Transition-Metals Catalyzed Intramolecular Amination and Hydroamination Reactions of Allenes

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Abstract. Progresses in the field of intramolecular additions of nitrogen nucleophiles to allenes and domino reactions involving intramolecular C-N bond formation are reviewed under catalysis with different transition metals.

Keywords: Catalysis, hydroamination, carboamination, unsaturated systems, transition metals, nitrogen nucleophiles

INTRODUCTION

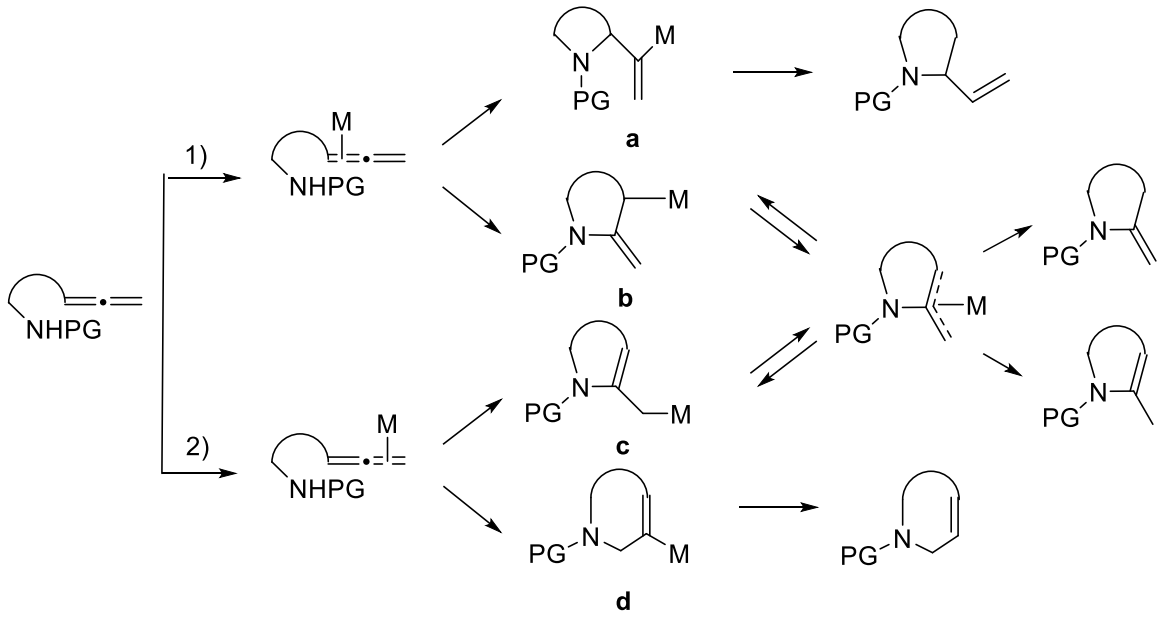
The allenes show unique physical and chemical properties and their high reactivity is the key to make this class of unsaturated systems particularly attractive to be used as substrates for different kind of reactions, with or without catalysts. Compared to alkenes and alkynes, the presence of three unsaturated carbons allows to achieve highly substituted derivatives, in particular through a domino processes. Moreover, a particular feature of allenes is the possibility to exhibit axial chirality. The axial chirality in general affects the diastereoselectivity in functionalization of substrates and can be transferred to the product derivatives.[1]

An effective strategy to transform allenes in more complex structures is to employ the transition metal-catalyzed reactions. In particular, reactions of allene derivatives containing proximate nucleophilic amino groups allowing to achieve functionalized heterocycles or heteropolycycles as highly atom-economy process.[2] In all the cases the regioselectivity is a significant problem. In general, the C-N bond formation proceeds with good or excellent regio- and stereoselectivity, affording high yields of the products. Placing the amino group at such a distance that five- or six-membered rings are formed, should solve the selectivity problems because normally larger rings are unfavored (Scheme 1).

The mechanism of the cyclization may be different depending on the transition metals used and on the substrate. The nature of the transition-metal plays a fundamental role and the problem is to find the proper catalyst, also in term of efficiency, stability and inexpensiveness. The metals with soft Lewis acids characteristics as silver and gold act through the complexation of the unsaturated system and its activation toward the nucleophilic attack. In other cases, such as palladium, the metal plays a dual role as activator of the allene and as promoter of the eventual functionalization reaction subsequent to the cyclization.

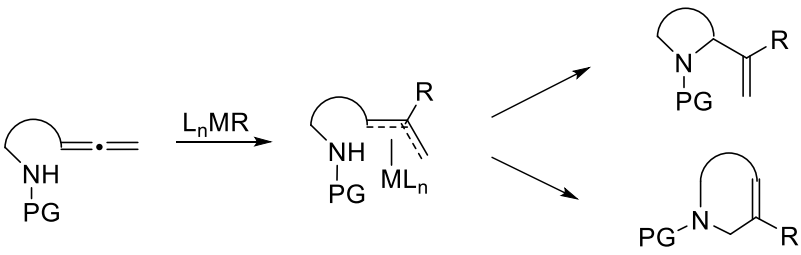
Regarding the regioselectivity, when the metal is a hard Lewis acid as palladium, the interaction with the more electron-rich double bond of the allene is favored, resulting in the formation of a vinyl substituted

nitrogenated ring (Scheme 1, Eq. 1). If the metal is a soft Lewis acid such as gold, it prefers to coordinate with the terminal double bond of the allene, promoting the reaction to the less hindered side of the unsaturated system to yield regioisomeric products (Scheme 1, Eq. 2). In this contest *endo-trig vs exo-dig vs endo-dig vs exo-trig* cyclization is reported. Four are the possible complexes formed, **a-d**, two of which are in equilibrium with the same π-allyl-complex. In a hydroamination process the final protodemetallation step affords the product and regenerates the metal catalyst.



[Scheme 1. Regioselective hydroamination processes]

In the case of a domino process as the carboamination, the reaction with aryl halide forms a metal-π-allyl-complex intermediate (Scheme 2). In most cases a palladium(II)-species is employed, arising from oxidative addition of the metal to the organic halide. The subsequent intramolecular nucleophilic attack of the NH group on the π-allyl-complex results in a functionalized heterocycle, in a regioselective fashion.



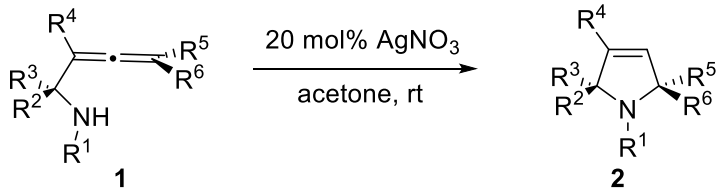
[Scheme 2. Regioselective carboamination processes]

Different types of C-N functionalities may be formed by addition of nitrogen nucleophiles to allene moiety. In this review we consider an update of methodological progresses on this topic. Also, significative previous works are reported. The reaction typologies considered herein are hydroaminations as: 1) simple C-N bond formation, and 2) domino reactions including: carboaminations, aminocarbonylations, diaminations and aminohalogenations of allenes, reported as both intra-intermolecular and intra-intramolecular processes.

HYDROAMINATION OF ALLENES

Different transition metals were exploited in order to obtain the intramolecular hydroamination of allenes. Allenylamines, allenylamides, allenylsulfonamides, allenylcarbamates, such as allenylhydroxylamines and allenylureas are all suitable substrates to give intramolecular process affording nitrogenated rings. The ring size of the heterocycles obtained, such as pyrrolidines and piperidines, is depending on the alkyl chain length between the allene and the nitrogen nucleophile, as shown in the next paragraphs.

The allenylamines are the simplest substrates for the intramolecular hydroamination process under different transition-metal catalysts. The reactions of substituted primary and secondary α-allenylamines **1** with $AgNO_3$, in acetone as solvent at room temperature, resulted in the formation of 3-pyrrolines **2** in very good yields, through an *endo*-cyclization process.[3] Also α-allenyl aminoacids were used as substrates affording functionalized 3-pyrrolines with complete control of the stereoselectivity (Scheme 3).[3d,e]



1 **2**

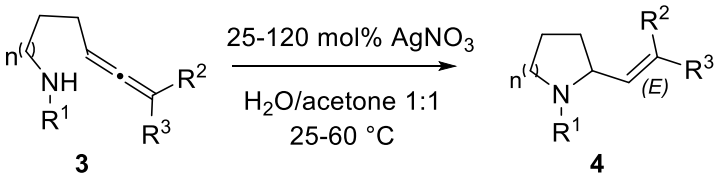
R^1 = H, Me; R^2 = H, CO_2Me
R^3 = H, Me, Bn, *i*-Bu
R^4 = H, TMS, *n*-Bu, Ph, $Ph(CH_2)_3$-, $PhCO_2(CH_2)_2$-
R^5, R^6 = H, Me, Ph, Bn, TMS, -$(CH_2)_5$-, -$(CH_2)_6$-, *i*-Pr, *n*-Bu, *t*-Bu, -$(CH_2)_5OH$, *n*-heptyl

21 examples,
54- 99% yields,
up to 99% *ee*

[Scheme 3. Cyclization of α-allenylamines]

This synthetic process was efficiently applied in the total synthesis of natural products such as: 1) in the crucial step for the synthesis of γ-aminoacid (-)-detoxinine to furnish the *syn*-dihydropyrrole derivative,[4] 2) in the synthesis of the two enantiomers of the antibiotic anisomycin,[5] 3) in the total synthesis of the alkaloids clavepictines A and B,[6] the alkaloid (-)-205B,[7] and the indolizidines (-)-223AB, 239AB and 239CD,[8] where the key-step of the allene cyclization afforded piperidines with exceptional control of the diastereoselectivity.

Also the γ– and δ-allenylamines **3** were successfully used as substrates to afford 2-alkenyl-pyrrolidines and 2-alkenyl-piperidines **4** using different amount of $AgNO_3$ in a mixture of acetone-water (1:1).[9] The reaction through a 5- (or 6-) *exo*-trig cyclization was regioselective and stereoselective giving only the *trans* isomer (Scheme 4).



