PALLADIUM-CATALYZED DOMINO CARBOPALLADATION/CYCLIZATION OF ALLENES

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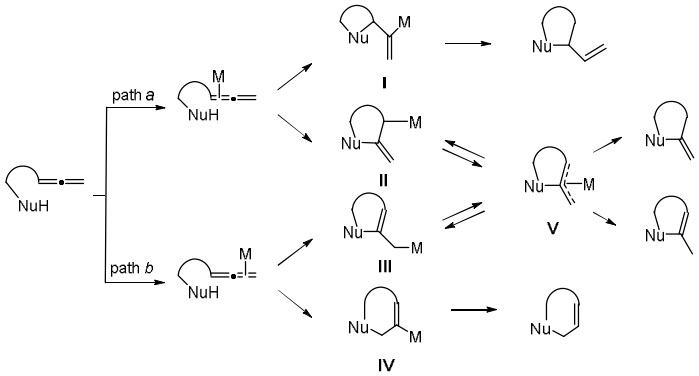
Abstract. *Allenes bearing a nucleophile are fruitful building blocks for heterocyclization reactions, providing a wide number of differently substituted heterocyclic structures. In particular, domino processes involving inter- or intra-intramolecular sequences are good tools to access substituted- or bicyclic heterocycles in a single step. Among the methods of the activation of the allenic moiety, palladium catalysis typically occupies a pivotal role. Progress in the field of carbopalladation/cyclization reactions by C-N, C-O or C-C bond formation to allenes under palladium catalysis is focused in this review.*

Contents

1. Introduction

Among the unsaturated systems, allenes are a class of compounds particularly attractive for different kind of reactions due to their unique physical and chemical properties.[1] The presence of two cumulative carbon-carbon double bonds allows to achieve different skeletons, in particular through domino reactions which involve intramolecular processes. One of the most effective strategies to convert allenes in structurally complex products is based on the activation by transition metal catalysis. In particular, reactions of allene derivatives containing nucleophilic groups allow to achieve functionalized heterocycles or heteropolycycles by highly atom-economy processes.[2] The cyclization process can occur with regio- and stereoselectivity problems, which are however depending on the feature of the chain that connects the reactant groups (Scheme 1).



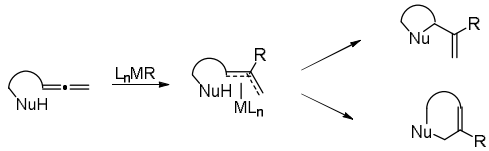
Scheme 1. General procedures for the transition metal-catalyzed cyclization of allenes bearing a nucleophile.

If the nucleophile occupies a position suitable for the formation of five- or six-membered rings, the selectivity of the reaction is largely predominant because normally smaller or larger rings are unfavoured.

The mechanism of the cyclization is depending on the transition metal used and on the substrate structure. The nature of the transition-metal plays a crucial role in term of efficiency, stability and inexpensiveness. Palladium plays a dual role, as activator of the allenic moiety and as promoter of the further functionalization reaction subsequent to the cyclization.

While a soft Lewis acid such as gold prefers the coordination with the terminal double bond of the allene (Scheme 1, path *b*), a hard Lewis acid such as palladium supports the interaction with the more electron-rich double bond of the allenyl group, typically resulting in the formation of a vinyl substituted nitrogenated ring (Scheme 1, path *a*). In this context, *endo-trig vs exo-dig vs endo-dig vs exo-trig* cyclizations are possible by intervention of the four complexes **I-IV**, two of which are in equilibrium with the same π-allyl-complex **V**. In a hydroamination process the final protodemetalation affords the product and regenerates the metal catalyst.

The treatment of allenes with some transition metal can undergo to generation of metal-π-allyl-complexes which are suitable intermediates for reaction with a nucleophile (Scheme 2). In most cases, this behavior involves palladium(II)-species, arising from oxidative addition of a palladium(0)-species to an organic halide. The subsequent intramolecular nucleophilic attack of the NH group on the π-allyl-complex results in a domino process with formation of functionalized heterocycles in regioselective manner.



Scheme 2. Cyclization of allenes involving π-allyl-complexes.

In this review, we focus our attention on palladium-catalyzed domino reactions of allenes bearing a nucleophile, which occur by carbopalladation/cyclization processes to provide hetero(poly)cycles. Nitrogen, oxygen, and carbon nucleophiles are suitable for these procedures and the presentation of the matter follows the kind of nucleophile involved in the reaction.

2. Carboamination of allenes

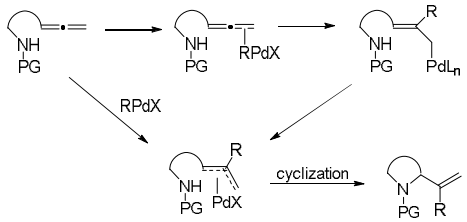
Intramolecular palladium-catalyzed reactions between nitrogen nucleophiles and allenes, combined with a further carbon-carbon bond formation, are important tools in organic synthesis, providing a number of three to ten-membered heterocycles. Coupling reactions of aryl or vinyl halides with allenes bearing an amino group play a relevant role in this context, as demonstrated by the examples reported in the literature by several research groups. The reaction occur by an initial carbopalladation which can be achieved at inter- or intramolecular level. The palladium-catalyzed reactions performed in the presence of chiral ligands result in a complete stereoselective cyclization processes.

2.1. Palladium-catalyzed intermolecular coupling/intramolecular amination processes

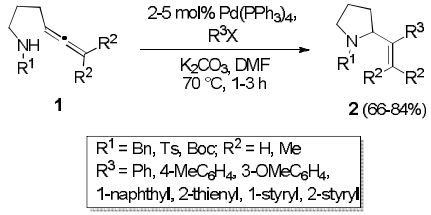
Allenes bearing nucleophiles such secondary amines, amides sulfonamides, and carbamates undergo carboamination when treated with Pd(0)-catalysts and aryl, allyl or vinyl halides. Typically, the reaction proceeds by formation of an intermolecular carbon-carbon bond by a Pd(II)-complex obtained by oxidative addition of the starting Pd(0)-species to the halide derivative. The so generated π-allyl-complex undergoes intramolecular nucleophilic attack from the NH group, which is crucial for the kind of the heterocyclic product (Scheme 3). Alternatively, the first-formed Pd(II)-species can act as the cyclization trigger through a π-olefin-complex. The latter pathway is preferred to justify the attack of the nitrogen nucleophile to the central carbon of the allenyl moiety.

The cyclization of γ-amino-substituted allenes **1** to yield 2-vinyl-substituted pyrrolidines **2** was reported in 1993 by Gallagher and co-workers (Scheme 4).[3] $Pd(PPh_3)_4$ was used as the catalyst, combined

with a wide range of aryl and vinyl halides, to trigger the formation of the electrophilic species essential for the generation of the organopalladium(II) intermediate.

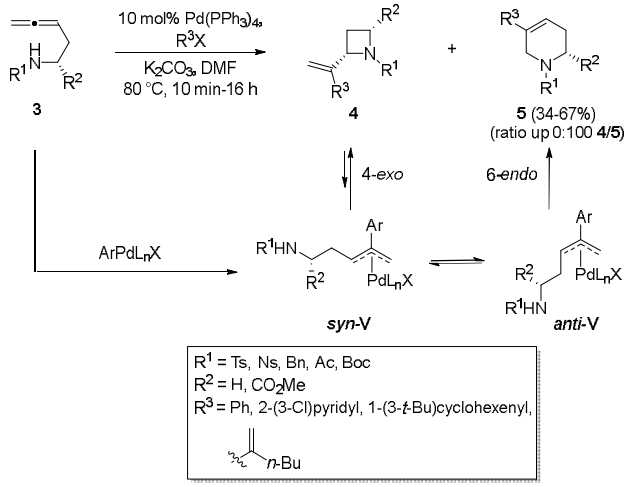


Scheme 3. General procedure for intermolecular carbopalladation/intramolecular amination of aminoallenes.



Scheme 4. Conversion of γ-aminoallenes into 2-vinyl-substituted pyrrolidines.

As shown in Scheme 5, β-aminoallenes **3** furnished the four- or six-membered nitrogen-containing heterocycles **4** and **5** by treatment with catalytic $Pd(PPh_3)_4$ and K_2CO_3 in the presence of aryl and heteroaryl halides or triflates.[4] The regioselectivity of the cyclization depends on the substituents of the starting material and the four- or six-membered ring formation resulted from the attack of the nitrogen onto one of the sp^2-allene carbon atoms. The geometry of the π-allyl intermediate is the crucial point of the mechanistic pathways that diverge according to the size of the formed heterocycle. In particular, the effect of the N-H protecting group as well as the nature of aryl halide for the selective 4-*exo*- vs 6-*endo*-allylic cyclization could be explained with its influence on the initial generation of the more stable *syn*-π-allylpalladium complex *syn*-**V**, which could be converted into the more hindered isomer *anti*-**V**.

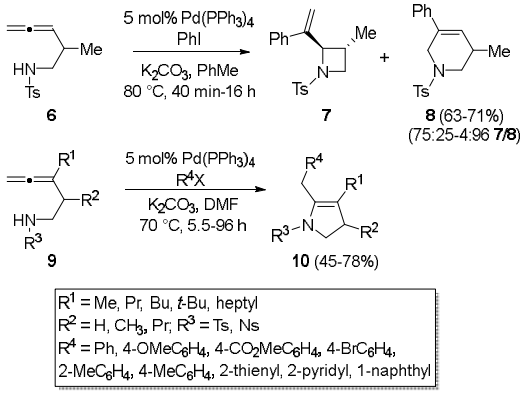


Scheme 5. Conversion of β-aminoallenes into azetidine and tetrahydropyridine derivatives.

The kinetic product azetidine **4**, obtained by 4-*exo* cyclization of the *syn*-intermediate, could undergo $Pd(PPh_3)_4$-mediated ring opening and through the *anti*-**V** the preferred 6-*endo* cyclization provided the thermodynamically more stable six-membered ring **5**. In detail, for an alkenyl triflate it was more difficult to generate the intermediate complex, so that its isomerization occurred slowly giving preferentially the four-membered ring. On the other hand, the better ability as leaving group of the nosyl than tosyl enhanced the isomerization process in such a way that the four-membered ring was no longer observed.

