PALLADIUM-CATALYZED HETEROCYCLE SYNTHESIS FROM ALLENES

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Abstract. *Bearing two cumulated carbon-carbon double bonds, allenes display distinctive reactivity to alkenes and alkynes. In the presence of palladium, allenes show diversified interactions to palladium and can been converted to various of organic compounds efficiently. In particular, palladium-catalyzed cyclization reactions involving allenes constitute a versatile platform for the construction of heterocyclic compounds. Two different mechanisms are involved concerning the cyclization of allenes, including the Pd^0 and Pd^{II} initiation pathways. The allene cyclization reaction enables effective synthesis of oxygen and nitrogen heterocycles and oxazolines, which are described in detail. Moreover, heterogeneous palladium-catalyzed heterocyclic synthesis features high activity, unique selectivity and palladium recyclability, which would be attractive to industrial chemists and are introduced at the end of the chapter.*

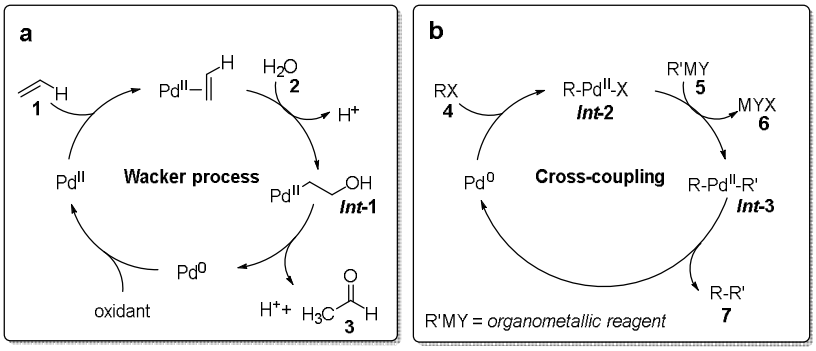
Contents

1. Introduction

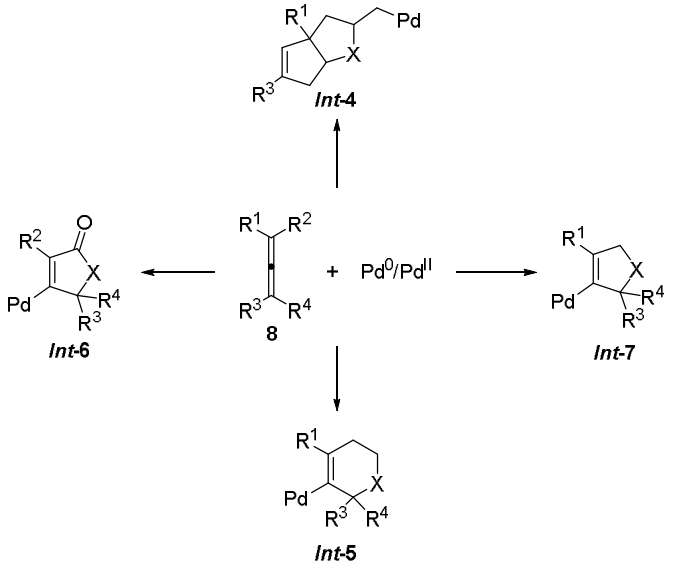
Being one of the most powerful transition metals for catalysis, palladium plays pivotal roles in many chemical industrial processes, such as the Wacker process[1] (Scheme 1a), in which the alkene **1** is converted to the aldehyde **3** *via* ***Int*-1** in the presence of **2**. The Wacker process was responsible for an annual production of one billion pounds of acetaldehyde from ethylene at one point. It also attracted considerable attention in basic research, and has promoted the in-depth understanding of elementary reactions in organometallic chemistry.[2] Thus, palladium-catalyzed processes have been involved in Nobel Prize in Chemistry for many times, for instance, the 2010 Nobel Prize in Chemistry for palladium-catalyzed cross-coupling reactions[3] (Scheme 1b). Specifically, a halide complex **4** undergoes oxidative addition to give ***Int*-2**. The next transmetallation process between ***Int*-2** and **5** gives ***Int*-3** and the byproduct **6**. A reductive elimination of ***Int*-3** would finally produce the desired compound **7**. Allenes are three-carbon functional groups possessing two cumulated carbon-carbon double bonds.[4-7] The two π-orbitals belonging to the two carbon-carbon double bonds are perpendicular to each other. This structural feature allows distinctive reactivity of allenes compared to the other carbon-carbon unsaturated compounds, such as alkenes and alkynes. Nowadays allenes have been recognized as reasonably stable functional groups and been involved in organic synthesis for the construction of many unique structures.[8]

The combination of palladium chemistry and allene chemistry has triggered the discovery of many new organic transformations.[9] In particular, palladium-catalyzed cyclization of allenes **8** has been developed as a versatile platform for the construction of heterocyclic compounds *via* ***Int*-4**–***Int*-7**[10,11] (Scheme 2). Herein, we focus on this topic and give a detailed description on the palladium-catalyzed heterocyclic synthesis from allenes. Ma group leads the research in this area. Besides, the main protagonists in this field are the groups of Jan-E. Bäckvall, Reinhold Zimmer, Norbert Krause, Corinne Aubert, *etc.* We will start by discussing the two main initiation pathways of palladium-catalyzed cyclization of allenes: the Pd^0-catalyzed pathway and the Pd^{II}-catalyzed pathway. The synthetic application for the construction of oxygen and

nitrogen heterocycles and oxazolines are summarized next. Finally, a heterogeneous version for the palladium-catalyzed heterocyclic synthesis from allene is introduced, which shows different catalytic activity and selectivity to the corresponding homogeneous palladium catalysis.



Scheme 1. Illustration of: a) Pd^{II}-catalyzed Wacker process; b) Pd^{0}-catalyzed cross-coupling reactions.



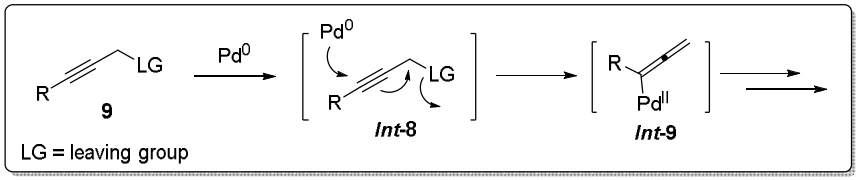
Scheme 2. Palladium-catalyzed heterocyclic synthesis.

2. Palladium-catalyzed cyclization of allenes initiated from Pd^{0}

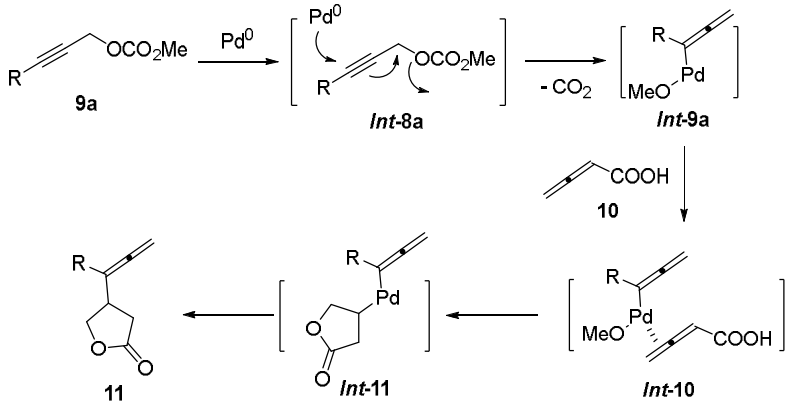
Palladium-catalyzed transformations of propargylic species have been developed as a useful chemistry for the generation of allenic moieties (Scheme 3).[12] Since the pioneering work by Tsuji *et al.* in 1985, this reaction has been used for constructing carbon-carbon and carbon-heteroatom bonds. Specifically, Pd^{0} initiates this process *via* an oxidative addition to the propargylic compounds **9**, which should bear a leaving group (LG). This process triggers the formation of an allenic palladium intermediate ***Int*-9** *via* ***Int*-8**, which can be further transformed to form heterocycles.

To give an example (Scheme 4),[13] in the irreversible oxidative addition of propargylic carbonate **9a** with Pd^{0}, carbon dioxide (CO_2) is released with concomitant formation of an allenylpalladium intermediate ***Int*-9an** from ***Int*-8a**. This key intermediate is able to coordinate with the carbon-carbon unsaturated bond of another molecular of allenoic acid **10**, giving ***Int*-10**. The activated carbon-carbon unsaturated bond would

be easily attacked by the oxygen atom of the carboxyl acid moiety, forming a new intermediate ***Int*-11**. A reductive elimination of ***Int*-11** produces the final heterocycle **11**.



Scheme 3. The key intermediate generated from Pd^0 catalysis.



Scheme 4. Synthesis of heterocycles *via* Pd^0-catalyzed allene formation.