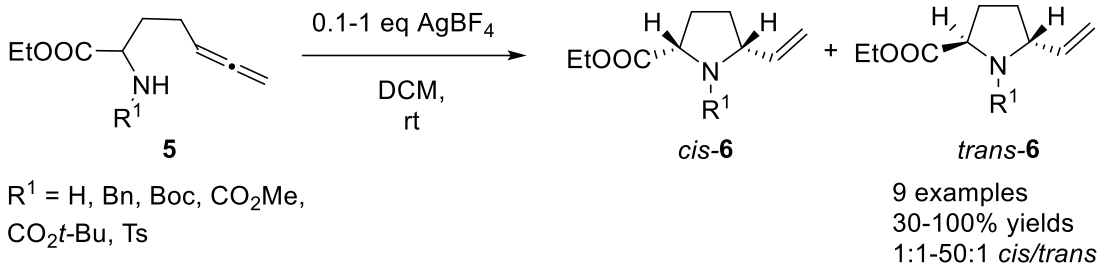
3 **4**

R^1 = *n*-Pr, Bn, Ph,
R^2, R^3 = H, Me, Et
n = 1, 2

9 examples
71-95 % yields
E/Z > 95:5

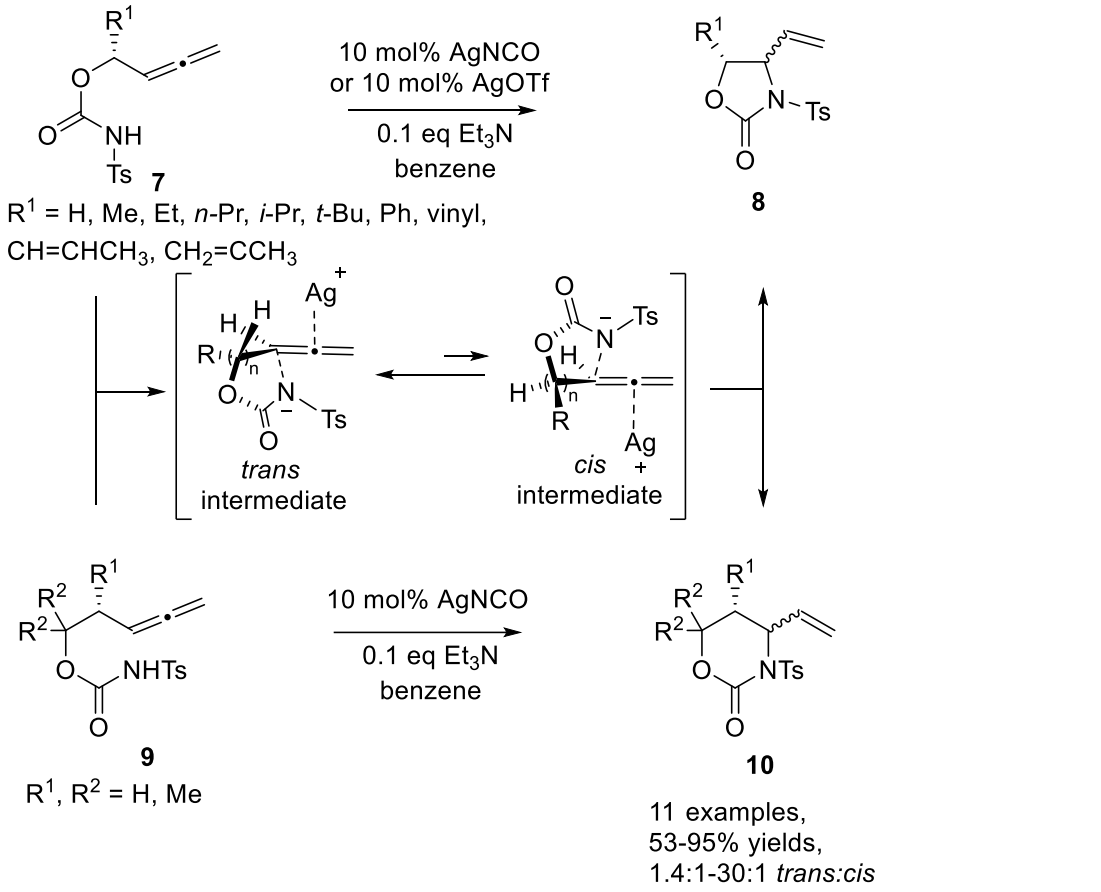
[Scheme 4. Cyclization of γ– and δ-allenylamines]

Working on γ-allenyl aminoesters **5** substituted with groups of different size at the nitrogen, the 2,5-disubstituted pyrrolidines **6** were achieved with *cis* stereoselectivity. The physical bulkiness of the substituent at the nitrogen seemed to be the determining factor in terms of stereoselectivity (Scheme 5).[10]



[Scheme 5. Cyclization of γ-allenyl aminoesters]

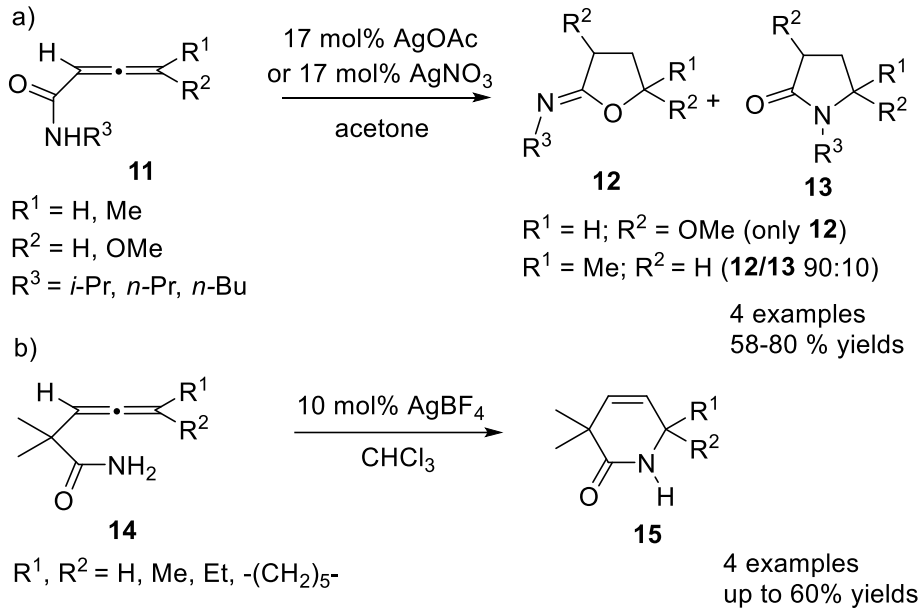
The *N*-Ts-2,3-butadienyl carbamates **7** and *N*-Ts-3,4-pentadienyl carbamates **9** reacted in the presence of AgOTf or AgNCO and triethylamine (10 mol% each) providing 4-vinyl-1,3-oxazolidin-2-ones **8** and 4-vinyl-tetrahydro-1,3-oxazin-2-ones **10** in good yields.[11] The observed *trans* selectivity of the substituents depended on the steric bulk of the R^1 group. In the case of *t*-Bu only the *trans* isomer was reported. The explanation may be due to the different stability of the transition states, in one case (*cis* isomer) showing a gauche repulsion between the R^1 group and C-3 of the allenyl moiety (Scheme 6).[12]



[Scheme 6. Cyclization of α- and β-allenyl carbamates]

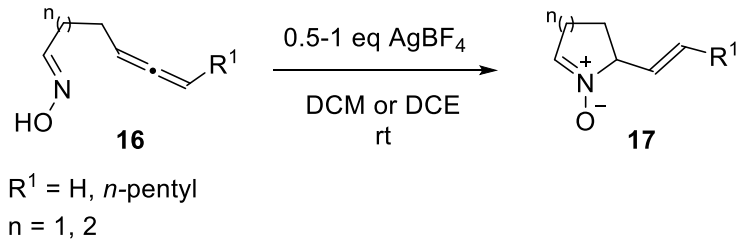
Alpha- and β-allenylamides **11** and **14** have also been tested using AgOAc or $AgNO_3$ as catalysts. In the case of *N*-monosubstituted amides a mixture of products, dihydrofuran and dihydropyrrole derivatives **12** and **13**

were formed, arising from the nitrogen- or oxo-nucleophilic attack of the enol form to the allene-silver complex.[13] The cyclization of the β-allenylamides **14** in $CHCl_3$ at reflux afforded the dihydro-2-pyridones **15** (Scheme 7).[14]



[Scheme 7. Cyclization of α- and β-allenylamides]

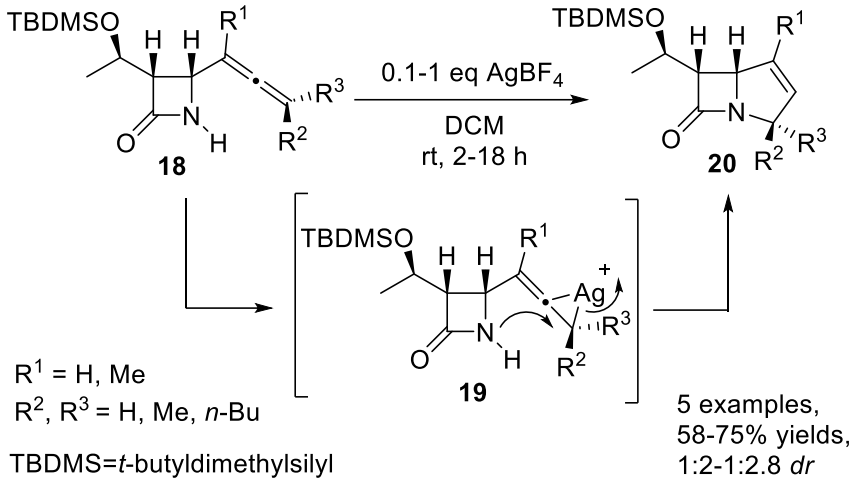
The $AgBF_4$ catalyzed also the cyclization of allenyl oximes **16** providing 2-vinyl nitrones **17**, suitable intermediates for the stereoselective synthesis of *trans*-2,6-disubstituted piperidines and *trans*-2,5-disubstituted pyrrolidines[10] and of pyrrolizidine alkaloids (Scheme 8).[15]



[Scheme 8. Cyclization of allenyl oximes]