Analogous 2,4-*cis*-disubstituted azetidines are accessible by carbopalladation/cyclization of *N*-arylsulfonyl-substituted β-aminoallenes.[5]

Studies of Ma and co-workers confirmed the determinant role of the substituents on β-aminoallenes for the outcome of their reactions in Pd-catalyzed coupling-cyclization in the presence of aryl halides.[6] Starting from 3,4-allenamides **6**, azetidines **7** and/or 1,2,5,6-tetrahydropyridines **8** were isolated with high *de,* by treatment with aryl halides, catalytic $Pd(PPh_3)_4$ and K_2CO_3 in toluene at 80 °C, while 2,3-dihydro-1*H*-pyrroles **10** were proven to be the cyclization products when 3-substituted-5-unsubstituted-3,4-allenamides **9** were treated in same conditions in DMF at 70 °C (Scheme 6). Plausibly, in the former case, the reaction proceeded through carbopalladation forming a π-allylic palladium intermediate, while in the latter case by a nucleometallation-reductive elimination pathway.



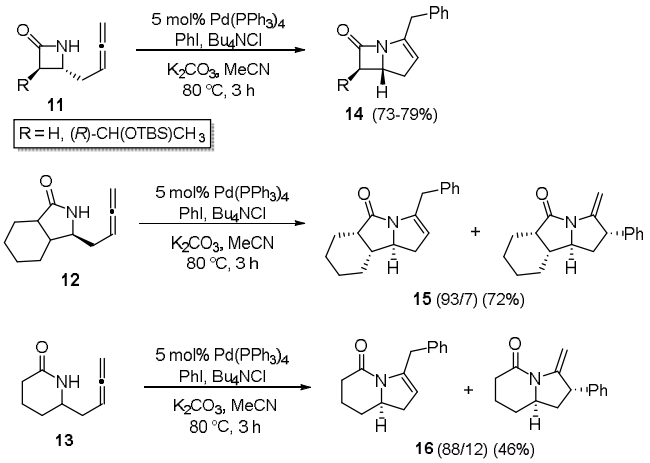
Scheme 6. Ring-size in carboamination of β-aminoallenes depending on the substituent.

Hiemstra and co-workers investigated the cyclization of the allenyl lactams **11-13**, which allowed to access five-membered fused-ring such as carbapenem **14**, pyrrolizine **15** and indolizine **16** structures by using $Pd(PPh_3)_4$ as catalyst, K_2CO_3 as the base, Bu_4NCl as the additive and iodobenzene (Scheme 7).[7] Due to the uncommon tendency of a π-allyl-complex to undergo attack on the central carbon, the reaction involving the central allene carbon is explicable by the generation of a π-olefin-complex as the key intermediate.

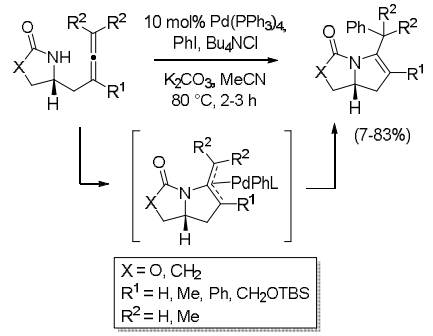
Under the same conditions, enantiopure allenyl lactams furnished enantiopure bicyclic enamides (Scheme 8).[8]

Also α-aminoallenes can undergo carbopalladation/cyclization reaction. In 1999, Ibuka, Tanaka, Ohno and their group reported conversion of substrates **17** to aziridine derivatives **18** working in the presence of iodobenzene, Pd(0)-catalyst, K_2CO_3 and 1,4-dioxane as solvent (Scheme 9).[9] The expected aziridine products were achieved in good yield also using 4-iodotoluene or β-bromostyrene. 1,4-Dioxane was proven to be crucial for the 3-*exo*-allylic cyclization. Thus, using the same conditions in DMF as the solvent, the 5-*endo*-allylic path was favored, affording to 2,5-dihydropyrrole derivatives **19** as the sole products.

Analogously, 1,4-dioxane resulted effective to obtain selective *exo*-allylic cyclization of β-aminoallenes. The treatment of **20** and iodobenzene with Pd(0)-catalyst and base afforded the 2,4-*cis*-4-alkyl-2-alkenylazetidines **21** as exclusive products. No formation of the possible regioisomeric six-membered ring was observed unless the presence of a strong electron-withdrawing 4-nitrophenylsulfonyl group on the nitrogen atom (Scheme 10).



Scheme 7. Carboamination of allenyl lactams.



Scheme 8. Carboamination of allenyl lactams in enantioselective manner.

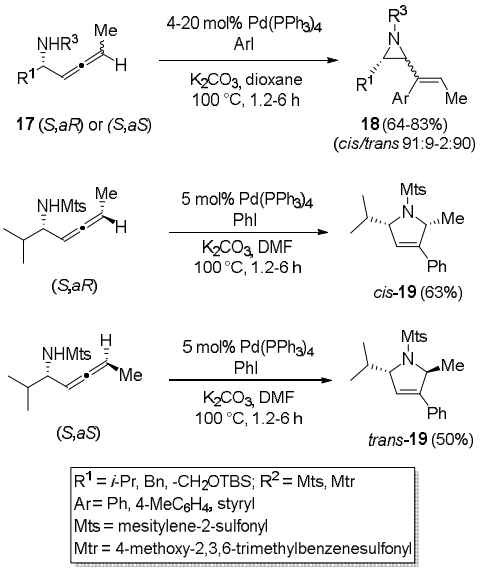
The carboamination of optically active γ-amino-allenamides **22** was performed with a catalytic amount of $Pd(PPh_3)_4$, an excess of K_2CO_3 in DMF at 100 °C affording the 4-imidazolidinones **23** in enantiopure form (Scheme 11).[10] The reaction proceeds through a carbopalladation/5-*exo*-allylic amination sequence with the π-allyl intermediate **VI**. The intramolecular carbopalladation investigated on substrates **24** worked successfully providing the tricyclic fused-ring imidazolidinones **25**. The styryl derivatives **23**, after deprotection and suitable functionalization, were conveniently used as intermediates for the preparation of a new class of tetracyclic benzodiazepine derivatives.[11]

This carboamination procedure was further developed exploiting the indole nitrogen of the *N*-allenyl amides **26** (Scheme 12).[12] The use of classical reaction conditions in acetonitrile as the solvent at reflux, furnished the styryl-substituted imidazoindole derivatives **27**. The reaction proceeded through the π-allyl-complex **VII** which selectively underwent the amination process on the internal carbon, whereas the possible formation of the C-C involving the nucleophilic 3-position of the indolyl nucleus was never observed.

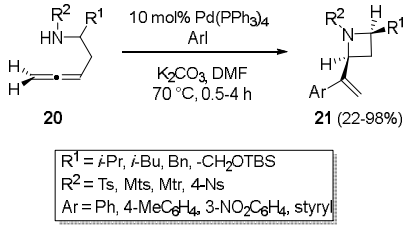
The anthranilic allenamides **28** treated with aryl iodides in the classic carbopalladation conditions were proven useful substrates for the preparation 2-(α-styryl)quinazolin-4-one derivatives **29** (Scheme 13).[13]

Working once again at reflux with acetonitrile as the solvent, Boc-protected allenyl derivatives of the 2-aminophenols and 1,2-phenylenediamine **30** reacted with (hetero)aryl iodides providing the 2-substituted dihydrobenzoxazoles and dihydrobenzimidazole **31** by treatment with a catalytic amount of $Pd(PPh_3)_4$ and K_2CO_3 (Scheme 14).[14] In terms of regioselectivity, the cyclization of *N*-allyl-1,2-phenylenediamine strongly

depended on the protecting group tethered to the nitrogen atoms, switching the reaction toward the seven-membered ring product **32**.



Scheme 9. Regioselective carbopalladation/amination of α-aminoallenes.



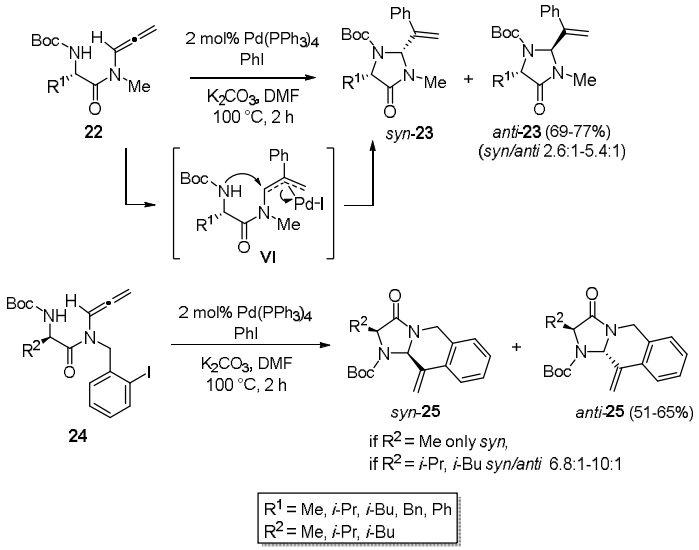
Scheme 10. Regioselective carbopalladation/amination of β-aminoallenes.

The same catalytic system is able to promote the cyclization of ω-aminoallenes to ten-membered azacycle products. Indeed, the Pd(0)-catalyzed reaction of compound **33** with iodobenzene in dimethylacetamide gave the benzo[*c*]azecine derivative **34** as the sole product by a 10-*endo*-allylic cyclization (Scheme 15).[15]

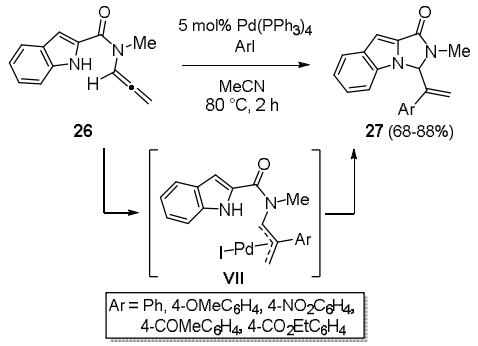
The regio- and *trans*-diastereoselective intermolecular coupling/intramolecular amination of 2,4-unsubstituted α-allenyl-hydrazines **35** with aryl iodides providing the *trans*-1,2-diazetidines **36** was reported in 2008 by Ma and co-workers (Scheme 16).[16] Conversely, a different regioselectivity with formation of the 2,3-dihydro-1*H*-pyrazoles **37** was observed when the reaction was carried out on substrates bearing a substituent in 2-position.[17]

The same research group performed a highly diastereoselective synthesis of pyrazolidines. The asymmetric reaction was based on a Pd(0)-catalyzed carboamination between the optically active β-allenyl- hydrazines **38** and (hetero)aryl halides in the presence of Ag_3PO_4 as the base and a chiral ligand in THF as the solvent (Scheme 17).[18] (*R,R*)-Bn-Box **39** was proven the most efficient chiral ligand, giving (3*R*,5*S*)-pyrazolidines **40** in good yields, often with very high enantiopurities (>99%) and high diastereoselectivities (up to 95:5). The absolute configurations of the newly formed chiral centers in the pyrazolidines depend on the configuration of substrates **38**, whereas enantio- and diastereoselectivities of the

pyrazolidine products are co-controlled by the structure of the allenes as well as by the efficiency of the chiral catalysts.



