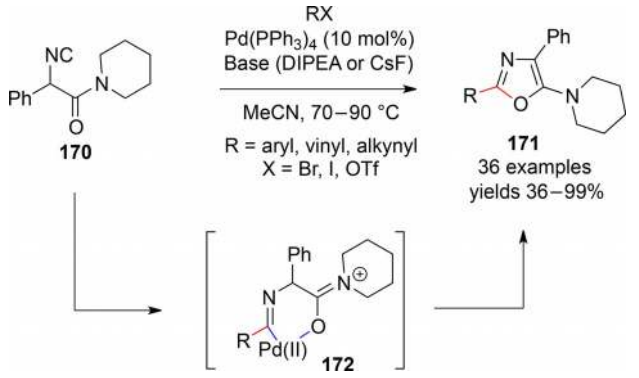
Scheme 48. Isocyanide insertion cascade for the production of 4-aminoquinoline derivatives.

arylimidates **168** (Scheme 49).[70] The reaction generated the products in modest to excellent yields, with higher yields for the pyrido[2,3-*d*]pyrimidines compared to the pyrido[3,2-*d*]pyrimidines.



Scheme 49. Isocyanide insertion in heteroarylimidates.

Zhu et al. reported the use of an intramolecular isocyanide coupling for the formation of oxazoles **171** (Scheme 50).[71] The authors propose an initiation by the palladium-catalyzed insertion of the isocyanide in the initial organopalladium intermediate. Subsequently, the amide oxygen is coupled to the imidoyl moiety *via* the formation of palladacycle **172**, reductive elimination, and deprotonation, yielding the product. The reaction is compatible with various alkynyl, alkenyl, and aryl (pseudo)halides and generally provides the products in excellent yields.

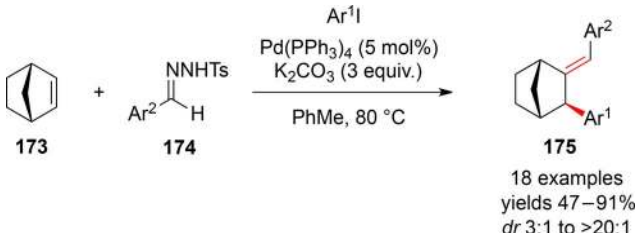


Scheme 50. Isocyanide insertion strategy for the synthesis of oxazoles.

2.2.3 Palladium-Catalyzed Carbene Insertion

Carbene insertion is similar to the insertion of carbon monoxide and isocyanides. However, carbenes are obviously much more reactive, and the corresponding cascade reactions typically involve *in situ* carbene generation. Carbene insertion results in an alkyl-Pd(II) species which can undergo either a β-hydride elimination or carbopalladation. This divergent reactivity makes palladium-catalyzed carbene insertion a versatile reaction.

In 2014, Wang et al. reported the synthesis of norbornene derivatives **175** by a diastereoselective three-component reaction of norbornene (**173**), aryl iodides and *N*-tosyl hydrazones **174** (Scheme 51).[72] The reaction tolerates small *para*-, *meta*-, and *ortho*-substituents at Ar^1, while variation at Ar^2 is limited *para*- and *meta*-substituents. The reaction generally provides the products in good to excellent yields with fair to excellent diastereoselectivity.



Scheme 51. Carbopalladation/carbene insertion of norbornene.

The authors propose a reaction mechanism initiated by carbopalladation of norbornene by the aryl-Pd(II) intermediate. The diastereoselectivity is governed by addition to the sterically less hindered *exo*-face. The base triggers formation of a diazo species from the *N*-tosyl hydrazone, subsequently leading to formation of a Pd(II)-carbene complex with loss of N_2. Insertion of the carbene then leads to a new alkyl-Pd(II) species, which is converted to the product by β-hydride elimination.

Gu and co-workers reported a carbopalladation/carbene insertion for the synthesis of benzo-fused carbo- and heterocycles **177** (Scheme 52).[73] The initial intramolecular carbopalladation forms the benzo-fused (hetero)cycle and subsequent carbene insertion yields the alkyl-Pd(II) intermediate **178**. β-Hydride elimination then generates the final product **177**. The reaction tolerates a diversity of tethers (Y, Z) without re-

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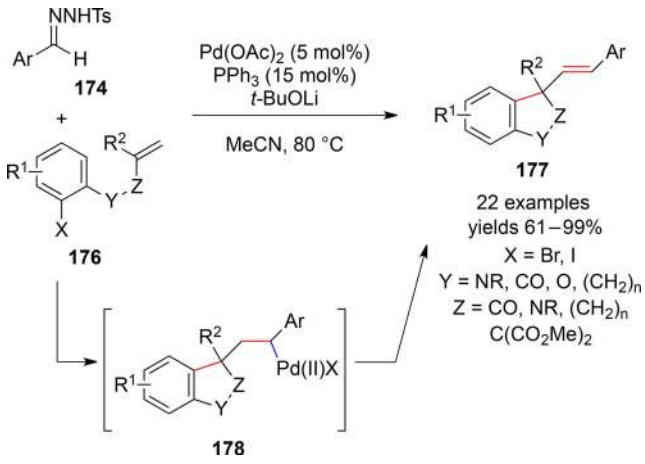
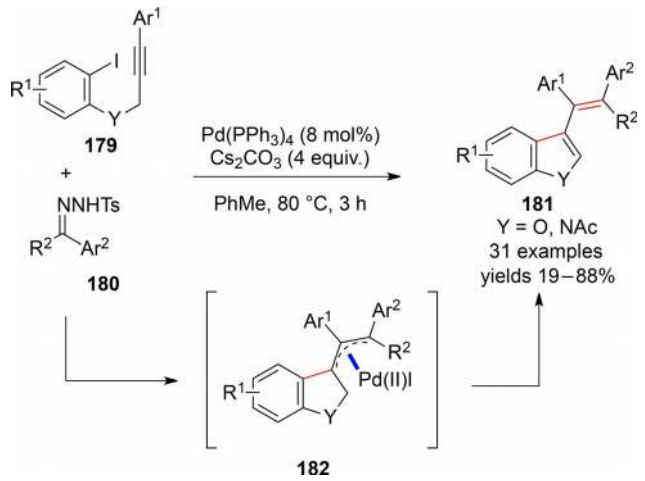


Scheme 52. Carbopalladation/carbene insertion cascade.

quiring a change in reaction conditions. Furthermore, various Ar groups were shown to be compatible, with the exception of *para*-nitrophenyl which did not provide the desired product.

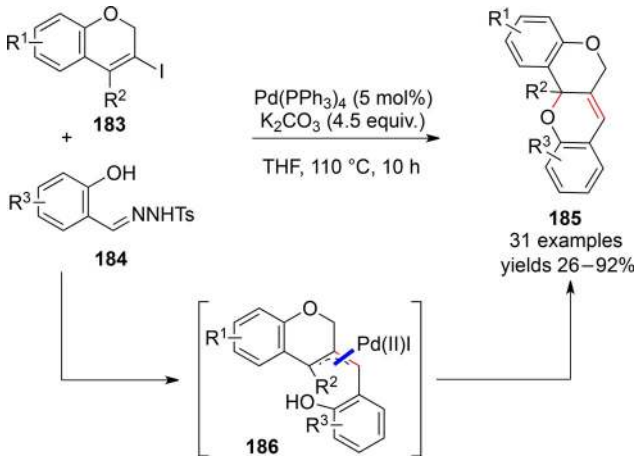
A carbopalladation/carbene insertion reaction for the synthesis of indoles and benzofurans **181** from the corresponding propargyl aryl ethers and propargyl arylamines **179** was reported by the group of Wang (Scheme 53).[74] The reaction tolerated various Ar^2 substituents with R^2 being phenyl or hydrogen. Furthermore, different (hetero)aromatic Ar^1 groups were compatible, while the use of terminal alkynes diminished the yield significantly. The yields of the reaction varied from poor to excellent.

The reaction mechanism proposed by the authors proceeds *via* a 5-*exo*-*dig* carbopalladation followed by the insertion of the *in situ* generated carbene. The resulting allyl-Pd(II) complex **182** then undergoes β-hydride elimination to give the fused heteroaromatic ring system.



Scheme 53. Carbopalladation/carbene insertion cascade.

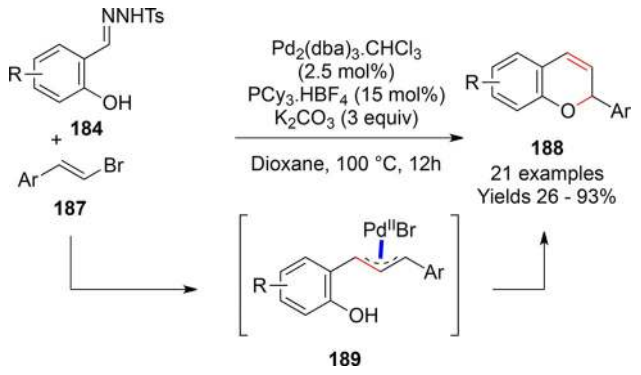
In 2015, Liu et al. reported the synthesis of chromeno[4,3-*b*]chromene derivatives **185** from 4-substituted 3-iodo-2*H*-chromenes **183** and salicaldehyde-derived *N*-tosyl hydrazones **184** (Scheme 54).[75] The proposed



Scheme 54. Cascade reaction involving carbene insertion and subsequent C–O bond formation.

mechanism is initiated by insertion of the carbene, followed by the isomerization of the allyl-Pd(II) complex **186** and a Tsuji–Trost type etherification to form the product. Various R^1 substituents were compatible, while the use of aromatic R^2 substituents was preferred. The yields of the reaction were generally good and even excellent in selected cases. Shang et al. also reported a fairly similar reaction with (2-iodophenyl)-propargylic ethers and the phenol-based *N*-tosyl hydrazones, generating spiro[benzofuran-3,2′-chromene] frameworks.[76]

Wang and co-workers reported a carbene insertion/etherification cascade for the formation of 2*H*-chromenes **188** from styryl bromides **187** and salicaldehyde-derived *N*-tosyl hydrazones **184** (Scheme 55).[77]



Scheme 55. Synthesis of 2*H*-chromenes by carbene insertion/etherification cascade.

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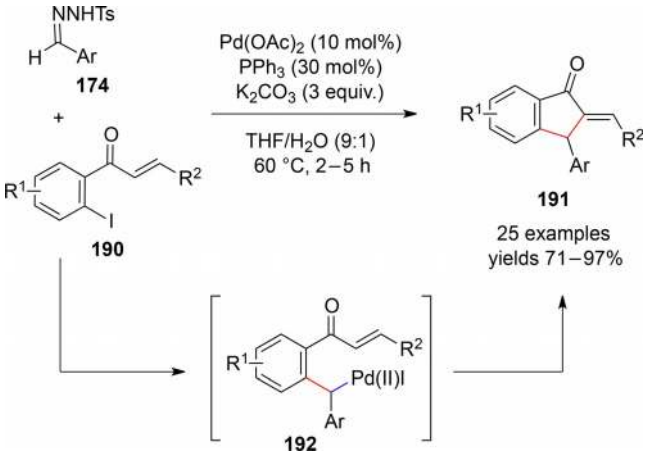
The authors propose an initiation *via* carbene insertion in the alkenyl-Pd(II) species. Subsequently, the formed allyl-Pd(II) complex **189** undergoes a Tsuji–Trost type etherification with the phenol. The reaction does not tolerate electron-withdrawing R substituents and lower yields are observed for highly electron-donating substituents. However, the reaction provides the products in good to excellent yields for compatible substituents.

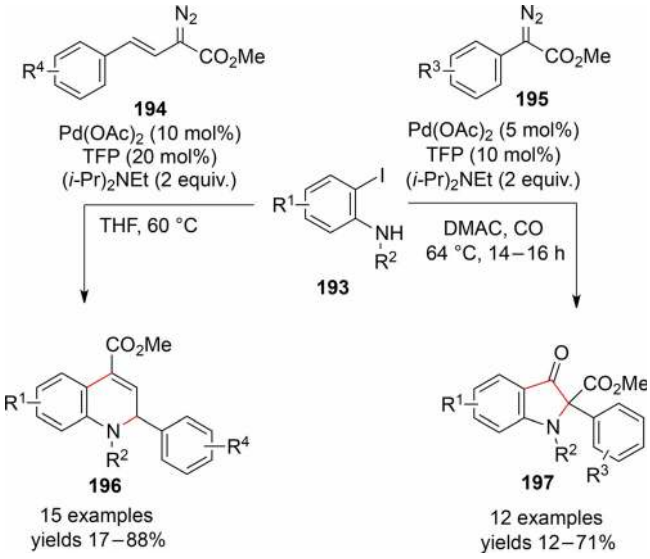
The synthesis of 2-alkylideneindanone derivatives **191** from 1-(2-iodoaryl)propenones **190** and *N*-tosyl hydrazones **174** *via* a palladium-catalyzed cascade reaction was reported by Sekar et al. (Scheme 56).[78] The authors propose a mechanism initiated by carbene insertion (leading to **192**) followed by a 5-*exo*-*trig* Heck reaction. The reaction tolerates a variety of aromatic R^1 and R^2 substituents, however electron-poor Ar groups proved to be incompatible. The products were obtained in good to excellent yields.



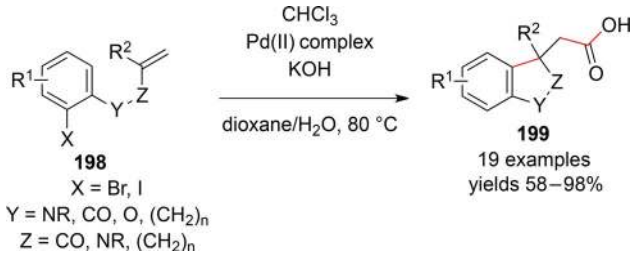
Scheme 56. Carbene insertion/Heck cascade.

In 2013, Liang et al. reported the synthesis of cyclic amino esters **197** by a CO insertion/carbene insertion/Buchwald–Hartwig amination cascade (Scheme 57).[79] α-Amino acids are important structures in many naturally occurring compounds, especially with a quaternary α-position. The reaction affords the products in mostly modest yields. The synthesis of γ-amino acids **196** using similar starting materials was reported in the same paper. This reaction is initiated by a carbene insertion, followed by isomerization of the allyl-Pd(II) complex and a Buchwald–Hartwig amination. A similar synthesis of γ-amino acids was reported by Sun and co-workers.[80]

A carbene insertion involving chloroform was reported in 2015 by Gu and co-workers, based on a carbopalladation/carbene-mediated carboxylation (Scheme 58).[81] The substrates **198** for the reaction were varied extensively, while only minor modifications of the reaction conditions were required.



Scheme 57. Synthesis of α- and γ-amino acids by palladium-catalyzed cascade reaction.



Scheme 58. A carbopalladation/carbene insertion cascade reaction with subsequent carbene hydrolysis.

Chloroform was used as the carbene precursor, which was hydrolyzed after formation of the carbene-Pd complex. The yields of **199** in the reaction were good to excellent, thus providing a viable alternative for the use of CO in palladium-catalyzed carboxylations.

2.3 C–X Activation with Two or More Propagation Steps

Thus far, the examples presented in this review contained a single propagation step. However, more complex systems can be constructed when more propagation steps are incorporated in the catalytic cycle. Regioselectivity becomes even more important in these complex cascade reactions, since multiple reactive sites may be available. To ensure the formation of a single product, most multiple propagation cascade reactions are used to form ring systems.

In 2012, Wu and co-workers reported a palladium-catalyzed cascade reaction with two propagation steps by using 2-alkynylbromoarenes **200** and 2-(2-alkynylaryl)malonates **201** (Scheme 59).[82] The authors pro-

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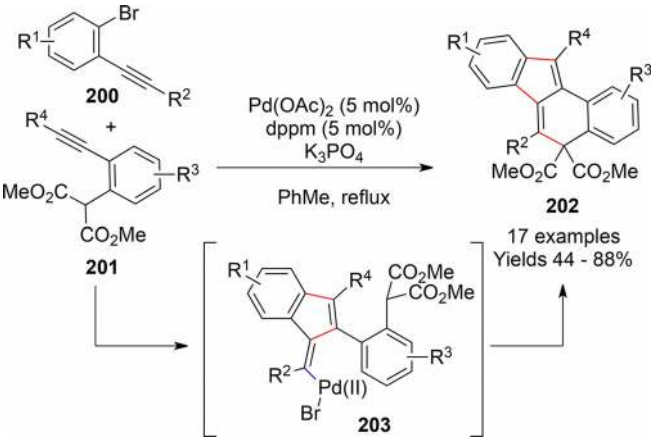
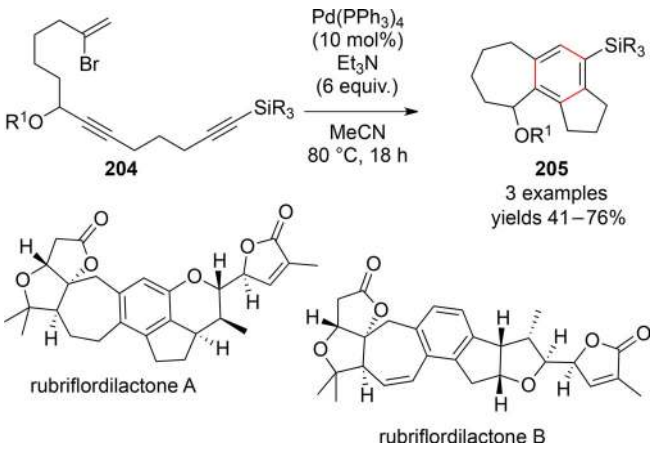


Scheme 59. Cascade reaction involving two carbopalladations.

pose a mechanism initiated by regioselective intermolecular carbopalladation of the aryl-Pd(II) species to the alkyne of **201**. The resulting alkenyl-Pd(II) complex undergoes a 5-*exo-dig* carbopalladation, forming indene-based alkenyl-Pd(II) intermediate **203**. Coupling of the malonate to palladium followed by reductive elimination generates product **202**.

Changes in both the R^1 and R^3 substituents did not influence the yield significantly, while a variety of aryl and alkyl R^2 and R^4 substituents was tolerated. The moderate to good yields and lack of side reactions demonstrate the robust and well-designed nature of the reaction.

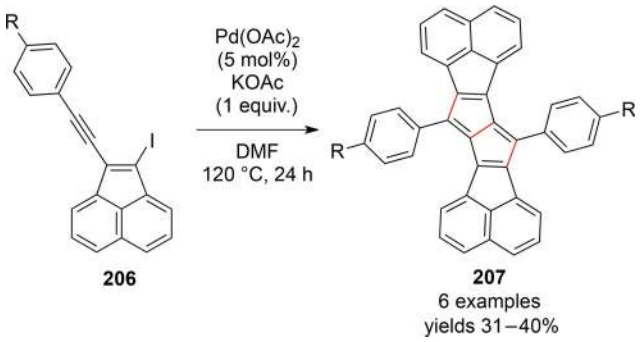
Anderson and co-workers reported the synthesis of hydrocyclohepta[*e*]indenes **205**, which can be used in the production of rubriflordilactones A and B (Scheme 60).[83] The authors did not propose a mechanism, but it most likely involves consecutive 7-*exo-dig* and 5-*exo-dig* carbopalladations terminated either by 6π-electrocyclization and β-hydride elimination or a 6-*endo-trig* Heck reaction. The reaction is limited to



Scheme 60. Cyclization cascade involving double/triple carbopalladation.

protected alcohols and internal alkynes and the yield is highly dependent on the substituents. The same authors later increased the substrate scope, allowing variation of the fused ring (cycloheptane in Scheme 60).[84]

In order to gain more insight into aromaticity, Plunkett and co-workers focused on pentalene derivatives.[85] However, the instability of pentalenes limited this study. The group synthesized pentaleno[1,2-*a*:4,5′]diacenaphthylenes **207**, since these oligoquinanes are more stable (Scheme 61). The yield of the reaction is fair at best and no reaction mechanism was proposed by the authors. Most likely, the cascade involves both an intermolecular and an intramolecular alkyne carbopalladation, followed by a (reductive) cross-coupling.



Scheme 61. The synthesis of pentalene derivatives for aromaticity studies.

In 2016, Suffert and co-workers reported the synthesis of cyclooctatetraenes **209** *via* multiple carbopalladations, electrocyclization, and termination by a Stille coupling (Scheme 62).[86] Especially the proposed initial 4-*exo-dig* carbopalladation to form bicycle[4.2.0]octane **210** is remarkable and exceedingly rare in palladium-catalyzed cascade reactions. The cascade is continued by a 5-*exo-dig* carbopalladation, yielding alkenyl-Pd(II) species **211**.

Either an 8π- or a 6π-electrocyclization occurs, with the 8π-electrocyclization leading to strained cyclic allene **212**, followed by an allyl-Pd(II) isomerization to **213** and Stille coupling to give **209**. The competing 6π-electrocyclization yields the main side product, responsible for the poor to fair yield of the reaction. R^1 substituents were mainly limited to Me_3Si, while R^2 substituents were either phenyl or *n*-pentyl. R^3 could be varied over a range of vinylic and heteroaryl substituents, as well as allyl and alkynyl groups. The yields of the reaction are typically modest but still impressive given the complexity of the cascade. The remarkable and complex proposed mechanism was supported by DFT calculations.