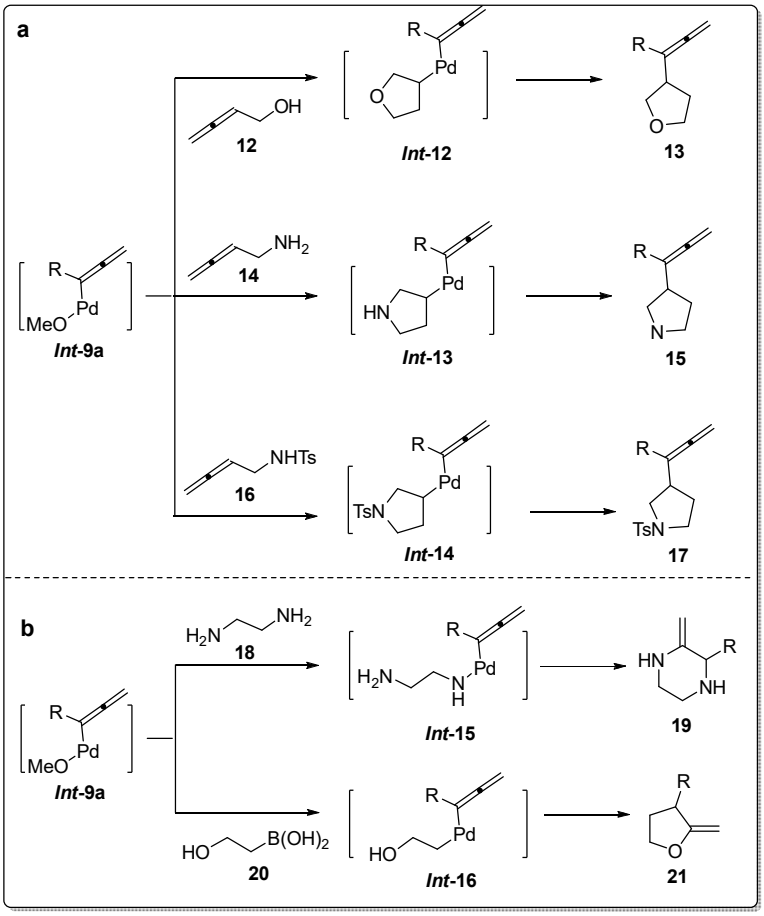
Notably, the key allenylpalladium intermediate ***Int*-9a** can be applied as a versatile platform and reacts with different partners for the construction of diversified heterocycles.[11] As shown in Scheme 5a, the Pd^{II} in ***Int*-9a** would interact with the allenol **12**, allenylamine **14**, and allenylamide **16** apart from the allenoic acid, affording the corresponding intermediates ***Int*-12**, ***Int*-13**, and ***Int*-14**. The reductive elimination of these intermediate would give the corresponding heterocycles **13**, **15** and **17**. On the other hand, the allenylpalladium intermediate ***Int*-9a** is able to be involved as a part of the obtained heterocycles (Scheme 5b). Two potential pathways were shown here. ***Int*-9a** would proceed *via* a ligand exchange with a diamine **18**, affording ***Int*-15** which undergoes a cyclization and a reductive elimination sequentially to give the heterocycle **19**. ***Int*-9a** can also proceed *via* a transmetallation with a boronic acid **20**, affording ***Int*-16** which undergoes a cyclization and a reductive elimination sequentially to give the heterocycle **21**. Various of similar reaction pathways can be designed and applied for the synthesis of different kinds of heterocycles.

3. Palladium-catalyzed cyclization of allenes initiated from Pd^{II}

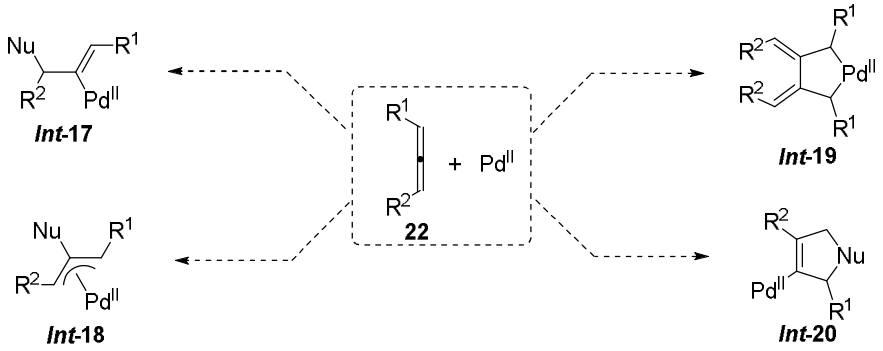
Palladium-catalyzed allene cyclizations initiated from Pd^{II} are more versatile than the ones initiated from Pd^0.[10] Some typical intermediates (***Int*-17**–***Int*-20**) generated from Pd^{II}-catalyzed allene **22** transformations are shown below (Scheme 6). Their cascade process would then furnish heterocycles *via* different pathways. It should be noted that these reactions can be summarized as two processes generally, that is, the nonoxidative process and the oxidative process. For the former one, the reaction partners are electrophilic, while the reaction partners are generally nucleophilic for the latter one. Two examples are given in Scheme 7 and 8 for clarification.

As shown in Scheme 7, allenoic acid **23** reacted with allylic bromide **24**, giving the heterocycle **25** at room temperature.[14] The reaction was initiated from the coordination of Pd^{II} with one of the carbon-carbon double bonds of allenoic acid **23** to promote cyclic nucleopalladation ***Int*-21** leading to intermediate ***Int*-22**, which then underwent insertion with the unsaturated carbon-carbon bond of **24** to give ***Int*-23**. A β-Br

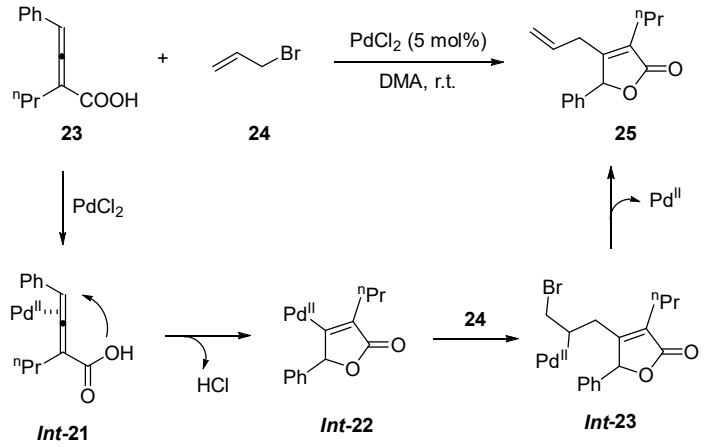
elimination process gave the final product **25** and regenerated Pd^{II} for the next catalytic cycle. Notably, the configuration was kept during the catalysis. Thus, the enantiomeric excess (ee) of allenoic acid **23** was introduced into the product **25**.



Scheme 5. Some examples for the construction of heterocycles *via* Pd^0-catalyzed allene formation.

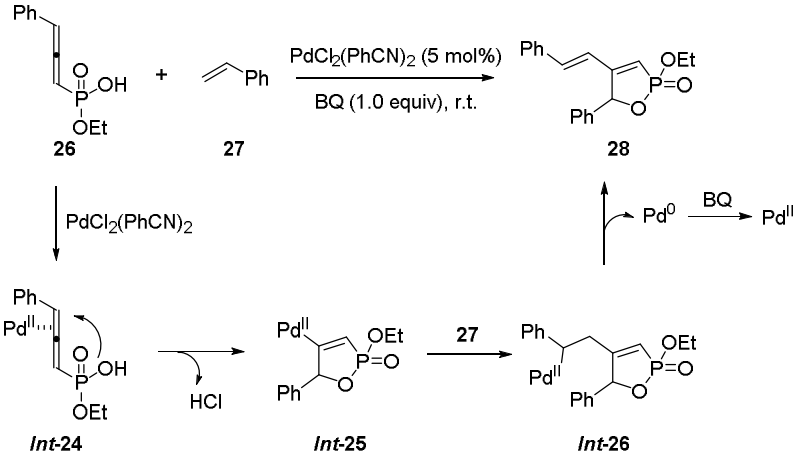


Scheme 6. Some key intermediates generated from Pd^{II} catalysis.



Scheme 7. The example for Pd^{II}-catalyzed allene cyclization *via* nonoxidative process.

Being different from the nonoxidative process shown in Scheme 7, equivalents of oxidants are required if the reaction partner is nucleophilic in the reaction.[15] Monoesters of 1,2-allenyl phosphonic acids **26** reacted with the simple alkene **27** to afford the heterocycle **28** under the presence of 1.0 equivalent of benzoquinone (Scheme 8). The reaction was also initiated from the coordination of Pd^{II} ***Int*-24** with one of the carbon-carbon double bonds of **26** to promote cyclic nucleopalladation leading to ***Int*-25**, which then underwent insertion with the unsaturated carbon-carbon bond of **27** to give ***Int*-26**. A β-H elimination gave the final product **28** and produced Pd^0, which was oxidized by benzoquinone to regenerate Pd^{II} for the next catalytic cycle.