Scheme 11. Carbopalladation/amination of optically active γ-amino-allenamides.



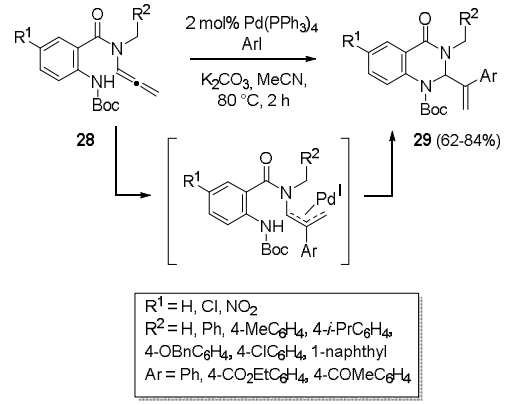
Scheme 12. Carbopalladation/amination of indole 2-carboxylic acid allenamides.

A spirooxazolidine chiral ligand (*Ra*,*S*,*S*)-**41** was fruitfully applied to the enantioselective cyclization of allenyl hydrazines **42** with (hetero)aryl iodides, affording pyrazolidines **43** in high yields and enantiomeric excesses (Scheme 18).[19] Control experiment revealed that the high enantioselectivity strongly depended on the spiro skeleton and the α-naphthylmethyl group.

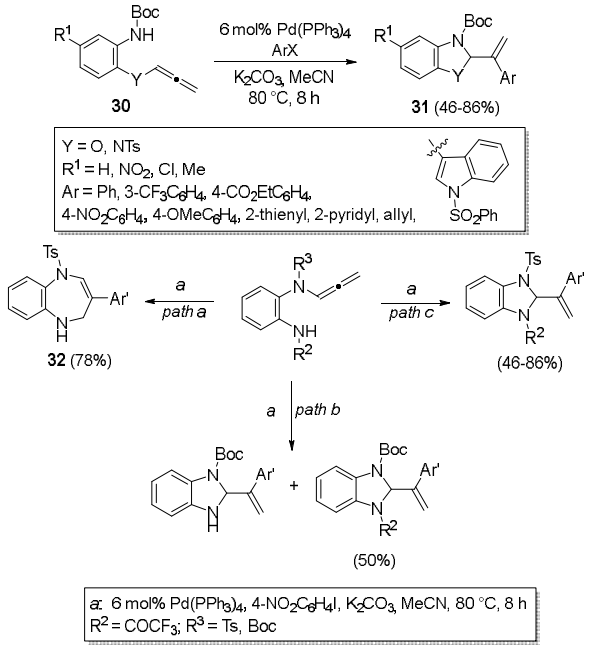
A synthetic protocol to access vinyl-substituted 1,4-benzodiazepinones **45** has been reported by a phosphine-free Pd(0)-catalyzed carbopalladation/allylic amination domino sequence starting from allenyl anthranyl amides **44** in the presence of aryl iodides (Scheme 19).[20] The Pd(0)-species required to start the reaction was generated from $PdCl_2(MeCN)_2$ in DMSO using 2 equiv. of BuLi as *in situ* reducing agent. This pure domino reaction occurs with total regioselectivity furnishing the desired 1,4-benzodiazepin-5-ones as the sole products. Indeed, benzo[1,5]diazoninone derivatives, arisen from the much more disfavoured 9-*endo* cyclization, were never observed (Scheme 20).

α-Aminoallenes **46**, after coupling with aryl iodides, can react intramolecularly giving either 3-pyrrolines or pyrroles (Scheme 21).[3a] Working with catalytic $Pd(PPh_3)_4$, K_2CO_3, and Bu_4NCl in DMF at

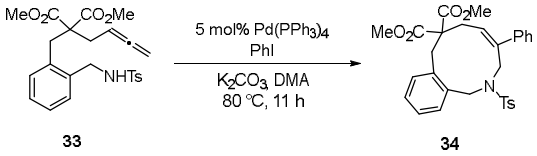
25 °C, the carboamination afforded 3-aryl-3-pyrrolines **47**. Conversely, the use of the same conditions at higher reaction temperatures gave the corresponding pyrroles **48**, bearing an aryl group at the C-3 position.



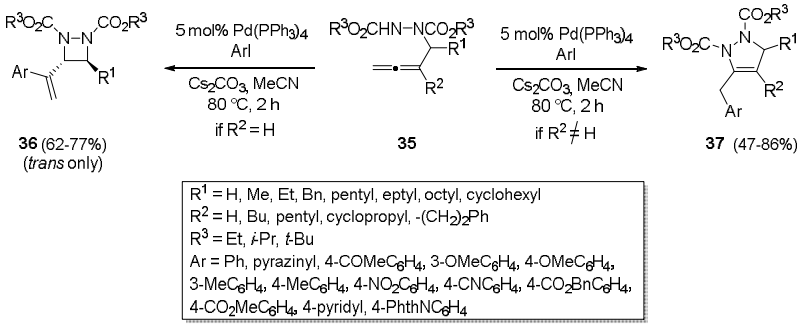
Scheme 13. Carbopalladation/amination of anthranilic allenamides



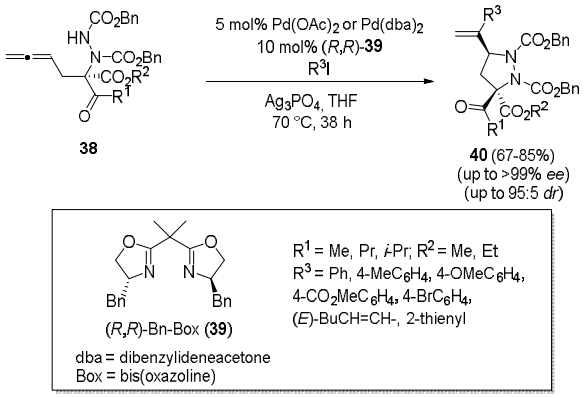
Scheme 14. Carbopalladation/amination of allenyl 2-aminophenols and 2-phenylendiamine.



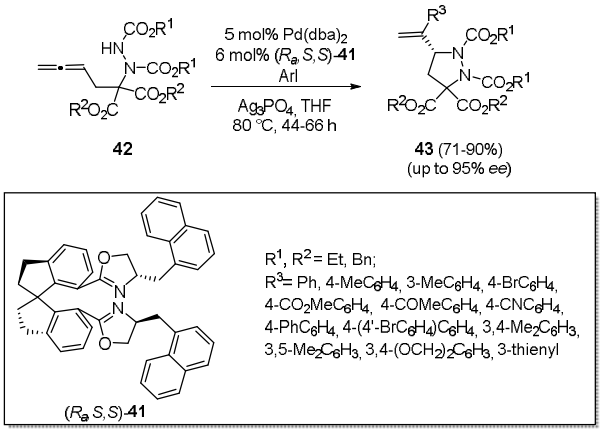
Scheme 15. Carbopalladation/amination of ω-aminoallenes.



Scheme 16. Regioselective carbopalladation/amination of α-allenyl-hydrazines.



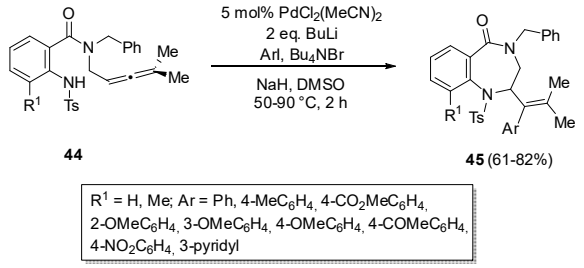
Scheme 17. Stereoselective carbopalladation/amination of β-allenyl-hydrazines.



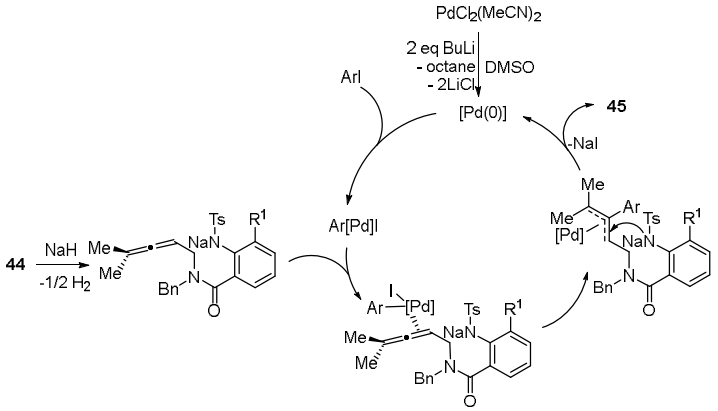
Scheme 18. Enantioselective carbopalladation/amination of β-allenyl-hydrazines.