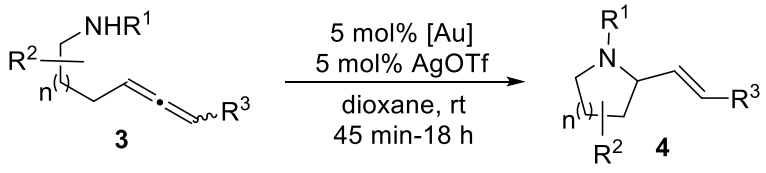
Among the reactions of usefulness to obtain heterocycles, the substituted allenyl hydroxylamines treated with $AgBF_4$ afforded isoxazolidines, precursors of the alkaloid (+)-sedamine[16] and of the tricyclic piperidine alkaloid Porantheridine.[17]

A particular application of the intramolecular reactivity of the allene was devoted to the construction of the β-lactam antibiotics carbapenem. Starting from 4-allenyl-azetidinones **18** and using $AgBF_4$ as catalyst in DCM at r.t., the Δ^1-carbapenems **20** were obtained in a stereospecific fashion probably through the Ag-bridged cation **19**, as showed in Scheme 9, with stereochemical control of substituents at C-3.[18] Similar cyclization was obtained on terminal allenes, performing the hydroamination with 5 mol% $AuCl_3$ with the same solvent at r.t..[19] Moreover, an analogous result was reported using 5 mol% $PtCl_2$ as catalyst in toluene at a temperature ranging from 40 °C to 80°C.[20]



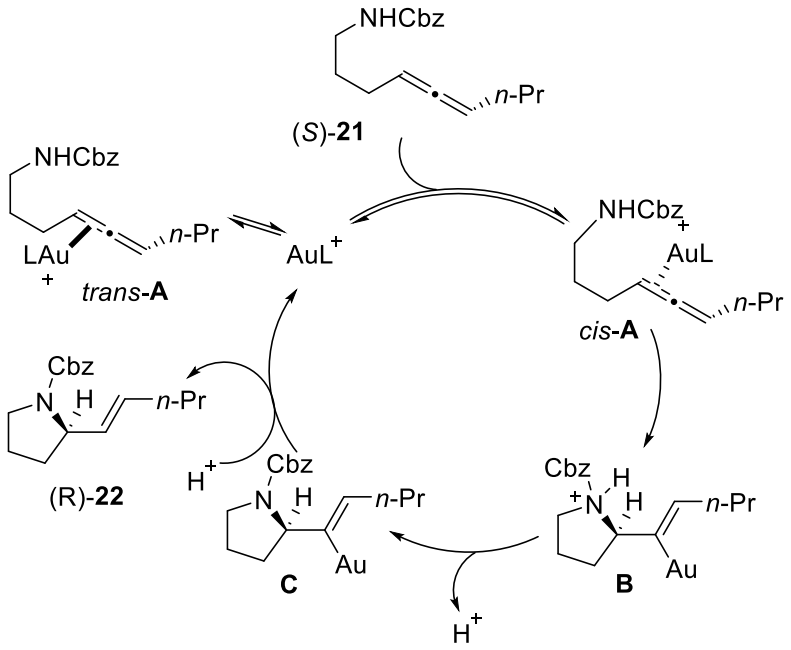
[Scheme 9. Cyclization of allenyl β-lactams]

In contrast to silver salts, wider literature studies were performed on the reactions catalyzed by gold catalysts, due to the major reactivity of the gold complexes and the less amount used. Hydroamination of different substituted γ- and δ-aminoallenes **3** afforded 2-alkenyl-pyrrolidines and piperidines **4** through an *exo*-trig cyclization, in which the new C-N bond was created with a new chiral center at position α to the N atom. *N*-Allenyl carbamates which possessed an axial chirality, underwent cyclization at room temperature in acetone, giving *E*-alkene with total selectivity. Both Au(I) and Au(III) gave similar results, although, AuCl was preferred because of its air stability.[21] Employment of a mixture of gold and silver catalysts was crucial for high activity. In particular, the sterically hindered Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl activated by AgOTf, where the silver salt acted as activator for the precatalyst gold complex. These results were reported by the Widenhoefer research group, which made a massive work on the gold-catalyzed hydroamination (and hydroalkoxylation) of aminoallenes (Scheme 10).



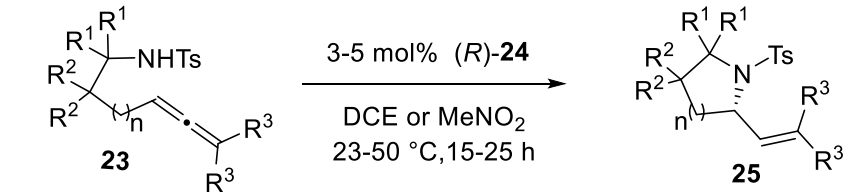
[Scheme 10. Au/Ag-catalyzed cyclization of γ– and δ-allenylamines]

The synthetic utility of this process was enhanced by the reported stereoselectivity. In fact, in the case of enantiopure aminoallene the cyclization gave pyrrolidine with complete chirality transfer. The suggested mechanism for the stereospecific conversion of (*S*)-**21** to (*R*)-**22** implicated the nucleophilic *anti*-attack of the nitrogen atom on the Au-complexed allene intermediate in the *cis*-**A** form, probably through a rapid interconversion from a more stable *trans*-**A**. The cationic product **B** underwent deprotonation to give the neutral complex **C** and subsequent protonolysis of the Au-carbon bond afforded the heterocycle with *E*-alkene substituent and regeneration of the cationic gold complex (Scheme 11).

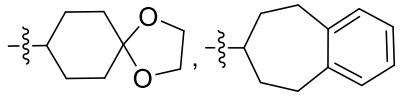


[Scheme 11. Au-catalyzed cyclization of (S)-*N*-Cbz-nona-4,5-dienamine]

In this context, the use of new chiral gold(I)-phosphine complexes resulted in the formation of enantiopure 2-vinyl pirrolidines and piperidines. The enantioselectivity was sensitive to substitution on the alkyl chain.[22] The protocol tolerated substitution at the C-1 or C-2 position of the 4,5-hexadienyl chain and alkyl disubstitution at the terminal allenyl carbon atom. Moreover, a remarkable counterion effect to increase the yields was discovered, in particular phosphine-gold(I)-bis-*p*-nitrobenzoate was the most efficient catalyst. Treatment of trisubstituted *N*-tosyl allenamides **23** with the catalytic (*R*)-xylyl-BINAP(AuOPNB)$_2$ [(*R*)-**24**] confirmed the influence of the substrate structure on the enantioselectivity, leading to predominant formation of one of the possible 2-vinyl pyrrolidine stereoisomers **25** (Scheme 12).[23]

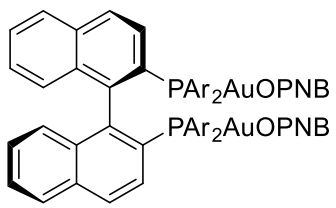


R^1 = H, Me
R^2 = H, Me, Ph, -$(CH_2)_5$-, -$(CH_2)_6$-
R^3 = H, Me, Et, -$(CH_2)_5$-, -$(CH_2)_6$-



n = 1, 2

16 examples
41-99% yields,
up to 99% *ee*



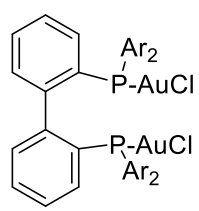
24 [(*R*)-xylyl-binap(AuOPNB)$_2$]

PNB = *p*-nitrobenzyl Ar = 3,5-xylyl

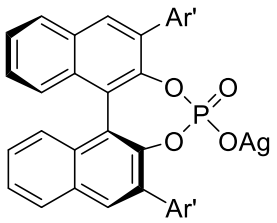
[Scheme 12. Enantioselective cyclization of N-Ts allenamides]

Subsequently an in depth study on the role of chiral counterions and on the ligands for hydroamination processes highlighted the efficiency of mononuclear gold(I) and gold(III) complexes in combination with silver salts to afford stereoselective cyclization.[24]

Chiral ligands **26** on gold can be combined additively with chiral phosphate counterions **27** to improve the enantioselectivity in the formation of 2-vinyl-tetrahydropyrroles.[25] In particular pairing one chiral ligand with two opposite enantiomers of the chiral counterion did not lead to the same improvement in enantioselectivity, indicating that the two pairs combine in a "matched" or "mismatched" fashion.[26] Moreover the degree of enantioinduction was dependent on the proximity of the counterion to the cationic gold center. Then, the use of apolar solvent as benzene proved to be the optimal medium (Scheme 13).



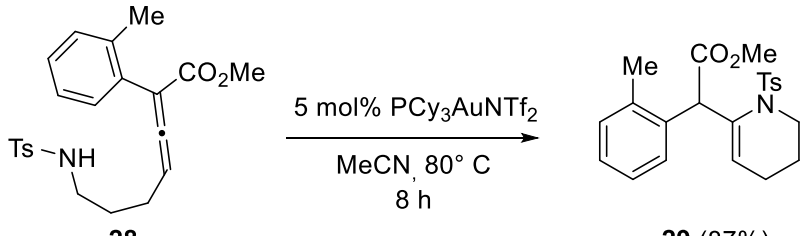
26
Ar = Ph, 3,5-$Me_2C_6H_3$



27
Ar' = Ph, 3,5-$(CF_3)_2C_6H_3$, 2,4,6-*i*-$Pr_3C_6H_2$, biphenyl

[Scheme 13. Chiral ligands and phosphate counterions]

A subsequent study on aminoallene **28,** substituted with an electron-withdrawing group on the terminal carbon of the 1,2-diene, discovered that in the presence of 5 mol% of PCy_3AuNTf_2 the intramolecular hydroamination afforded only the *N*-tosyl tetrahydropyridine **29**, highlighting the pivotal role of the substituents on the ring closure selectivity. In fact, when two electron-donor groups were present in the γ-position, 5-*exo*-trig hydroamination was reported, resulting in the 2-vinyl-pyrrolidines (Scheme 12). When the allene bears an EWG in the same position, the hydroamination occurred at the β-position through a formal 6-*exo*-dig or 6-*endo*-dig cyclization to give the tetrahydropyridine **29** (Scheme 14).[27]



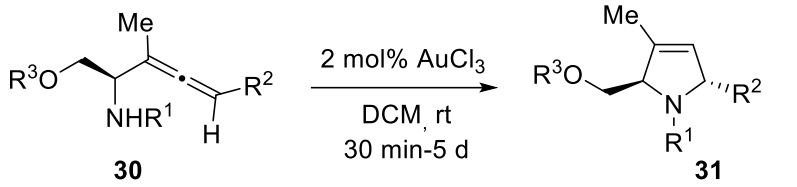
28 **29** (87%)