In 2017, Zhang et al. reported the synthesis of 4-substituted benzo(hetero)arenes **216** from (2-alkynyl)-

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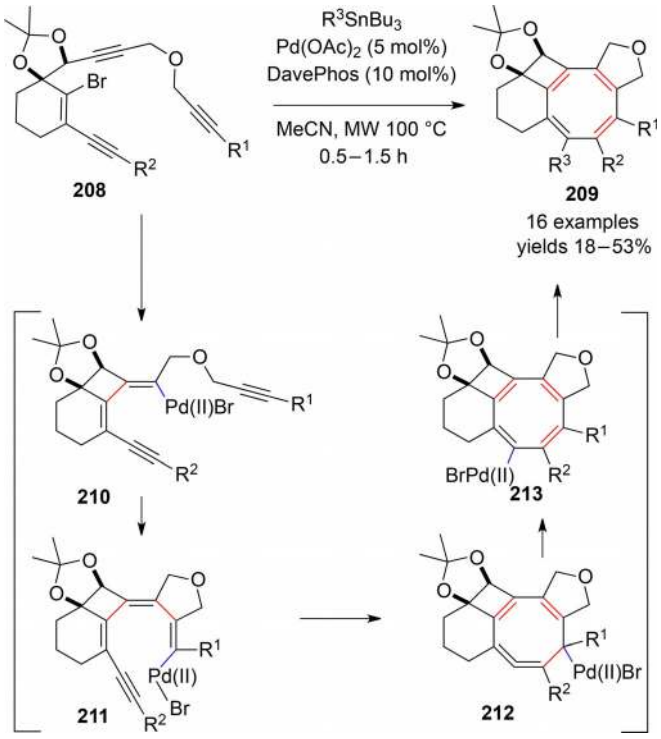
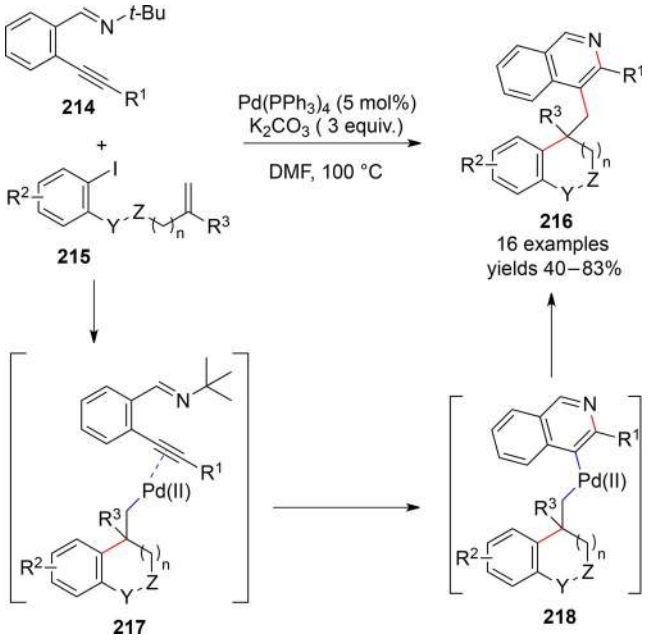
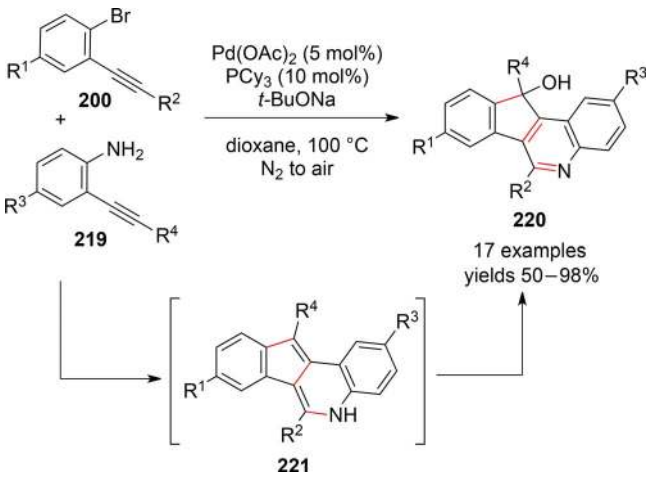


Scheme 62. Double carbopalladation, 8π-electrocyclization and Stille coupling cascade reaction.



Scheme 63. Cascade reaction involving carbopalladation and π-system activation, with reductive coupling of the organic fragments.



Scheme 64. Cascade reaction involving two carbopalladations and Buchwald–Hartwig termination.

benzylidene imines **214** (Scheme 63).[87] The reaction is initiated by an intramolecular carbopalladation forming alkyl-Pd(II) intermediate **217**, followed by π-system activation, with intramolecular attack of the imine nitrogen on the Pd(II)-activated alkyne to give diorganopalladium intermediate **218**. The mechanism of the reaction will be discussed in more detail in the next section. Reductive elimination and loss of isobutene generate the product. Silyl and electron-deficient aryl groups were not tolerated as R^1 substituents. However, the tether (Y, Z, n) could be varied without reducing the generally good yields.

In 2011, Wu et al. reported a palladium-catalyzed cascade reaction between 2-alkynyl-bromobenzenes **200** and 2-alkynylanilines **219**, generating 5*H*-cyclopenta[*c*]quinoline derivatives **220** (Scheme 64).[88] The reaction proceeds *via* intermolecular carbopalladation, followed by a 5-*exo*-*dig* carbopalladation and Buchwald–Hartwig amination to give tetracycle **221**. Oxidation of the tetracycle forms the final product **220**. Small variations of R^1 and R^3 substituents were tolerated. Furthermore, the use of aryl and alkyl R^4 substituents proved to be compatible.

The yields of the cascade reaction were excellent, especially considering the complexity of the sequence. The starting materials of the cascade have been further expanded over the years, now including 2-alkynylphenols,[89] 2-alkynylbenzamides[90] and 1-bromo-2-(cyclopropylidenemethyl)benzenes.[91] In a similar approach, the group of Wu also reported the synthesis of cyclopenta[*c*]quinolines,[92] cyclopenta[*c*]chromenes[93] and 6*H*-benzo[*f*]cyclopenta[*d*][1,2]thiazepine 5,5-dioxides.[94]

The insertion of benzynes into organopalladium complexes is similar to the propagation by alkyne insertion. However, instead of the alkene functionality introduced by the alkyne, an aromatic ring is inserted. The instability of benzynes requires their *in situ* generation. The most common benzyne precursors are 2-trimethylsilylaryl triflates, which react with fluoride to eliminate the silyl group and triflate to form the corresponding benzyne.

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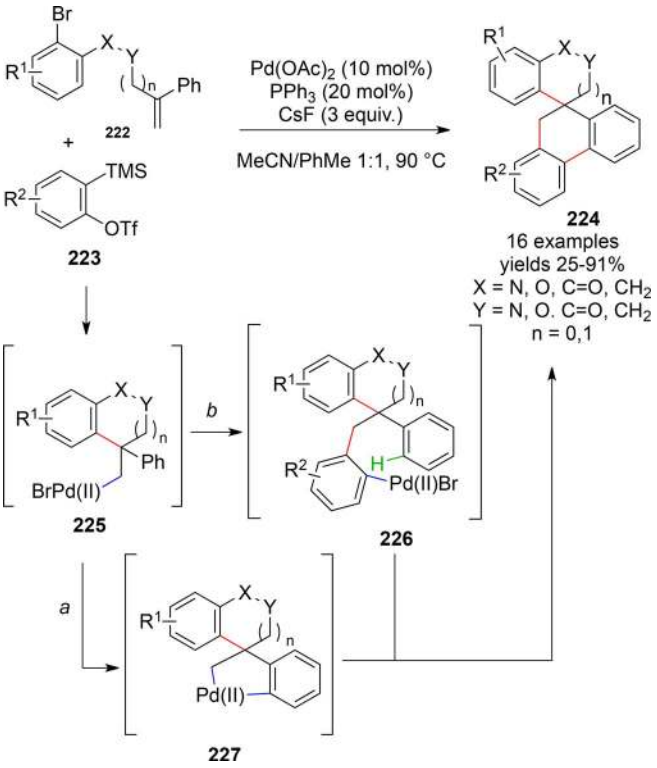
In 2016, Pérez-Gómez and García-López reported the synthesis of spiro-fused 9,10-dihydrophenanthrenes **224** using 2-trimethylsilylaryl triflates **223** as benzyne precursors (Scheme 65).[95] The authors propose two different mechanisms for the reaction, both

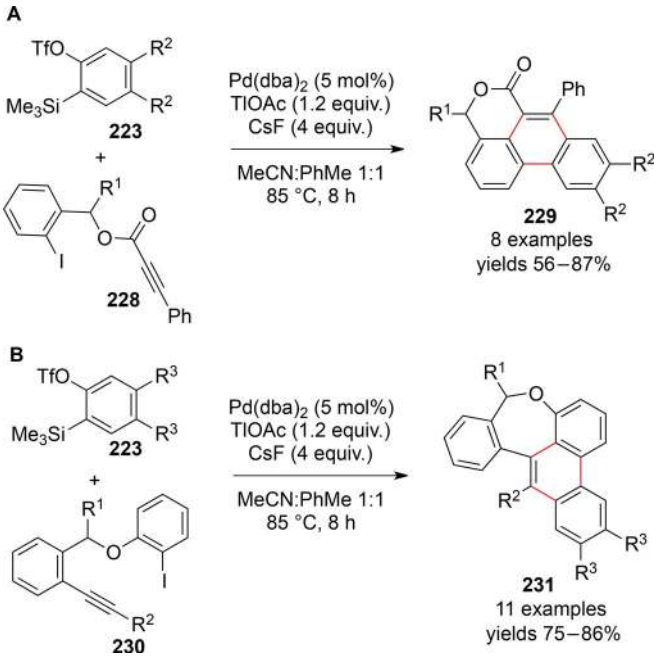


Scheme 65. Cascade reaction comprising carbopalladation, benzyne insertion and C–H activation.

starting with an intermolecular carbopalladation. The resulting common intermediate **225** can then either undergo C(sp^2)–H activation to give diorganopalladium complex **227** (pathway *a*) or benzyne insertion to aryl-Pd(II) species **226** (pathway *b*). In the case of C–H activation, the palladium center adds to benzyne and is consecutively inserted in both the alkyl-Pd(II) and aryl-Pd(II) bonds, generating the product. From intermediate **226**, C(sp^2)–H activation leads to the product.

The reaction proceeds very efficiently for the synthesis of spiro compounds containing five-membered rings (n = 0). However, when the method is extended to six-membered rings (n = 1), a major side product is formed. Furthermore, the reaction is not regioselective when using unsymmetrically substituted benzynes. While the reaction involves a complex sequence of steps, the yields of the reactions are quite good. A similar strategy was developed around the same time by Lautens and co-workers.[96]

In 2012, Cheng et al. reported the synthesis of fused isochromenones **229** and oxepines **231** (Scheme 66).[97] Both mechanisms are proposed to involve an intramolecular carbopalladation (6-*exo-dig* in the case of isochromenones and 7-*exo-dig* in the



Scheme 66. Cascade reaction involving carbopalladation, benzyne insertion and C(sp^2)–H activation.

case of oxepines), followed by C(sp^2)–H activation. The resulting diaryl-Pd(II) complex then undergoes benzyne insertion, forming two new C–C bonds. The role of TlOAc during the reaction is not well understood, but may involve removal of iodide, facilitating formation of the proposed diorganopalladium intermediate. However, replacing TlOAc by a halide scavenger did not result in formation of the desired product. The yield of the reaction was excellent, especially considering the complexity of the reaction and the lack of side products.

3 π-System Activation by Palladium(II)

The previous chapter focused on palladium-catalyzed cascade reactions initiated by the insertion of Pd(0) in (hetero)aryl or vinyl (pseudo)halide bonds. However, Pd(II) catalysts are able to activate the π-system of alkenes and alkynes. Coordination of Pd(II) increases the electrophilicity of the π-system and triggers nucleophilic tack, generating both a new C–Y (Y = O, N or C) bond and a new C–Pd(II) bond (Scheme 67). Generally, the addition of the nucleophile to the π-system leads to an *anti* geometry in the product.

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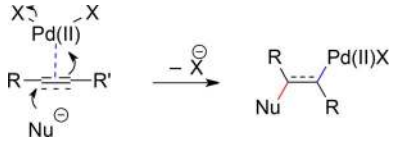


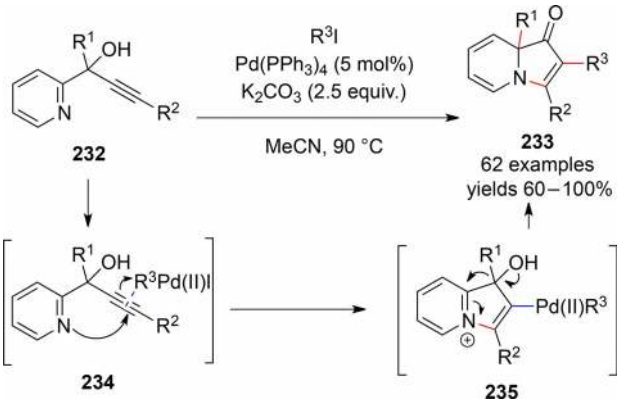
Scheme 67. π-System activation by Pd(II) and attack of a nucleophile, yielding the *anti* organopalladium complex.

Especially the activation of alkynes provides many opportunities for cascade reactions since it leads to the formation of stable alkenyl-Pd(II) intermediates, which can undergo subsequent propagation and termination steps. Typically, palladium needs to be reoxidized after the cascade since most cross-coupling (termination) reactions proceed *via* reductive elimination, forming a Pd(0) species. This chapter will continue the classification presented in the introductory section.

3.1 π-System Activation/Direct Termination

Alk(en)yl-Pd(II) intermediates can undergo direct termination by any of the cross-coupling reactions or by C–H activation. This section includes the termination reactions as described in Section 2.1. However, propagation steps are not required, since the initiation already involves an additional bond formation.

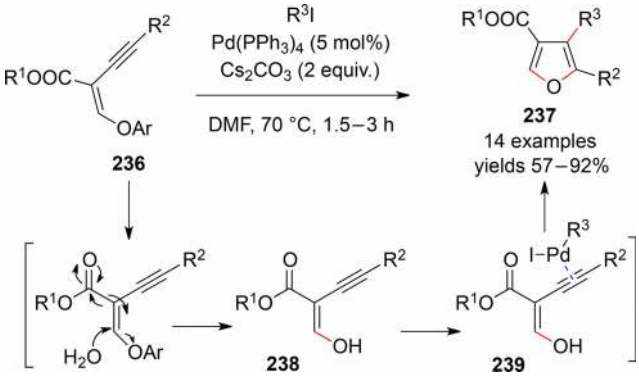
Aminopalladation by π-system activation has been elegantly used for the synthesis of indolizinones **233** from propargylic alcohols **232** (Scheme 68).[98] The authors propose a catalytic cycle initiated by the oxidative insertion of Pd(0) into the aryl iodide bond. Then, the aryl-Pd(II) complex facilitates a 5-*endo-dig* aminopalladation by π-system activation to afford intermediate **234**, instead of a carbopalladation. Evidence for this process is the formation of an *anti* intermediate, generally favored by a Pd(II) alkyne activation. A [1,2]-aryl shift then forms indolizinone ring **235** and a reductive elimination generates the product. The authors produced many examples in good to excellent yields and the reaction tolerates almost every imaginable aryl iodide.



Scheme 68. Aminopalladation/reductive elimination cascade.

Similar substrates were employed to produce 2-aroylindolizines[99] *via* aminopalladation and to realize the carbonylative arylation of 2-propargylpyridines, and indolizines[100] *via* aminopalladation and carbonylative esterification of alkynylpyridines.

In 2012, Li and co-workers reported the use of aryloxyenynes **236** and aryl halides for the synthesis of 2,3,4-trisubstituted furans **237** (Scheme 69).[101] The proposed mechanism is initiated by the conjugate addition of water (to give **238**). Subsequently, Pd(0) inserts into the Ar–I bond and the Pd(II) complex activates the alkyne (**239**), after which the oxygen of the enol attacks the alkyne. The desired product is then obtained by reductive elimination.



Scheme 69. Synthesis of furans *via* a π-system activated oxypalladation and reductive elimination.

The reaction was shown to be compatible with alkyl and aryl R^2 substituents. Furthermore, a highly diverse substitution pattern at the aryl iodide was tolerated. Most reactions were carried out using ethyl esters, which showed higher yields than their methyl counterparts. Yields were fair to excellent, but no clear correlation between yield and substitution pattern was observed.

Wang and co-workers reported the synthesis of 2,3,5-trisubstitued furans **241** from conjugated enynones **240** (Scheme 70).[102] The reaction is proposed to be initiated by a 5-*exo-dig* π-system-activated oxypalladation, forming the furanium intermediate **242**. Subsequently, a Suzuki cross-coupling and isomerization forms the furan ring. The scope of the boronic acids was limited to alkenyl and aryl substituents, and electron-rich systems were preferred. A decrease in yield and *E/Z* selectivity was observed when R^2 was not an electron-withdrawing substituent. Furthermore, the R^3 and R^4 substituents were limited to single substitution ($R^3 \neq R^4 = H$) or cyclic substituents (R^3 and R^4 are linked).

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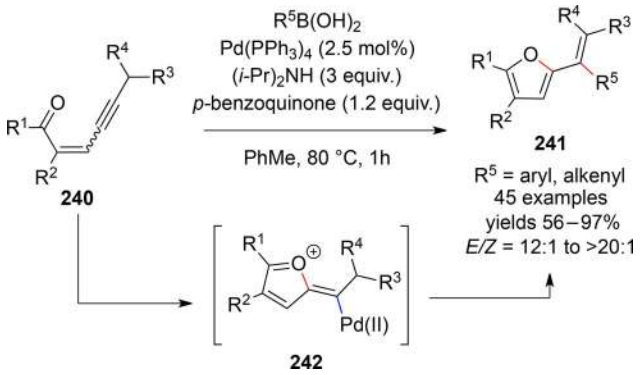
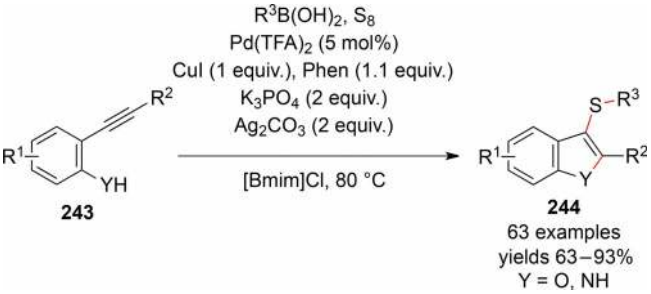


Scheme 70. Cascade reaction involving π-system oxypalladation and Suzuki coupling.

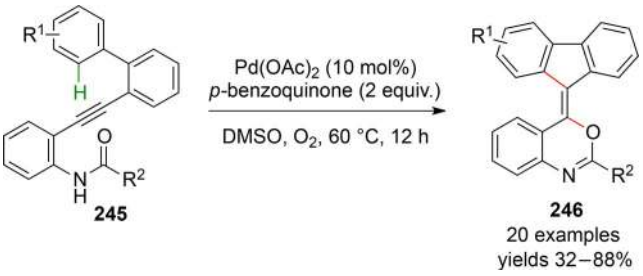
In 2016, Jiang et al. reported the synthesis of 3-sulfenylindoles and 3-sulfenylbenzofurans **244** *via* sulfurization with elemental sulfur in ionic liquids (Scheme 71).[103] A copper/phenanthroline-mediated sulfurization of the boronic acid generates an organocopper thiolate complex. After a 5-*endo-dig* heteropalladation, a transmetallation transfers the thiolate to the organopalladium complex, similarly to the Liebeskind–Srogl cross-coupling.[104] Reductive elimination then forms the product, while the catalyst is reoxidized by Ag(I) to the active Pd(II) species.



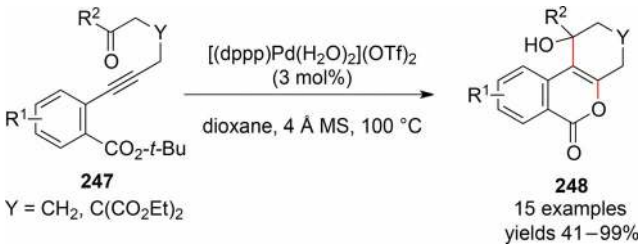
Scheme 71. Cascade reaction involving π-system activation/sulfurization reaction with boronic acids.

Ji et al. reported the synthesis of 4-(9*H*-fluoren-9-ylidene)-4*H*-benzo[*d*][1,3]oxazines **246** (Scheme 72).[105] The proposed mechanism proceeds *via* a π-system activation/6-*exo-dig* oxypalladation/C(sp^2)–H activation sequence, requiring the reoxidation of Pd(0) to Pd(II) after every catalytic cycle. Halides and electron-donating R^1 substituents were compatible with the reaction. Furthermore, diverse R^2 substituents were tolerated. Only one example with a *meta* R^1 substituent was reported, which exclusively afforded the product resulting from activation of the sterically more accessible C–H bond.

A 6-*endo-dig* oxypalladation by π-system activation/carbonyl addition cascade for the synthesis of cyclohexane-fused 1*H*-isochromen-1-ones **248** was reported by Lu et al. in 2016 (Scheme 73).[106] The reaction tolerates a wide variation of aldehydes, as well as aromatic and aliphatic ketones (R^2 = H, aryl, alkyl).