The palladium-catalyzed intermolecular carbopalladation/intramolecular amination can also be achieved using allyl halides. Seminal works on this procedure was reported by Tamaru and co-workers, who reported the cyclization of the allenyl tosylcarbamates **49** to the 4-pentadienyl-substituted oxazolidinones **50** (Scheme 22).[21] The reaction was carried out using catalytic $PdCl_2(PhCN)_2$ and triethylamine in THF with an

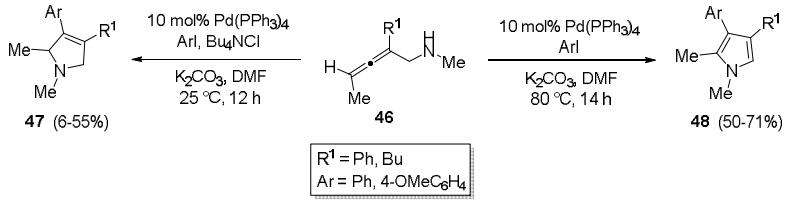
excess of allylic chlorides. The tosyl-protection was proven to be essential for the cyclization. If the final oxazolidinones were 4,5-disubstituted, high *trans*-stereoselectivity was observed. The outcome of this aminocyclization depended on the use of the Pd-catalyst. $Pd_2(dba)_3 \cdot CHCl_3$ and $PdCl_2$ might be used with similar efficiency as of $PdCl_2(PhCN)_2$. Working with $Pd(PPh_3)_4$, only *N*-allylation of the tosylcarbamate was queerly observed. Moreover, performing this reaction with $Pd(PPh_3)_4$ in the absence of an allylating agent, a formal dimerization of the substrate occurred, with formation of the oxazolidinone products **51**.



Scheme 19. Carbopalladation/amination of α-allenyl-anthranylamides.



Scheme 20. Plausible mechanism for carbopalladation/amination of α-allenyl-anthranylamides.

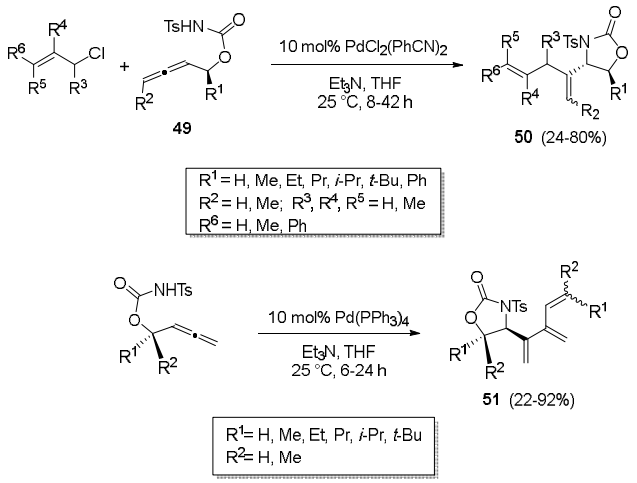


Scheme 21. Carbopalladation/amination of α-aminoallenes for the synthesis of pyrrole derivatives.

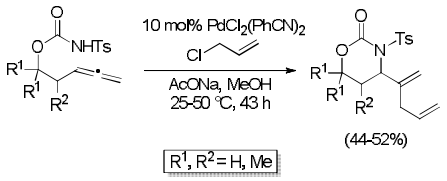
The reaction conditions cannot be extended to the synthesis of the six-membered ring analogues. Only in the case of *N*-tosyl-1,1-dimethyl-3,4-pentadienylcarbamate, in the presence of AcONa as base, the expected *N*-tosyl-6,6-dimethyl-4-(1-allylvinyl)-tetrahydro-1,3-oxazin-2-one was obtained (Scheme 23).

The reaction mechanism plausibly involves the intervention of the π-allyl intermediate **VIII**, which proceeds following two possible pathways (Scheme 24). Complex **VIII** could coordinate the internal double bond of the allene moiety promoting the nucleophilic attack of the carbamate nitrogen with generation of the vinyl-palladium(II) intermediate **IX**, which is converted into the final product by reductive elimination of the

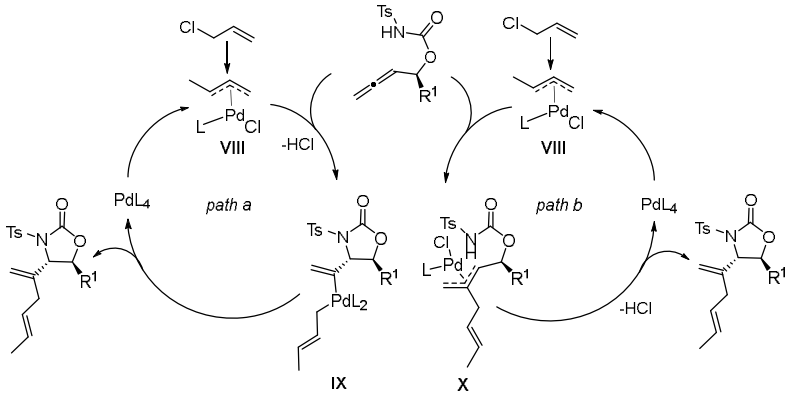
metal (*path a*). Otherwise, **VIII** could generate the π-allyl-palladium complex **X**, which undergoes nucleophilic substitution by the carbamate anion furnishing the oxazolidinone product and a Pd(0)-species (*path b*). Between these pathways, the former seems preferable due to speculative considerations, although the latter could not be ruled out.



Scheme 22. Carbopalladation/amination of *N*-tosylamides-α-aminoallenyl carbamates with allyl halides.

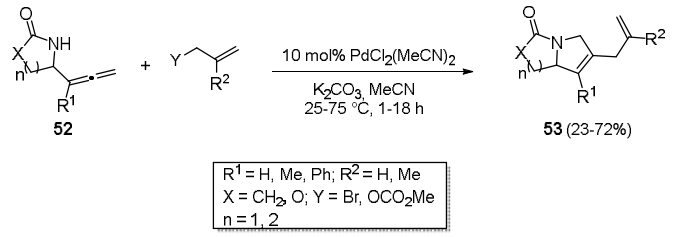


Scheme 23. Carbopalladation/amination of *N*-tosylamides-β-aminoallenyl carbamates with allyl chloride.



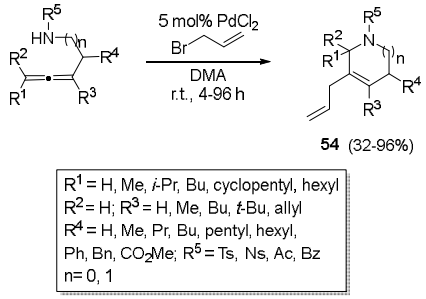
Scheme 24. Mechanism for the cyclization of *N*-tosylamides-β-aminoallenyl carbamates with allyl chloride.

The same behavior was observed with the treatment of the cyclic allenamides **52** with allyl chlorides in the presence of $PdCl_2(MeCN)_2$ as the catalyst and K_2CO_3 in acetonitrile to give the allyl-substituted bicyclic heterocycles **53** (Scheme 25).[22]



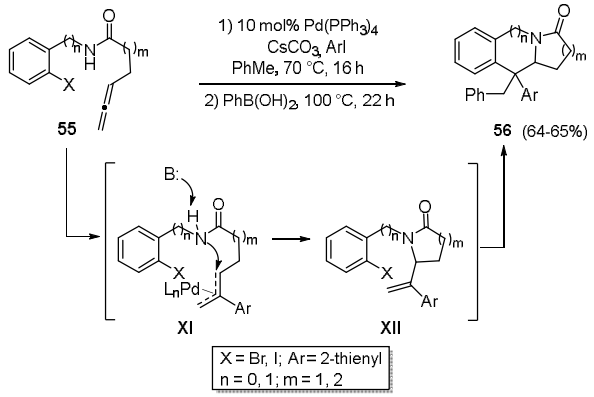
Scheme 25. Carbopalladation/amination of cyclic aminoallenes.

This procedure works well also with α- or β-aminoallenes. Performing the reaction in the presence of allyl bromides and DMA as solvent at r.t., the 3-allyl-3-pyrrolines and 3-allyl-1,2,3,6-tetrahydropyridines **54** were obtained in moderate to high yields (Scheme 26).[23]



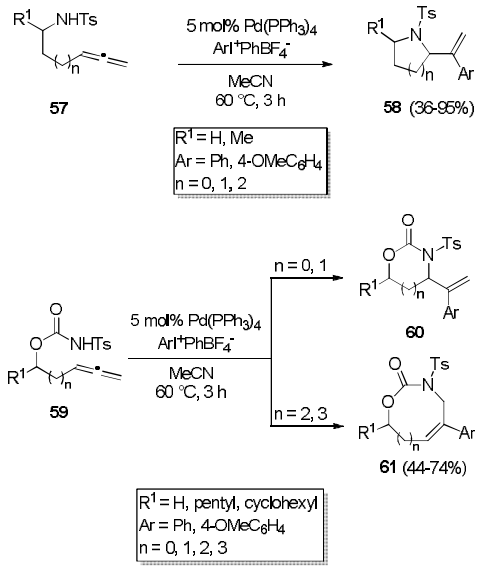
Scheme 26. Carbopalladation/amination of aminoallenes with allyl bromide.

The *exo*-cyclization of allenes bearing a nitrogenated nucleophile in the presence of aryl halides leads to heterocycles suitable for further functionalization due to the presence of the styryl moiety. The intramolecular amination on the π-allyl-palladium complexes **XI** generated from allenamides **55** and aryl iodides in the presence of $Pd(PPh_3)_4$ and K_2CO_3 led to a first cyclized products **XII** (Scheme 27).[24] These latter evolved again by a Pd-catalyzed cyclization involving phenylboronic acid to yield the tricyclic systems **56**.



Scheme 27. Dual cyclization of aminoallenes involving a carbopalladation/amination process.

Kang and co-workers developed an alternative version of the palladium-catalyzed intermolecular coupling-intramolecular amination reaction, based on the use of hypervalent iodonium salts instead of aryl halides.[25] Diphenyl iodonium tetrafluoborate has been used with *N*-tosyl aminoallenes **57** in the presence of catalytic amount of $Pd(PPh_3)_4$ in acetonitrile, affording the styryl-substituted heterocyclic products **58** (Scheme 28). Application of these conditions to allenyl carbamates **59**, either *exo*- or *endo*-cyclization were observed, providing oxazolidinones and 1,3-oxazin-2-ones **60** as well as higher membered 1,3-*N,O*-heterocycles **61**. Compared to similar Pd-catalyzed coupling-cyclization reactions of aminoallenes, this procedure required only a slight excess of the aryl component and the reaction worked at lower temperature in shorter reaction times.