PCy = tricyclohexylphosphine

[Scheme 14. Regioselective cyclization of N-Ts allenamides]

In the case of *N*-protected or *N*-unprotected-α-aminoallenes **30**, five membered heterocycles **31** were obtained through *endo*-cyclization process, and both Au(I) and Au(III) were working as catalysts.[28] The AuCl was much more effective than $AuCl_3$, reducing the reaction times from several days to a few hours. In this case, the authors presumed that Au(I) was the catalytic active species even when the reaction started with a Au(III) precatalyst.[29] The 3-pyrrolines were obtained from good to high yields with low catalyst loading (2

mol%) and very mild reaction conditions. The treatment of enantiopure aminoallene gave pyrrolidine with complete chirality transfer (Scheme 15). Functionalized 3-pyrrolines are important natural products with different biological activities.[30]

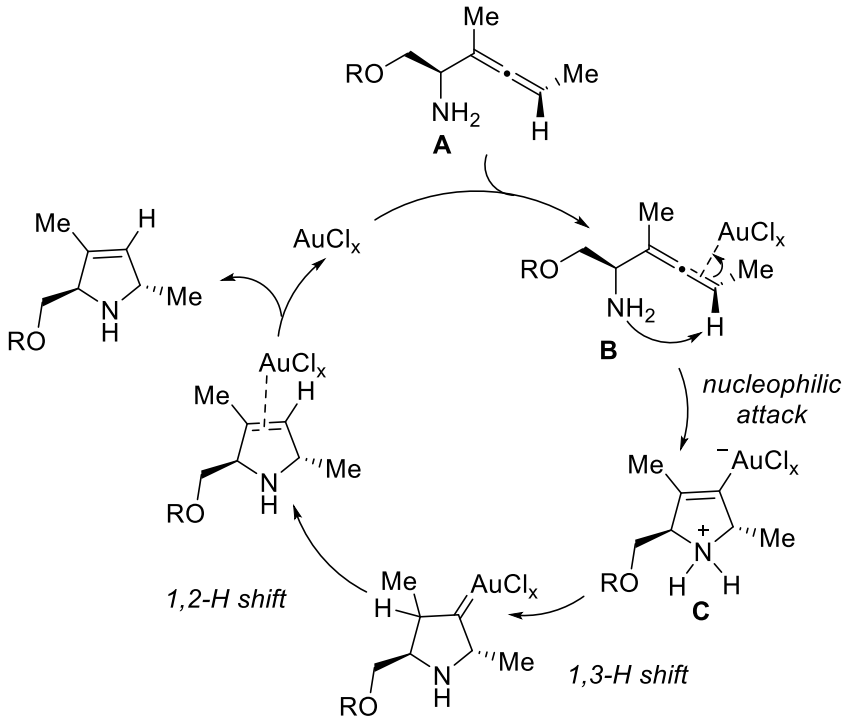


R^1 = H, Ms, Ts, Ac, Boc
R^2 = H, Me, *i*-Pr, *n*-hexyl, Ph
R^3 = Bn, TBS

9 examples,
61-95% yields
46:54 - 99:1 dr

[Scheme 15. Stereoselective cyclization of α-allenylamines]

The reaction mechanism was studied in depth through the DFT calculations. In this case the coordination of the metal was on the distal double bond of the allene (**B**), then after the formation of the zwitterionic intermediate **C,** the proton shifts followed by demetalation affording the 3-pyrroline. The calculation confirmed that the 1,3-proton shift was assisted by a second molecule of α-aminoallene as the assisting catalyst (Scheme 16).[31]

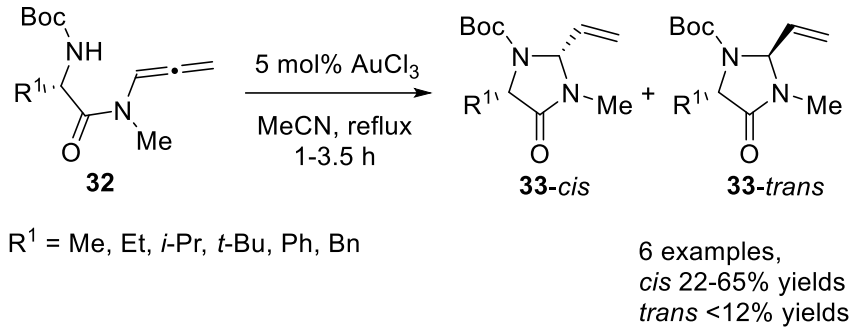


[Scheme 16. Au-catalyzed α-aminoallene cyclization mechanism]

An application of gold-catalyzed cycloisomerization of α-aminoallenes was exploited to obtain the azafuranomycin, the aza-analogue of the antibiotic furanomycin.[32]

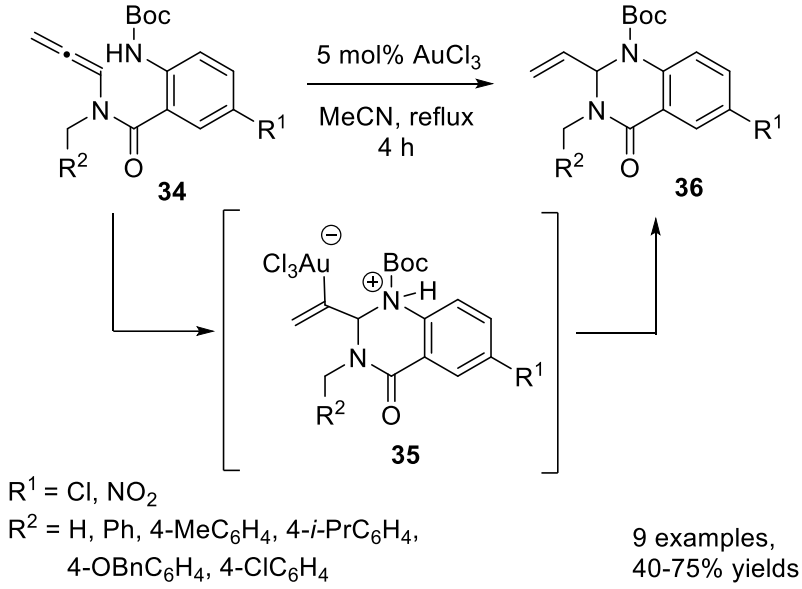
Starting from allenamides **32** arising from α-aminoacids, the gold-catalyzed *exo*-heterocyclization was an efficient path to obtain enantiopure imidazolidinones **33**, bearing a useful vinyl substituent in position 2. The

reaction performed in acetonitrile at reflux, afforded a mixture of *cis/trans* diastereoisomers, where the *cis* isomer was always the major product (Scheme 17).[33]



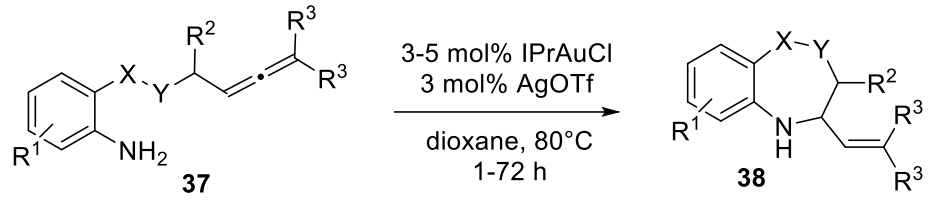
[Scheme 17. Cyclization of α-aminoacid allenamides]

The hydroamination of anthranilic allenamides **34** with $AuCl_3$ in acetonitrile as solvent resulted in the formation of 2-vinyl-quinazolinones **36** (Scheme 18).[34] The π-olefin complex generated through the coordination of the gold to the internal double bond of the 1,2-diene afforded the zwitterionic intermediate **35** that evolved, after protodeauration, giving the product.



[Scheme 18. Cyclization of anthranilic allenamides]

An intramolecular 7-*exo*-*trig* hydroamination of unprotected anilines *o*-substituted with allenyl pendant **37** was reported affording 1,5-benzoxazepines and 1,4-benzodiazepines **38**.[35] The reaction tolerated both electron-donor and electron-withdrawing substituents at the aromatic ring, but terminal allenes gave very poor results. Furthermore, anilines with electron-withdrawing protecting groups did not undergo cyclization, probably due to an insufficient nucleophilicity of the nitrogen. The chiral allenes allowed the transfer of the chirality to the final products (Scheme 19).

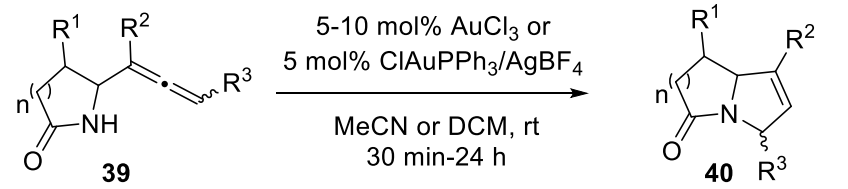


R^1 = 3-NHCbz, 4-Me, 4-OMe,
4-CO_2Me, 4-F, 5-OMe, 5-CN,
5-CO_2Me, 5-CF_3, 5-*t*-Bu, 6-Me
R^2 = H, Me, *n*-Pr
R^3 = H, Me, -$(CH_2)_5$-
X= CH_2, O; Y = CH_2, NTs

17 examples,
54-89% yields

[Scheme 19. Cyclization of *o*-substituted anilines]

The use of α-allenyl lactams of different ring sizes **39,** as substrates in the aminocyclization afforded pyrrolizidine systems **40**, useful scaffolds for the synthesis of pyrrolizidine alkaloids.[36] The cyclization was performed using $AuCl_3$ in acetonitrile for unsubstituted allenes or the cationic gold complex, generated in situ from $ClAuPPh_3$ and $AgBF_4$ in DCM, for substituted allenes (Scheme 20).