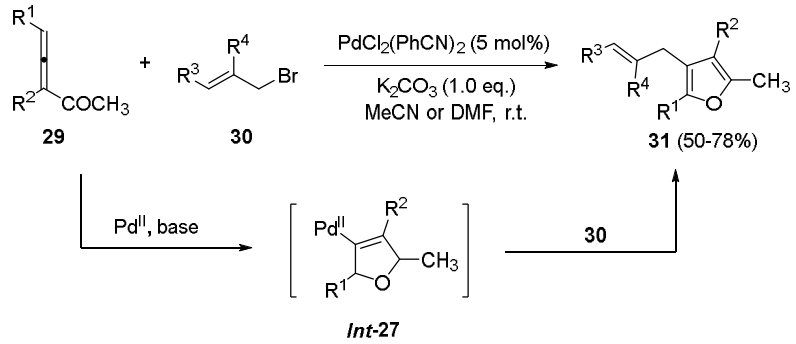


Scheme 8. The example for Pd^{II}-catalyzed allene cyclization *via* oxidative process.

4. Oxygen heterocycles synthesis from palladium-catalyzed allene chemistry

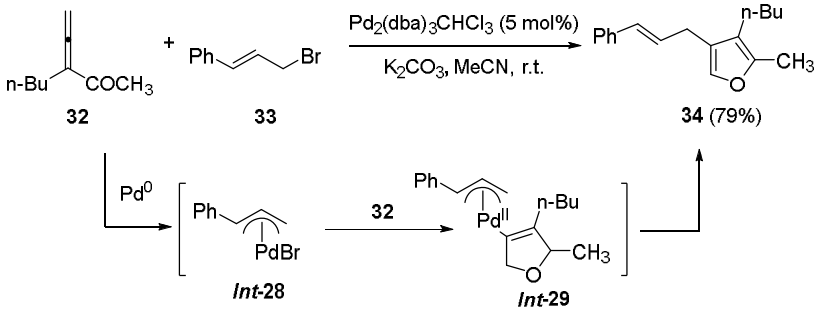
Oxygen heterocycles such as furans play a significant role in organic synthesis. Meanwhile, they broadly exist in natural products and useful materials. Great efforts have been made for the construction of this kind of cyclic compounds. Although gold-based catalysts are generally applied for the synthesis of oxygen heterocycles from allenes or alkynes, palladium-catalyzed allenic cyclization provides a straightforward and efficient pathway to them. Ma and coworkers developed a regio- and stereoselective reaction between 1,2-allenyl ketones **29** and allylic bromides **30** for the synthesis of the substituted furan **31**

(Scheme 9).[16] The addition of equivalents of K_2CO_3 was found to be critical for the coupling-cyclization products in satisfactory yields. The furanyl palladium species ***Int*-27**, which was generated *via* a cyclic oxypalladation of 1,2-allenyl ketones **29** in the presence of $PdCl_2(PhCN)_2$, was proposed to react with allyl bromide **30** to give **31** and regenerate Pd^{II} species possibly *via* a direct replacement of the bromide atom.



Scheme 9. Synthesis of furan *via* Pd^{II}-catalyzed allene cyclization.

Interestingly, it was observed that the reaction was also catalyzed by Pd^0 species, which probably proceed *via* cyclic oxypalladation of **32** with the generated Pd^{II} intermediate ***Int*-28** from **33**, forming the cyclized ***Int*-29**. A regioselective reductive elimination will then furnish the final product **34** (Scheme 10).[16] This process may also account for the regioselectivity of the nonsymmetric allylic halides. The comparison of the two cases indicates that palladium catalysis is very flexible for the allenic cyclization, thus being a powerful route to the oxygen heterocycles.

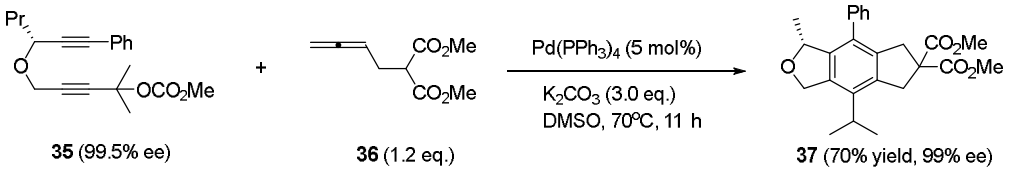


Scheme 10. Synthesis of furan *via* Pd0-catalyzed allene cyclization.

Apart from the simple oxygen heterocycles, structurally complex oxygen heterocycles and related bioactive molecules were readily synthesized by Pd-catalyzed allene cyclization reactions. In 2015, Ma and coworkers developed a palladium-catalyzed tandem reaction of 2,7-alkadiynylic carbonates with allenes bearing a carbon nucleophilic site, such as the malonate and bis(phenylsulfony)methane.[17] Fused tricycles such as 3,5,6,7-tetrahydro-*1H*-indeno[5,6-*c*] furan, 1,2,3,5,6,7-hexahyrocyclopenta[*f*] isoindole, and 1,2,3,5,6,7-hexahyro-*s*-indacene derivatives were efficiently synthesized according to the reaction. The Pd^0-catalyzed cyclization involving allenes features high stereoselectivity. For example, when the optically pure 2,7-alkadiynylic carbonates **35** containing a central chirality were mixed with allene **36** (Scheme 11), the reaction gave the oxygen heterocycle **37** in 70% yield without loss of enantiomeric purity (99% ee).

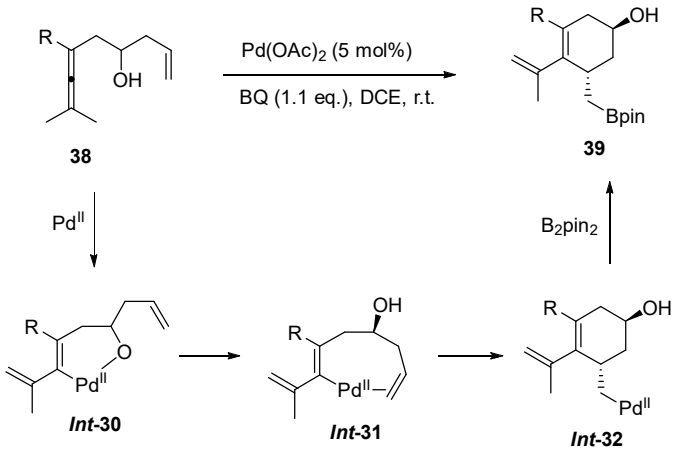
Alkoxyallenes are especially useful for the construction of oxygen heterocycles. They have been successfully employed for the synthesis of bioactive compounds, such as sugars, alkaloids, *etc.* Bäckvall *et al*. reported the Pd^{II}-catalyzed allenic C-H oxidative carbocyclization, which provides an effective way to the

bioactive oxygen compounds when oxygen substituents are introduced into the allene moiety (Scheme 12).[18] A highly regio- and diastereoselective palladium-catalyzed oxidative carbocyclization of enallenes **38** bearing a weakly coordinating oxygen-containing group (*e.g.* hydroxyl, alkoxide and ketone) occurred affording functional cyclohexene derivatives **39**. The reaction proceeds *via* a ligand exchange of the weakly coordinating group with an olefin group from ***Int*-30** to ***Int*-31**, thus giving ***Int*-32** with high diastereoselectivity. The assisting effect was investigated to be indispensable, and determined the stereoselectivity of the final product. Notably, equivalents of benzoquinone (BQ) were essential for the regeneration of the Pd^{II} catalyst.



35 (99.5% ee) **36** (1.2 eq.) **37** (70% yield, 99% ee)

Scheme 11. Synthesis of complex oxygen heterocycles *via* Pd-catalyzed allene cyclization



38 **39** ***Int*-30** ***Int*-31** ***Int*-32**

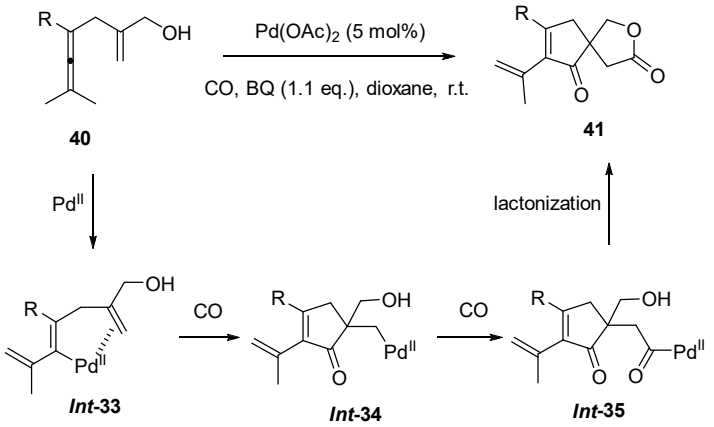
Scheme 12. Synthesis of bioactive oxygen monocycles *via* Pd-catalyzed allene cyclization.

In 2017, the same research group realized the synthesis of spirolactones *via* the Pd^{II}-catalyzed carbonylative spirocyclization of enallenes **40** (Scheme 13).[19] In this reaction, simultaneous coordination of the olefin and the allene units of **40** to the palladium center triggers an allene attack on Pd^{II} *via* C–H bond cleavage, producing ***Int*-33**, which the undergoes a cascade carbon monoxide and olefin insertion to give ***Int*-34**. The latter intermediate undergoes an additional CO insertion ***Int*-35** followed by a lactonization, giving the final product **41** bearing an all-carbon quaternary stereocenter. The reaction demonstrates high chemoselectivity and good tolerance for various functional groups. Notably, when chiral benzoquinone was used in replacement of BQ, **41** was obtained with a relatively low *ee* (26%). This result suggests that the quinone coordinates to palladium in the enantio-discrimination step. A higher ee (66%) of the product **41** was obtained when a chiral phosphoric acid was utilized as a cocatalyst in toluene. This result confirms the potential of the palladium-catalyzed allene cyclization for the construction of bioactive oxygen heterocycles.