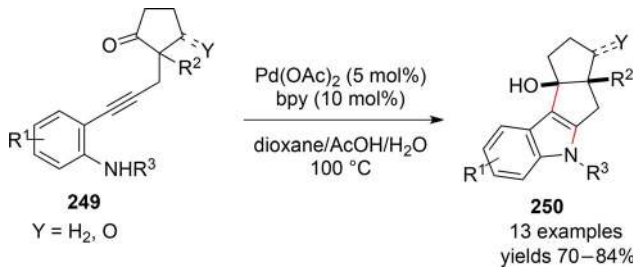


Scheme 72. π-System activation/C(sp^2)–H activation cascade reaction.



Scheme 73. π-System activation/carbonyl addition cascade reaction.

Similarly, a 5-*endo-dig* aminopalladation by π-system activation/carbonyl addition cascade was employed by the same group to synthesize pentaleno[2,1-*b*]indoles **250** (Scheme 74).[107] The reaction tolerates a variety of substituents on the aromatic system, ranging from electron-withdrawing to electron-donating functional groups. The reaction provides the products in good to excellent yields.



Scheme 74. Cascade reaction involving π-system activation and carbonyl addition.

Reddy et al. reported the synthesis of 2,3,4-trisubstituted quinolines **252** from 1-(2-aminoaryl)propargyl alcohols **251** (Scheme 75).[108] The reaction is initiated by a 6-*endo-dig* aminopalladation followed by a copper-free Sonogashira cross-coupling. Elimination

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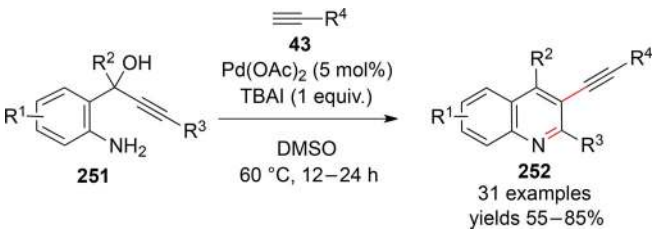
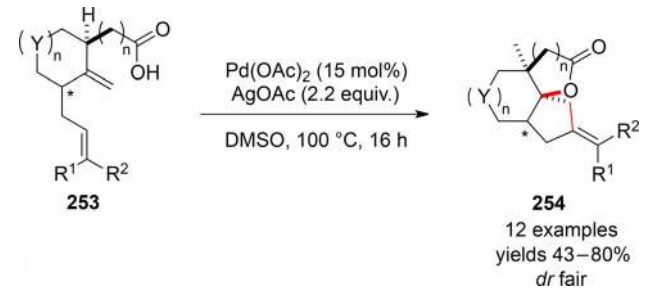


Scheme 75. Aminopalladation/copper-free Sonogashira cascade reaction.

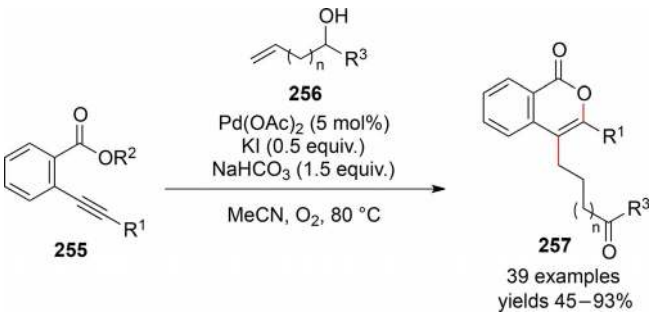
of water generates the quinoline and provides the final product. The catalytic cycle was closed by the apparent oxidation of Pd(0) by DMSO. This oxidation process was supported by the foul odor of dimethyl sulfide after the reaction. Various R^4 substituents proved to be compatible with the reaction and yields were generally good.

An elegant synthesis of spiranoid lactones **254** using an intramolecular oxypalladation/5-*exo*-*trig* Heck cascade was reported by Tsvelikhovsky and co-workers (Scheme 76).[109] A wide variety of cyclization precursors was employed showing the versatility of the cascade reaction, which even tolerated different ring sizes. Furthermore, high diastereoselectivity was observed for simple starting materials, while more complex starting materials often produced mixtures of diastereomers.



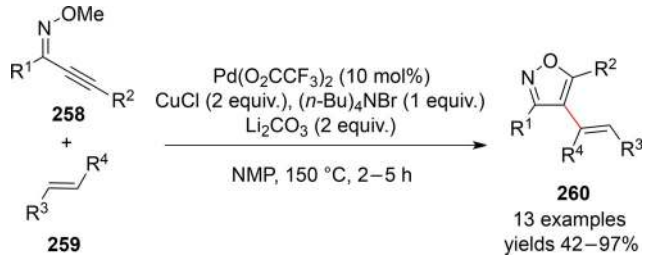
Scheme 76. Oxypalladation/Heck cascade reaction.

In 2016, Jiang and co-workers reported the synthesis of 1*H*-isochromen-1-ones **257** *via* a 6-*endo*-*dig* oxypalladation/intermolecular Heck reaction sequence (Scheme 77).[110] The authors performed an extensive study of the scope of the reaction, showing that it was compatible with many R^1 substituents with the exception of highly electron-withdrawing groups. Furthermore, varying the alkenes only led to lower yields for internal alkenes. While the mechanism of the reaction is not spectacular, the shift of the alkene in the final product to the alcohol is noteworthy. This occurs even over extended chain lengths, always forming the carbonyl. A similar study was reported earlier by Li and co-workers.[111]



Scheme 77. Oxypalladation/Heck cascade reaction with alkene shift.

Chen et al. reported the synthesis of 3,5-disubstituted 4-alkenylisoxazoles **260** from 2-alkyn-1-one *O*-methyloximes **258** and alkenes **259** (Scheme 78).[112]



Scheme 78. Heteropalladation/Heck cascade reaction to isoxazoles.

The authors propose a 5-*endo*-*dig* oxypalladation by π-system activation, where the methyl is presumably removed by a halide ion from the oxonium by nucleophilic substitution. A subsequent Heck reaction provides the product, after which the Pd catalyst is reoxidized from Pd(0) to Pd(II) by Cu(I). The reaction is compatible with alkyl and aryl substituents at both R^1 and R^2, providing the products in good to excellent yields. The regioselectivity of the Heck-type coupling to the alkene is governed by electronics (R^3 = EWG, R^4 = H or R^3 = H, R^4 = EDG).

In 2010, de Lera and co-workers reported the synthesis of polysubstituted indoles, isoquinolones and benzofurans **263** (Scheme 79).[113] The mechanism is the same for the various product types, starting with a 5/6-*exo*-*dig* heteropalladation. Subsequently, an intermolecular Heck reaction forms the product, while the Pd catalyst needs to be reoxidized. However, the optimal catalyst was dependent on the Y–C coupling, slightly limiting the generality of the reaction. The strategy was later further extended to produce 1*H*-isochromen-1-imines and benzofuran-1(3*H*)-imines as well.[114,115]

Nakazaki et al. reported the synthesis of 2,3-dihydro-4*H*-pyran-4-one systems **266** and **267** from β-hydroxy ynones **264** with a specific LiBr additive effect

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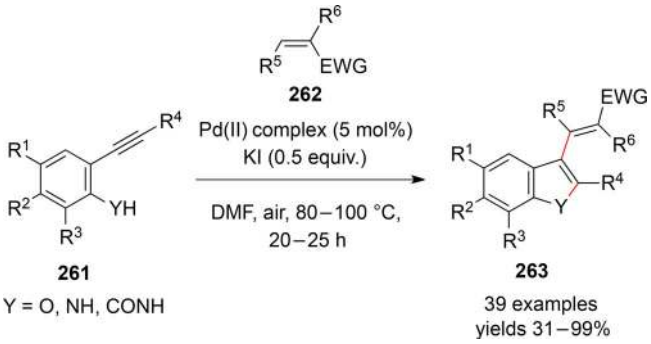
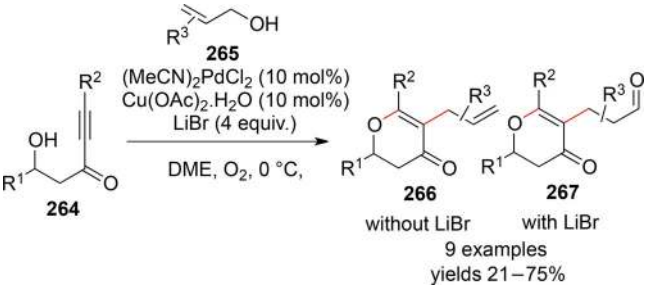


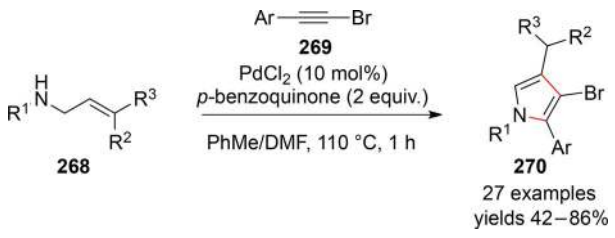
Scheme 79. Heteropalladation/Heck cascade reaction.

(Scheme 80).[116] The proposed mechanism starts with a 6-*endo-dig* oxypalladation, forming the dihydropyrone ring. Subsequently, an intermolecular carbopalladation couples the allylic alcohol to the ring. At this stage LiBr influences the final elimination of the reaction. In the absence of LiBr, a β-OH elimination forms a new allylic system. However, the addition of LiBr favors a Heck-type reaction pathway (β-hydride elimination), possibly by coordination of the LiBr to the alcohol.



Scheme 80. A π-system activated oxypalladation/Heck cascade reaction.

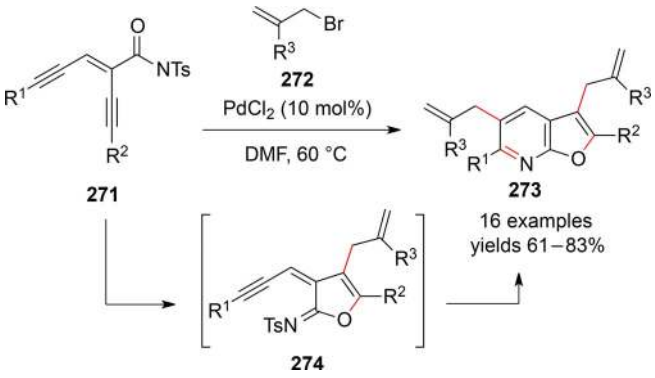
In 2015, Jiang and co-workers reported the synthesis of 3-bromo-2-arylpyrroles **270** from allylic amines **268** and bromoalkynes **269** (Scheme 81).[117] The proposed mechanism is initiated by an intermolecular aminopalladation followed by a 5-*exo-trig* Heck reaction. The reaction is compatible with aryl-substituted bromoalkynes, preferably electron-rich systems. A



Scheme 81. A π-system activated aminopalladation/Heck cascade reaction.

wide variety of aromatic R^1 substituents is tolerated and the reaction provided the products in generally good to excellent yields.

Ma and co-workers reported the synthesis of polysubstituted furo[2,3-*b*]pyridines **273** from enediynes **271** *via* a combination of two palladium-catalyzed cascade reactions (Scheme 82).[118] The proposed mechanism is initiated by a 5-*endo-dig* oxypalladation followed by intermolecular carbopalladation and β-bromide elimination, forming intermediate **274**. After the first cascade, a second cascade is initiated by a 6-*endo-dig* aminopalladation forming the pyridine ring, while the tosyl group is removed from the amide. The aryl-Pd(II) complex again undergoes an intermolecular carbopalladation and β-bromide elimination, forming the final product.



Scheme 82. Double heteropalladation cascade reaction.

3.2 π-System Activation/CO Insertion

The insertion of CO into alk(en)yl-Pd(II) complexes generated by π-system activation is more straightforward to predict than Pd(II) complexes generated by oxidative insertion. The main reason for this is the fact that the first alk(en)yl-Pd(II) is often only formed after the initial reaction. Therefore, CO insertion after π-system activated nucleopalladation is more common.

In 2014, Mancuso and Gabriele reported the synthesis of benzofurans **276** and **277** from 1-(2-allyloxyaryl)-2-yn-1-ols **275** (Scheme 83).[119] The initial study focused on the same reaction using the corresponding free phenols, however, the instability of these compounds when R^5 is an alkyl group reduces the feasibility of the reaction. Therefore, the phenolic OH had to be protected as an allyl ether. The allyl ether is cleaved under Pd(0) catalysis by a Tsuji–Trost-type insertion. The reaction is compatible with electron-rich aromatic systems, while the use of electron-withdrawing substituents was not tested.

The proposed mechanism is initiated by a Tsuji–Trost type insertion of Pd(0) in the allylic ether, yield-

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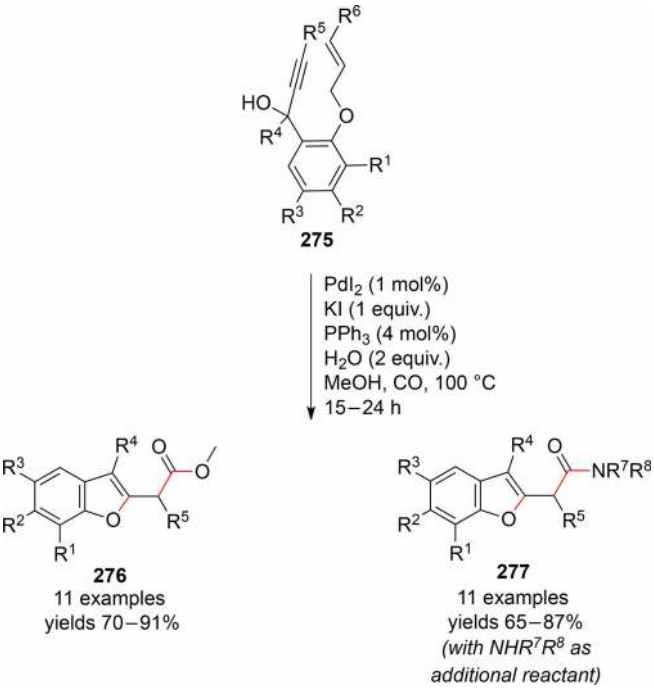
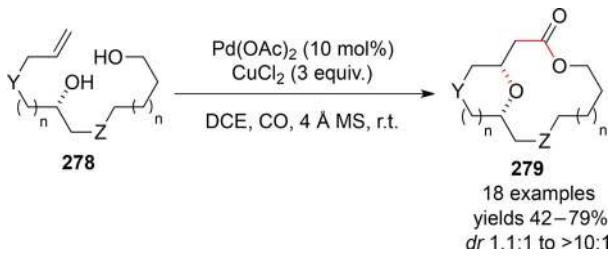


Scheme 83. Cascade reaction involving an oxypalladation/carboxesterification (-amidation) sequence.

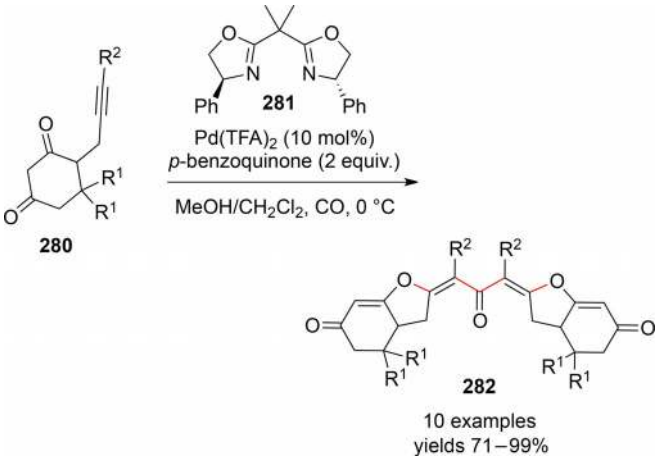
ing the phenol or phenoxide. Subsequently, a 5-*exo-dig* oxypalladation by π-system activation closes the hydrofuran ring and the alkenyl-Pd(II) undergoes a carbonylative esterification or amidation. HPd(II)I-mediated dehydration/aromatization then forms the final product.

Dai et al. reported the synthesis of tetrahydropyran/tetrahydrofuran-containing macrolides **279** *via* intramolecular oxypalladation and subsequent carbonylative esterification (Scheme 84).[120] Most syntheses of macrolides involve numerous protection and deprotection steps of the alcohols and carboxylic acids required for the lactonization. Furthermore, the conditions necessary for the macrolactonization are generally harsh and stoichiometric amounts of activators are required. These tetrahydropyran-containing macrolides are found in the naturally occurring neopeltolide, lyngbyaloside B and exiguolide, which all show anti-cancer activity.[121–123]



Scheme 84. Synthesis of macrolides by intramolecular oxypalladation/carboxesterification.

The synthesis of symmetrical oxabicycle-substituted ketones **282** was reported by Kato and co-workers in 2012 (Scheme 85).[124] The proposed mechanism starts with a 5-*exo-dig* oxypalladation, followed by carbonylation of the alkenyl-Pd(II) species. Subsequently, the acyl-Pd(II) complex catalyzes the 5-*exo-dig* oxypalladation of a second molecule of **280**. Reductive elimination then forms the product. The reaction tolerates various substituents on the alkyne, with electron-rich aryls leading to lower yields. The same paper also reports two similar reactions. Furthermore, the authors used this strategy for the synthesis of similar symmetrical ketones.[125–128]



Scheme 85. Double oxypalladation and dimerization *via* CO coupling.

3.3 π-System Activation/Isocyanide Insertion

Compared to carbon monoxide insertion, isocyanide insertion is less common in π-system activation reactions. There is no clear explanation for this, but it is in line with the limited use of isocyanide insertion in palladium-catalyzed cascade reactions in general.

In 2014, Reddy et al. reported the synthesis of α-indolyl- and α-benzofurylacetamides **284** *via* heteropalladation and isocyanide insertion (Scheme 86).[129] The authors propose an intriguing mechanism initiated by a 5/6-*exo-dig* heteropalladation to furnish bicyclic system **285**. Subsequently, isocyanide insertion followed by the formation of imidate **286** occurs. The ring strain of the imidate facilitates the insertion of Pd(0) in the original C–O bond. Protonolysis liberates the carboximic acid **287**, which isomerizes to the product. The reaction is compatible with alkyl isocyanides and the aromatic substitution pattern (R^1) does not decrease the generally good yields.

Wu and co-workers reported the synthesis of indolecarboxamides **289** from *N,N*-dimethyl-2-alkynylanilines **288** (Scheme 87).[130] The reaction is proposed to be initiated by a 5-*endo-dig* aminopalladation fol-

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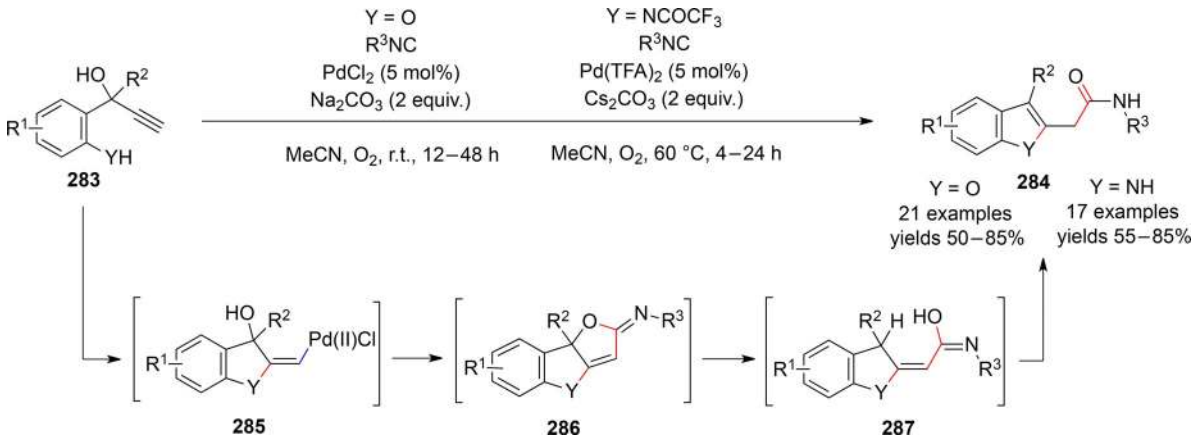
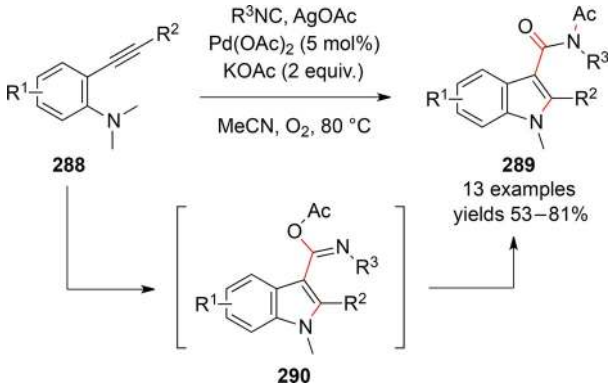
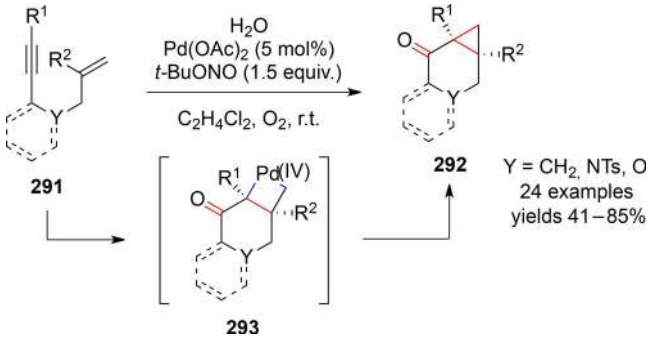


Scheme 86. Heteroapalladation/isocyanide insertion cascade reaction.