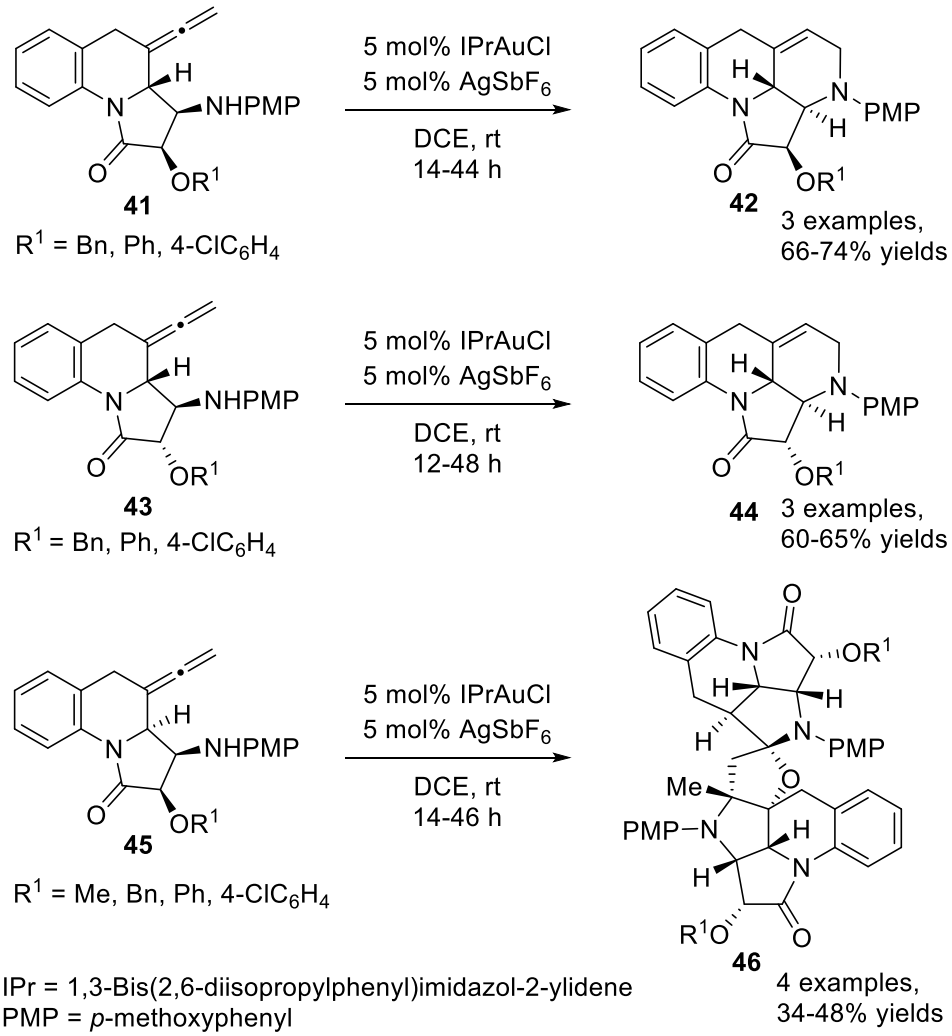


R^1 = H, OAc
R^2 = H, Me, *n*-Pr, CH_2OAc, CH_2OBn
R^3 = H, *n*-Pr; n = 1, 2, 3

14 examples,
up to 92% yields

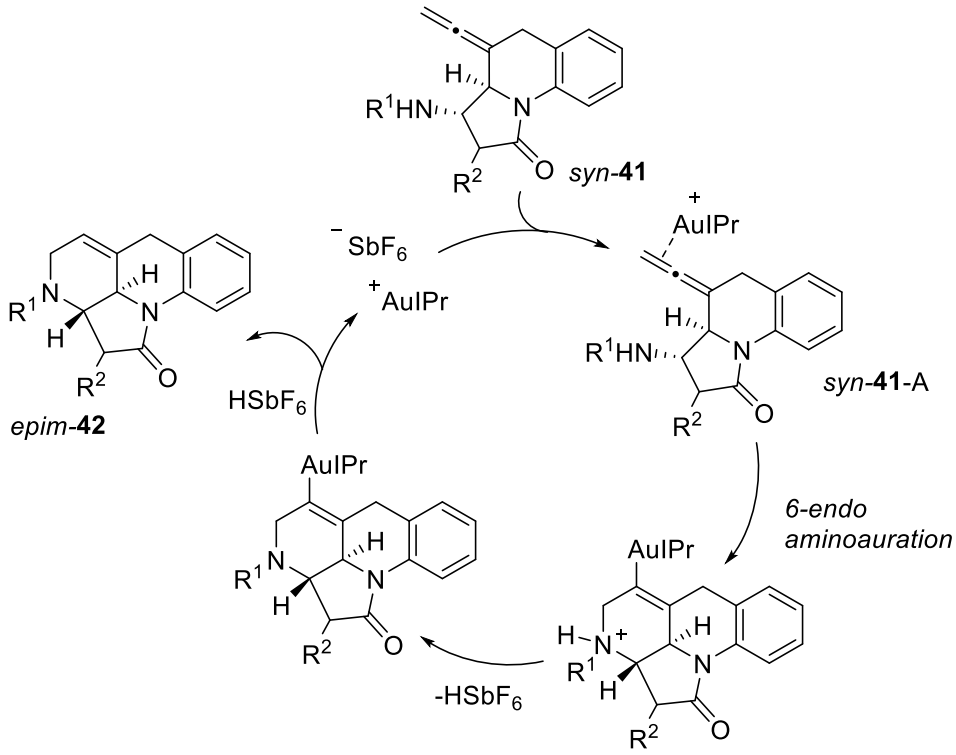
[Scheme 20. Cyclization of α-allenyl lactams]

A particular tricyclic indolizidinone substrates **41** bearing allenyl substituent were submitted to gold-catalyzed reactions resulting in a stereoselective aminocyclization and pointing out the influence of the stereochemistry of the allene precursor on the outcome of the reaction. In fact, a divergent reactivity was observed depending on the *syn* or *anti*-disposition of both protons at the α– and β-allenic stereocenters. The *syn*-precursors **41** and **43** led to tetrafused benzo[*b*]pyrrolonaphthyridin-1-ones **42** and **44** through 6-*endo* cyclization, while starting from the *anti*-allenes **45** a tandem process of heterocyclization/dimerization through 5-*exo* amino-ketalization-spirocyclization involving the adventitious water was reported affording **46**. The reaction was performed using IPrAuCl and $AgSbF_6$ both need to form the cationic catalyst. The reaction did not work in the absence of $AgSbF_6$ which indicated that the counterion controlled the Au-catalyzed cycloisomerization of the α-aminoallenes (Scheme 21).[37]



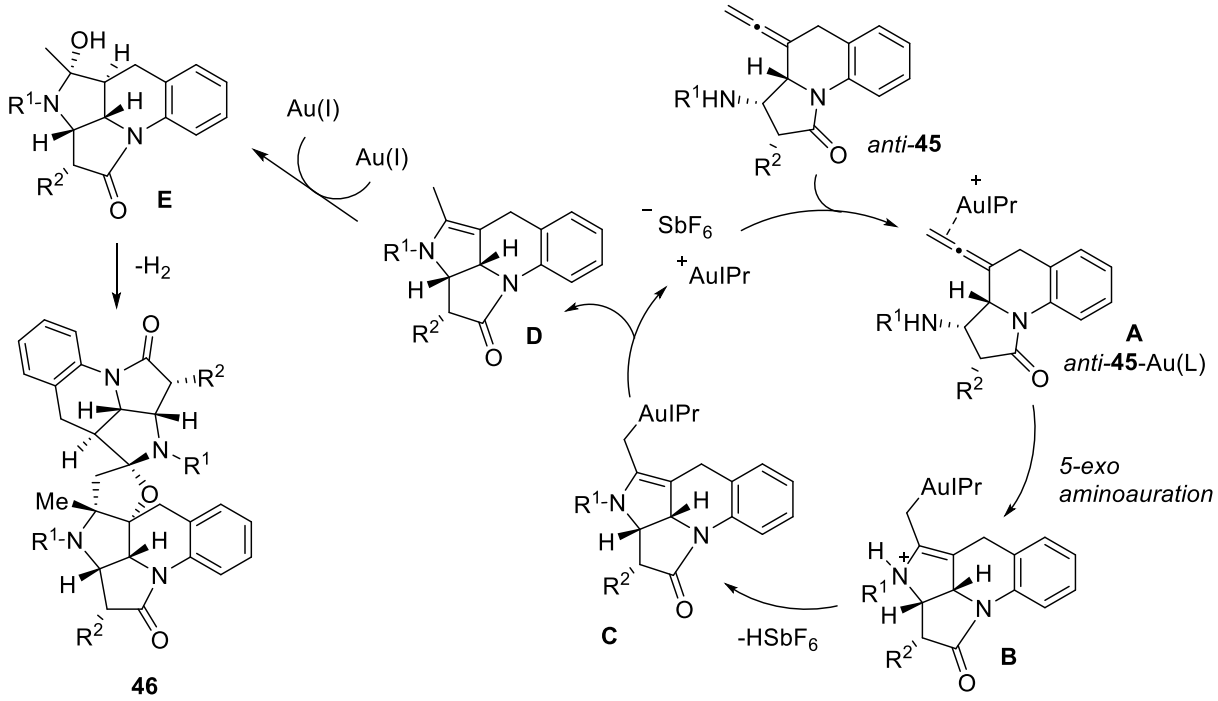
[Scheme 21. Cyclization of allenyl tetrahydropyrrolo[1,2-a]quinolinones]

DFT calculations were carried out to gain insight into the different outcome of the epimers *syn* and *anti* and a mechanism was proposed to explain the divergent reactivity. From the data obtained, under both kinetic and thermodynamic control it was clear that the aminoauration reaction involving the *syn* epimer exclusively led to the formation of the 6-*endo* adduct **42**, in view of the considerably higher activation energy for the formation of the alternative 5-*exo*-adduct (Scheme 22).



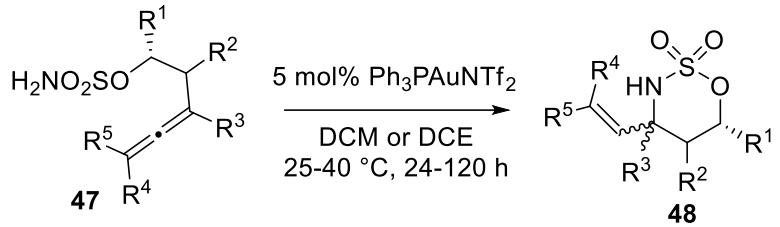
[Scheme 22. Mechanism for benzo[b]pyrrolonaphthyridinones]

A completely different situation was computed for the epimer *anti*, in this case the calculations suggested that the 5-*exo* aminocyclization was kinetically and thermodynamically preferred over the alternative 6-*endo* cyclization. This led to the formation of the cationic intermediate **B**, which upon protonolysis of the corresponding C-Au bond produced the corresponding tetracyclic species **D**. Species **D** may evolve to *N,O*-acetal **E** via gold-catalyzed nucleophilic addition of water. Subsequent oxidative coupling between **D** and **E** with the elimination of H_2, afforded spirocycles **46** (Scheme 23).