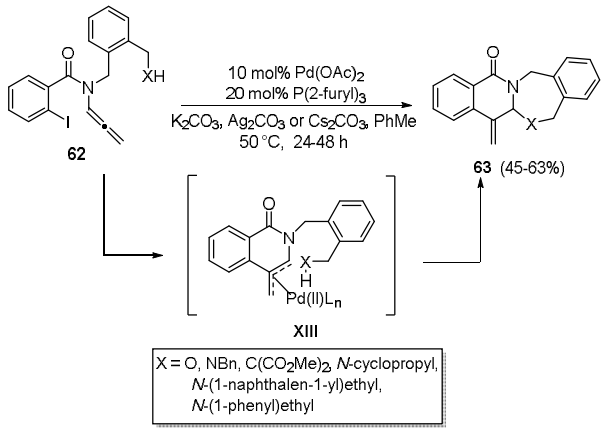
Scheme 28. Carbopalladation/amination reactions with iodonium salts.

2.2. Palladium-catalyzed intramolecular coupling/intramolecular amination processes

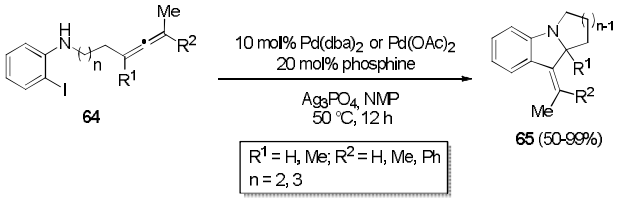
Grigg reported the Pd-catalyzed intramolecular carbopalladation of the allenyl aryl iodides followed by an intramolecular nucleophilic addition which intercepted the firstly generated π-allyl-palladium complex, leading to polyheterocycles. This dual intramolecular carbopalladation/amination process was performed starting from substrates **62** in the presence of K_2CO_3 or Ag_2CO_3 with formation of the tetracyclic isoquinolinone derivatives **63** (Scheme 29).[26] After oxidative addition of Pd(0) to the aryl iodide, a selective carbopalladation/cyclization onto the central allenic carbon would first generate the π-allyl-palladium complex **XIII** which was intramolecularly captured by a nucleophile giving the final product.

The 2-iodoanilines bearing an allenyl moiety **64** were converted into the indole derivatives **65** by treatment with a Pd(0)-catalyst, a phosphine ligand and triethylamine in acetonitrile (Scheme 30).[27] Also in this case the reaction proceeds by intramolecular carbopalladation of allenes followed by intramolecular amination of π-allylpalladium complexes. An asymmetric version of this procedure has been developed using a chiral phosphine ligand.[28] The enantioselectivity was found to be depended on the chiral ligand and the solvent used. (*S*)-(-)-BINAP or (*S*)-Tol-BINAP resulted the most useful chiral ligands examined, using *N*-methylpiridone (NMP) as solvent.

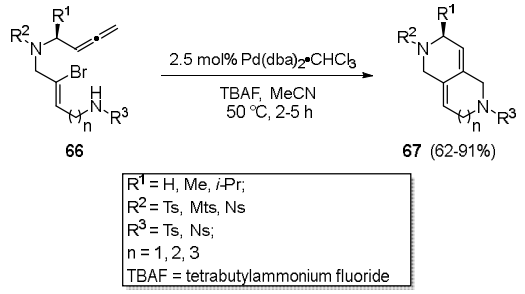
Bromovinyl-substituted aminollenes are suitable candidates for domino Pd(0)-catalyzed reaction which afford bicyclic heterocycles in good to high yields.[29] Using a catalytic amount of palladium(0) in the presence of TBAF or Cs_2CO_3 in acetonitrile, allenes **66** were converted into the fused six-six-, six-seven-, or six-eight-membered bicyclic products **67** (Scheme 31).



Scheme 29. Intramolecular carbopalladation/amination of allenyl 2-iodobenzamides for the synthesis of tetracyclic systems.



Scheme 30. Intramolecular carbopalladation/amination of allenyl 2-iodobenzamides for the synthesis of tricyclic systems.

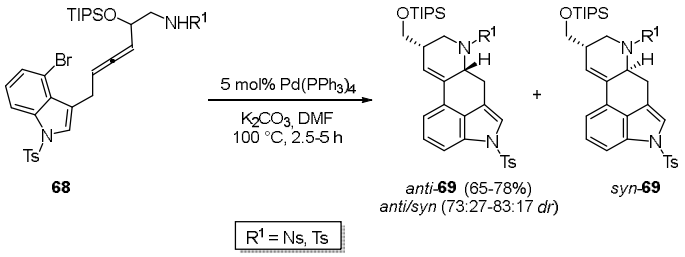


Scheme 31. Intramolecular carbopalladation/amination of allenyl bromoalkenylamines.

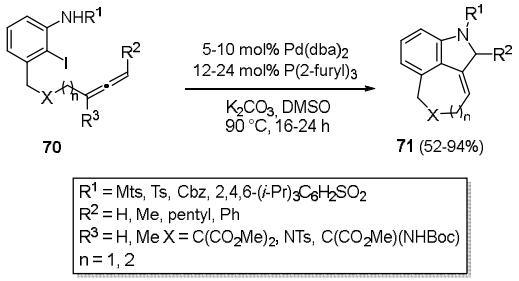
This strategy was applied to the 4-bromoindolyl allenes **68** in the total synthesis that leads to a tetracyclic structure, precursor of the biologically important ergot alkaloids (Scheme 32).[30] The key step, performed with Pd(0)-catalysis and K_2CO_3 in DMF, allowed the direct construction of the C/D ring system of the ergot alkaloids skeleton **69**, precursors of lysergol, isolysergol, and lysergic acid.[31] This procedure could be performed in enantioselective manner using optically active substrates prepared from a chiral 1,3-aminoalcohol. The C5 stereogenic center was generated with transfer of the allenyl axial chirality to the central chirality.

In 2015, Nemoto and co-workers developed an intriguing Pd-catalyzed domino cyclization by a dual intramolecular coupling/amination sequence.[32] Allenes tethered at the *meta-position* of 2-iodoaniline derivatives **70** reacted with Pd(0)-catalyst in the presence of K_2CO_3 in DMSO providing 3,4-fused tricyclic

indoline derivatives **71**, which were divergently transformed into three types of indole derivatives (Scheme 33).



Scheme 32. Intramolecular carbopalladation/amination of bromoindolyl allenes to ergot alkaloids skeleton.

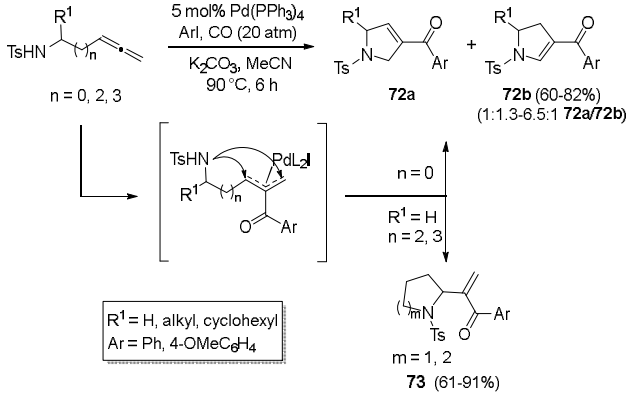


Scheme 33. Intramolecular carbopalladation/amination of allenyl 2-iodoanilines to tricyclic indole products.

2.3. Carbonylative carbopalladation/intramolecular amination processes

The palladium-catalyzed carbonylation of aromatic halides is one of the most versatile and convenient processes for the preparation of aromatic carbonyl compounds. The carbopalladation/intramolecular amination process carried out in the presence of carbon monoxide allows the interception of the CO species prior to or after the cyclization. In the former case, a carbonyl group was inserted inside or outside the ring, while in the latter case ketone or ester functional groups were obtained.

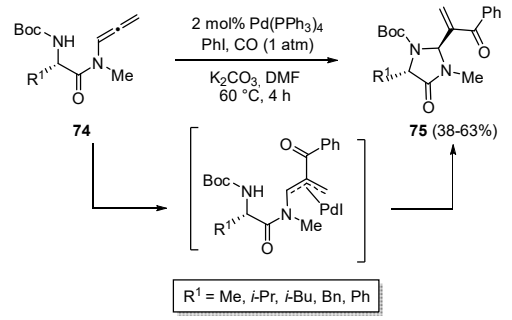
Cyclization of *N*-tosyl α-, γ- and δ-aminoallenes, performed in the presence of ArI with catalytic $Pd(PPh_3)_4$ and K_2CO_3 in acetonitrile and CO atmosphere, arises in *exo*- or *endo*-manner depending on the length of the chain between the allene and amine moieties (Scheme 34).[33]



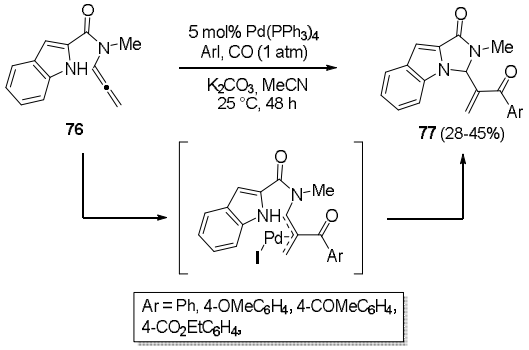
Scheme 34. Carbonylative carbopalladation/amination of *N*-tosyl aminoallenes.

The oxidative addition to generate the organopalladium(II) species involved carbon monoxide giving 3-acyl- or 2-vinylpyrrolines **72** or **73**, respectively.

When used under CO atmosphere, the reaction conditions which successfully promoted the intermolecular coupling/intramolecular amination reaction of allenamides **74** and **76** afforded imidazolidines **75** and indoloimidazoles **77** bearing an enone moiety (Schemes 35 and 36, respectively). Also in these cases, the carbopalladation-5-*exo*-*dig* amination was selectively observed with variously substituted aryl iodides through aryl palladium π-allyl intermediates.



Scheme 35. Carbonylative carbopalladation/amination of α-aminoacid allenamides.



Scheme 36. Carbonylative carbopalladation/amination of 2-carboxylic acid allenamides.

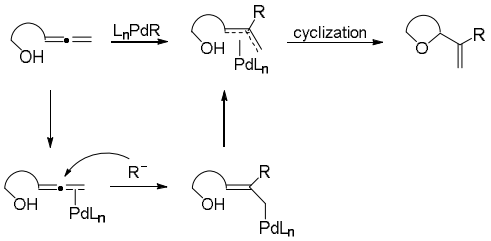
3. Carboalkoxylation of allenes

Domino palladium-catalyzed reactions involving oxygen nucleophiles and allenes, via formation of a C-C and a C-O bonds are important tools providing functionalized heterocycles. In literature various examples of carbopalladation of allenes followed by the attack from an oxygenated functional group are reported for the synthesis of oxygenated heterocycles rings. The four-five-six oxygen containing heterocycles always play an important role due to their great presence in natural and biologically active products. The efficiency of Pd-catalyzed reactions toward the regioselective and, in case, the enantioselective control warrants high value to this cyclization process.