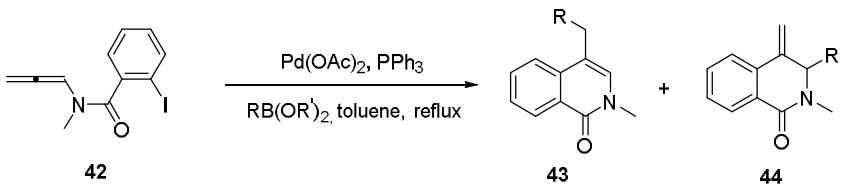
5. Nitrogen heterocycles synthesis from palladium-catalyzed allene chemistry

Nitrogen heterocycles constitute one of the most important cyclic compounds in nature. Palladium-catalyzed allene cyclization provide an efficient way toward this kind of molecules. Allenes carrying nitrogen moieties are readily utilized as the starting materials for the construction of nitrogen heterocycles. Grigg and co-workers developed a palladium-catalyzed tandem cyclization-anion capture

process using allene as the terminating species.[20,21] As shown in Scheme 14, the allene **42** undergoes a monocyclization reaction in 6-*exo-dig* fashion to give six-membered nitrogen heterocycles **43** and **44** as the final products. Pd^0 catalysis was observed to initiate the reaction, where the allene moiety was applied as a nucleophilic group.



Scheme 13. Synthesis of bioactive oxygen bicycles *via* Pd-catalyzed allene cyclization.



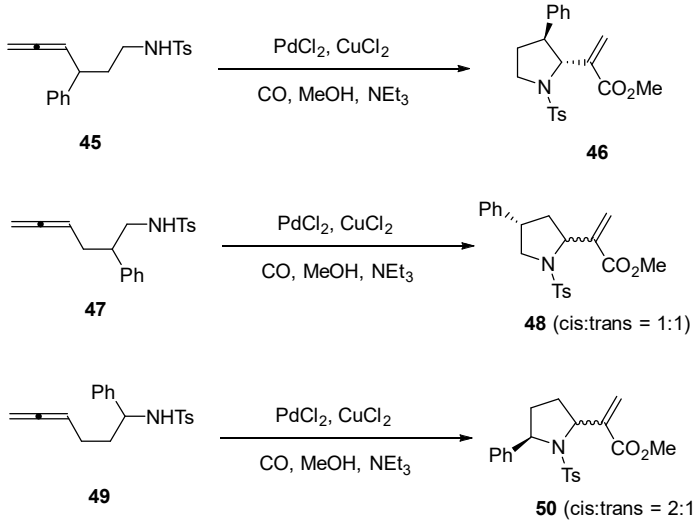
Scheme 14. Nucleophilic attack of allene for the construction of nitrogen heterocycles.

The allene moiety can also serves as an electrophilic group for the construction of nitrogen heterocycles from allenes carrying nitrogen moieties. Gallagher, Walkup, *et al.* reported the intramolecular amino- and amidopalladation-methoxycarbonylations of allenes.[22,23] These reactions initiate from Pd^{II}, which coordinates with the carbon-carbon double bonds of allene and facilitates the following nitrogen-based nucleophiles' attack. Stoichiometric amounts of oxidants such as $CuCl_2$ are required during the catalysis for the regeneration of the Pd^{II} catalyst. The reactions undergo with high regioselectivity, while the stereoselectivity depends on the position and types of the substituents. Based on the reactions, substituted tetrahydropyrroles such as **46**, **48** and **50** were obtained in satisfactory yields from allenes **45**, **47** and **49** (Scheme 15).

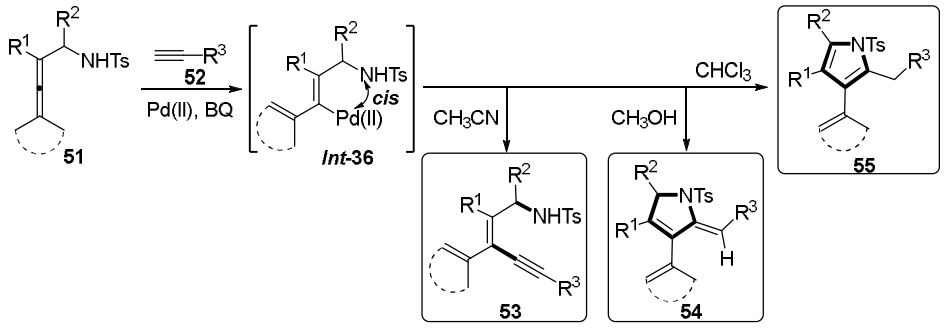
Dihydropyrroles and pyrroles were also available by palladium-catalyzed allene cyclization reactions. In 2019, Bäckvall *et al*. reported the palladium-catalyzed stereospecific oxidative cascade reaction of allenes with the alkynes **52** for the construction of pyrrole-related rings.[24] The tosylamide group on the allene **51** is verified to be crucial for triggering the allene attack on Pd^{II}, which generates the key intermediate ***Int*-36** for the formation of the desired products. Solvent-controlled selectivity of the cascade reaction was realized for divergent synthesis of tetra-substituted olefins **53**, 2,5-dihydropyrroles **54**, and pyrroles **55** (Scheme 16). In addition, enantioenriched 2,5-dihydropyrrole were readily synthesized by chirality transfer *via* this approach. This strategy for the divergent and stereospecific construction of 2,5-dihydropyrroles and pyrroles is beneficial in synthetic and material chemistry.

Apart from the intramolecular cyclization, the intermolecular reactions of allenes with nitrogen nucleophiles have also been widely developed for the synthesis of nitrogen heterocycles. The elegant method for the regioselective heterocyclization of disubstituted allenes **56** or **60** employing functionally substituted

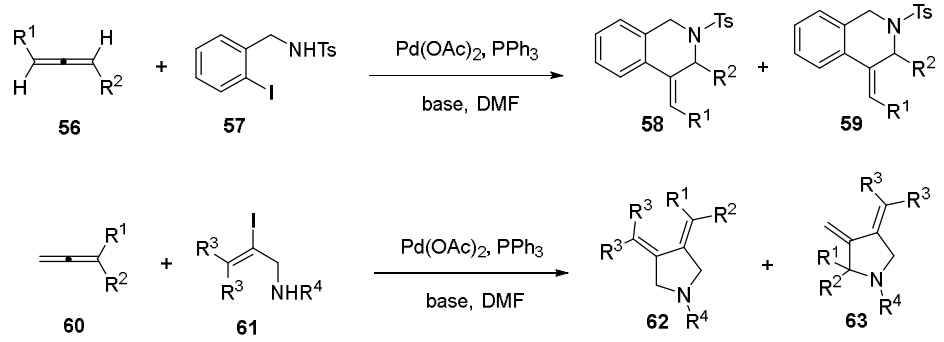
aryl or alkenyl halides **57** or **61** has been subjected to detailed investigation by Larock and co-workers.[25-27] A wide range of five- and six-membered nitrogen heterocycles **58**, **59**, **62**, and **63** have been formed by this method (Scheme 17).



Scheme 15. Nucleophilic attack of nitrogen groups for the construction of nitrogen heterocycles.

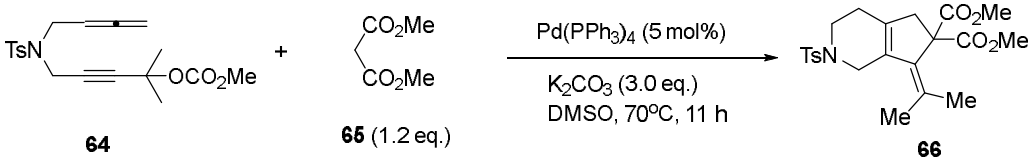


Scheme 16. Pyrroles synthesis from palladium-catalyzed allene cyclizations.



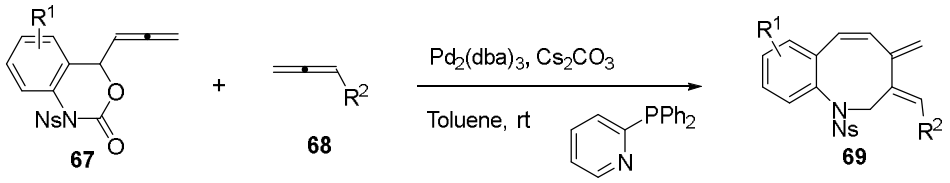
Scheme 17. Intermolecular reactions for the construction of nitrogen heterocycles.

Ma group made significant contribution in the construction of nitrogen heterocycles by palladium-catalyzed allene cyclizations. In 2013, they developed an allene relay reaction, in which a fused nitrogen heterocycle **66** was efficiently synthesized by a palladium-catalyzed bicyclization of allene-propargylic carbonates **64** with geminal bis(nucleophoile)s **65** (Scheme 18).[28] The ability to generate functionalized bicycles, including optically active ones, from the easily accessible starting materials in a single step is the most important feature of the method. Moreover, mechanistic investigations revealed that the MeOH generated in situ in the first step played a pivotal role in the second step of this transformation.