Scheme 87. Aminopalladation/isocyanide insertion cascade reaction.



Scheme 88. Oxypalladation/oxidative carbocyclization cascade reaction.

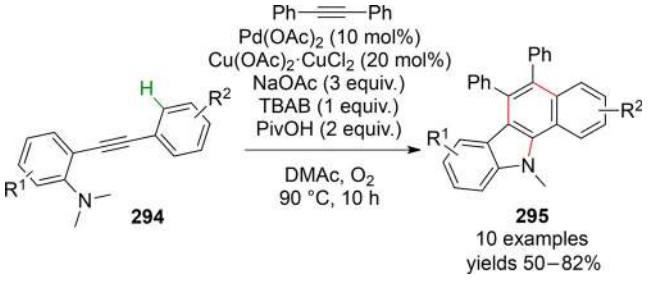
lowed by isocyanide insertion. Reductive elimination of the imidoyl-Pd(II)OAc complex forms *O*-acetyl imidate **290** which rearranges to form the amidate. The generated iminium loses a methyl group *via* a nucleophilic attack of acetate. The reaction tolerates various substituents and produced the indoles in typically good yield.

3.4 π-System Activation/Carbopalladation Propagation

Similarly to carbopalladation following oxidative insertion, the π-system-activated nucleopalladation yields an alk(en)yl-Pd(II) intermediate, which can be used for subsequent reactions. This section will discuss carbopalladations on alkenes and alkynes.

In 2015, Li et al. reported the synthesis of bicyclo[4.1.0]heptan-5-one derivatives **292** from 1,6-enynes **291** (Scheme 88).[131] The proposed mechanism is initiated by Pd(II) activation of the alkyne and subsequent attack of water, forming the alkenyl-Pd(II) complex. A 6-*exo*-*trig* carbopalladation forms the six-membered ring, while an oxidative cyclization mediated by NO_2 and O_2, generated *in situ* by the reaction between *t*-BuONO and H_2O, produces a Pd(IV)-containing palladacycle **293**. Reductive elimination closes the cyclopropane ring, regenerating Pd(II) and the product. Both electron-rich and electron-deficient aryl R^1 substituents were tolerated, as were alkyl substituents.

Liang et al. reported the synthesis of 11*H*-benzo[*a*]-carbazoles **295** from 2-(arylethynyl)anilines **294** (Scheme 89).[132] The reaction is proposed to proceed *via* a 5-*endo*-*dig* Pd(II)-catalyzed indole cyclization



Scheme 89. Cascade reaction involving an aminopalladation by π-system activation, carbopalladation and C(sp^2)–H activation.

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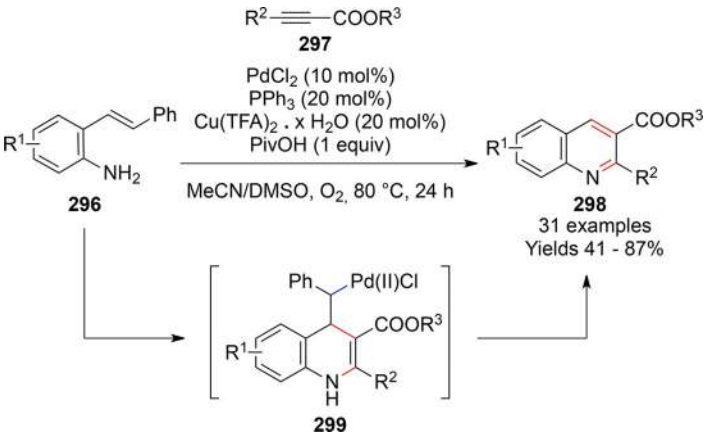
with concomitant nucleophilic displacement of one of the methyl groups, followed by intermolecular carbopalladation on diphenylethyne. The close proximity of the alkenyl-Pd(II) complex to the aromatic system then induces C(sp^2)–H activation, after which reductive elimination affords the product.

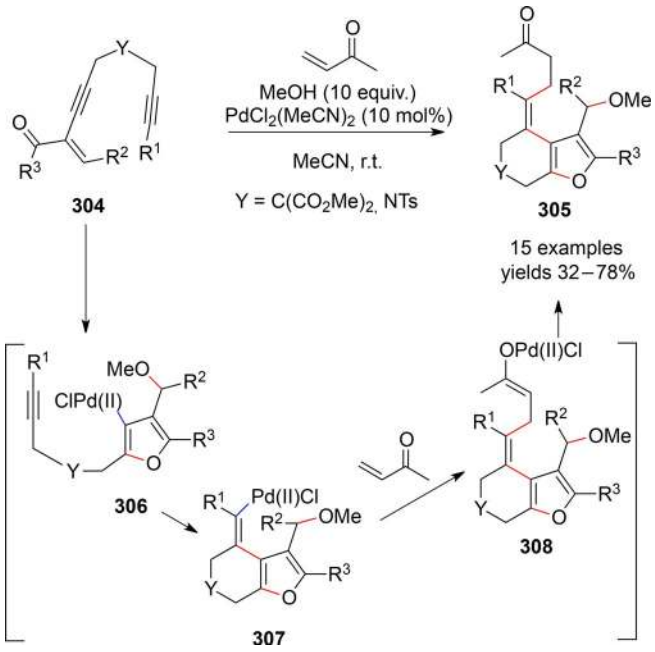
The synthesis of 2,3-disubstituted quinolines **298** from 2-styrylanilines **296** was reported by Jiang and co-workers in 2016 (Scheme 90).[133] The proposed reaction mechanism commences with an intermolecular aminopalladation. Subsequently, a 6-*exo*-*trig* carbopalladation forms dihydroquinoline ring **299**. The alkyl-Pd(II) is oxidized to the corresponding peroxopalladium(III) complex by copper catalysis, which rearranges to afford benzaldehyde and the product. The reaction is incompatible with alipathic alkynes, while R^1 substituents could be varied without lowering the yields.



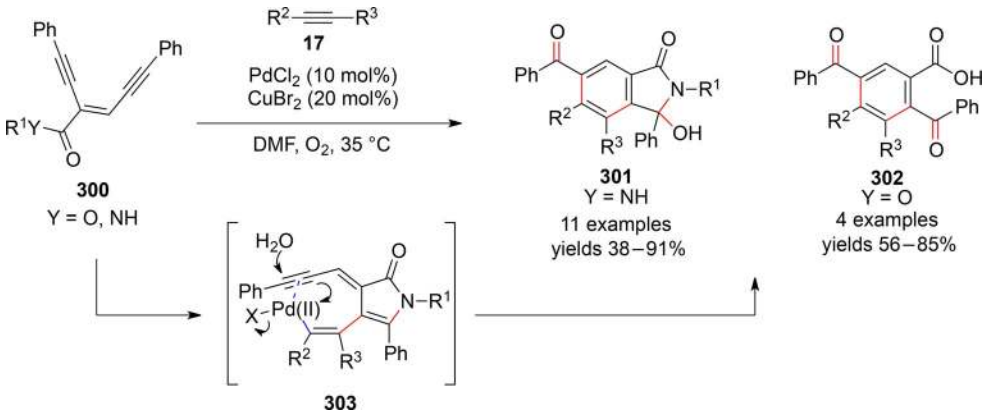
Scheme 90. A cascade reaction consisting of a π-system activated aminopalladation/carbopalladation/Heck reaction.

In 2014, Ma and co-workers reported the synthesis of isoindolinones **301** and 2,5-dibenzoylbenzoic acids **302** from enediynes **300** (Scheme 91).[134] The proposed mechanism is initiated by a 5-*endo*-*dig* heteropalladation by π-system activation followed by an intermolecular carbopalladation to intermediate **303**. The authors then propose a π-system-activated addition of water and coupling of both organic fragments. A final isomerization/oxidation of the intermediate yields the product. While 3-hydroxyisoindolines were stable after the reaction, the produced 3-hydroxyisobenzofuran-1(3*H*)-one isomerized to the 2,5-diacylbenzoylbenzoic acids. The selectivity for the carbopalladation on the external alkyne was poor, with highly polarized alkynes showing higher selectivities. Ma later extended the strategy to a reaction between two enediynes.[135]

In 2012, Zhang et al. reported a palladium-catalyzed three-component reaction of enediynones **304**, nucleophiles, and vinyl ketones (Scheme 92).[136] The reaction is compatible with aryl R^1, R^2 and R^3 sub-



Scheme 92. Cascade reaction involving oxypalladation/nucleophilic addition/carbopalladation/carbopalladation.



Scheme 91. Heteropalladation/carbopalladation/oxypalladation cascade reaction.

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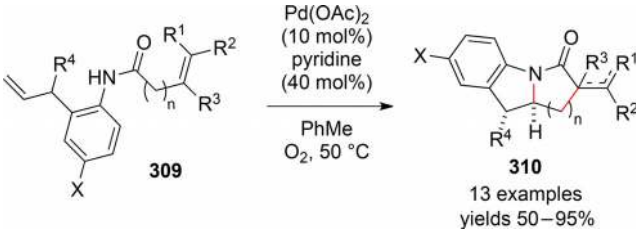
stituents, with no significant decrease in yields for either electron-poor or electron-rich aryls at R^3. However, the use of aliphatic R^1, R^2 and/or R^3 substituents leads to a tremendous decrease in yield. Methanol could be replaced by other alcohols with some decrease in yield.

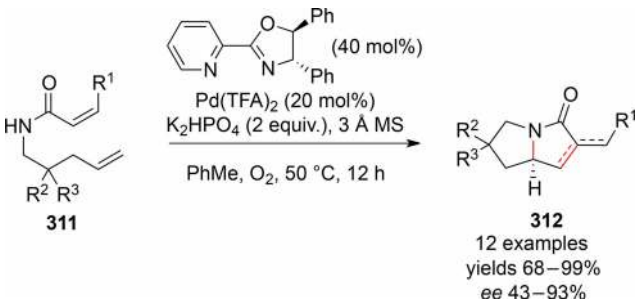
The mechanism proposed by the authors starts with a tandem 5-*endo-dig* oxypalladation and concomitant conjugate addition of methanol to give intermediate **306**. Subsequently, a 6-*exo-dig* carbopalladation forms bicyclic system **307**, and intermolecular carbopalladation forms palladium enolate **308**. Protonolysis of the Pd(II) complex with the generated HCl forms product **305**.

Yang and co-workers reported the diastereoselective synthesis of indoline-fused lactams **310** with the diastereoselectivity being determined by a *syn*-aminopalladation (Scheme 93).[137] The authors did not provide an explanation for the predominant *syn* addition, but only referred to the same observation by other authors. Furthermore, the authors provided only a few examples containing multiple stereocenters, and the selectivity seemed poor to excellent without any systematic explanation.



Scheme 93. Synthesis of polycyclic systems by 5-*exo-trig*/n-*exo-trig* cyclization cascade.

In 2017, Yang and co-workers reported a similar cascade for the enantioselective synthesis of bicyclic lactams **312** (Scheme 94).[138] The authors propose initiation by a 5-*exo-trig* aminopalladation with a subsequent 5-*exo-trig* Heck reaction. The overall *ee* of the reaction is excellent [using (*S,S*)-diPh-pyrox as a chiral ligand] and yields are generally good. However, the final alkyl-Pd(II) intermediate can undergo different termination processes, ranging from β-hydrogen eliminations to protonolysis, and the final products can differ in complexity.

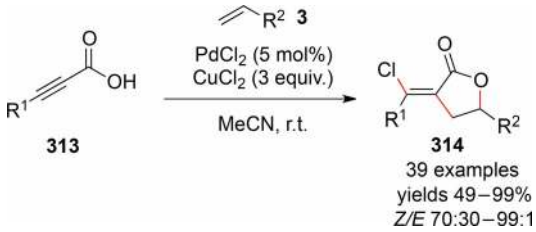


Scheme 94. Cascade reaction involving 5-*exo-trig* aminopalladation and 5-*exo-trig* Heck reaction.

3.5 π-System Activation with Halides

All of the reactions discussed so far in Section 3 involved a heteropalladation with oxygen or nitrogen. Halides are also able to undergo similar reactions. However, this reaction has only scarcely been studied.

In 2014, Jiang and co-workers reported the synthesis of 3-methylene-γ-lactones **314** from propiolic acids **313** and alkenes **3** (Scheme 95).[139] The reaction is initiated by a Pd(II)-mediated *anti* chloropalladation followed by an intermolecular carbopalladation. A Buchwald–Hartwig-type lactonization generates the final product with an *Z/E* ratio of ≥90:10. However, the *Z/E* ratio dropped when cyclopropylpropargylic acid was used, possibly due to Pd-catalzyed ring opening of the resulting vinylcyclopropane. Jiang and co-workers also reported a similar synthesis of lactones and other oxygen-containing heterocycles.[140–142]



Scheme 95. Halopalladation/C–O coupling cascade.

4 Specific Systems

While most of the palladium-catalyzed cascade reactions can be organized according to the classification used in Sections 2 and 3, some do not fit either category. This section of the review will provide insight in palladium-catalyzed cascade reactions involving particular building blocks with reactivities not readily categorized in the previous chapters. Furthermore, lesser known reactions or reaction types that do not fit the classification will also be discussed.

4.1 Tsuji–Trost-Based Cascade Reactions

The Tsuji–Trost reaction is initiated by the oxidative insertion of Pd(0) in allylic esters, carbonates, ethers, (pseudo)halides, or other allylic electrophiles. Usually, a nucleophile subsequently attacks the allyl-Pd(II) intermediate, generating a new C–C bond and regener-

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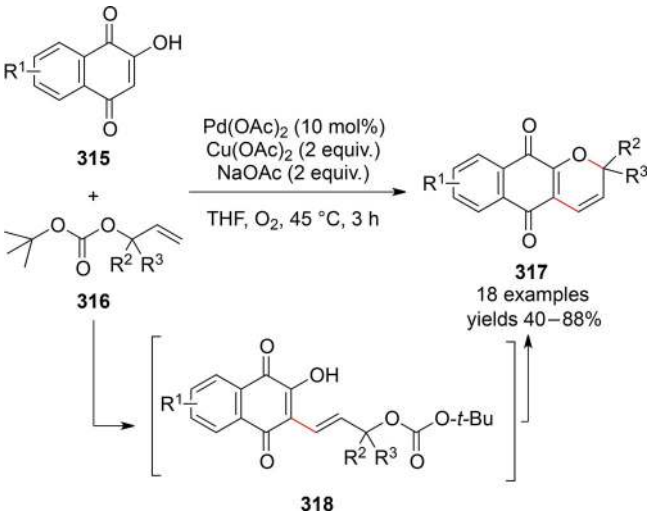
ating Pd(0). However, the allyl-Pd(II) species can also undergo carbopalladation and other propagation/termination steps.

The synthesis of 2*H*-pyranonaphthoquinones **317** from 2-hydroxy-1,4-naphthoquinones **315** and allylic carbonates **316** was reported by Zhang et al. in 2015 (Scheme 96).[143] The authors propose an initiation *via*

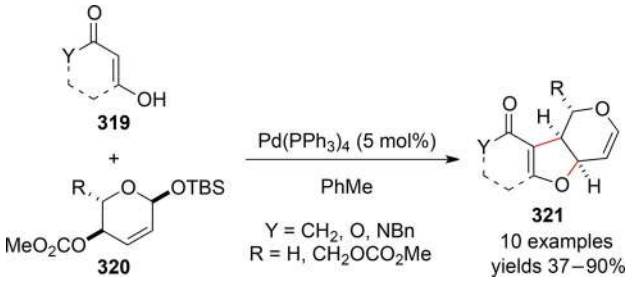


Scheme 96. C(sp^2)–H activation/Heck/Tsuji–Trost C–O coupling cascade reaction.

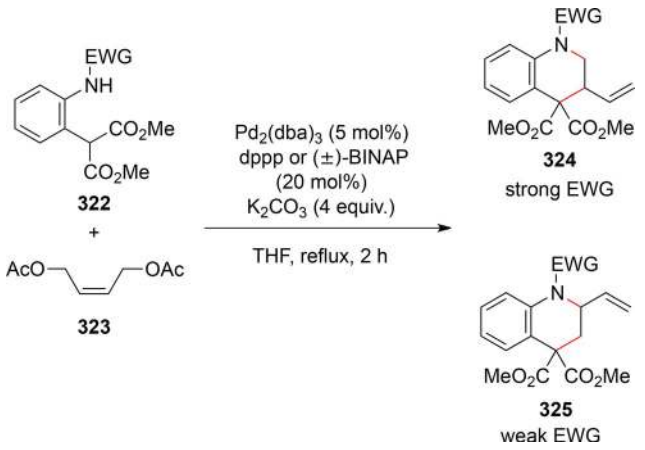
the coordination of the alkoxide to Pd(II) and subsequent C(sp^2)–H activation. The alkenyl-Pd(II) species then undergoes an intermolecular Heck reaction, generating the hydroxy-1,4-naphthoquinone allyl carbonate **318** and Pd(0) *via* the formation of acetic acid. The Pd(0) then facilitates a Tsuji–Trost-type insertion to generate the allyl-Pd(II) species, which undergoes etherification. The reaction is compatible with various R^1 substituents, generating the products in good yields. Increasing the length of the R^2 and R^3 sidechains led to lower yields, while electron-donating R^1 substituents were shown to counteract this decrease.

In 2013, Harvey and co-workers reported the synthesis of furo[3,2-*c*]pyrans **321** from dihydropyrans **319** and cyclic β-dicarbonyls **320** (Scheme 97).[144] The reaction is initiated by the formation of an allyl-Pd(II) species *via* a Tsuji–Trost-type insertion, followed by C(sp^2)–H activation and C–C coupling at the carbonyl α-carbon with net retention of stereochemistry. A second Tsuji–Trost-type insertion and etherification generates the desired product.

A year earlier, a double Tsuji–Trost cascade was reported by Yoshida et al. for the synthesis of tetrahydroquinolines **324** and **325** from 2-amidophenylmalonates **322** and allylic diacetate **323** (Scheme 98).[145] The position of the vinyl group in the product is dependent on the order of attack of the nucleophile of the amidophenylmalonate on the allyl-Pd(II) inter-



Scheme 97. Double Tusji–Trost cascade reaction including C(sp^2)–H activation.



Scheme 98. Regiodivergent double Tsuji–Trost cascade.

mediate. If the amide attacks the allyl-Pd(II) complex, product **324** is the major product, while **325** is the major product when the malonate attacks first. The nature of the electron-withdrawing group on the aniline moiety determines the relative reactivity of the two nucleophiles, and thus the outcome of the reaction. Highly electron-withdrawing EWGs favor the formation of the amide and therefore lead to **324** as the major product. An enantioselective cyclization was developed by the introduction of chiral phosphine ligands, with the *ee* depending on the electron-withdrawing group on the amine.

Trost and co-workers reported the use of two different oxidation states of palladium in their synthesis of trienes **329** *via* a Tsuji–Trost-initiated palladium-catalyzed cascade (Scheme 99).[146] A standard Tsuji–Trost coupling of malonate-type structure **326** and allylic acetate **327** affords **330**. Addition of 1,4-diene **328** and an oxidizing agent produces diallyl-Pd(II) intermediate **331**, which is then coupled to the conjugate base of **330** The yield and *E/Z* selectivity of the reaction were generally good. Efforts to perform the reactions simultaneously gave fair to good yields, showing the possibility of two different oxidation states of palladium co-existing in the same reaction mixture.

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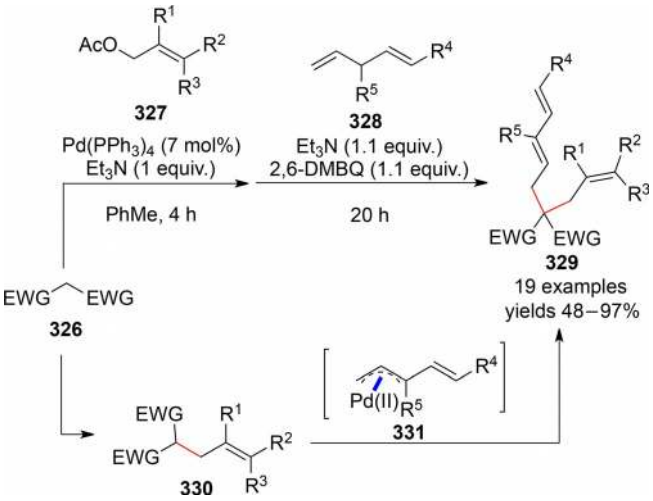
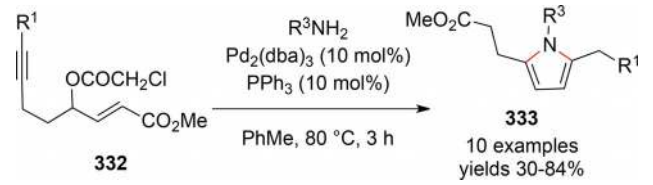


Scheme 99. Cascade reaction involving a Tsuji–Trost reaction and palladium-catalyzed allylation. 2,6-DMBQ = 2,6-dimethyl-*p*-benzoquinone.