3.1. Palladium-catalyzed intermolecular coupling/intramolecular alkoxylation processes

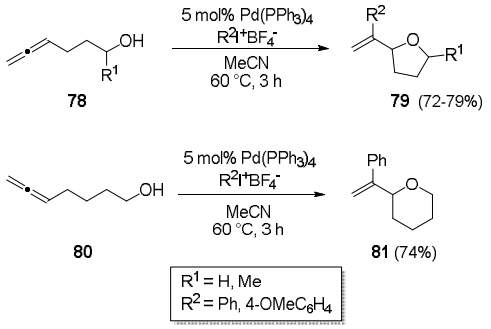
Allenyl compounds containing an oxygenated functional group (*i.e.* alcohols, ketones, carboxylic acids and esters) which act as nucleophile, can undergo to a cyclization process promoted by Pd(II)-catalysts in the presence of different kinds of aryl or allyl halides. The reaction can follow to possible pathways: in the first one, the formation of an intermolecular carbon-carbon bond between allene and halide function is followed by an intramolecular nucleophilic attack from the OH group on the π-allyl-complex, which determines the kind of heterocycle (Scheme 37). Conversely, in the second case, the Pd(II)-species preformed can act as the

cyclization starter for the π-olefin-complex and the following insertion of the R-group. The latter pathway can also explain the various kind of reactivity of the allenyl moiety towards the attack of the oxygenated nucleophile, in particular to the central carbon.



Scheme 37. General procedure for intermolecular carbopalladation/intramolecular alkoxylation of allenols.

In 1998, a first example of cyclization of γ- and δ-allenols **78** and **80** to access to 2-vinyl-substituted tetrahydrofurans and tetrahydropyrans **79** and **81** was reported by Kang and co-workers (Scheme 38).[34] The reaction was carried out using $Pd(PPh_3)_4$ as the catalyst and aryl iodonium salts to promote the formation of the electrophilic species involved in the cycle as organopalladium(II) intermediate.



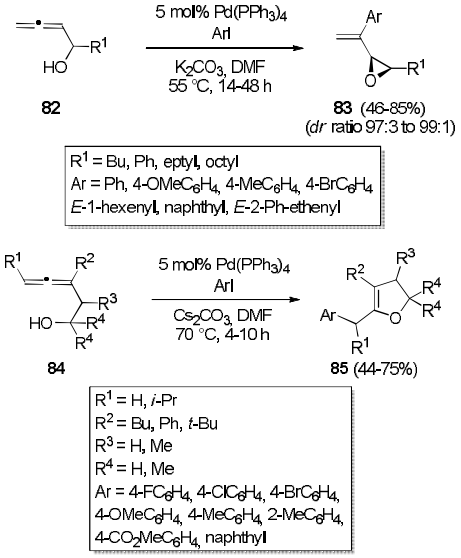
Scheme 38. Carbopalladation/alkoxylation reactions of γ,δ-allenols with iodonium salts.

From the synthetic point of view, products obtained by cyclization are not only due to the inner structural features of substrates, but also are influenced by the different regioselective pathways on the π-allyl intermediate. For example, while treating α-allenols **82** with $Pd(PPh_3)_4$, aryl iodide and K_2CO_3 gives solely the epoxides **83**,[35] the β-allenols **84** furnishes the products **85** (Scheme 39).[36] If the formation of products **83** are justified with the intervention of π-allyl-complexes that undergoes selectively cyclization in *exo*-allylic manner, the conversion of **84** into the 2,3-dihydrofuran derivatives follows a highly selective oxidative *exo*-mode oxypalladation of the terminal C-C double bond (Scheme 40).

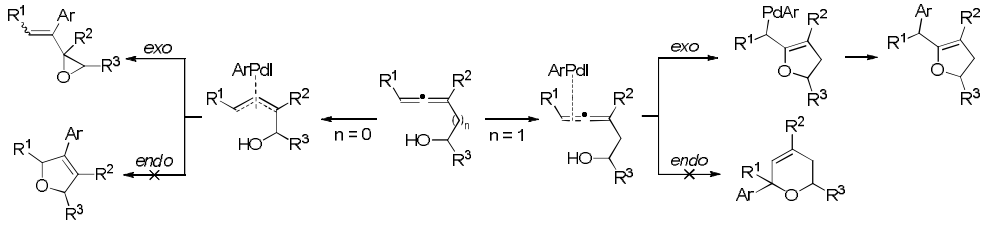
A similar Pd-catalyzed reaction starting from γ-allenols **86** was performed in enantioselective version by Xie and Ma in 2013, affording high enantioenriched 2-styryl substituted tetrahydrofurans **88** (Scheme 41).[37] Using the chiral biphosphine ligand (*R*,*R*)-**87** with a Pd(0)-catalyst in the presence of aryl iodides and K_2CO_3 in acetonitrile at 90 °C, the cyclization occurred in 60-87% yield and 85-92% *ee* towards the (*R*)-stereoisomer. Plausibly, the regioselective carbopalladation formed the ArPdI complex *in situ* involving the central carbon atom of the allenyl group, forming only one of the two possible π-allylic palladium complex due to the steric repulsion between the $-CH_2CH_2OH$ moiety and the chiral ligand which determines the unique cyclization product.

In 2015 Miao and coworkes developed a highly chemoselective cascade coupling-cyclization of allenols derivatives.[38] The reaction was carried out on substrate **89** using ArI, $Pd(PPh_3)_4$ as catalyst with PPh_3 in DMF. In this case authors suggest how the insertion of the aryl group in the central carbon to the

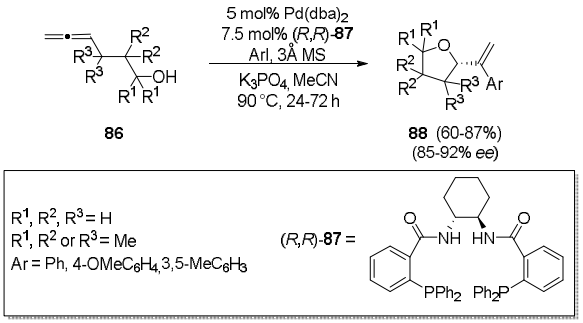
allenyl system makes the inner carbon more electrophile than the outer one, thus driving the pathway regio- and stereoselectively towards the formation of *trans*/*cis* 2-vinyl substituted benzofuran systems **90** (Scheme 42). Interestingly, the *cis*/*trans* isomers ratio is highly influenced by the electronic nature of the aryl iodine employed: the presence of electron-donating groups favors *trans* products (R^2=4-MeC_6H_4, *cis*/*tran*=1:3.5), while ratio is inverted with electron-withdrawing substituents (R^2=2-FC_6H_4, *cis*/*trans*=3.2:1).



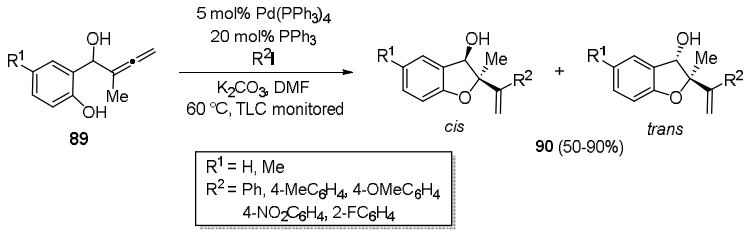
Scheme 39. Cyclization reactions of α,β-allenols with aryl iodide.



Scheme 40. Plausible mechanism for cyclization reactions of allenols with phenyl iodide.

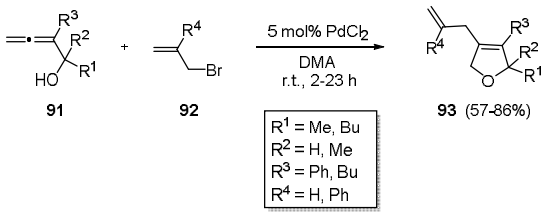


Scheme 41. Enantioselective carbopalladation/alkoxylation reactions of γ-allenols with aryl iodide.



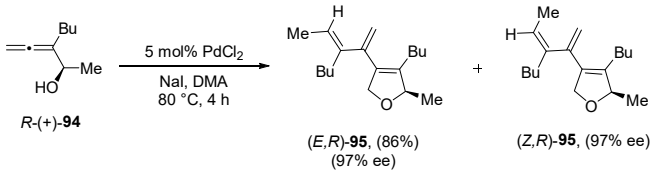
Scheme 42. Benzofuran synthesis from carbopalladation/alkoxylation of α-allenols **89**.

An unusual reaction pathway to the outer carbon of the allenyl system was reported in 2000 by Ma and Gao.[39] Their work was based on the use of the allyl bromides **92**, allowing the transformation of the allenyl derivates **91** into the two 4-alkenyl-2,5-dihydrofurans **93** in moderate to high yields (Scheme 43).



Scheme 43. Carbopalladation/alkoxylation reactions of α-allenols with allyl bromides.

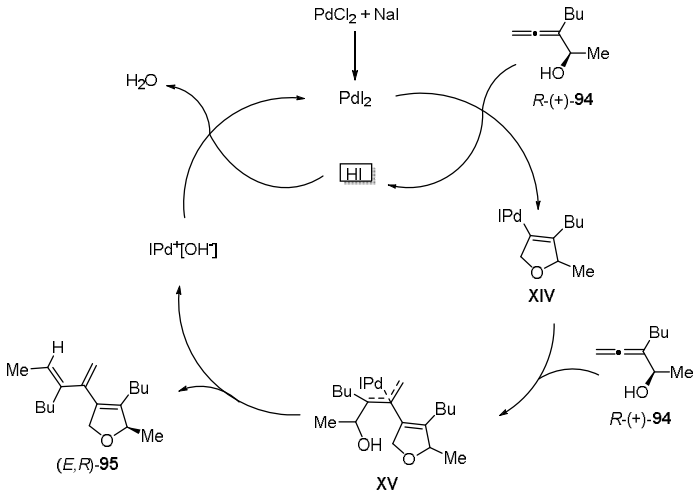
In 2008, Ma and Deng reported the homodimeric coupling reaction of α-allenols using $PdCl_2$ and NaI.[40] In this process, the most efficient cyclization step was observed on both the enantiopure allenes *R*-(+)- and *S*-(-)-**94** (depicted in Scheme 44 for the *R*-(+)-**94** enantiomer) that give rise to the intermediate **XIV** (Scheme 45). In turn, the latter undergoes the carbopalladation step with generation of the intermediate **XV** as the precursor of the homodimeric products **95**, obtained respectively in a *E*/*Z* ratio 95:5, with high *ee* for each diastereoisomer.