Scheme 18. Allene relay reaction for the construction of nitrogen heterocycles.

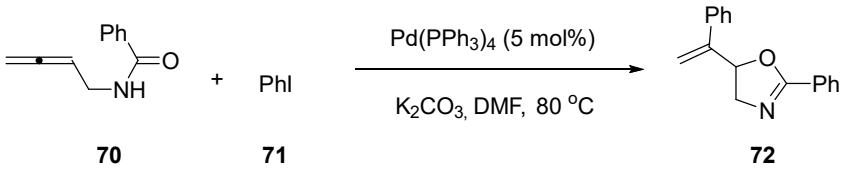
In 2023, they further realized the intermolecular reaction of two allenes for synthesis of benzazocines, which serves as the core structure of a variety of bioactive natural products, such as dehydroisolongistrobin, sulpinine C, shearinine C and asporyzin A.[29] An unexpected Pd-catalyzed formal [6+2]-cyclization of allenyl benzoxazinanones **67** with another allene **68** gave benzazocine derivatives **69** with high efficiency (Scheme 19). This reaction process represents a completely new reactivity of methylene-π-allyl palladium species, and provides a new concept for the formation of eight-membered rings. Notably, control experiments indicated that neither alkenes nor alkynes may replace allenes to react with allenyl benzoxazinanones to deliver the corresponding products.



Scheme 19. Benzazocines synthesis.

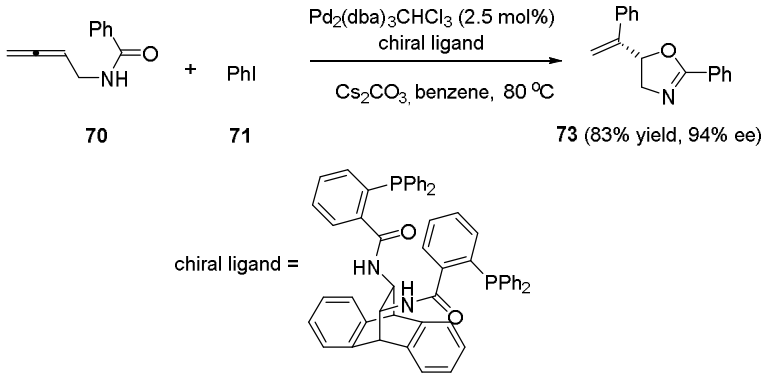
6. Oxazoline synthesis from palladium-catalyzed allene chemistry

As a very important class of heterocyclic compounds, oxazolines, especially the optically active oxazolines is not only present in many biologically active natural and unnatural compounds,[30-32] but also a versatile functional group in organic synthesis.[33,34] However, their synthetic routes are still very limited. In 2012, the Ma group developed a synthetic route to oxazoline derivatives **72** *via* the reaction between phenyl iodine **71** and *N*-(buta-2,3-dienyl)amides **70**, which was efficiently prepared from terminal *N*-propargyl amides.[35] $Pd(PPh_3)_4$ was used as the catalyst and the aryl iodine was applied as the reaction partner (Scheme 20). This method for the construction of oxazoline derivatives features mild reaction conditions, good functional group tolerance, low-catalyst loading and readily accessible starting materials with diversity, thus being promising potential in industrial chemistry and asymmetric catalysis.



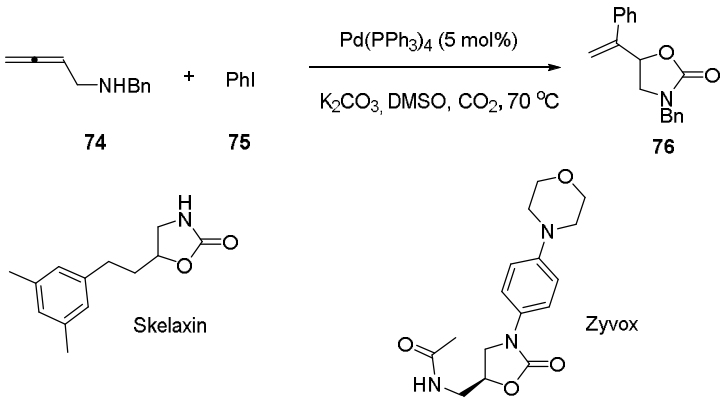
Scheme 20. Palladium-catalyzed coupling-cyclization for the synthesis of oxazoline derivatives.

After six years, they finally completed the asymmetric version of the reaction in 2018.[36] A chiral trost ligand was found to be beneficial for acquiring high enantio excess (Scheme 21). This method is quite different from the previous reports, in which the oxazoline derivatives **73** with a chiral center at the 5-position was synthesized by a ruthenium-catalyzed chemo- and enantioselective hydrogenation of the carbon-carbon double bond. 50 atm of hydrogen gas was needed for the conversion. Thus, the palladium-catalyzed coupling-cyclization reaction of allenes effectively overcomes the limitation of the starting materials and products.



Scheme 21. Palladium-catalyzed asymmetric coupling-cyclization for the synthesis of oxazoline derivatives.

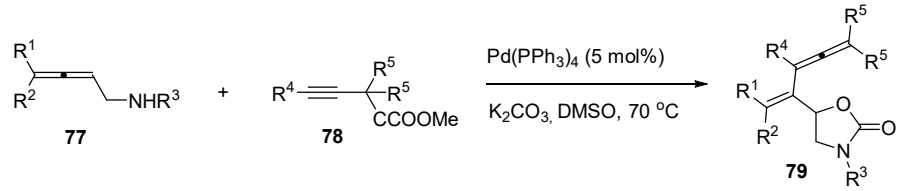
By employing the allenic amine as the starting material, the same group developed a synthetic method for the construction of 5-vinyloxazolidin-2-one **76** in the presence of CO_2 (Scheme 22). This highly efficient three-component reaction was still initiated by a oxidative addition of Pd^0 to the aryl iodine **75**, which was followed by a CO_2 insertion and finally the nucleophilic attack to the allene compound **74**. Oxazolidin-2-ones with various functional groups were readily obtained. This kind of compounds are widely used in pharmaceutical industry. For instance, the best-selling drugs, Skelaxin and Zyvox, both contain the oxazolidin-2-one skeleton.[37]



Scheme 22. Synthesis of 5-vinyloxazolidin-2-one from allenic amine.

This skeleton was achieved as well when propargylic carbonates **78** were employed, in which the CO_2 was not needed any more. The CO_2 generated in situ from propargylic carbonates is incorporated into the oxazolidin-2-one unit **77** with high efficiency, affording the desired products **79** in 70% to 92% yields

(Scheme 23).[38] The stereoselectivity on the olefin moiety was not satisfatory when $R^1 \neq R^2$. However, in the next work, they successfuly resolved this problem by utilizing a sterically hindered monophosohine ligand Gorlos-Phos. In the presence of this ligand, the palladium-catalyzed coupling-cyclization reaction furnished oxazolidin-2-ones **79** with high *Z* selectivity.[39]



Scheme 23. Synthesis of oxazolidin-2-one skeleton from allenic amine and propargylic carbonates.

7. Heterogeneous palladium-catalyzed heterocyclic synthesis from allene

The discussion above is based on homogeneous palladium catalysts, including palladium salts, palladium-ligand complexes, *etc.*[40] It should be noticed that among some of cases, the real catalytic species in the system were in-situ generated palladium clusters or particles. In 1995, the Hiemstra group reported that the $Pd(OAc)_2$/DMSO catalytic system efficiently catalyzed the oxidative cyclization of *N*-hydroxymethylamine.[41] Based on transmission electron microscopy (TEM), it was shown that Pd clusters were generated during the reaction and they could be isolated and reused without loss of catalytic activity. Results from the Sheldon group demonstrated that Pd nanoclusters, formed in-situ during the reaction, were catalytically active in the alcohol oxidation.[42] Stahl and coworkers found that in the oxidation of cyclohexanones and cyclohexenones to phenols with the $Pd(TFA)_2$/2-dimethylaminopyridine catalytic system, the initial Pd^{II} catalyst evolved to Pd clusters immediately and catalyzed the formation of phenols.[43] Additionally, Pd clusters exhibited distinct selectivity compared to monomeric palladium catalysts. Control experiments showed that monomeric palladium catalysts, disfavoring formation of Pd clusters, catalyzed oxidation of cyclohexanone to cyclohexenone without subsequent oxidation to phenol. It is noteworthy that the continual growth of Pd clusters to nanoparticles (>100 nm) leads to loss of activity in these oxidation reactions. These reports together suggest that Pd clusters with small size would overcome the mass-transfer issue, generally associated with heterogeneous catalysts, and provide high activity in oxidative cascade reactions. Moreover, these clusters can also alter the catalytic selectivity compared with the monomeric palladium catalysts. Additionally, the easy removal of Pd clusters from the reaction mixture enables catalyst recycling, which is highly beneficial for practical applications in the fine chemical and pharmaceutical industry.