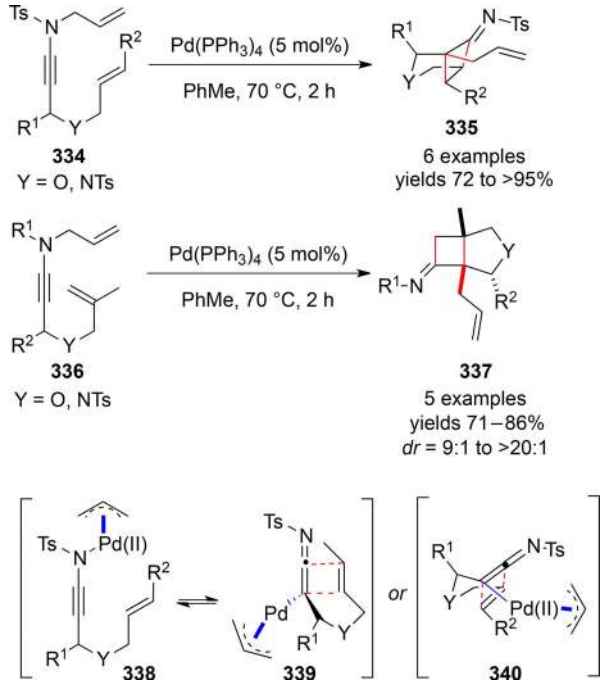
In 2012, Wang et al. reported the synthesis of 1,2,5-trisubstituted pyrroles **333** from enynyl esters **332** and primary amines (Scheme 100).[147] The authors propose initiation by the allylic amination of the enynol with subsequent intramolecular hydroamination and olefin isomerization. The reaction tolerates various amines and the best results were obtained with terminal alkynes ($R^1 = H$).



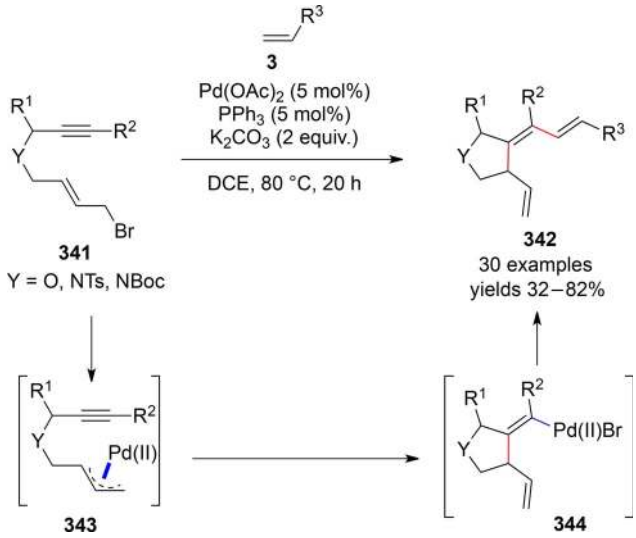
Scheme 100. Tsuji–Trost initiated Buchwald–Hartwig amination and hydroamination cascade.

A highly interesting use of the Tsuji–Trost-type insertion was reported by Hsung and co-workers in the rearrangements of *N*-allyl ynamides **334** and **336** to give bridged or fused cyclobutanes (**335** and **337**, respectively, Scheme 101).[148] Tsuji–Trost-type activation of the allylic sulfonamide results in intermediate **338**, which rearranges to produce a ketenimine that can either undergo a fused-[2+2] or crossed-[2+2] cycloaddition (*via* intermediate **339** or **340**, respectively). The selectivity of the type of cycloaddition is dependent on the substrate and the cascade provides the products in good to excellent yields.

In 2011, Wang et al. reported the synthesis of 3-allylidene-4-vinyltetrahydrofurans and 3-allylidene-4-vinylpyrrolidines **342** from 1,6-enynes **341** and alkenes **3** (Scheme 102).[149] The mechanism is a hybrid between a Tsuji–Trost-type reaction and the R–X activa-



Scheme 101. Palladium-catalyzed rearrangement of *N*-allyl ynamides.



Scheme 102. Tsuji–Trost-initiated carbopalladation/Heck cascade.

tion mechanisms described in Chapter 2. The authors propose initiation *via* formation of the allyl-Pd(II) complex **343**, followed by a 5-*exo*-*dig* carbopalladation to alkenyl-Pd(II) species **344** and an intermolecular Heck reaction to form the product. The reaction is compatible with electron-poor R^3 substituents, providing the products in generally good yield. However, the use of styrene ($R^3 = Ph$) significantly decreases the yield, and the use of aryl R^2 substituents is preferred.

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4.2 Propargylic Esters and Carbonates

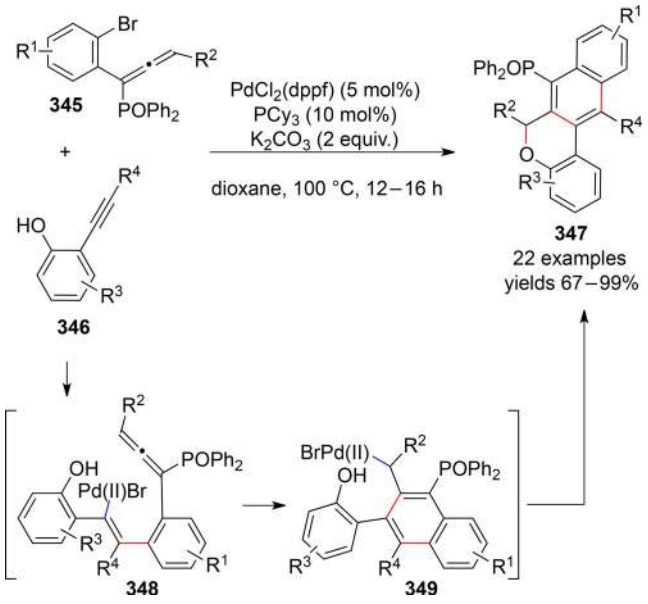
Propargylic esters and carbonates can undergo a Tsuji–Trost type insertion, resulting in an allenyl-Pd(II) complex. The organopalladium intermediate is formed at the γ-position of the original ester or carbonate functionality, offering various opportunities for propagation and termination steps. This chemistry was recently reviewed by Franckevičius and will therefore not be included in this overview.[150]

4.3 Allenes

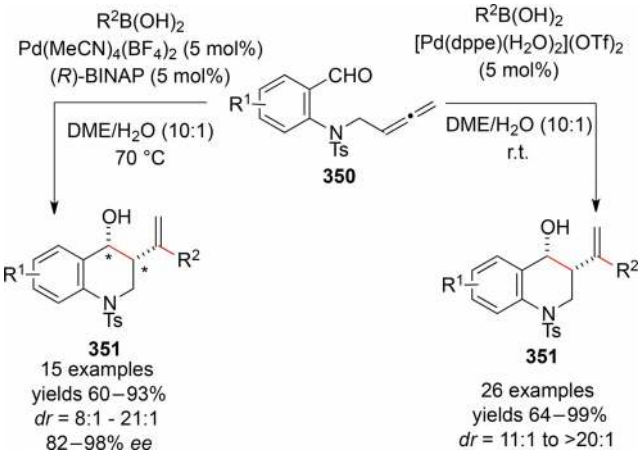
Allenes are versatile building blocks for palladium-catalyzed reactions and readily undergo carbopalladation, yielding allyl-Pd(II) intermediates. The reactivity of allenes has been reviewed by Lechel and co-workers, and we will therefore only discuss cascade reactions reported after this review (2013).[151]

In 2014, Wu and co-workers reported the synthesis of 6*H*-naphtho[2,3-*c*]chromenes **347** from 2-haloaryl allenes **345** and 2-alkynyl phenols **346** (Scheme 103).[152] The authors propose initiation *via* an intermolecular carbopalladation generating alkenyl-Pd(II) intermediate **348**. Subsequently, the geometry of the alkenyl-Pd(II) complex facilitates carbopalladation on the allene yielding intermediate **349**. The final product is formed by an etherification with the phenol. The reaction is compatible with a variety of aryl R^4 and R^2 substituents, with electron-rich aryls slightly decreasing the excellent yields.

An enantioselective synthesis of 3-hydroxy-2-vinyltetrahydroquinolines **351** from *N*-tosylaniline-tethered



Scheme 103. Cascade reaction involving alkyne carbopalladation/allene insertion and C–O cross-coupling.



Scheme 104. Boronic acid-mediated allene insertion/carbonyl addition cascade reaction.

allenyl aldehydes **350** was reported by Lu et al. (Scheme 104).[153] The reaction is initiated by the formation of the Suzuki complex from the arylboronic acid and subsequent addition of the aryl-Pd(II) complex to the allene. Addition of the allyl-Pd(II) intermediate to the carbonyl forms the final product. Initially, high diastereoselectivity of the reaction was observed, which was further developed into an catalytic asymmetric process using (*R*)-BINAP as a chiral ligand. The reaction provides the products in generally very high yields, with excellent enantio- and diastereoselectivities.

In 2013, Ye and Ma reported the synthesis of bicyclo[4.3.0] skeletons **353** from allene-functionalized propargylic carbonates **352** and malonates **326** (Scheme 105).[154] The authors propose two possible pathways both initiated by activation of the propargylic carbonate, generating allenyl-Pd(II) complex **354**.

In pathway *a*, the allenyl-Pd(II) intermediate **354** adds to the allene, and the resulting allyl-Pd(II) complex undergoes a Tsuji–Trost cross-coupling with the malonyl-type structure to furnish intermediate **355**. A base-mediated addition of the malonate-type structure to the allene then provides the product. The second pathway (*b*) involves the addition of the malonyl-type structure to the allenyl-Pd(II) complex, generating allyl-Pd(II) intermediate **356**. Addition of this complex to the allene then forms allyl-Pd(II) intermediate **357**, which forms the product *via* a Tsuji–Trost cross-coupling with the malonyl-type structure. The reaction is compatible with a variety of electron-withdrawing substituents. Remarkably, EWG combinations with weakly electron-withdrawing methyl ethers were tolerated with a slight decrease in yield. An increase in size of the R^3 and R^4 substituents decreased the yield slightly. Furthermore, chiral information of R^1 and R^2 was observed to be maintained

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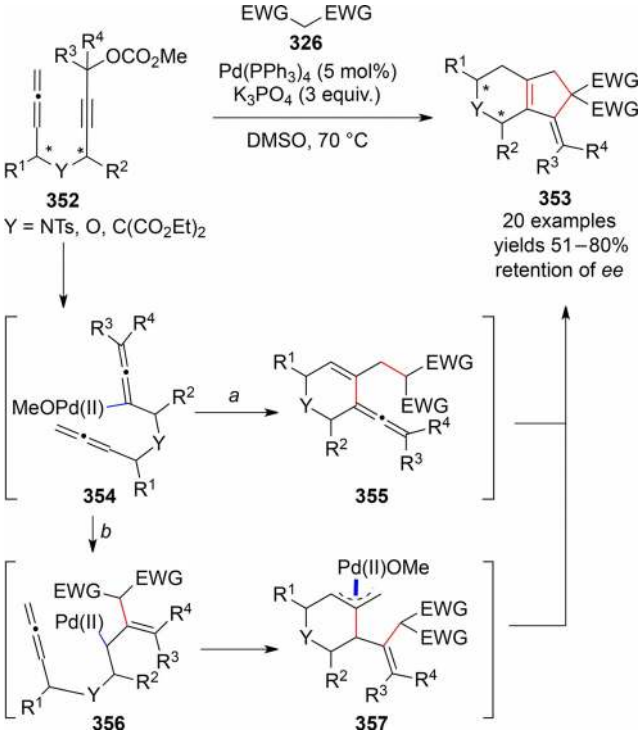
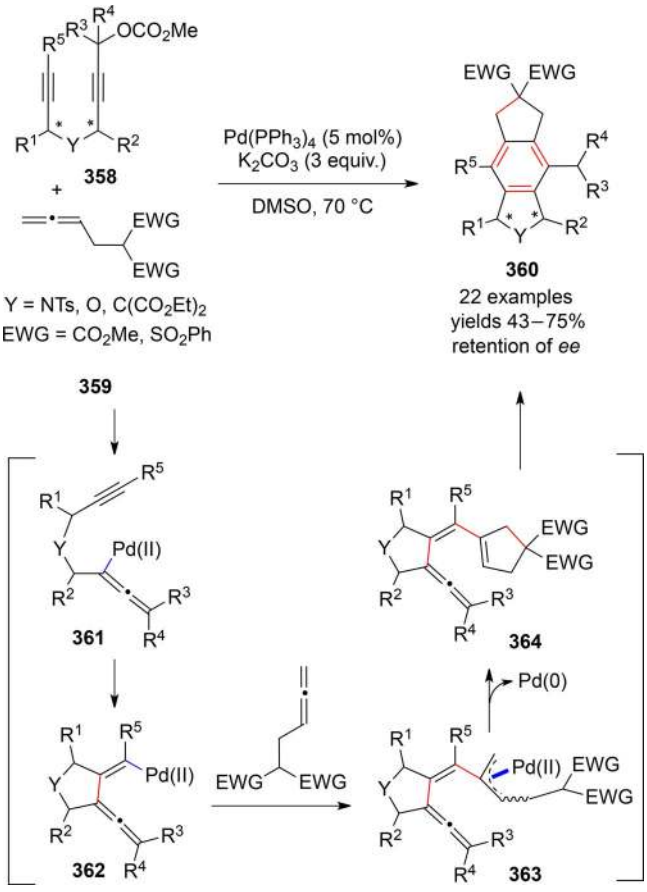
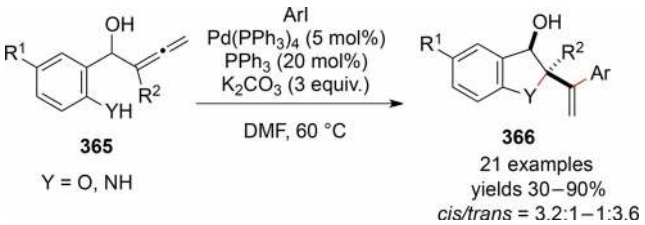


Scheme 105. Allene insertion *via* propargylic carbonate initiation.



Scheme 106. Double carbopalladation/Tsuji–Trost coupling/6π-electrocyclization cascade.



Scheme 107. Allene insertion/Tsuji–Trost cascade.

during the reaction. The geometry of the exocyclic alkene appears to be governed by sterics; if $R^3 \neq R^4$, the reaction primarily affords the *E*-configured product (R^3 = alkyl, R^4 = H).

The same group reported another cascade reaction derived from the previous example for the synthesis of tricyclic systems **360** from alkyne-functionalized propargylic carbonates **358** and allene-functionalized malonates **359** (Scheme 106).[155] The reaction is compatible with aryl and alkyl substitution and the propargylic carbonate and alkyne could be linked by ethers, amines or aliphatic chains. Furthermore, the reaction proceeds in good yields and chiral information on the tether is retained during the reaction.

The reaction is initiated *via* activation of the propargylic carbonate, forming allenyl-Pd(II) complex **361**. Subsequently, a 5-*exo-dig* carbopalladation generates alkenyl-Pd(II) intermediate **362**, which undergoes an intermolecular carbopalladation on the allene to form allyl-Pd(II) **363**. A Tsuji–Trost cyclization generates **364**, and the product is formed *via* a 6π-electrocyclization and isomerization.

In 2015, Li et al. reported the diastereoselective synthesis of dihydrobenzofuranols and indolinols **366** from allenols **365** and aryl iodides (Scheme 107).[156] The authors propose a mechanism initiated by organopalladation of the aryl-Pd(II) complex on the allene. Subsequently, the resulting allyl-Pd(II) species undergoes a 5-*exo-trig* Tsuji–Trost-type cyclization to form the product. The *cis*/*trans* selectivity is determined by the electronic nature of the aryl iodide, with electron-poor aryls favoring the formation of *cis* products, while electron-rich aryls favor *trans* stereochemistry.

Hamada et al. reported the synthesis of spiro[4.5]-cyclohexadienones **368** from allene-functionalized phenols **367** (Scheme 108).[157] The authors propose initiation by carbopalladation of the allene followed by an *ipso*-Friedel–Crafts-type reaction on the resulting allyl-Pd(II) intermediate. The reaction is compatible with both protected amines and malonyl-type structures in the tether (Y), while different substitution patterns on the aromatic ring were tolerated. Notably, modest to good diastereoselectivity was observed for unsymmetrically substituted aromatic systems.

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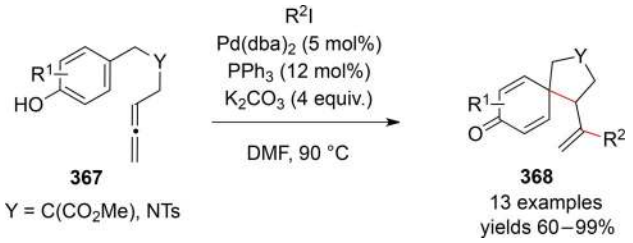
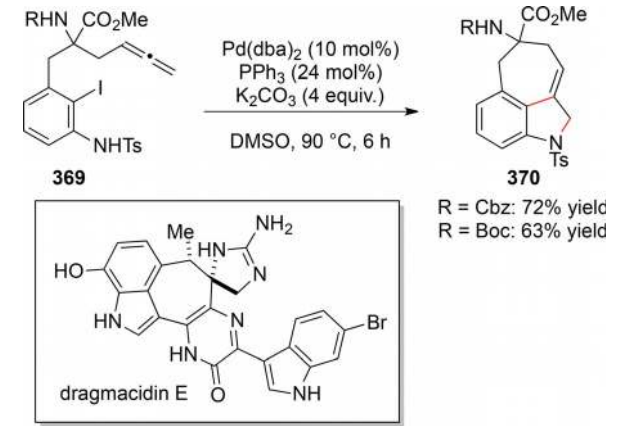


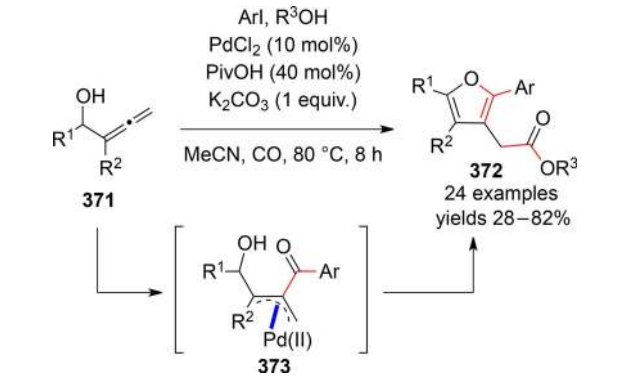
Scheme 108. Allene insertion/*ipso*-Friedel–Crafts cascade.

The same group reported the synthesis of the core structure (**370**) of dragmacidin E by 7-*exo-trig* carbopalladation followed by a Tsuji–Trost-type amination (Scheme 109).[158] Biological studies of dragmacidin E were hindered by the low yields of isolation from natural resources and a previous total synthesis had unavoidable epimerization issues.



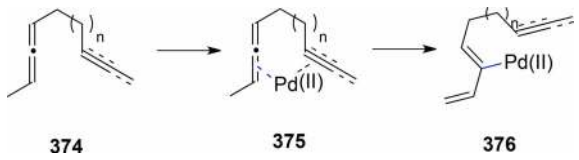
Scheme 109. Allene insertion/Tsuji–Trost amination cascade.

In 2015, Fan and co-workers reported the synthesis of 2-(3-furyl)acetates **372** from allenols **371**, alcohols and aryl iodides (Scheme 110).[159] The reaction is initiated by palladium-catalyzed carbonylative arylation of the allene, followed by the carbonylative esterification of allyl-Pd(II) intermediate **373**. The final product is obtained by cycloaromatization of the hydroxy ketone to give the furan ring. The reaction was shown to tolerate various aryl iodides, alcohols and aryl R^1 substituents, providing the product in typically fair yield.



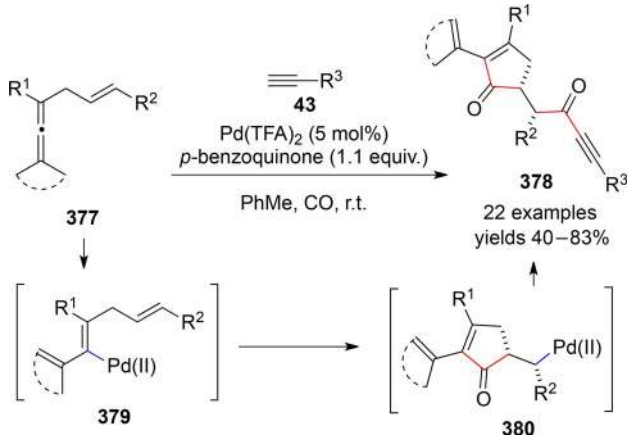
Scheme 110. Cascade involving carbonylative allene arylation and subsequent carbonylative esterification.

Allenynes, enallenes and bisallenes **374** can all undergo coordination of Pd(II) to afford complex **375**, in turn generating alkenyl-Pd(II) species **376** (Scheme 111). This specific type of reactivity has been extensively exploited by the group of Bäckvall.



Scheme 111. Addition of allenes to Pd(II).

In 2015, Bäckvall and co-workers reported a palladium-catalyzed Pd(II) addition/carbonylation/carbocyclization/carbonylative Sonogashira sequence of enallenes **377** (Scheme 112).[160] The mechanism is initiated by the above-mentioned key reaction step, generating the alkenyl-Pd(II) species **379**.



Scheme 112. Allene insertion/carbonylation/carbopalladation/carbonylative copper-free Sonogashira cascade.

Subsequently, CO insertion and 5-*exo-trig* carbopalladation close the cyclopentenone ring, and alkyl-Pd(II) intermediate **380** undergoes a carbonylative copper-free Sonogahsira reaction to give the final product **378**. The generally good yields of the reaction are only slightly influenced by varying alkyl and aryl R^3 substituents. The use of internal alkenes ($R^2 \neq H$) provided single diastereomers of the corresponding products, albeit in significantly lower yields.