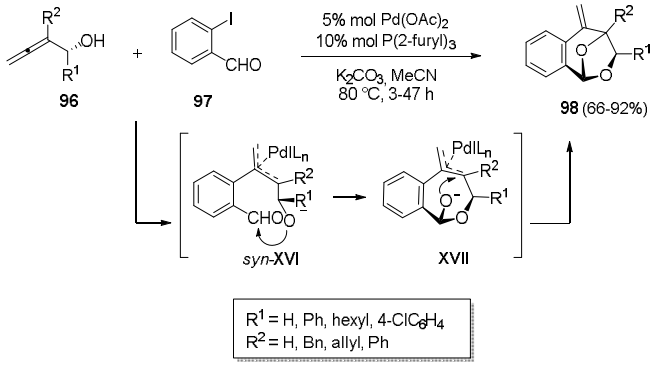
Scheme 44. Homodimeric coupling reaction of α-allenols.

In 2010 an useful method for one pot synthesis of oxa-bridged benzocycloheptanes,[41] the core structure of a class of compounds with pharmacological activity, was developed using 2-iodobenzaldehyde **97** in the presence of catalytic $Pd(OAc)_2$, tri-(2-furyl)phosphine as ligand and K_2CO_3 in acetonitrile at 80 °C. After the first carbopalladation step of **96**, the intermediate *syn*-**XVI** promotes the intramolecular 1,2-addition of the alkoxyl anion to the aldehyde functionality to give **XVII**, which furnishes the product **98** by intramolecular allylation (Scheme 46).

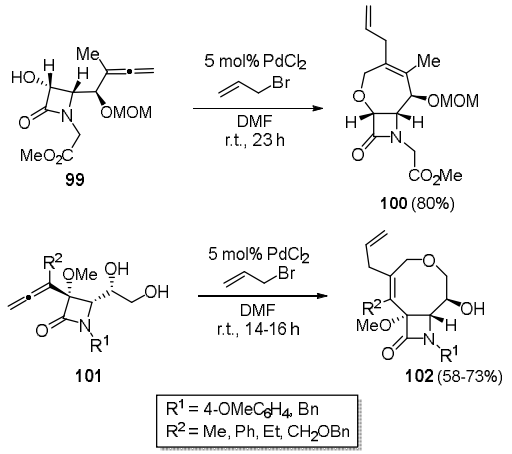
The behavior of allenyl β-lactams and allyl bromide with palladium-catalysts was reported by Alacaide and coworkers respectively in 2007 and 2009. Undergoing 2-azetidinone **99** containing a γ-allenol moiety to oxypalladation step in presence of $PdCl_2$ and an allyl bromide in DMF, the seven membered product **100** was isolated as the sole product arising from a 7-*endo*-*trig* cyclization.[42] Similarly, the γ,δ-bisallenol substrates **101** in the same conditions provided the oxycine fused bicyclic structures **102** in moderate yields through a regioselective 8-*endo*-*trig* pathway involving selectively a hydroxyl group (Scheme 47).[43]



Scheme 45. Mechanism of homodimeric coupling reaction of α-allenols.

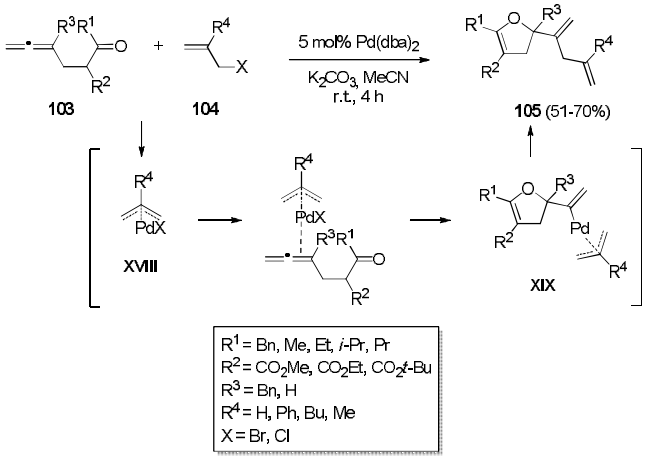


Scheme 46. Carbopalladation/alkoxylation of allenols for the synthesis of oxa-bridged benzocycloheptanes.



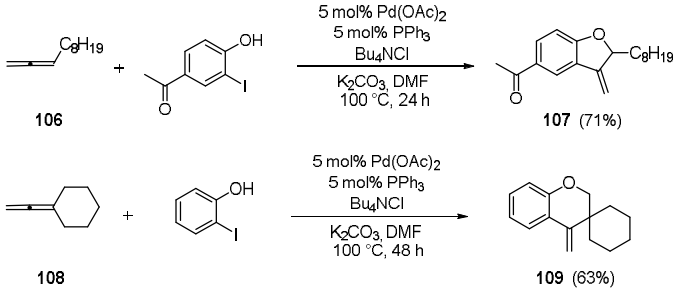
Scheme 47. Carbopalladation/alkoxylation of allenyl β-lactams.

A palladium-catalyzed intermolecular coupling combined with an intramolecular alkoxylation is achievable using different sources of allenes with allyl halides. A work based on this procedure was reported by Ma and co-workers for the cyclization of the γ-allenyl acetylacetates **103** to the 4-pentadienyl-substituted dihydrofurans **105** (Scheme 48).[44] The reaction was carried out using 5 mol% $Pd(dba)_2$, K_2CO_3 in acetonitrile with substituted allylic halides **104**. The reaction mechanism plausibly involved the formation of a π-allyl intermediate **XVIII**, which proceeds by coordination of the allene internal double bond promoting the nucleophilic attack of the acetylacetates oxygen. The generation of the vinyl-palladium(II) specie **XIX** is then converted into the final product by reductive elimination of the metal.



Scheme 48 Carbopalladation/alkoxylation of γ-allenyl acetylacetates with allyl halides.

A procedure of intermolecular carbopalladation/cyclization avoiding the use of allenols has been reported in 1991 by Larock and co-workers starting from 2-iodophenols and allenes (Scheme 49).[45] The cyclization step involves again the attack by a hydroxyl group on a π-allyl-palladium complex, although supported on the aryl halide, as shown for substrates **106** and **108** to give the products **107** and **109**, respectively. This approach has been developed also with a 2-iodobenzyl amine and a 2-iodoaniline to provide nitrogenated heterocycles.



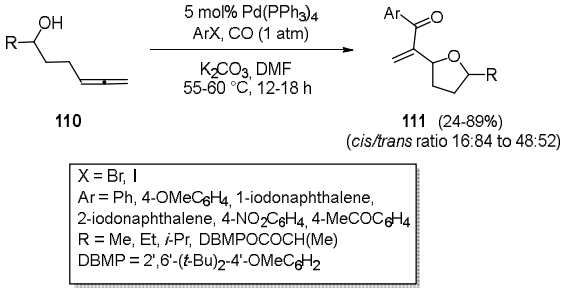
Scheme 49. Carbopalladation/cyclization starting from 2-iodophenols and allenes.

3.2. Carbonylative carbopalladation/intramolecular alkoxylation processes

The carbopalladation of allenes with aryl halides in presence of carbon monoxide can occur with insertion of CO into the heterocyclic ring giving a conjugated unsatured system or with formation of an ester functional group. This process follows the typical pathway of carbopalladation step, with formation of an

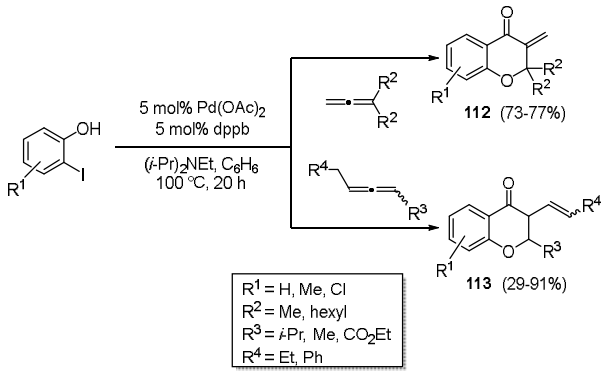
aroyl-Pd(II) intermediate, originated by oxidative addition, which can consequently be trapped by a nucleophilic partner with final insertion.

γ-Allenols **110** undergo cyclization-carbonylation-coupling with aryl and vinyl halides in the presence of catalytic $Pd(PPh_3)_4$, base, and CO to form aryl (tetrahydrofuran-2-yl)vinyl ketones **111** (Scheme 50).[46] The reaction is strongly temperature dependent because at 80 °C the CO insertion does not readily occur, while at 55-60 °C the ketone products are achieved in good yields.



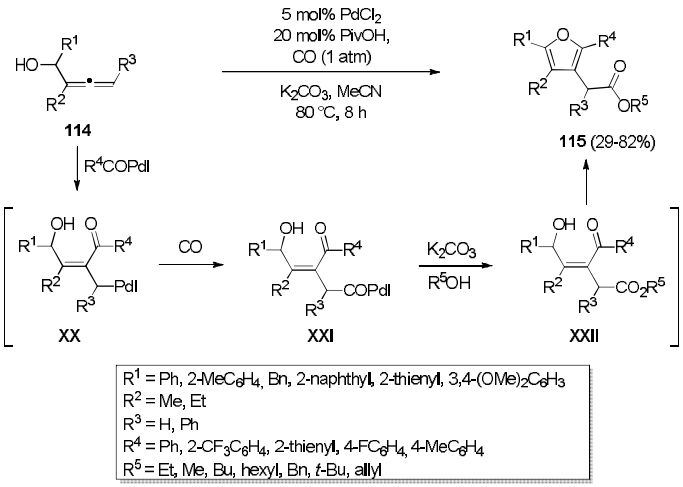
Scheme 50. Carbonylative carbopalladation/alkoxylation of γ-allenols.