In this section, we will discuss some examples on heterogeneous palladium catalyzed heterocyclic synthesis from allenes, which were developed by Bäckvall and Li. The heterogeneous palladium catalyst was synthesized by a one-pot wet chemical reduction method. Specifically, siliceous mesocellular foam (MCF) was used as the solid support, which was functionalized with 3-aminopropyltrimethoxysilane to introduce an amino group. Aminopropyl-functionalized MCF (AmP-MCF) was then impregnated with Li_2PdCl_4 to furnish the Pd^{II}-AmP-MCF, which was reduced by $NaBH_4$ to give Pd^0-AmP-MCF. Pd^{II}-AmP-MCF or Pd^0-AmP-MCF was utilized as the Pd^{II} or Pd^0 catalyst for the palladium-catalyzed allene cyclization reactions. The pore and window sizes of Pd^{II}-AmP-MCF and Pd^0-AmP-MCF were measured and found to be essentially the same as those in non-functionalized MCF: 29 nm and 15 nm (Figure 1). TEM images showed an average cluster size of Pd^0-AmP-MCF to be 1-2 nm, while the unreduced catalyst Pd^{II}-AmP-MCF bears much smaller palladium clusters.[44]

It is generally considered that heterogeneous palladium catalysts are less active and selective than their homogeneous counterparts, as a result of the mass-transfer issue. However, the heterogeneous Pd^{II}-AmP-MCF was found to be highly efficient in oxidative cascade reactions of allenes. Bäckvall and Li developed an oxidative alkynylation-cyclization reaction of enallenols with alkynes, which is efficient for the synthesis of furans (Figure 2). The yields and TONs of $Pd(OAc)_2$ and Pd^{II}-AmP-MCF are shown for comparison. The use of 1 mol% of $Pd(OAc)_2$ led to a catalytic reaction, giving only 36% yield of furan **83**

with over half of the starting material **80** being recovered, while Pd^{II}-AmP-MCF with the same Pd loading (1 mol%) gave an 82% yield of **83**. It is noteworthy that the addition of a bidentate N-ligand to the homogeneous $Pd(OAc)_2$ results in catalyst passivation, probably due to the strong coordination disfavoring the formation of ***Int*-37** (Figure 2).[45]

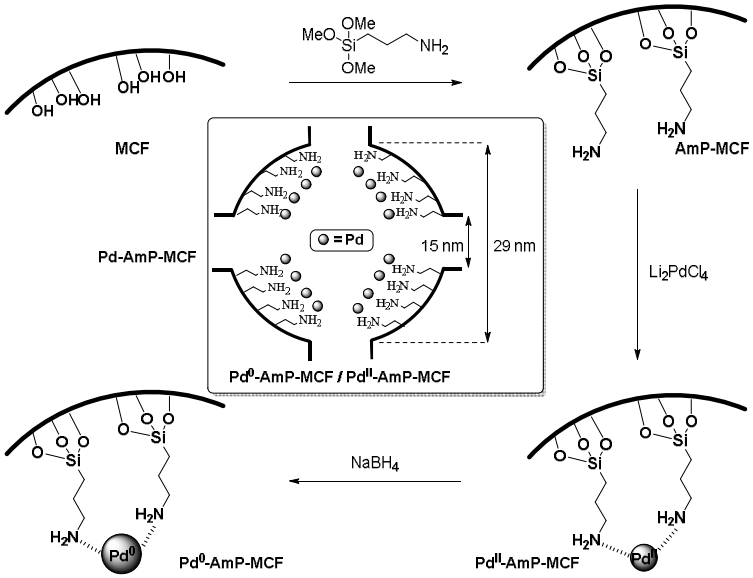


Figure 1. Synthesis of the heterogeneous palladium catalyst

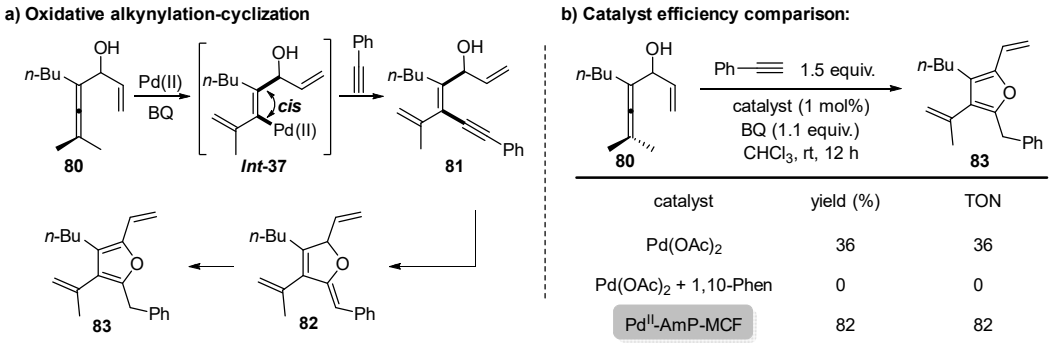
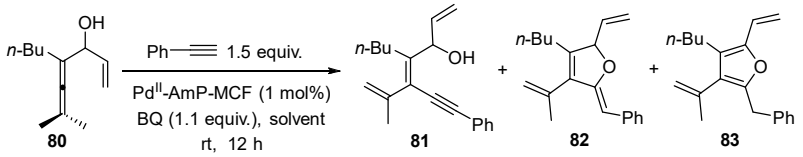


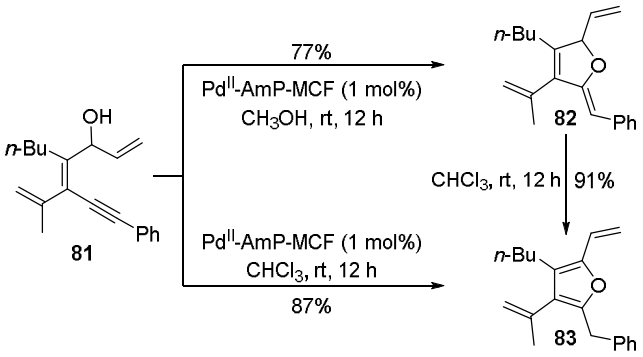
Figure 2. Heterogeneous palladium-catalyzed allene cyclization for the synthesis of furans.

Interestingly, the Pd^{II}-AmP-MCF-catalyzed oxidative cascade reactions of enallenols involving terminal alkynes as the reaction partner exhibited a solvent-controlled chemoselectivity. In the reaction of enallenol **80** with alkyne, (*Z*)-tetrasubstituted olefin **81**, 2,5-dihydrofuran **82** or tetrasubstituted furan **83** was isolated as the major product using CH_3CN, CH_3OH or $CHCl_3$, respectively, as the solvent (Scheme 24). We speculated that **82** and **83** were generated from the Pd^{II}-catalyzed intramolecular cyclization of **81** and isomerization of **82**, respectively, which was confirmed by the further control experiments (Scheme 25). The solvent-controlled selectivity could be explained by a) interaction of CH_3CN with Pd^{II} inhibiting the subsequent Pd-catalyzed cyclization of **81**, b) the protic solvent (CH_3OH) promoting transformation of **81** to **82**, as a proton is essential during the process, and c) the relatively acidic reaction conditions ($2CHCl_3 + O_2 \rightarrow 2COCl_2 + 2HCl$) favoring the isomerization from **82** to **83**.[45]



solvent	yield of **81** (%)	yield of **82** (%)	yield of **83** (%)
CH_3CN	90	0	0
CH_3OH	0	75	8
$CHCl_3$	0	0	82

Scheme 24. Solvent-controlled selectivity in heterogeneous palladium-catalyzed allene cyclization.

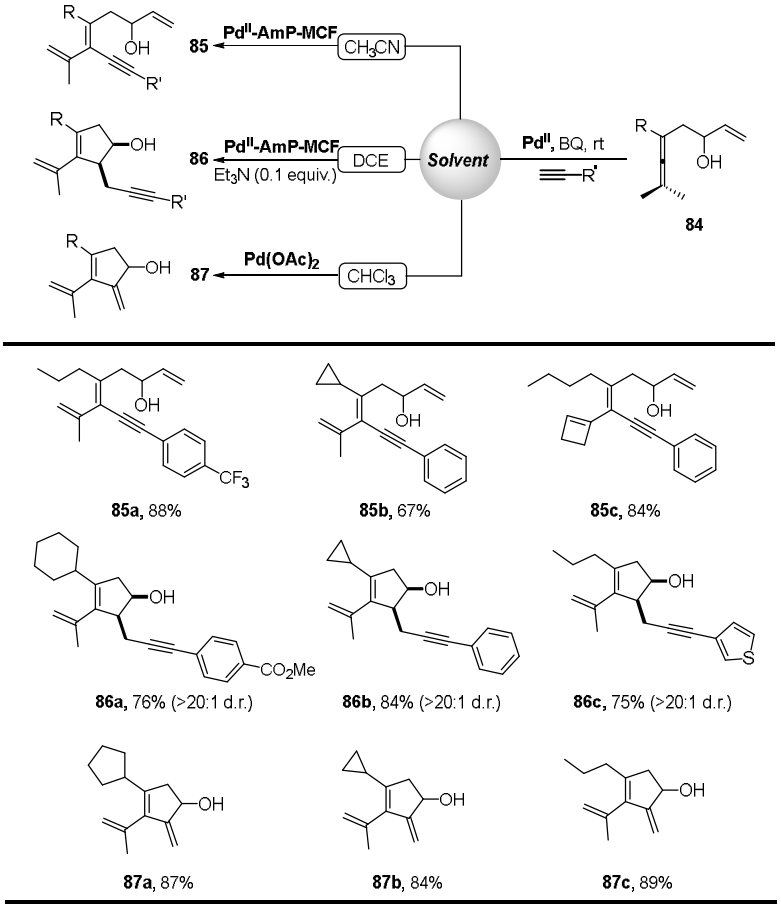


Scheme 25. Control experiments for the selectivity.