[Scheme 23. Mechanism for the spirocycle dimers formation]

Gold-catalyst was effective also in the cyclization of β-allenylsulfamates **47** enabling the formation of cyclic sulfamidates **48**, under mild reaction conditions. The hydroamination was effective also for substrates bearing a substituent in γ-position affording N-substituted quaternary centres, a very rare outcome for catalytic hydroamination. Sulfamates bearing adjacent substituents were unreactive. (Scheme 24).[38]

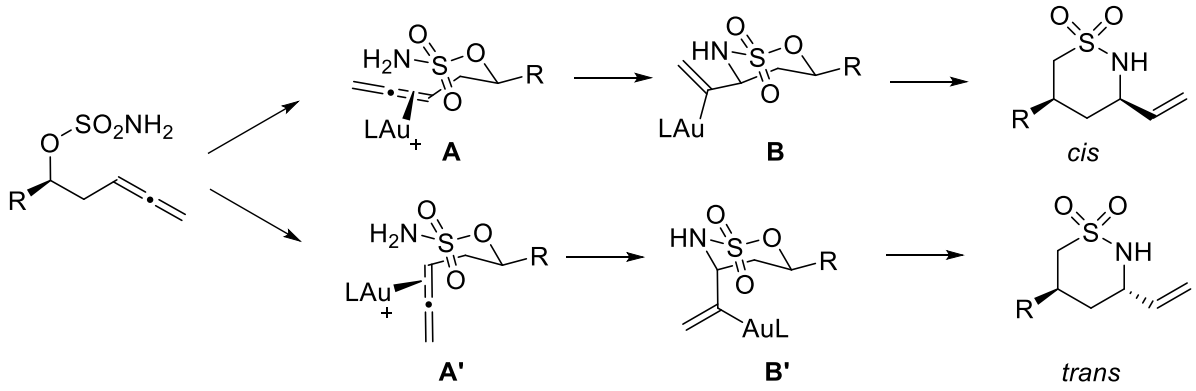


R^1 = H, *i*-Bu, *t*-Bu, -$(CH_2)_2$Ph
R^2 = H, Me
R^3 = H, *n*-Pr, *i*-Pr, *n*-hexyl, -CH_2-cyclohexyl, -$(CH_2)_2$OBn, -CH_2OBn, -CH_2OMe
R^4 = H, -$(CH_2)_5$-; R^5 = H, *n*-pentyl

13 examples,
up to 95% yields,
cis/trans 1.8:1-3:1

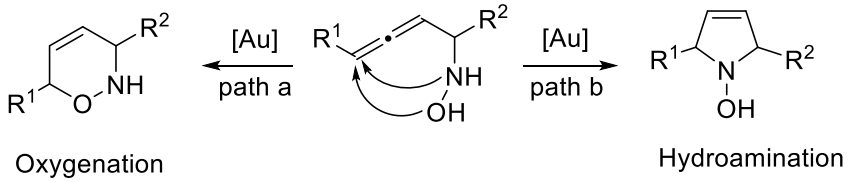
[Scheme 24. Cyclization of β-allenylsulfamates]

The reaction occurred *via* outer-sphere mechanism leading to the *anti* amino-auration of the activated allene. Different conformation of the coordinated unsaturated system as in **A'**, could result as the *cis* and *trans* diastereomeric products, being the *cis* product favored due to the formation of intermediate **B** which has both the substituent R and the allene in equatorial position (Scheme 25).

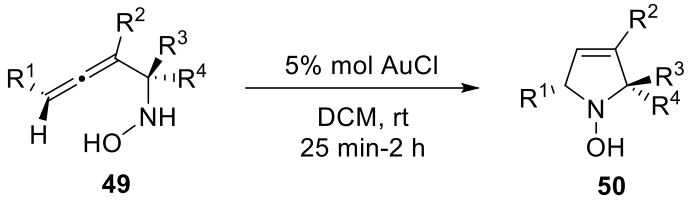


[Scheme 25. Mechanism of the stereoselective cyclization]

When the substrates were *N*-allenyl hydroxylamines **49** or *O*-allenyl hydroxylamines **51**, the gold catalysed cyclization showed a regio- and stereoselective route to three different heterocycles, *N*-hydroxy-pyrrolidines, dihydroisoxazoles and dihydro-1,2-oxazines depending on the *endo*- or *exo*-selective cycloisomerization. In general, the *endo*-cyclization of α-functionalized allenes to five-membered heterocycles was faster than the formation of six-membered heterocycles (Scheme 26). The cyclization can also be carried out in water using chloroauric acid as catalyst (HAuCl).[39] A complete computational investigation was reported with respect to the substrate structure (allenyl hydroxylamines and *O*-amino-α-hydroxyallenes), to the different catalytic properties of the Au(I) catalyst (neutral or cationic), to the control of the nucleophilicity (N or O), to the ring formation member (five and six member respectively) and to the regioselectivity (5-*endo* vs. 6-*endo*) (Scheme 27).



[Scheme 26. Regioselective cyclization of allenyl hydroxylamines]

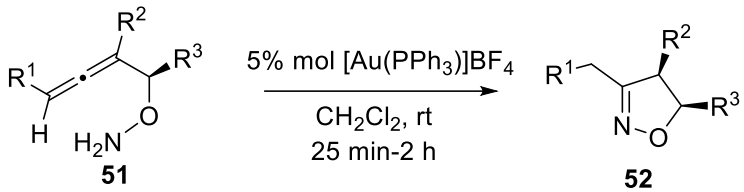


R^1 = Me, *i*-Pr, *n*-Bu, Ph
R^2 = H, Me; R^3 = H, $-CH_2OBn$
R^4 = H, $-CH_2OBn$, $-(CH_2)_2Ph$, $-(CH_2)_2CO_2Et$

6 examples,
67-80% yields

[Scheme 27. Cyclization of *N*-allenyl hydroxylamines]

In the case of O-allenyl hydroxylamines **51**, where the heteroatoms position was exchanged, the formation of five- or six-membered ring formation depended of the catalyst applied. In the presence of cationic gold(I) complexes a complete regioselectivity was in favour of the five membered ring affording dihydroisoxazoles **52**, with *cis* selectivity for disubstituted substrates (Scheme 28).

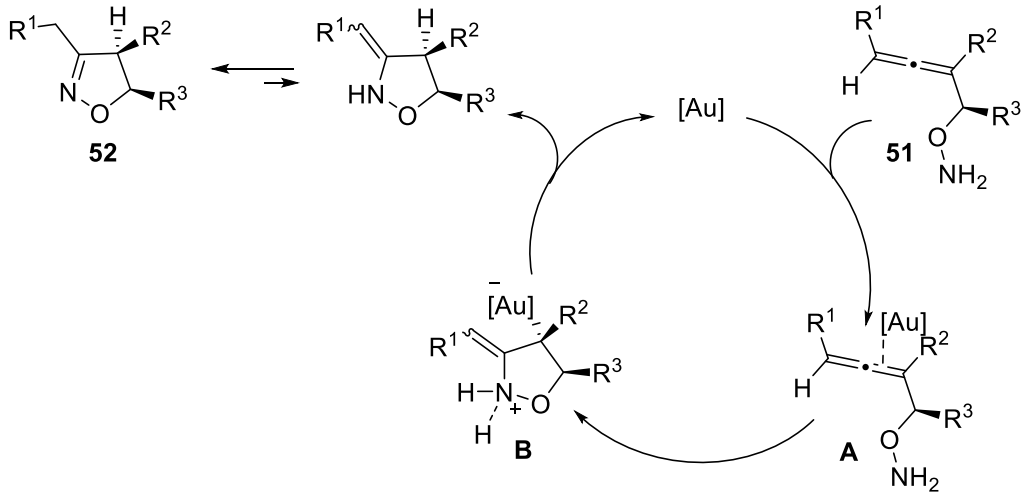


R^1 = H, Me, *i*-Pr, *n*-Bu
R^2 = H, Me; R^3 = H, $-CH_2OBn$
R^4 = Me, $-CH_2OBn$, $-CH_2OTBS$, $-(CH_2)_2Ph$, $-(CH_2)_2CO_2Et$

6 examples,
72-86% yields,
up to 95:5 *dr*

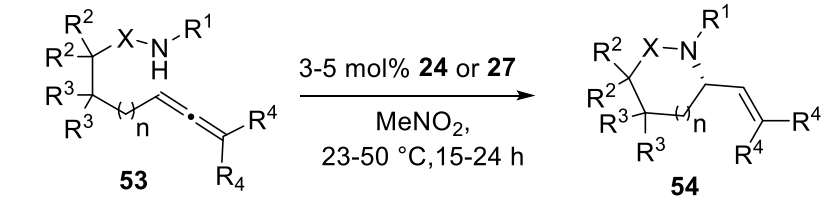
[Scheme 28. Cyclization of *O*-allenyl hydroxylamines]

That result could be justified supposing the formation of π-olefin-complex **A** and the attack of the nitrogen nucleophile on the central carbon of the allene system providing the zwitterionic species **B**. The bulky gold group was preferentially situated trans to the R^3 group in order to minimize the steric interactions. Protodemetalation afforded the product followed by isomerization to the more stable dihydroisoxazole (Scheme 29).



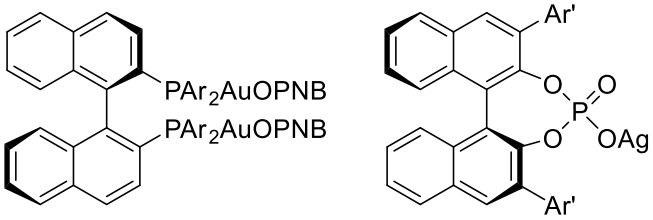
[Scheme 29. Mechanism of the dihydroisoxazoles formation]

After that work, chiral gold(I) complexes **24** used with chiral silver salts **27** catalysed the hydroaminations of hydrazine and hydroxylamine allenic derivatives **53** allowing rapid method to access chiral vinyl isoxazolidines, oxazines and pyrazolidines **54** with *ee* up to 89% (Scheme 30).[40] The presence of substituents on the linker chain enhanced the yields, presumably through the Thorpe-Ingold effect.