In 1997 Alper and co-worker proposed the preparation of substituted benzopyranones starting from 2-iodophenols in the presence of an allenyl substrate and CO atmosphere by a reaction that takes place in a regioselective manner.[47] Treatment of 2-iodophenols and allenes using a catalytic system containing $PdCl_2$-dppb in the presence of $(i\text{-Pr})_2NEt$ in benzene at 100 °C for 20 h under 20 atm of carbon monoxide resulted in the formation of 3-methylene-2,3-dihydro- or 3-vinyl-4*H*-1-benzopyran-4-one derivatives **112** and **113** (Scheme 51). The required ratio of the allene to 2-iodophenol is 2:1, and that of allene to $PdCl_2$ and dppb is 40:1:1, and the presence of dppb was proven to be essential to gain satisfactory yields.



Scheme 51. Carbonylative carbopalladation/alkoxylation starting from 2-iodophenols and allenes.

More recently a new palladium-catalyzed one-pot multi-component reaction of allenols was developed for the preparation of substituted 2-(furan-3-yl)acetates.[48] The reaction involving α-allenols **114** underwent in presence of $PdCl_2$ (5 mol%) and PivOH as ligand, K_2CO_3, under CO atmosphere (1 atm), in acetonitrile at 80 °C (Scheme 52). The initial oxidative addition of the Pd(0) species with the aryl iodide undergoes the carbonylation step affording an acyl palladium complex **XX**. The acylation of the allene system **XXI** is indeed followed by nucleophilic displacement with the alcohol to give the product **XXII** which, after intramolecular nucleophilic addition gives the final product **115**.

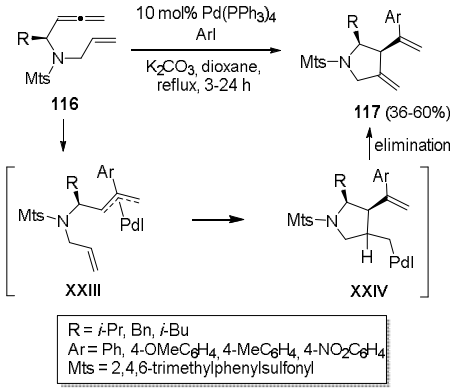


Scheme 52. Multi-component reaction of α-allenols for the preparation of substituted 2-(furan-3-yl)acetates.

4. Carboalkylation of allenes

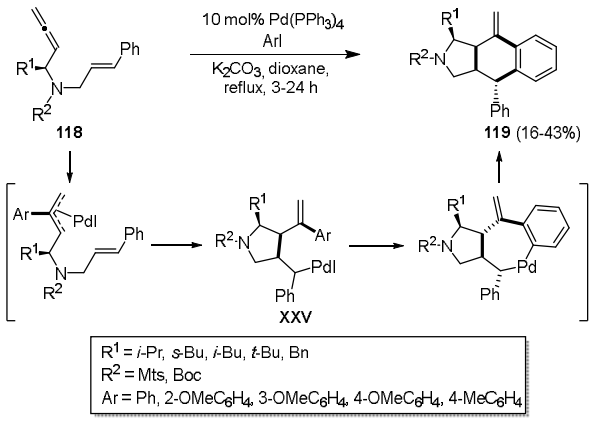
The π-allylpalladium intermediates generated *in situ* from allenes and arylpalladium complexes, in turn arising by reaction of aryl halides with palladium(0), can react also with carbon nucleophiles. In this case, the process afford to heterocycles if at least a heteroatom is contained in the tether that binds the reaction centers.

In 2003 Ohno and co-workers described a series of reactions of allenenes which evolve differently depending on the structure of the substrates as well as on the reaction conditions. Treatment of allenenes **116** with an aryl halide and K_2CO_3 in the presence of catalytic amount of $Pd(PPh_3)_4$ in dioxane affords the 2,3-*cis*-pyrrolidines **117** in a stereoselective manner (Scheme 53).[49] Carbocyclization on the double bond of **XXIII** and subsequent β-hydride elimination of the resulting σ-alkylpalladium intermediates **XXIV** allow the formation of the final products.



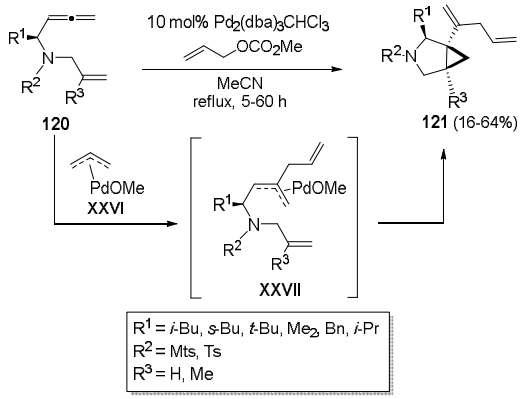
Scheme 53. Carbopalladation/alkylation of allenenes.

Interestingly, the presence of a substituent at the terminal position of the olefin **118** inhibits the β-hydride elimination from **XXV** permitting a further cyclization involving the aryl group (Scheme 54). This tandem reaction proceeds with the formation of three carbon-carbon bonds yielding tri- or tetracyclic heterocycles **119** by a C-H bond functionalization of the (hetero)arene introduced in the first carbopalladation step.



Scheme 54. Carbopalladation/alkylation of allenenes with further cascade step.

In sharp contrast, cyclization of the allenenes **120** using catalytic $Pd_2(dba)_3{\cdot}CHCl_3$ in the presence of allyl methyl carbonate in acetonitrile leads to stereoselective formation of a 3-azabicyclo[3.1.0]hexane framework (**121**) in moderate yields (Scheme 55).[50] The key intermediate is the π-allylpalladium(II) methoxide **XXVII**, arisen from reaction between the starting allenenes and the π-allylpalladium(II) **XXVI**, in turn derived from allyl carbonate and palladium(0).



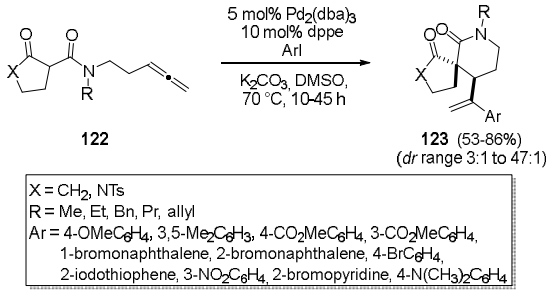
Scheme 55. Carbopalladation/alkylation of allenenes with allyl methyl carbonate.

In 2010 Dixon and co-worker proposed a cascade procedure in which two new carbon-carbon bonds and one new heterocyclic ring are created to produce spiroderivatives which should be of high value in complex natural product synthesis.[51] The diastereoselective arylative carbocyclization of the allenes **122** with (hetero)aryl halides was performed using $Pd_2(dba)_3{\cdot}CHCl_3$ as the catalyst in the presence of dppe and K_2CO_3 in DMSO at 70 °C furnishing the spirocyclic lactam **123** (Scheme 56).

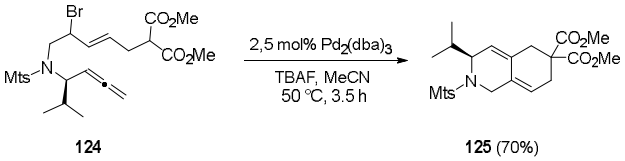
The same conditions shown in Scheme 31 for the cyclization of allenyl bromoalkenes **66** were proven to be effective also for the domino carbocyclization of the malonate derivative **124**, which afforded the hexahydroisoquinoline dicarboxylate **125** in 70% yield (Scheme 57).[29]

Recently, exploiting an initial intramolecular carbopalladation step, an arylative carboxylation of allenes has been fruitfully developed for the synthesis of 3-substituted indole-2-carboxylic acids.[52] The reaction was carried out treating the allenes **126** with the catalytic system $PdCl_2/P(4\text{-}CF_3C_6H_4)_3$ and $ZnEt_2$ under CO_2 atmosphere (Scheme 58). The obtained products **127** could be efficiently converted into 3-substituted indole-2-carboxylate derivatives. The first-formed β,γ-unsaturated carboxylic acids **XXIX** is

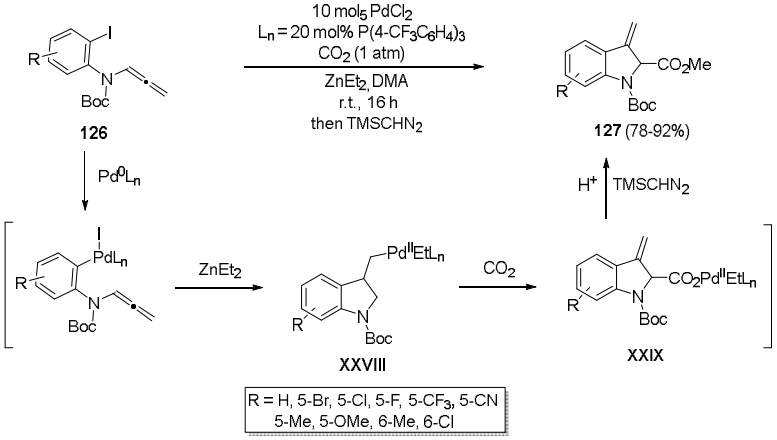
efficiently converted by acidic catalysis and $TMSCHN_2$ in the final products **127**. The key intermediate of the cyclization/carboxylation sequence is the allylethylpalladium complex **XXVIII**, which reacts with CO_2 at the γ-position of palladium.



Scheme 56. Carbopalladation/alkylation for the synthesis of spiro-compounds.



Scheme 57. Carbopalladation/alkylation for the cyclization of allenyl bromoalkenes.



Scheme 58. Arylative carboxylation of allenes.

5. Conclusions

The reactions described in this review demonstrate the wide potential associated with the carbopalladation/cyclization processes for the synthesis of heterocycles. The intervention of a π-allylpalladium intermediates, easily generated from allenes with aryl or vinyl halides in the presence of a palladium(0)-catalyst, allows the attack by various kind of nucleophile, affording differently substituted hetero(poly)cycles. The examples herein reported show that the use of this procedure can provide a platform useful to identify novel intermediates for the synthesis of natural products and biologically active compounds, containing important structural elements otherwise difficult to obtain using conventional organic chemistry.

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