Bäckvall extended the work on enallenes to allenes **381**, and introduced a second carbocyclization

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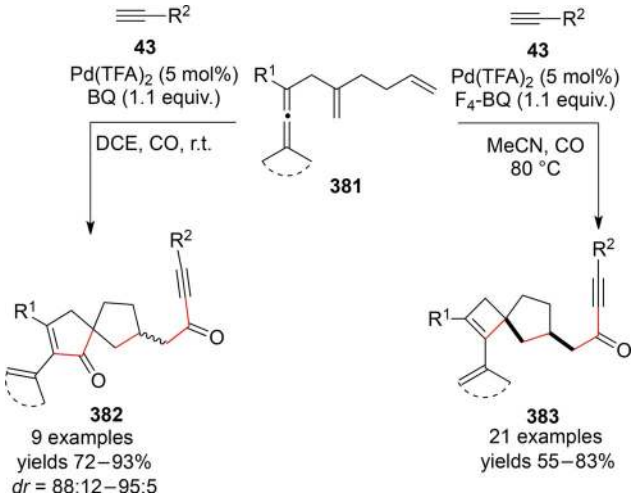
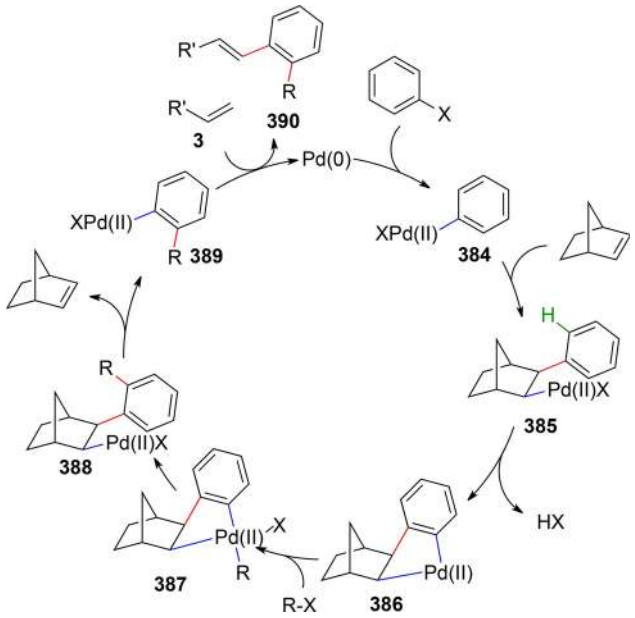


Scheme 113. Extension of Pd(II) allene addition/carbopalladation/carbonylation/copper-free Sonogashira cascade. BQ = *p*-benzoquinone; F_4-BQ = 2,3,5,6-tetrafluoro-*p*-benzoquinone.



Scheme 114. Mechanism of the Catellani reaction.

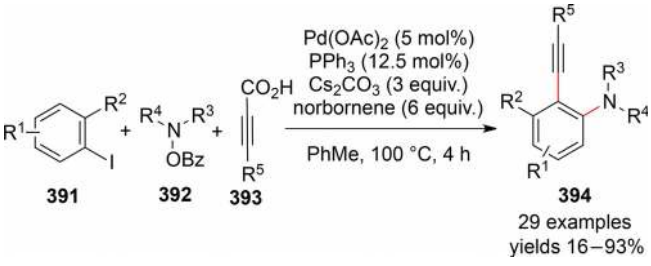
(Scheme 113).[161] After formation of the key alkenyl-Pd(II) intermediate, carbonylation and 5-*exo-trig* carbopalladation form the cyclopentenone as depicted in Scheme 112. However, direct 4-*exo-trig* cyclization can also occur, depending on the solvent. Both alkyl-Pd(II) intermediates then undergo a 5-*exo-trig* cyclization followed by a carbonylative copper-free Sonogashira reaction to give **382** and **383**, respectively. The formation of the spirocyclobutenes **383** is fully diastereoselective and provides the products in good yields. The diastereoselectivity of the reaction affording spirocyclopentenones **382** is excellent and tolerates various aryl R^2 substituents with good to excellent yields. Bäckvall and co-workers have reported many similar reactions and achieved tremendous progress in the field of allene additions to Pd(II).[162–166]

4.4 Norbornene and the Catellani Reaction

Throughout this review, the importance of C–H activations in palladium-catalyzed cascade reactions has been highlighted. Usually, C–H activation is initiated by the close proximity of a Pd(II) complex to a C–H bond. In 1997, Catellani developed the use of strained olefins to catalyze the *ortho* C–H activation of aryl halides (Scheme 114).[167] The mechanism of the norbornene-catalyzed C(sp^2)–H activation is initiated by formation of aryl-Pd(II) complex **384** from the corresponding aryl (pseudo)halide and Pd(0). A carbopalladation then couples the norbornene to the aryl, forming norbornyl-Pd(II) complex **385**, which cannot undergo *syn* β-hydride elimination. The close proximity of Pd(II) to the arene *ortho* C–H bond(s) facilitates C(sp^2)–H activation with loss of HX, generating palladacycle **386**. Coupling with an organohalide (or other coupling partner) *via* Pd(IV) intermediate **387** yields the norbornyl-Pd(II) complex **388**. This complex undergoes a retro-carbopalladation to generate aryl-Pd(II) species **389**. Coupling of the generated aryl-Pd(II) **389** with a coupling partner, e.g., alkene **3**, yields product **390**.

An important feature of the reaction is the possibility of double *ortho* C(sp^2)–H activation, which can be countered by the use of mono *ortho*-substituted aryl halides. The Catellani reaction itself is already a palladium-catalyzed cascade reaction and this section will present recent uses of the reaction.

In 2015, Sun and Gu reported the synthesis of 2-alkenylanilines **394** from aryl iodides **391**, *O*-benzoylhydroxylamines **392** and alkynoic acids **393** (Scheme 115).[168] Norbornene facilitates C(sp^2)–H activation of the *ortho* position, which undergoes a Buchwald–Hartwig-type amination. After the loss of norbornene *via* retro-carbopalladation, the aryl-Pd(II) is coupled to the alkynoic acid to afford the aromatic ring *via* a decarboxylative process.



Scheme 115. Catellani reaction with decarboxylative alkynylation.

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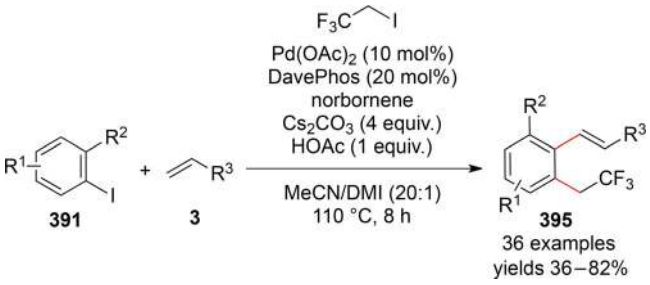
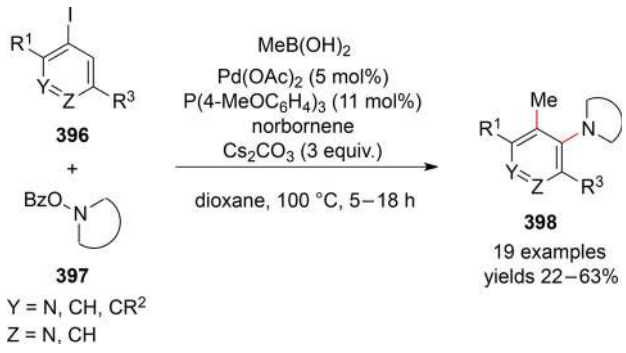
The reaction tolerates various substituents on the aromatic ring, with electron-donating groups slightly decreasing the generally good yields. Furthermore, different secondary amine donors are compatible with the reaction, while the use of alkynes with electron-deficient aryl groups decreased the yield significantly. A later study by the same authors showed the possibility of replacing the amine by benzoyl chlorides or anhydrides, producing diaryl ketones.[169]

In a similar approach, Liu et al. reported the synthesis of *ortho*-trifluoroethylstyrenes **395** from iodoarenes **391**, alkenes **3** and trifluoroethane (Scheme 116).[170] The authors propose norbornene-assisted *ortho* trifluoroethylation, retro-carbopalladation and intermolecular Heck reaction as the mechanism for the reaction. A major side reaction is the cross-coupling of the norbornene palladacycle. However, the reaction provides the desired products in fair to good yields, predominately as the *E* isomers.



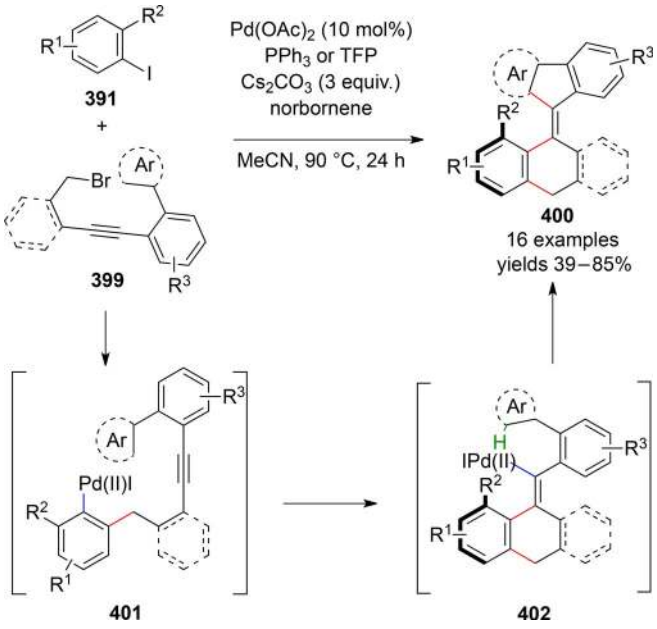
Scheme 116. Catellani reaction with trifluoroethylation. DMI = 1,3-dimethyl-2-imidazolidinone.

Another example of the Catellani reaction was reported by Wilson who described the synthesis of *ortho*-methyl(hetero)arylamines **398** (Scheme 117).[171] The *ortho* position of **396** is coupled with *O*-benzoyl-hydroxylamines **397** *via* C(sp^2)–H activation with norbornene with a subsequent *ipso* Suzuki methylation. The reaction provides the products in fair yields, on par with another palladium-catalyzed cascade two-step synthesis of the same products.[172]



Scheme 117. Catellani reaction involving norbornene-assisted Buchwald–Hartwig-type amination and Suzuki coupling.

In 2012, Lautens and co-workers reported the synthesis of tetrasubstituted helical alkenes **400** from iodobenzenes **391** and tethered alkynes **399** (Scheme 118).[173] *ortho* C(sp^2)–H activation and subsequent coupling of the alkyl bromide *via* a Pd(IV) intermediate produce aryl-Pd(II) species **401**. Loss of norbornene and a 6-*exo*-*dig* carbopalladation then generate alkenyl-Pd(II) complex **402**. The final product is formed by a second C(sp^2)–H activation and reductive elimination. The reaction is compatible with various aromatic systems and Lautens even showed an asymmetric version of the reaction.



Scheme 118. Cascade reaction involving Catellani-type benzylation/carbopalladation/C(sp^2)–H activation.

Liang et al. reported the synthesis of spiroindolenines **404** from 3-(3-bromopropyl)indoles **403** and iodoarenes **391** (Scheme 119).[174] Coupling between the *ortho* position of the iodoarene and 3-(3-bromopropyl)-indoles occurs *via* the standard Catellani mechanism, producing aryl-Pd(II) intermediate **405**, after which nucleophilic attack of the 3-position of the indole produces a seven-membered palladacycle. Reductive elimination then provides the products in modest to reasonable yields.

In 2011, Lautens and co-workers reported the synthesis of benzo[*c*]phenanthridines **408** from aryl triflates **406** and benzaldimines **407** (Scheme 120).[175] The reaction is initiated by the norbornene-mediated *ortho* activation of the aryl triflate. Cross-coupling between the two aryl moieties and retro-carbopalladation produce aryl-Pd(II) species **409**, which finally un-

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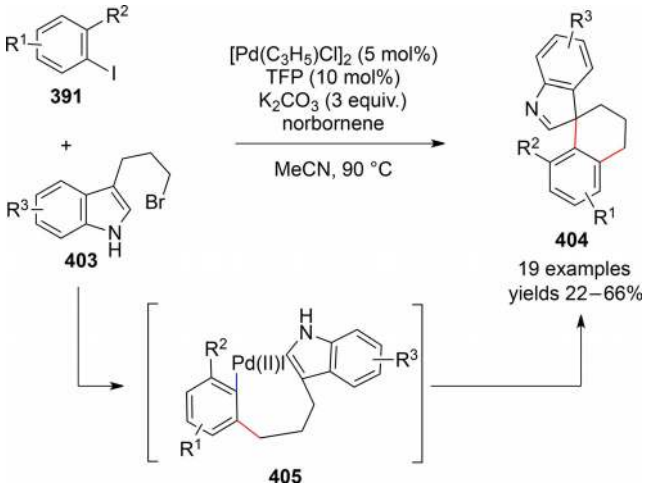
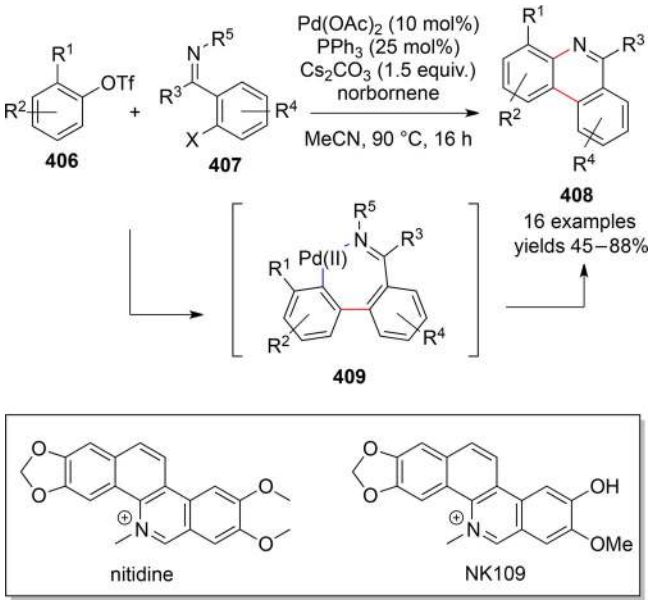


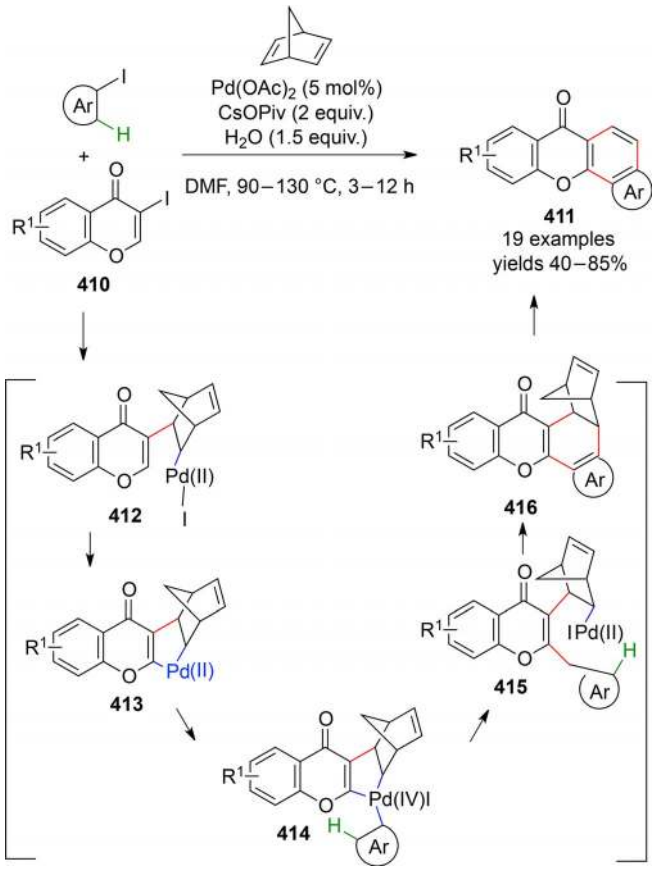
Scheme 119. Synthesis of spiroindolenines *via* a Catellani cascade reaction.



Scheme 120. Cascade reaction including a norbornene-mediated *ortho* C(sp^2)–H activation and Buchwald–Hartwig amination.

dergoes a Buchwald–Hartwig amination to afford the products **409** in generally good yields. To show the utility of this strategy in total synthesis, the authors included formal syntheses of nitidine and NK109 in the report, showing the same good yields.

The use of norbornadiene was reported by Hu et al. for the synthesis of annulated xanthones **411** (Scheme 121).[176] The reaction is proposed to proceed *via* the Catellani mechanism, including the insertion of norbornadiene to form norbornyl-Pd(II) complex **412**. C(sp^2)–H activation subsequently forms palladacycle **413**, and coupling of the iodoarene generates



Scheme 121. Introduction of an ethene fragment *via* norbornadiene addition and retro-Diels–Alder reaction.

415 *via* Pd(IV) intermediate **414**. Additionally, a second C(sp^2)–H activation occurs, generating ring system **416**. A retro-Diels–Alder reaction with loss of cyclopentadiene finally provides the product.

4.5 C–H Activation

C–H activation is a versatile and useful process in palladium-catalyzed reactions and has proven its value in cascade reactions initiated by both R–X-activation and π-systemactivation . Even the Catellani reaction is based on this process. This section will continue the C–H activation cascade reactions and will primarily include cascade reactions initiated by C–H activation.

In 2012, Ohno et al. reported the synthesis of polyheterocycles **418** *via* a double C–H activation cascade involving intermediates **441** and **442** (Scheme 122).[177] The reaction was shown to be compatible with aryls bearing both electron-donating and electron-withdrawing substituents at the *para* position and showed a correlation between regioselectivity and electron-withdrawing properties of the *meta* substituents. However, the use of nitro groups proved incompatible. Even (hetero)aryl systems were shown to be compati-

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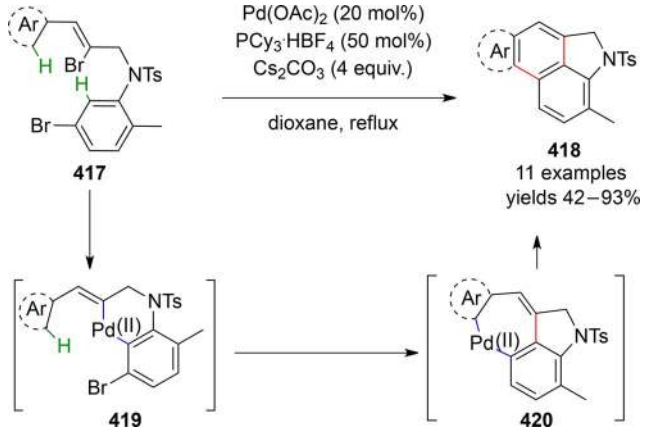
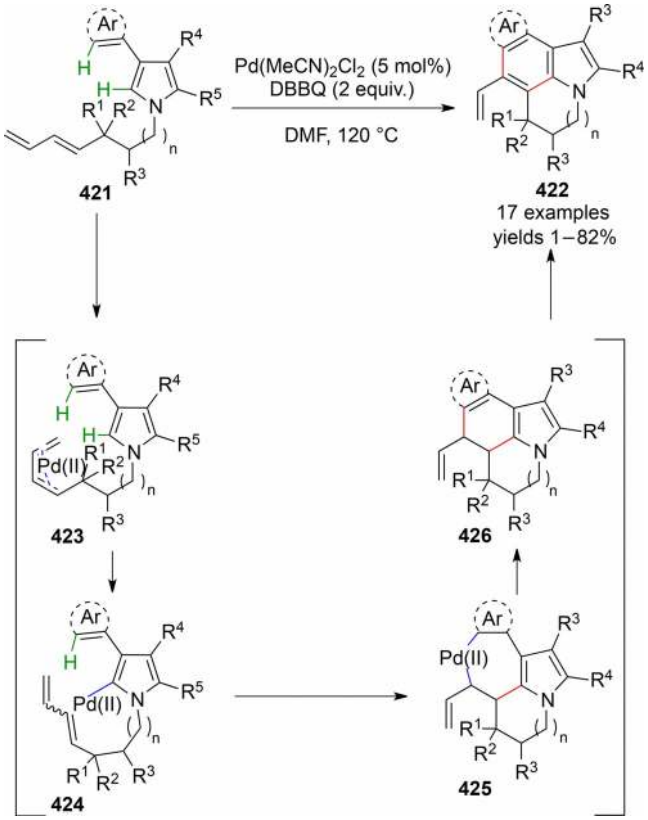


Scheme 122. Double C(sp^2)–H activation cascade.

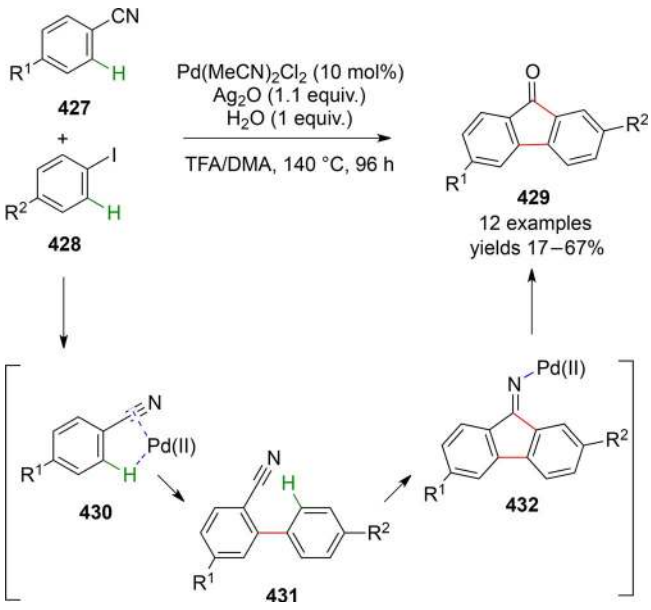
ble and the reaction provides the products in fair to excellent yields.