R^1 = Boc, Mts; R^2, R^3 = H, Me
R^4 = H, Me, -$(CH_2)_4$-, -$(CH_2)_5$-
X = O, NBoc; n = 0,1

11 examples,
63-98% yields,
up to 99% *ee*



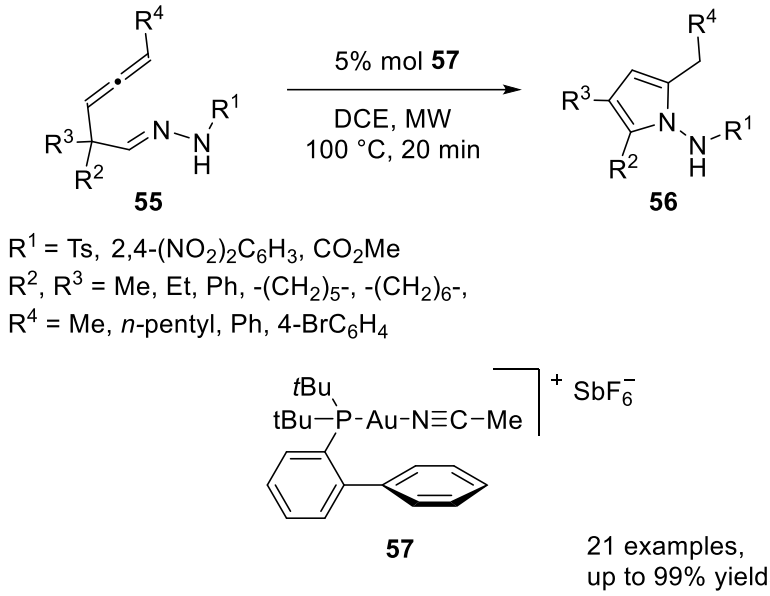
24 [(*R*)-xylyl-binap(AuOPNB)$_2$]
Ar = 3,5-xylyl

27 [(*S*)-TriPAg
Ar' = 2,4,6-*i*-$Pr_3C_6H_2$

PNB = *p*-nitrobenzyl

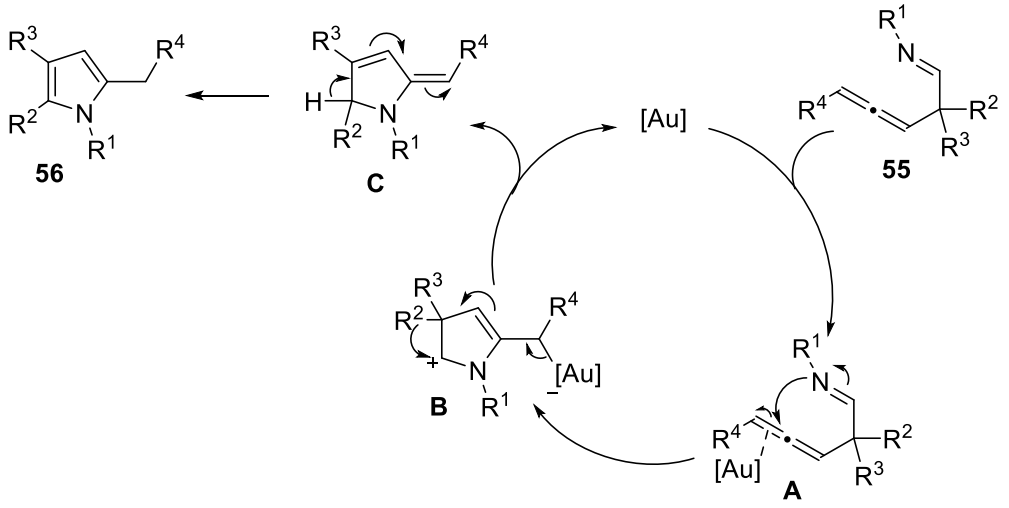
[Scheme 30. Stereoselective cyclization of allenyl hydroxylamines and hydrazines]

A new intramolecular cyclization of alkyl- or aryl-substituted α-allenylhydrazones **55** allowed the formation of 2,3,5-substituted pyrroles **56**. The protocol was effective for a broad range of substituents and tolerated both alkyl and aryl groups at the terminal allenyl carbon. The reaction was performed only with the catalyst **57** or PPh_3AuNTf_2 in DCE as solvent, in a short reaction time under microwave heating (Scheme 31). [41]



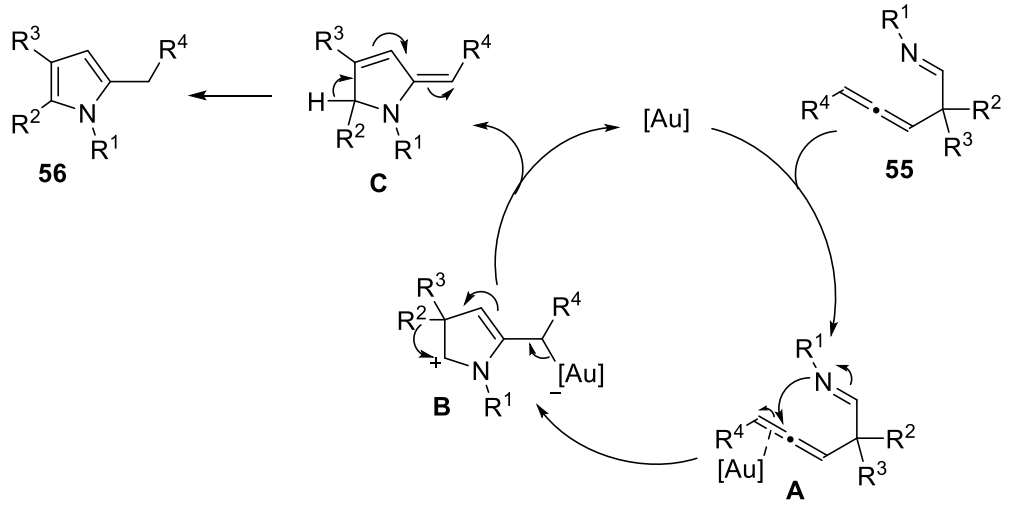
[Scheme 31. Cyclization of α-allenylhydrazones]

The product was the result of a selective intramolecular (1,2) alkyl or aryl shift, as the key step of the proposed reaction mechanism, involving first the usual metal-allene complexation and the subsequent nucleophilic attack of the nitrogen to the central atom of the allene with formation of the zwitterionic intermediate **B**. The final rearomatization of **C** provided the pyrrole **56** (Scheme 32).



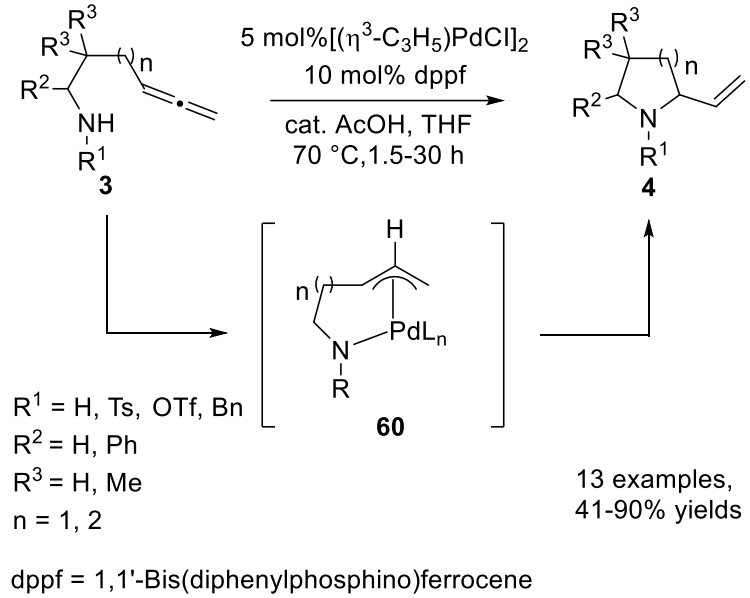
[Scheme 32. Mechanism of the pyrroles formation]

Expanding the scope of that gold(I)-catalyzed hydroamination process, different achiral N-allenyl ureas **57** were used as substrates in enantioselective fashion to form functionalized 2-vinyl pyrrolidines **58** with up to 93% *ee*. The reaction was performed at room temperature and was catalyzed by an enantiomerically enriched bis(gold) phosphine complex **59**, in the presence of $AgBF_4$ as co-catalyst, necessary to generate the active dicationic bis gold(I) complex (Scheme 33).[42] The cyclization was effective also on allenes without gem-disubstituents along the main chain. Allenyl ureas that possessed an axially chiral allenyl moiety underwent intramolecular process with high enantioselectivity and low diastereoselectivity.