The solvent-controlled selectivity was also utilized for the chemodivergent synthesis of highly substituted olefins **85** and cyclopentenols **86** and **87** from enallenol **84** (Scheme 26). Notably, the heterogeneous palladium-catalyzed oxidative cascade reactions not only displayed good chemoselectivity, but also showed excellent stereoselectivity. Cyclopentenols **86** were isolated as single *cis*-diastereomers in high yield in each case, and olefins **85** were obtained with stereodefined double bonds under the reaction conditions (Scheme 26).[46]

Pd^{II}-Catalyzed oxidative carbonylation constitutes an efficient approach towards synthesis of organic molecules with carbonyl groups.[47-51] Bäckvall and Li designed an oxidative cascade route involving carbonylation[52] for the construction of ring fused γ-lactone **12**, which is a core structure of many bioactive compounds, such as the strigolactone family members.[53] The envisioned cascade process (Scheme 27) for the construction of this skeleton involves four steps of bond formation including CO insertions twice in the reaction sequence. The possible side reactions of each palladium intermediate ***Int*-38**–***Int*-42** result in difficulties of controlling the chemoselectivity of the cascade reaction and **88**, **89** and **90** were all possible products.[54]

In the presence of $Pd(TFA)_2$, **89** and **88** were obtained in 65% and 28% yields, respectively. However, when Pd^{II}-AmP-MCF was used in place of the homogeneous palladium catalyst, the selectivity of the reaction was completely reversed, leading to **88** in 68% yield. A slight modification of the oxidant under the heterogeneous reaction conditions improved the yield of **88** to 80%. The homogeneous $Pd(TFA)_2$-catalyzed reaction, with 10 mol% of AcOH as an additive, gave **89** in 86% yield. The unique selectivity of Pd^{II}-AmP-MCF-catalyzed oxidative carbocyclization-carbonylation reaction allows the chemodivergent construction of γ-lactone **89** and fused γ-lactone **88**.[52] It is noteworthy that **88** bearing two chiral centers were obtained with high diastereoselectivity as the *cis*-product (Scheme 28).

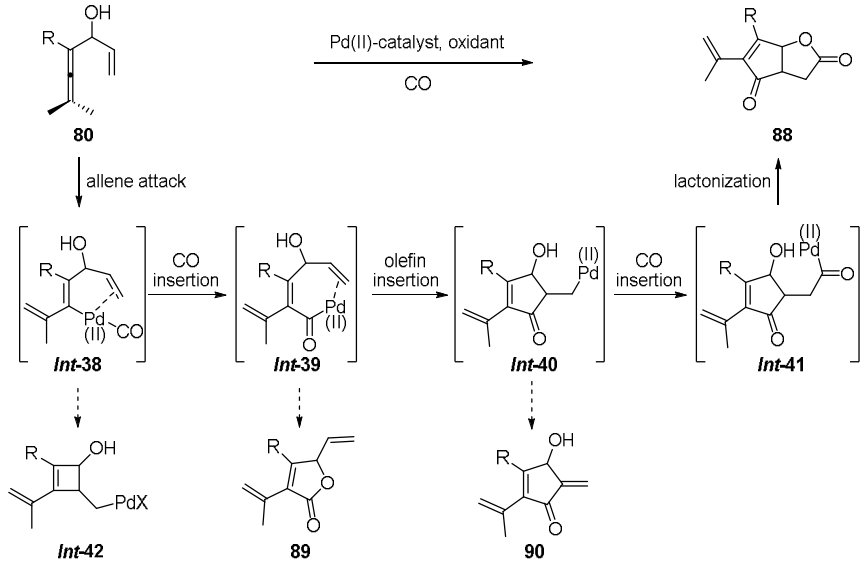


Scheme 26. Solvent-controlled chemodivergent syntheses.

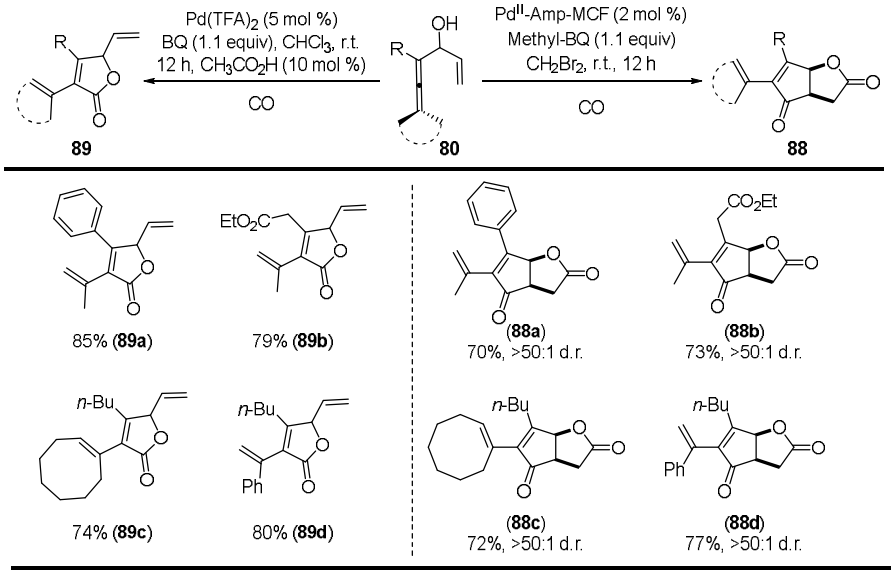
The results of control experiments[52] suggest that the distinct chemoselectivity between $Pd(TFA)_2$ and Pd^{II}-AmP-MCF originated from their different adsorption (coordination) capacity for CO. The high surface area of Pd^{II}-AmP-MCF and presence of Pd^0 atoms favor adsorption and coordination of CO in the catalyst, which results in the aggregation of CO in Pd^{II}-AmP-MCF. The local high CO concentration would promote the generation of ***Int*-39** from ***Int*-38** with subsequent carbocyclization to give ***Int*-40**. A second CO insertion of ***Int*-40** would give **88**. On the other hand, a low CO concentration would favor the formation of ***Int*-41** from ***Int*-38** with subsequent reductive elimination to give **89** (Figure 3).

In 2019, Bäckvall and Li found that the sulfonamide group of α-tosylamide allenes **91** could undergo anionic ligand exchange with ligands on the Pd^{II} catalyst from ***Int*-44** to ***Int*-45**. The coordination of the sulfonamide group also triggered the allenic attack step and the subsequent alkynylation.[24] Inspired by this observation, they designed an oxidative carbonylation-cyclization process for the construction of pyrrolidones (Scheme 29).[55]

Initial attempts, however, gave very low yield of pyrrolidone **92** (<8%) and variation of solvent, oxidant, or temperature did not improve the yield with the starting material **91** being almost completely recovered. After screening different additives, finally they found that the addition of catalytic amounts of AgOTf (10 mol%) in Pd^{II}-AmP-MCF dramatically improved the yield of **92** to >90%. Further optimization of the reaction conditions showed that the loading of Pd^{II}-AmP-MCF and AgOTf could be reduced to 0.5 mol% and 1 mol%, respectively, furnishing **92** in satisfactory yield in 30 minutes.



Scheme 27. Palladium-catalyzed oxidative carbocyclization-carbonylation for the synthesis of γ-lactone.



Scheme 28. Chemodivergent syntheses of γ-lactone.

By using crystalline nanocellulose as the support, the authors prepared Pd^{II}-AmP-CNC as a catalyst by using the same procedure as the synthetic method of Pd^{II}-AmP-MCF. Pd^{II}-AmP-CNC also showed high catalytic activity with the addition of AgOTf in this oxidative cascade reaction. By contrast, homogeneous palladium catalysts such as $Pd(TFA)_2$ or Li_2PdCl_4 did not give satisfactory yields with AgOTf (Scheme 29).

For revealing the origin of the high activity of this catalytic system (Pd^{II}-AmP-CNC+AgOTf) in oxidative carbonylation-cyclization reaction, the authors further conducted control experiments.[55] The results show that the Cl/Pd molar ratio of Pd^{II}-AmP-CNC is 2.1/1 and 0.03/1 before and after treatment with

AgOTf, respectively. Analysis of XPS spectra indicates that the Pd3d binding energy of Pd^{II}-AmP-CNC treated by AgOTf is higher than that of untreated catalyst. These results suggest that the chloride on the palladium clusters of Pd^{II}-AmP-CNC has been completely removed by AgOTf, generating cationic palladium[56,57] with high activity in the oxidative carbonylation-cyclization reaction (Figure 4). The addition of AgOTf to homogeneous palladium also results in an improvement of production of **92**, which supports the generation of cationic palladium. However, the homogeneous catalytic system did not give satisfactory yield, probably due to the immediate deactivation of the palladium species under the reaction conditions.