Cooper and Booker-Milburn reported the synthesis of polyheterocycles **422** from tethered 1,3-dienylpyrroles **421** (Scheme 123).[178] The authors propose initiation of the reaction by coordination of the diene to Pd(II), forming the diene-Pd(II) complex **423**. This complex mediates C(sp^2)–H activation of the pyrrole, yielding intermediate **424**. Intramolecular carbopalladation produces allyl-Pd(II) species **425**. This intermediate is proposed to undergo a Friedel–Crafts-type attack by the Ar system to give polycycle **426**. However, a pathway involving C(sp^2)–H activation cannot be excluded. Oxidation to the aromatic system leads to the final product. The reaction is compatible with electron-rich Ar systems and provides the products with modest to good yields.



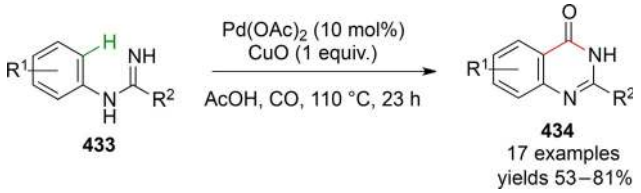
Scheme 123. Cascade reaction of two C(sp^2)–H activations. DBBQ = 2,4-di-*tert*-butyl-*o*-benzoquinone.

The synthesis of fluorenones **429** from benzonitriles **427** and aryl iodides **428** was reported by Hsieh et al. in 2013 (Scheme 124).[179] The authors propose C(sp^2)–H activation at the *ortho* position of the benzonitrile *via* Pd(II) complex **430**, after which a cross-coupling to diaryl **431** with the iodoarene occurs *via* a Pd(IV) intermediate. A second C(sp^2)–H activation and silver-assisted nitrile coupling produces the fluoreneimine-Pd(II) species **431**, which is hydrolyzed during work-up to give the fluorenone. The reaction tolerates small R^1 and R^2 substituents, but yields decreased with increasing substituent size.



Scheme 124. Double nitrile-assisted C(sp^2)–H activation.

Zhu and co-workers reported the synthesis of quinazolin-4(3*H*)-ones **434** *via* intermolecular C(sp^2)–H activation and carboxamidation of *N*-arylamidines **433** (Scheme 125).[180] The authors propose initiation



Scheme 125. The carboxamidation of *N*-arylamidines *via* C(sp^2)–H activation.

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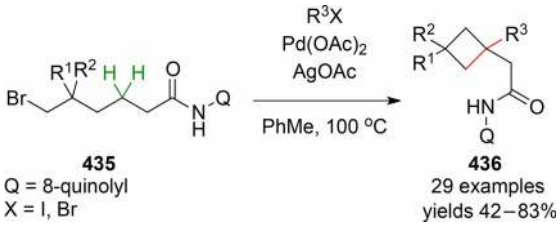
by palladium-catalyzed N–H functionalization of the amidine followed by the C(sp^2)–H activation of the arene and carboxamidation. The reaction is compatible with different aryl and alkyl R^2 substituents and electron-donating R^1 substituents.

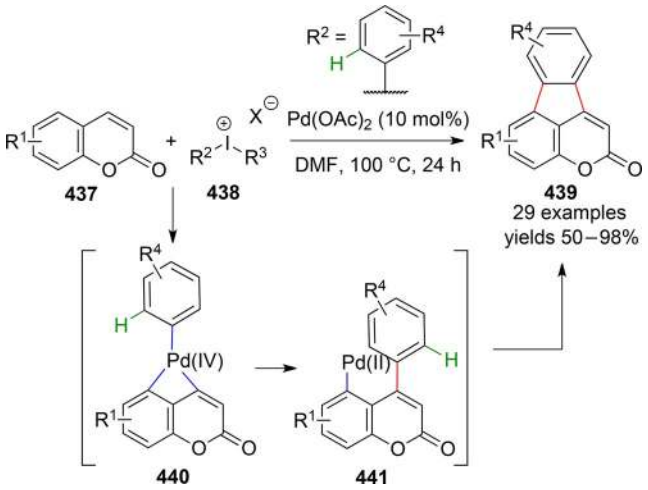
Recently, Rao et al. reported the synthesis of cyclobutanes **435** *via* a directing group-assisted C(sp^3)–H activation (Scheme 126).[181] The authors propose β-C(sp^3)–H activation and coupling of the alkyl bromide



Scheme 126. Directing group-mediated double C(sp^3)–H activation.

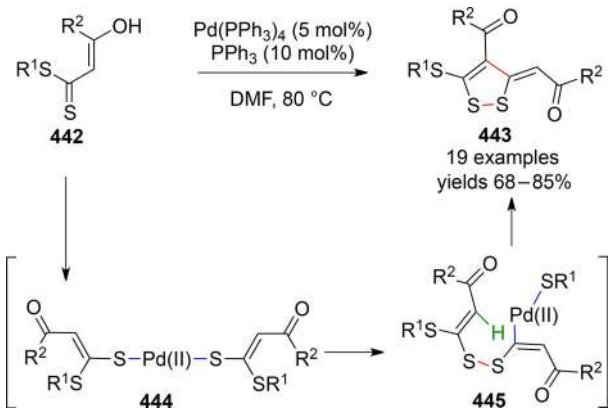
via a Pd(IV) complex, generating the cyclobutane ring. A second β C(sp^3)–H couples the haloaryl to the cyclobutane ring, again *via* a Pd(IV) intermediate. The authors showed the necessity of first forming the cyclobutane ring for the second β C(sp^3)–H activation. The reaction required modification of the reaction conditions between different substrates, with many substrates requiring the addition of additional Pd(II) and additives during the reaction. Nevertheless, a broad range of cross-coupling partners (R^3X) was shown to be compatible with the reaction.

In 2015, Wang and co-workers reported the synthesis of 4,5-benzocoumarins **439** from diaryliodonium salts **438** and coumarins **437** (Scheme 127).[182] The authors propose initiation by activation of the diaryliodonium with Pd(II). Double C(sp^2)–H activation produces organopalladium(IV) complex **440**, which undergoes reductive elimination to give aryl-Pd(II) complex **441**. Another C(sp^2)–H activation and cross-coupling yields the product. A similar reaction was used for the synthesis of dibenzo[*a*,*c*]carbazoles.[183]



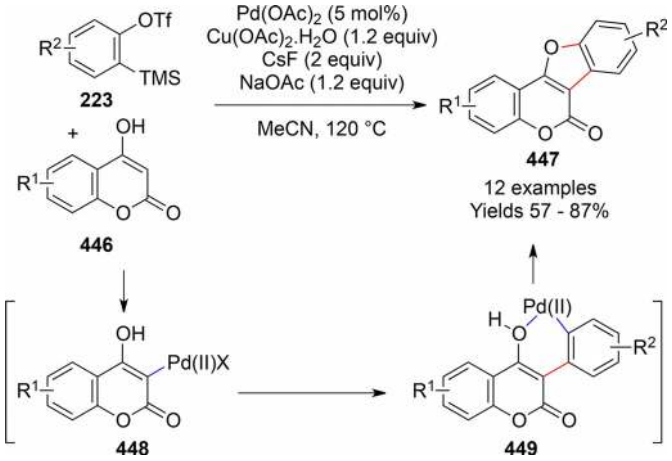
Scheme 127. Triple C–H activation reaction.

Singh et al. reported the synthesis of 3,4,5-trisubstituted 1,2-dithioles **443** from α-enolic dithioesters **442** (Scheme 128).[184] The authors propose initiation by cross-coupling between the thioenolates *via* Pd(II) complex **444**, forming a new S–S bond. The oxidative insertion of Pd(0) in the thioether bond forms the alkenyl-Pd(II) complex **445** and C(sp^2)–H activation forms the final product. The reaction tolerated various (hetero)aryl R^2 substituents with minimal decrease of the typically very good yields.



Scheme 128. Palladium-catalyzed cascade reaction involving S–S and C–C bond formation.

In 2016, Gogoi et al. reported the synthesis of coumestans **447** from 4-hydroxycoumarins **446** and benzyne precursors **223** (Scheme 129).[185] The authors propose C(sp^2)–H activation assisted by the coordina-



Scheme 129. C(sp^2)–H activation/benzyne insertion/C–O coupling cascade.

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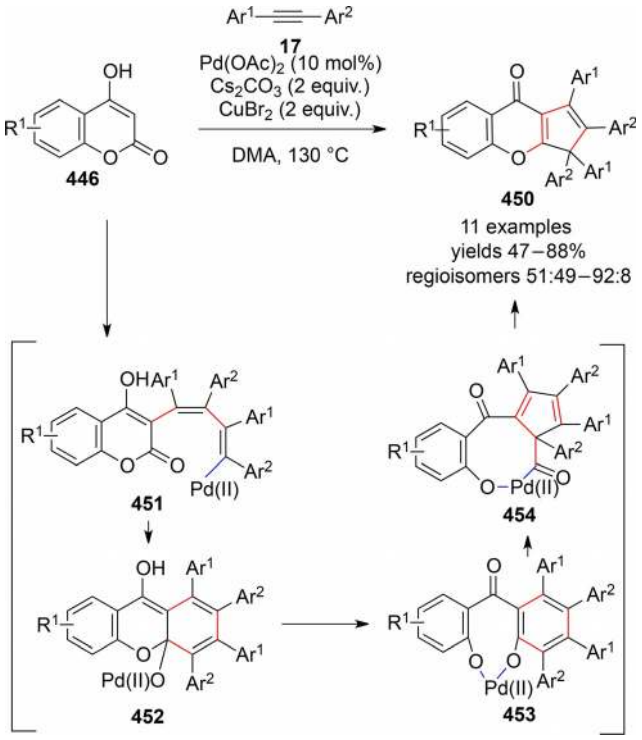
tion of Pd(II) to the alcohol for the formation of coumaroyl-Pd(II) complex **448**. Insertion of the benzyne forms intermediate **449** and a Buchwald–Hartwig-type etherification forms the product. Broad variation of the R^1 substitution is tolerated, providing the coumestans in good yields. No regioselectivity was obtained when the benzyne was unsymmetrically substituted.

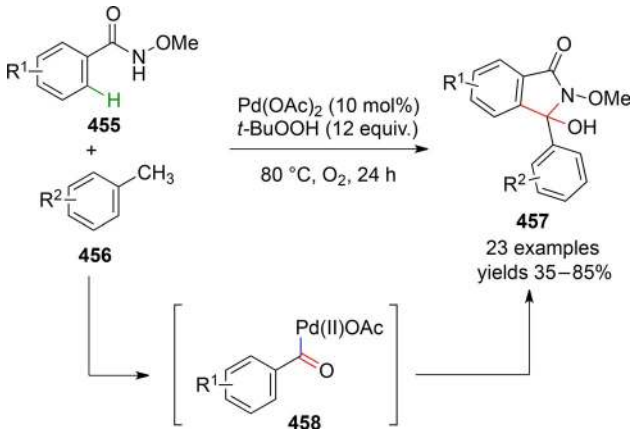
A synthesis of cyclopentadiene-fused chromones **450** by a double coupling of alkynes **17** and coumarins **446** was reported by Wang et al. in 2011 (Scheme 130).[186] The authors propose a complex mechanism initiated by the same C(sp^2)–H activation



Scheme 130. C(sp^2)–H activation/double carbopalladation/carbonyl addition/ring contraction/decarbonylation cascade.

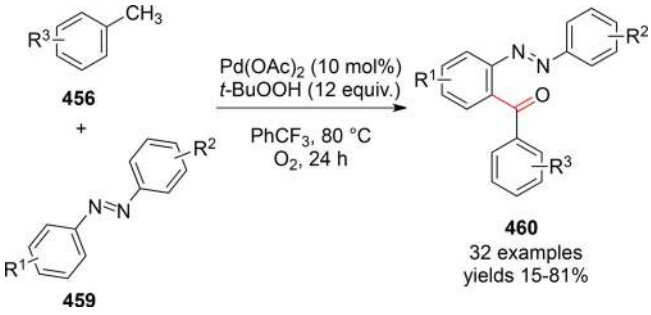
as mentioned above (Scheme 129), followed by an alkyne carbopalladation to give intermediate **451**. Nucleophillic addition of the alkenyl-Pd(II) complex to the lactone carbonyl closes the six-membered ring. The resulting alkoxy-Pd(II) species **452** then rearranges to intermediate **453**. A ring contraction yields intermediate **454**, which undergoes decarbonylation (loss of CO) followed by C–O coupling and a [1,2]-aryl shift to yield the product **450**.

A remarkable type of reactivity is observed when toluene derivatives are subjected to a Pd(II) catalyst and oxidants at high temperature. These conditions generate aroyl-Pd(II) species **458**, similar to the product of CO insertion in an aryl-Pd(II) complex. Zhang et al. reported the synthesis of 3-hydroxyisoindolin-1-ones **457** from toluene derivatives **456** and *N*-methoxybenzamides **455** using the aroyl-Pd(II) intermediate **458** (Scheme 131).[187] C(sp^2)–H activation couples the aroyl moiety and the benzamide and addition of the amide to the carbonyl closes the five-membered ring.



Scheme 131. Cascade reaction involving toluene oxidation/C(sp^2)–H activation.

Lu et al. reported a similar cascade involving benzylic oxidation and C(sp^2)–H activation (Scheme 132).[188] In their study, azobenzenes **459**



Scheme 132. Benzylic oxidation/C(sp^2)–H activation cascade.

were acylated at the *ortho* position with generally good yields. However, the reaction showed lower yields for electron-rich azobenzenes. Different R^3 substitution patterns did not decrease the yield significantly. In a similar approach, Kwong and co-workers reported the synthesis of *N*-alkyl-2-aminobenzophenones[189] and *ortho*-acylacetanilides.[190]

A palladium-catalyzed cascade reaction was reported during the total syntheses of dictyodendrins B and E by Jia et al. (Scheme 133).[191] Dictyodendrins B and E have interesting telomerase inhibiting activities, which are of potential interest for cancer treatment. The authors use the cascade reaction to construct the indolo[3,2-*d*]indole core of these alkaloids. The mechanism involves oxidative insertion of Pd(0) into the

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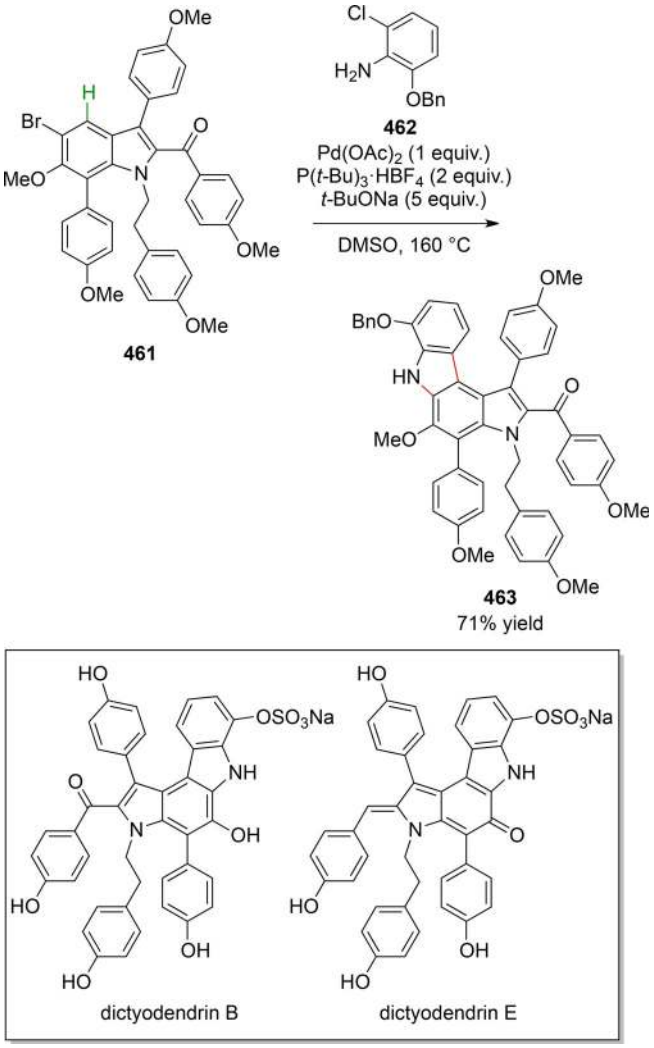
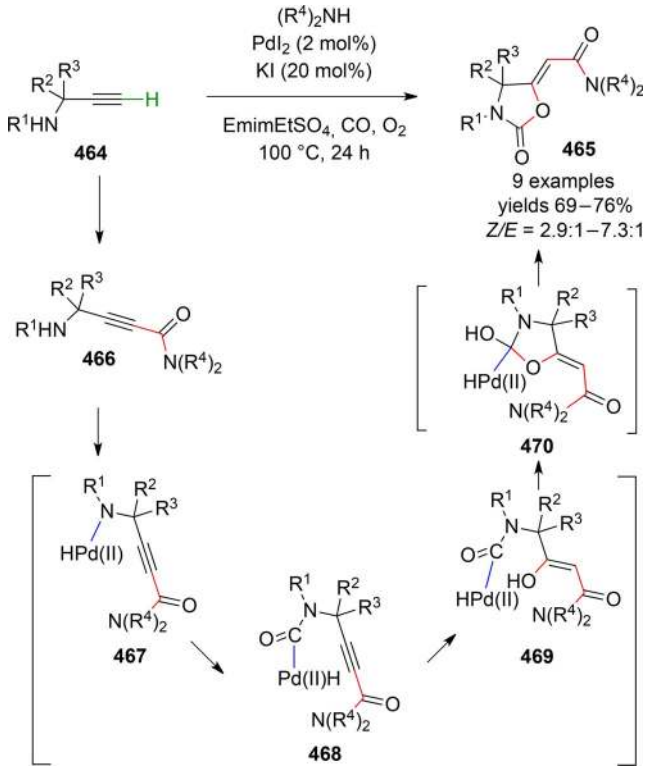


Scheme 133. The use of a palladium-catalyzed cascade reaction for the synthesis of dictyodendrins B and E.



Scheme 134. Cascade reaction with double catalytic cycle including double CO insertion.

aryl-Br bond in **461** and subsequent Buchwald–Hartwig amination with **462**. A second oxidative insertion in the aryl-Cl bond facilitates C(sp^2)–H activation, after which cross-coupling generates product **463**.

4.6 Miscellaneous

The majority of palladium-catalyzed cascade reactions could be classified in one of the previous sections. However, some reactions are stand-alone cases, where the initiation is not straightforward or involves palladium-catalyzed reactions which are not commonly described. Such cases will be discussed in this section.

In 2016, Gabriele and co-workers reported an aminocarbonylation/water-promoted oxidative cyclocarbonylation of propargylic amines **464** to oxazolidinones **465** (Scheme 134).[192] The reaction is performed with PdI_2 as the catalyst and KI as an additive. The authors propose a mechanism comprising two cycles, the first starting with C(sp)–H activation. Subsequently, CO insertion occurs followed by amidation of the acyl-Pd(II) complex. The resulting propiolamide derivative **466** undergoes N–H activation to give intermediate **467** and subsequent CO insertion to afford amidoyl-Pd(II) **468**. The authors then propose the formation of orthoamide **470** by the conjugate addition of water and attack of the resulting alcohol **469** on the carbonyl-Pd(II) complex, with expulsion of Pd(II) generating the desired oxazolidinone. However, a Buchwald–Hartwig-type lactonization is also a possibility. Different R^1 substituents were tolerated, as were various secondary amines as coupling partners. The reaction provided the products in good yields and with preference for the Z isomer.

Wang et al. reported an unusual synthesis of 1-aminonaphthalenes **472** (Scheme 135) and indenones **476** (Scheme 136) from acetophenones **471**.[193] The synthesis of 1-aminonaphthalenes **471** is initiated by the formation of enamine **473** and a subsequent Sonogashira coupling to give intermediate **474**. Pd(II)-catalyzed π-system activation triggers nucleophilic attack of the enamine to give alkenyl-Pd(II) complex **475**. The iminium ion then undergoes proton elimination, while reductive elimination of Pd forms the product. A minor side reaction under these conditions (further developed by the authors to a synthetic method in its

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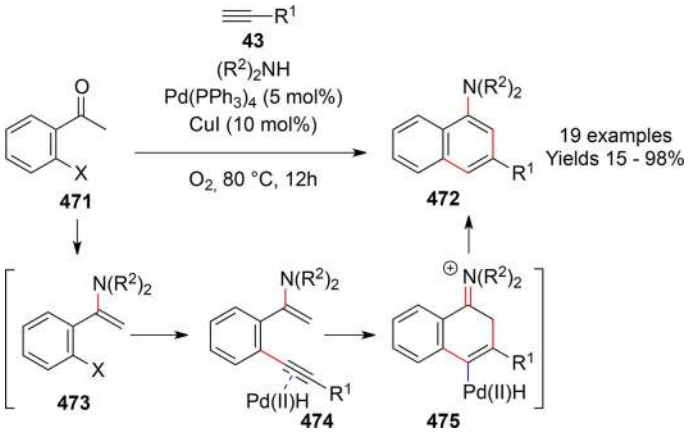
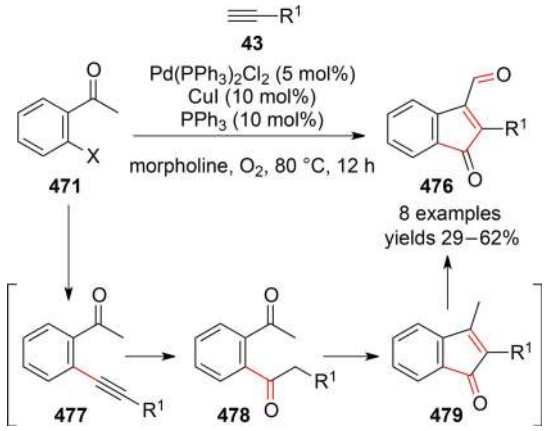


Scheme 135. Enamine formation/Sonogashira cascade.

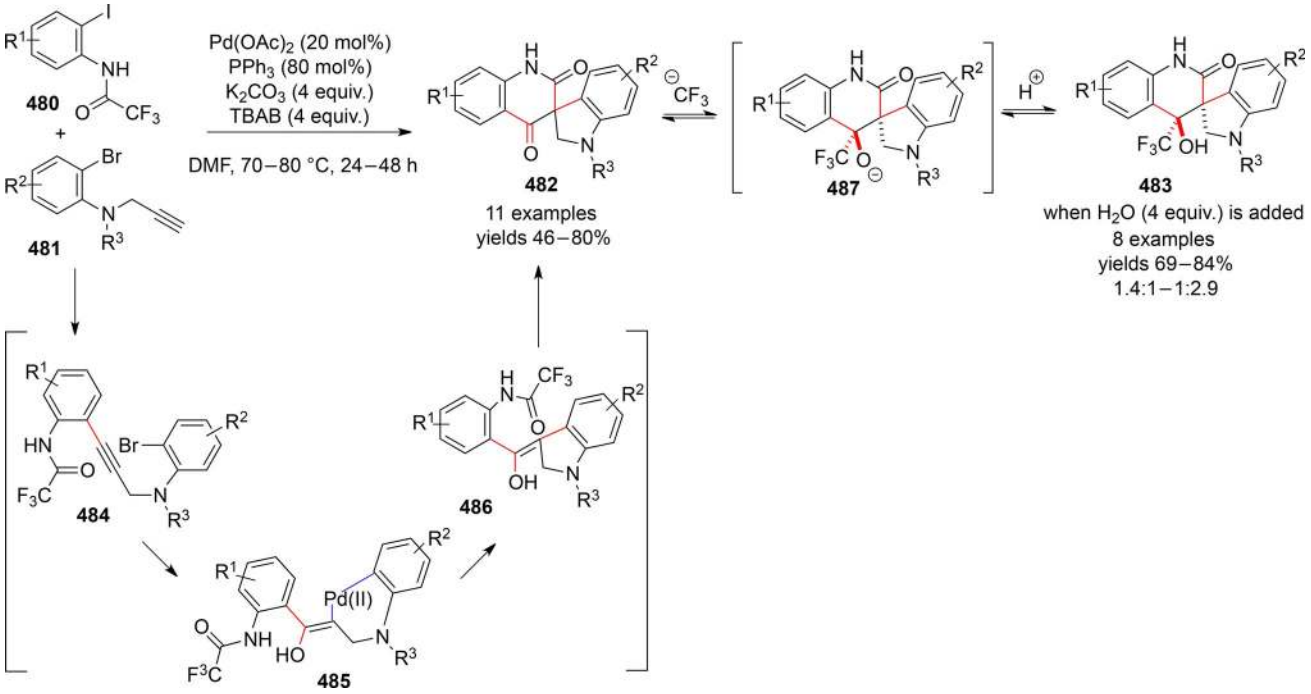


Scheme 136. Sonogashira/hydration/aldol condensation/allylic oxidation cascade.

own right) was the direct Sonogashira reaction of acetophenone **471** to give **477**, which can undergo palladium-catalyzed hydration to give diketone **478**. Aldol condensation then produces 3-methylindenone **479**, which is transformed by Pd-catalyzed allylic oxidation to 1-oxo-1*H*-indene-3-carbaldehyde **476**.

A palladium-catalyzed synthesis of spiro[indoline-3,3′-quinoline] derivatives **482** and **483** was reported by Wang et al. (Scheme 137).[194] The authors propose initiation by copper-free Sonogashira coupling between aryl iodide **480** and *N*-propargylaniline **481** affording **484**. Oxidative insertion into the aryl bromide bond and coordination of the Pd(II) complex to the alkyne activates the π-system toward attack of water to form palladacyclic intermediate **485**. Reductive elimination then forms the indoline system in **486**, after which the enolate can attack the trifluoroacetamide, forming the six-membered ring with loss of CF_3^- resulting in **482**. Additionally, the CF_3^- can attack on the ketone to give **483** *via* alkoxide **487**, with the presence or absence of water governing the product selectivity. Without the addition of water, the generated alkoxide **487** is instable and rearranges back to product **482**. However, in the presence of water (4 equiv.), alkoxide **487** is protonated and product **483** predominates.

In 2014, Qin et al. described an intermolecular cyclopropanation *via* an allylic palladium carbene (Scheme 138).[195] The cyclopropane structure **489** is a



Scheme 137. Copper-free Sonogashira/oxypalladation/enol addition cascade.

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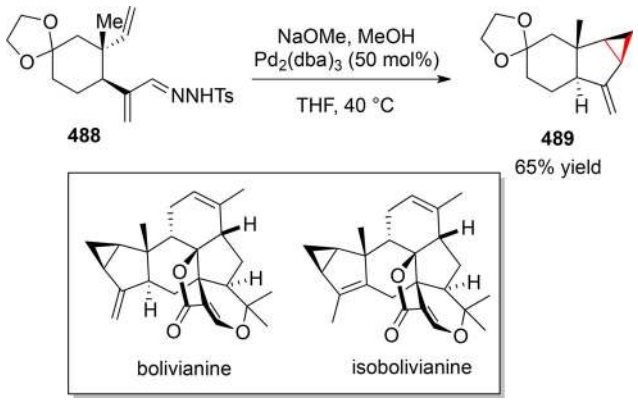
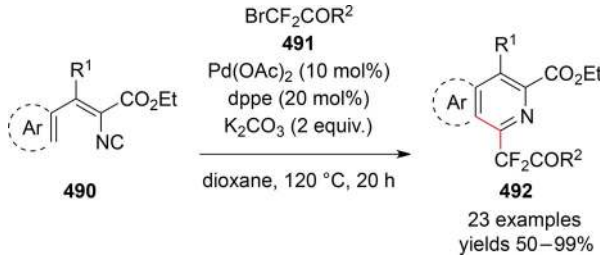
key intermediate in the total synthesis of bolivianine and isobolivianine. These sesterterpenoids with nine stereogenic centers, including three quaternary chiral centers were isolated in 2007, but have not shown any significant biological activity.



Scheme 138. The synthesis of the key intermediate towards bolivianine with palladium-catalyzed carbene insertion.

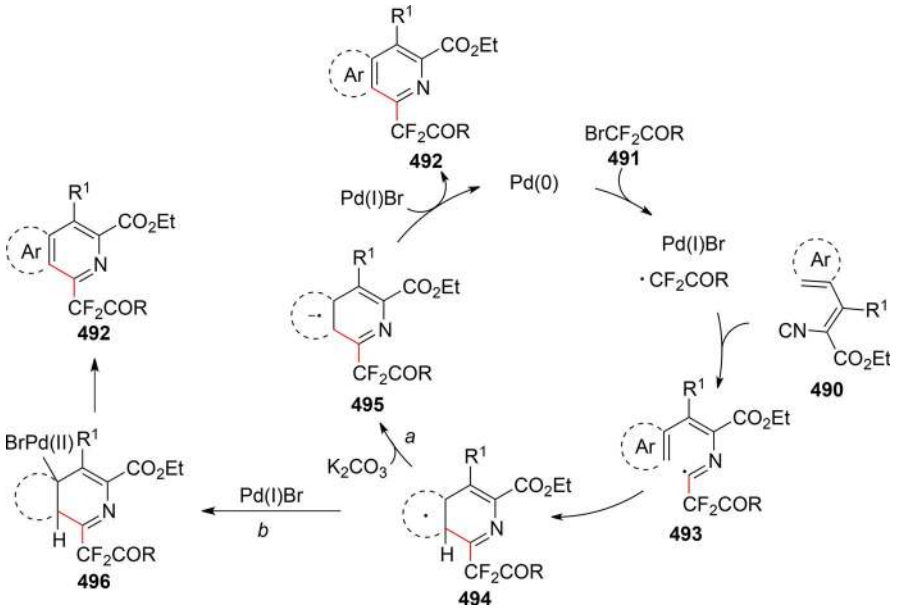
A radical cascade involving Pd(I) species was reported by Cai et al. for the synthesis of 1-difluoroalkylated isoquinolines **492** (Scheme 139).[196] The reaction provides the products in excellent yields for electron-rich aryl R^1 substituents and good yields for electron-poor aryl R^1 substituents. However, the use of alkyl R^1 substituents significantly lowers the yields. Furthermore, the difluoroalkyl chain could contain either an ester or an amide function without reducing the yields.



Scheme 139. Synthesis of 1-difluoroalkylated isoquinolines.

The authors propose a palladium-catalyzed radical initiation by bromine atom abstraction from **491** followed by the coupling to the isocyanide to give imidoyl radical intermediate **493** (Scheme 140). A 6-*endo-trig* radical cyclization occurs to give arene radical **494**, from which two pathways to the product are possible. Deprotonation of the ring system of radical **494** generates the radical anion **495** which is quenched by BrPd(I) to product **492** (pathway *a*). Alternatively, addition of BrPd(I) to **494** generates Pd(II) species **496**, which then provides the product *via* β-hydride elimination (pathway *b*). A similar radical cascade was employed by Liang et al. for the synthesis of difluoromethylated pyrrolidines.[197]

In 2014, Lei et al. reported the synthesis of 2,3,4-trisubstituted quinolines **498** *via* N–H activation followed by an aminopalladation, carbonyl addition and elimination of water leading to aromatization (Scheme 141).[198] This reaction resembles the Friedländer quinoline synthesis.[199] The reaction is compatible with aromatic, conjugated and aliphatic R^2 substituents. However, the use of highly electron-with-



Scheme 140. Mechanism of palladium-catalyzed radical cascade reaction.

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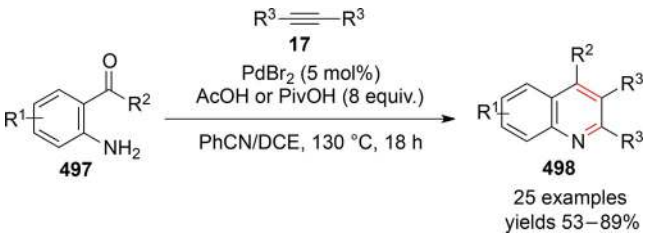


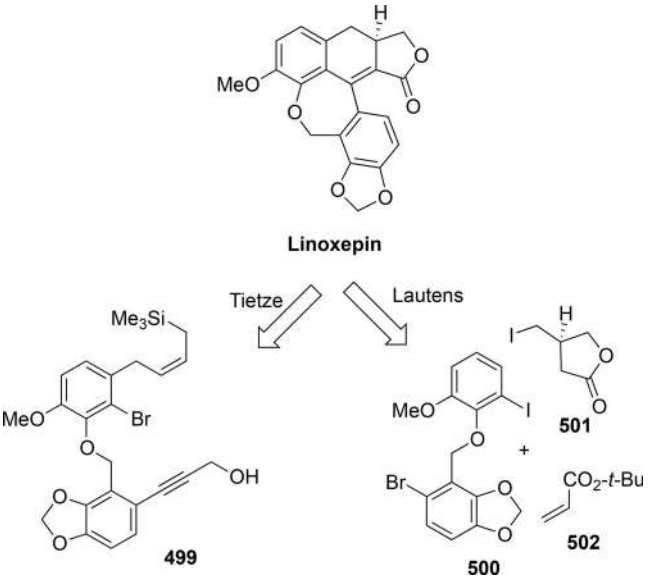
Scheme 141. Aminopalladation/carbonyl addition cascade.

drawing substituents on the aromatic system leads to significantly lower yields.

5 Palladium-Catalyzed Cascade Reactions in Total Synthesis: Linoxepin

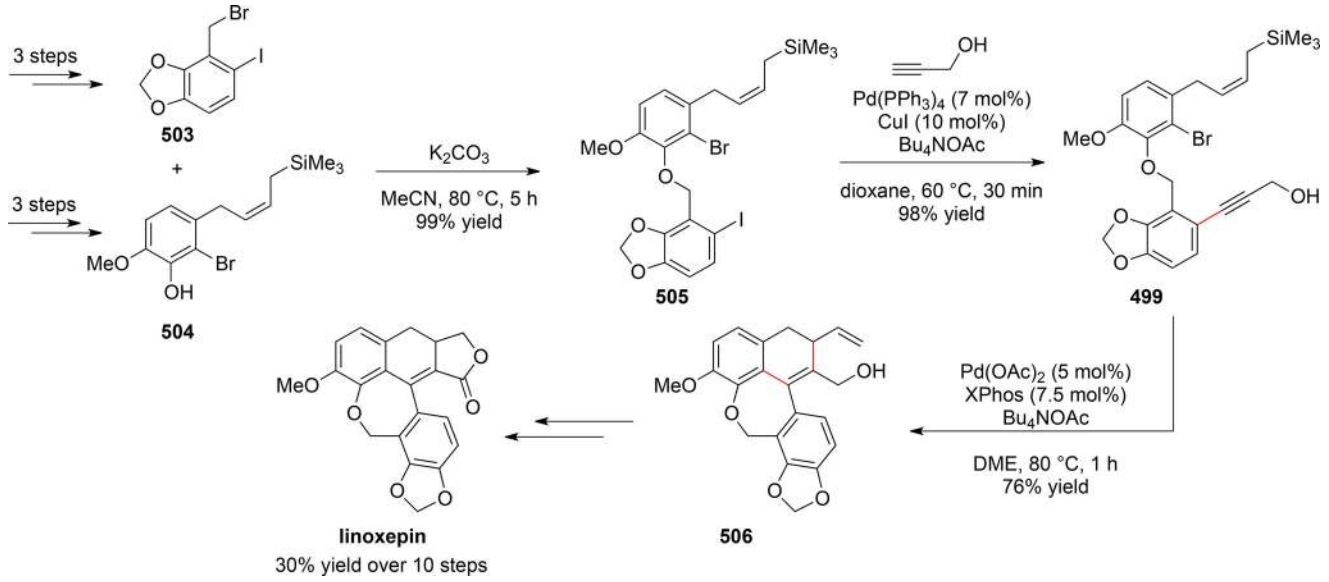
Most of the examples presented in this review relate to method development for the efficient generation of new molecules, often without a specific target in mind. However, palladium-catalyzed cascade reactions offer unique reactivity and astounding synthetic efficiency, making them of high potential utility in natural product total synthesis. As a showcase, we will present two different approaches to the total synthesis of the lignane natural product linoxepin reported by Tietze and Lautens in 2013 (Scheme 142).[47,200] Although both groups used a palladium-catalyzed cascade reaction as the key step, the approaches are conceptually completely distinct, both providing valuable insight in the field.

Tietze's method starts with the synthesis of bis(haloarene) **505** from benzylic bromide **503** and phenol



Scheme 142. Cascade approaches by Lautens and Tietze for the synthesis of linoxepin.

504, which were both produced in three steps (Scheme 143).[47] The original strategy involved a Sonogashira/carbopalladation/Heck cascade reaction. However, this approach resulted in the formation of a stable aromatic side product. Therefore, the Sonogashira reaction was performed first, generating propargylic alcohol **499**. A subsequent carbopalladation/Heck cascade then produces the key intermediate **506**. Four steps were required to transform alcohol **506** to (±)-linoxepin. To prepare the optically pure natural product, racemic **506** was resolved by chiral chromatography. This method gave the (+)- and (−)-



Scheme 143. Tietze's strategy for the synthesis of linoxepin.

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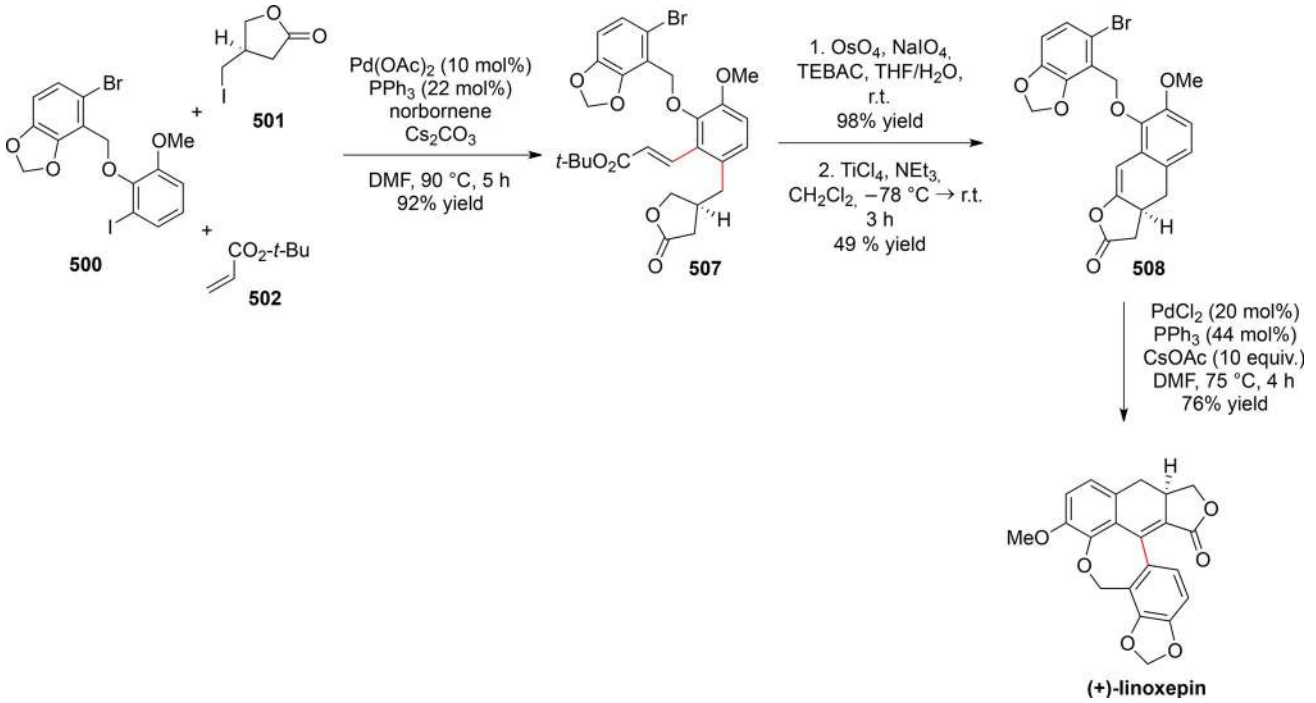

Scheme 144. Lautens' strategy for the synthesis of (+)-linoxepin.

enantiomers of **506** with 99% *ee* which was retained in subsequent reactions. The entire synthesis comprised ten steps and generated the natural product in 11% overall yield.

Lautens used the Catellani reaction for his synthesis of (+)-linoxepin (Scheme 144).[200] Most of the steps in the strategy are in fact required for the construction of aryl iodide **500**. The key Catellani reaction between aryl iodide **500**, alkyl iodide **501** and *tert*-butyl acrylate **502** produces the desired product **507** in excellent yield. Subsequently, the olefin was oxidatively cleaved to the aldehyde, which was then condensed with the lactone moiety to give dihydronaphthofuranone **508**. A final Heck cyclization was envisioned to complete the synthesis of (+)-linoxepin. However, initial results with Et_3N as the base showed the formation of (±)-isolinoxepin as the sole product. This product is formed by *syn* β-hydride elimination, while formation of the desired product needs to proceed *via anti* β-hydride elimination. Switching the base to cesium acetate completely shifted the product selectivity to (+)-linoxepin, although the authors were unable to explain this observation. This impressive synthesis produced the natural product in an excellent 30% overall yield over just eight steps.

Both strategies represent an elegant approach for the synthesis of linoxepin and used a palladium-catalyzed cascade reaction as the key step in the synthesis. With the growing interest in palladium-catalyzed cascade reactions, an increasing number of total syntheses using these cascade reactions is expected for the near future.

6 Conclusion

Palladium-catalyzed cascade reactions have proven their value over the recent years. Simple starting materials can be converted to complex products by the rational design of catalytic pathways. Furthermore, important medicinally and biologically active structures can be readily prepared in a single catalytic process.

This review has presented an overview of the various types of palladium-catalyzed cascade reactions and characterized the different components from which the cascades are derived. This classification was used as a basis for the structure of this review. While many cascade reactions and classifications were discussed, we do not claim that our overview is complete. This review rather aims to provide a basis for understanding the generality of this intriguing class of reactions.

The field of palladium-catalyzed cascade reactions is continuously expanding and far from complete. The coming years will mark an increase in complexity of new cascade reactions which should allow highly efficient synthetic access to diverse complex molecules, including natural products and pharmaceuticals.

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