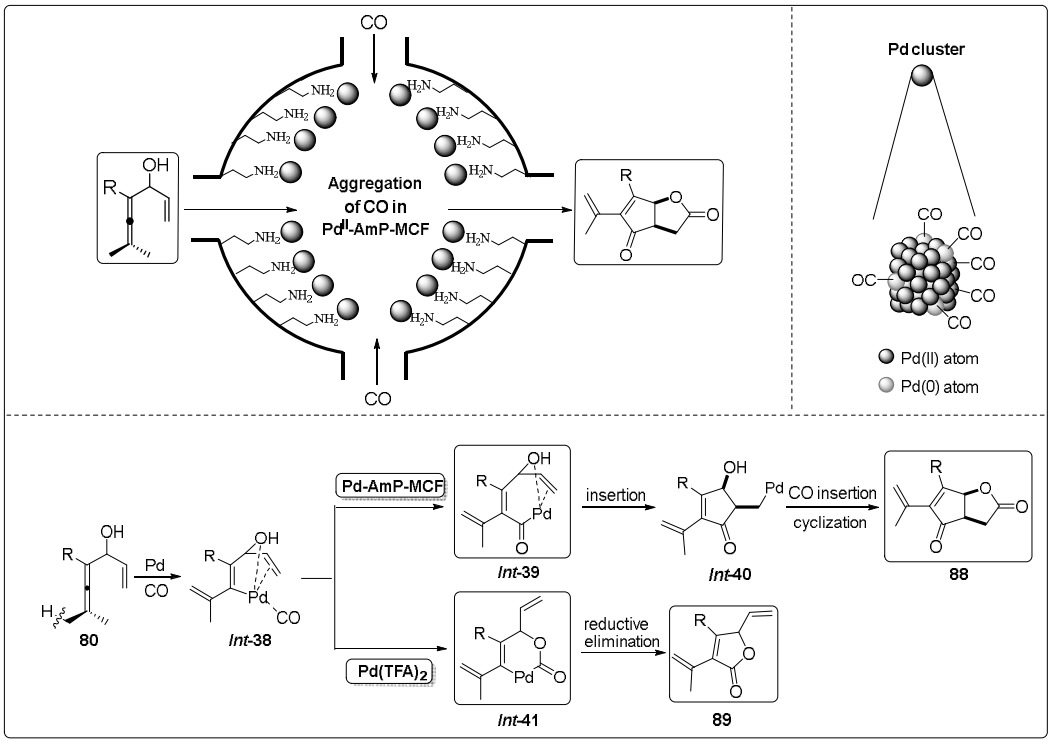
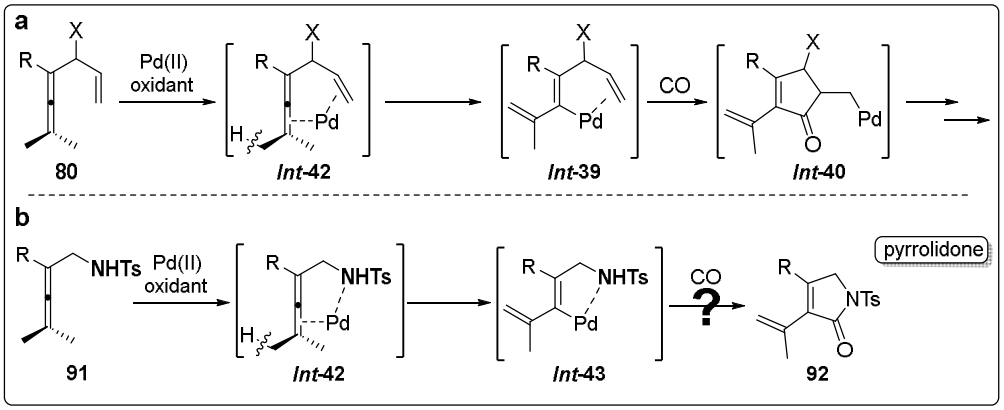


Figure 3. Origin of the selectivity.



Scheme 29. Oxidative carbonylation-cyclization process for the construction of pyrrolidone.

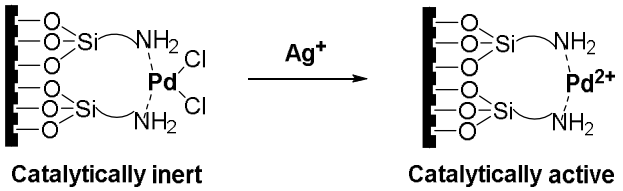
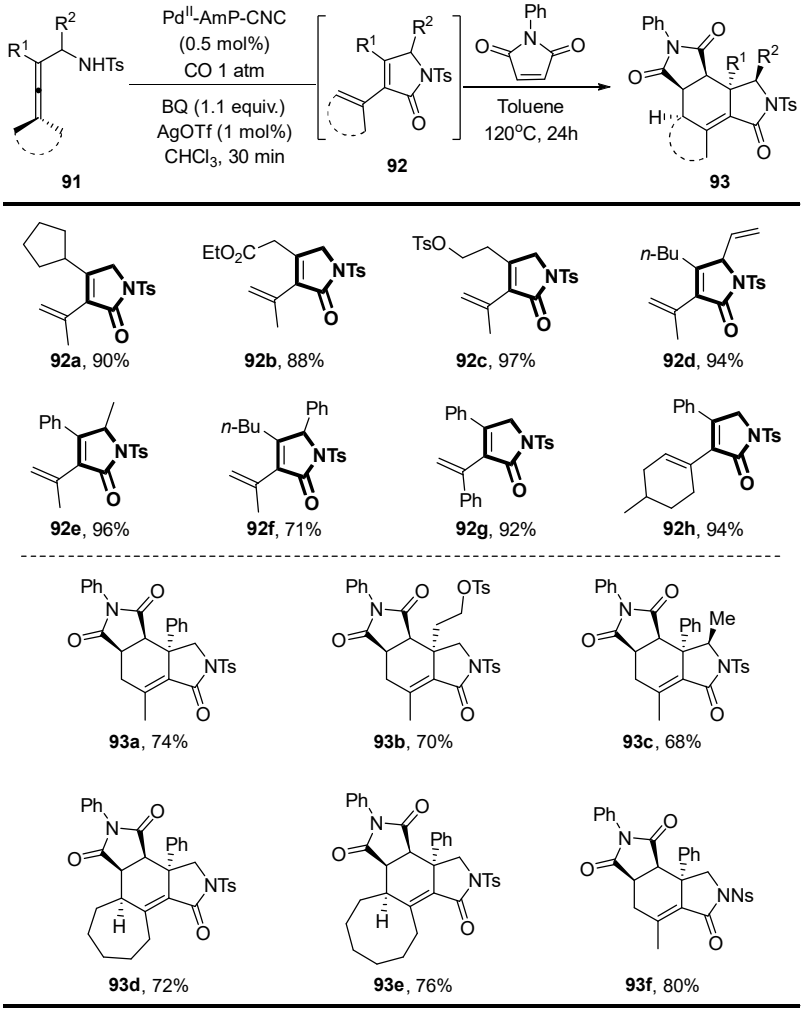


Figure 4. Identification of active palladium species.

This heterogeneous method allows rapid access to pyrrolidones with high efficiency, and has been utilized for the one-pot construction of polycyclic compounds with a subsequent Diels-Alder reaction (Scheme 30). It is noteworthy that polycyclic compounds **93** were obtained with high diastereoselectivity, and only 0.5 mol% of Pd^{II}-AmP-CNC catalyst and 1 mol% of AgOTf were needed in the oxidative cascade reaction.



Scheme 30. Rapid access to pyrrolidones and highly diastereoselective synthesis of polycycles.

7. Conclusions

In summary, here we introduced the advance of palladium-catalyzed heterocyclic synthesis from allenes. These reactions are initiated from either Pd^0 or Pd^{II} process. As one of the most powerful metals, palladium shows highly diversified pathways for catalyzing the transformation of allenes, thus allowing the construction of heterocycles with various structures, including oxygen heterocycles, nitrogen heterocycles, oxazolines, *etc.* Palladium salts and palladium complexes coordinated by different ligands were employed as the catalysts. These homogeneous palladium catalysts trigger the cyclization reactions with high activity and controlled selectivity. On the other hand, heterogeneous palladium catalysts such as the $Pd^{0/II}$-AmP-MCF features high catalytic efficiency, unique selectivity and palladium catalyst recyclability were developed.[58,59]

The heterogeneous processes provide an important supplement for the palladium-catalyzed allene cyclization because they would produce heterocycles that cannot be achieved by homogeneous catalysis and stimulate the development of industrial chemistry. To assess the potential of heterogeneous palladium catalysis in allene cyclizations, rational design of efficient catalysts is of great importance and the following approaches would significantly stimulate further development of the field: 1) Robust heterogeneous nanopalladium catalysts with ultra-small particle size would be able to overcome the mass-transfer issues and dramatically increase the catalytic activity. 2) Metal-doping in Pd nanoclusters would generate a novel heterogeneous palladium catalyst, where the new metal introduced (*e.g.* Cu, Au) can cooperate with palladium and synergistically catalyze cyclization reactions, realizing organic transformations that are difficult to achieve by mononuclear homogeneous palladium catalysts. 3) Design and synthesis of well-defined palladium nanoclusters with atomically precise structures[60-68] will be helpful for in-depth understanding of catalytic mechanisms, thus promoting the recursive optimization of structure and catalytic performance of heterogeneous palladium catalysts.

Acknowledgements

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