[Scheme 33. Enantioselective cyclization of allenyl ureas]

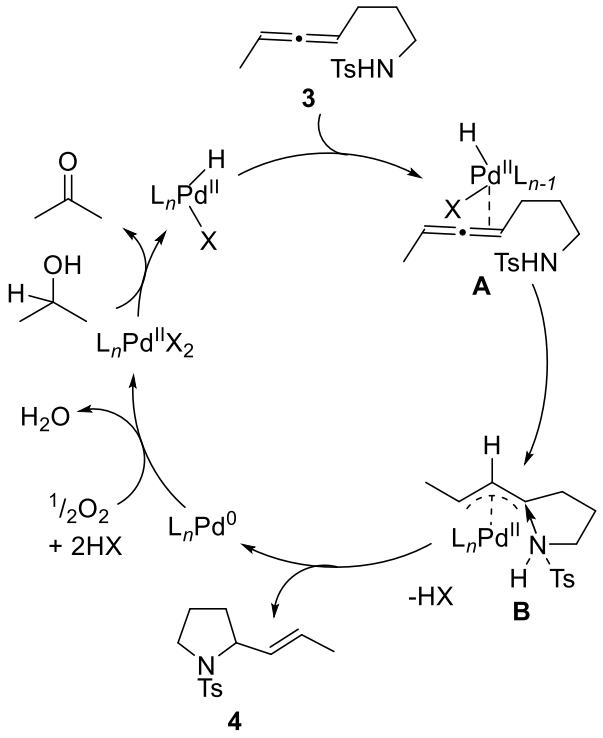
Among the vast work of Yamamoto's group on the transition-metal catalysed reaction in obtaining heterocycles, they reported the study on the Pd-catalyzed intramolecular hydroamination of aminoallenes **3**. The protecting group on the amine was fundamental. In fact, amine, benzylamine and tosylamide derivatives afforded the 2-vinyl-cyclized products **4**, while other protecting groups as acetyl, trifluoroacetyl and benzyloxycarbonyl did not give the desired product. The best reaction conditions involved the presence of $(\eta^3\text{-}C_3H_5)PdCl]_2$ catalyst, dppf as ligand and of AcOH that is oxidatively added to the metal producing the hydridopalladium species H-PdOAcL_2. Continuously, H-PdOAcL_2 is exchanged with the amine producing another hydridopalladium species H-PdNR_2L_2 able to form the π-allylpalladium complex **60**. The cyclization proceeds by 5-*exo*-trig or 6-*exo*-trig step in good to high yields, whereas no *endo*-cyclized product was observed (Scheme 34).[43]



[Scheme 34. Pd-catalyzed aminoallenes cyclization]

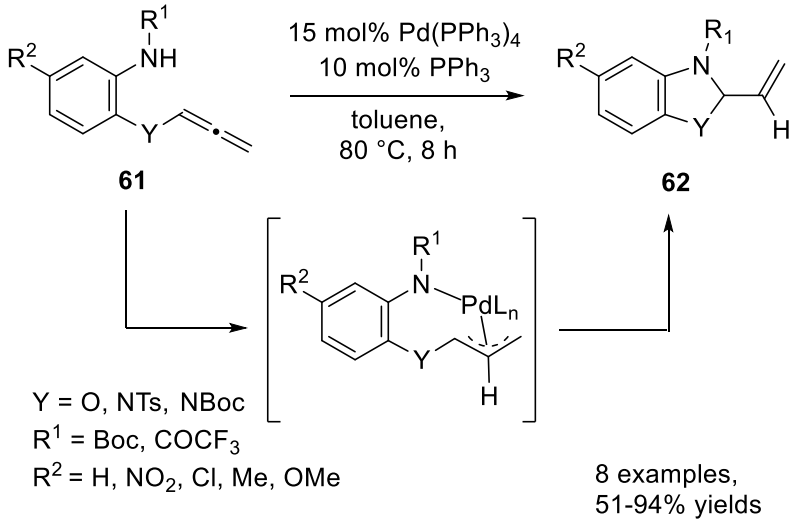
Analogously, internal γ-aminoallenes, also bearing substituents, underwent intramolecular hydroamination affording five- and six-membered aza-containing cycles with high regioselectivity and configuration exclusively *trans* at the resulting double bond. The reaction was performed in the presence of $PdCl_2$,

bathocuproine as ligand and isopropanol. In this case, the formation of Pd(II)-hydride species intermediate was based on the aerobic oxidation of alcohols. The insertion of Pd-H into the allene generated the π–allyl-Pd intermediate **B**, able to give cyclized product and Pd(0) which could be reoxidized to Pd(II) by molecular oxygen to complete the catalytic cycle (Scheme 35).[44]



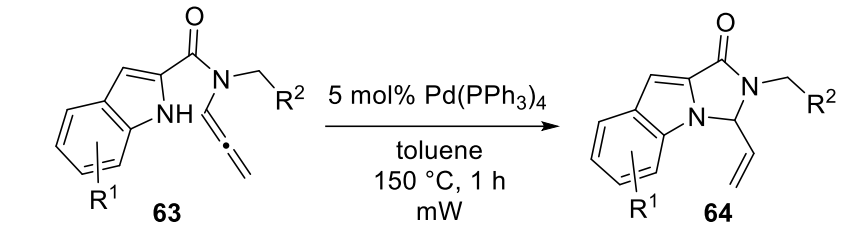
[Scheme 35. Mechanism of the pyrrolidine formation in aerobic conditions]

Allenyl ether and aminoallene derivatives **61** arising from 2-aminophenols and 2-phenylenediamine reacted intramolecularly providing 2-vinyl-dihydrobenzoxazoles and 2-vinyl-dihydrobenzimidazole **62**. The reaction was performed in toluene at 80 °C, with $Pd(PPh_3)_4$ as catalyst in the presence of PPh_3. The exact role of PPh_3 was unclear but the addition of 10 mol% of PPh_3 enhanced the yields, probably promoting the initial hydropalladation step (Scheme 36).[45]



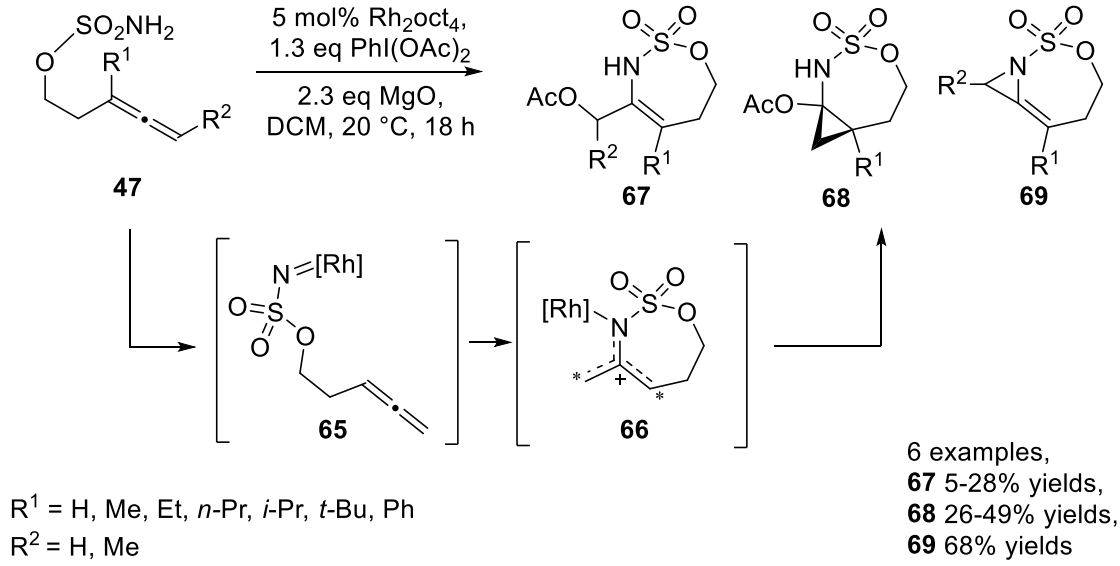
[Scheme 36. Cyclization of allenyl 2-aminophenols and 2-phenylendiamine]

Hydroamination process is applied also to indole 2-carboxylic acid allenamides **63** affording 3-vinyl substituted imidazo[1,5-*a*]indoles **64**, exclusively under microwave irradiation. On the same substrates in the presence of aryl halides carboamination reactions give 3-styryl imidazoloindoles under thermal or microwave heating. In both cases, the indole nitrogen acted as the nucleophile attacked in the allene group complexed with palladium (Scheme 37).[46]



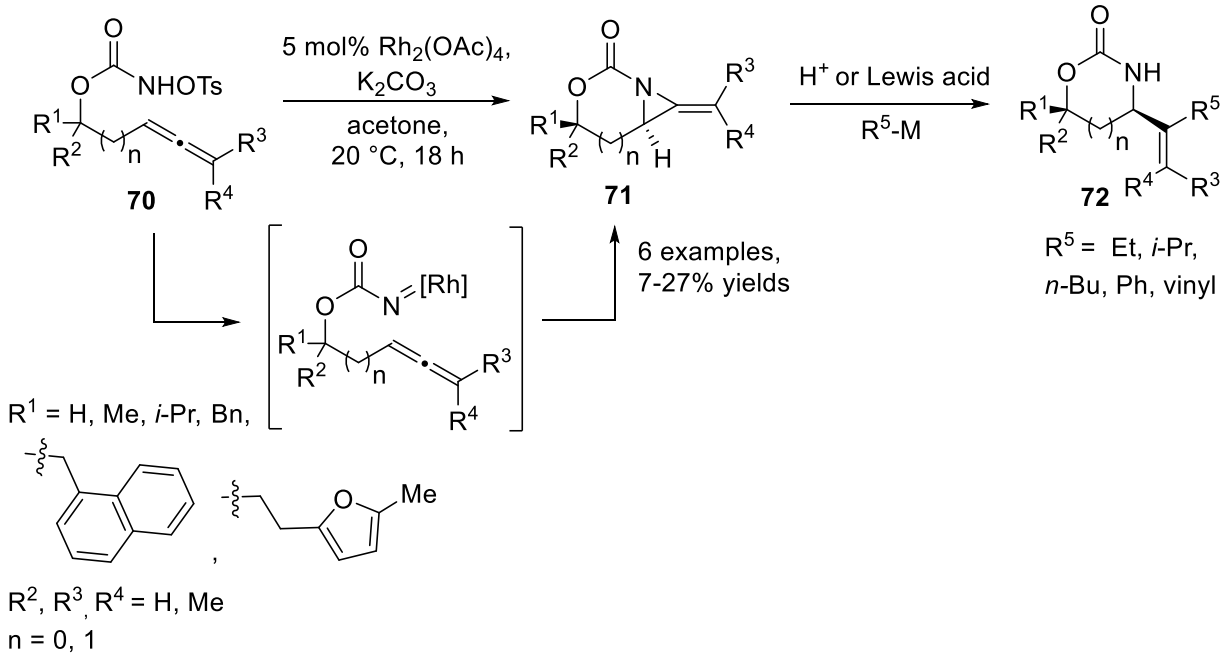
[Scheme 37. Cyclization of indole 2-carboxylic acid allenamides]

The treatment of alkyl substituted penta-3,4-dienyl sulfamates **47** with rhodium(II) octanoate dimer in the presence of $PhI(OAc)_2$ afforded three categories of cyclized products depending on the substitution pattern. The reaction pathway began, for all the products, with the formation of rhodium nitrenoid species **65** followed by nucleophilic attack to the tethered allene obtaining the intermediate **66**. Besides the expected *exo*-cyclization product **67**, the cyclopropyl products **68** and methylene aziridines **69** were formed, arose by ring-closure between two carbons of the allene moiety of **66**, or between the nitrogen and one carbon of the allene residue of **66** (Scheme 38).[47]



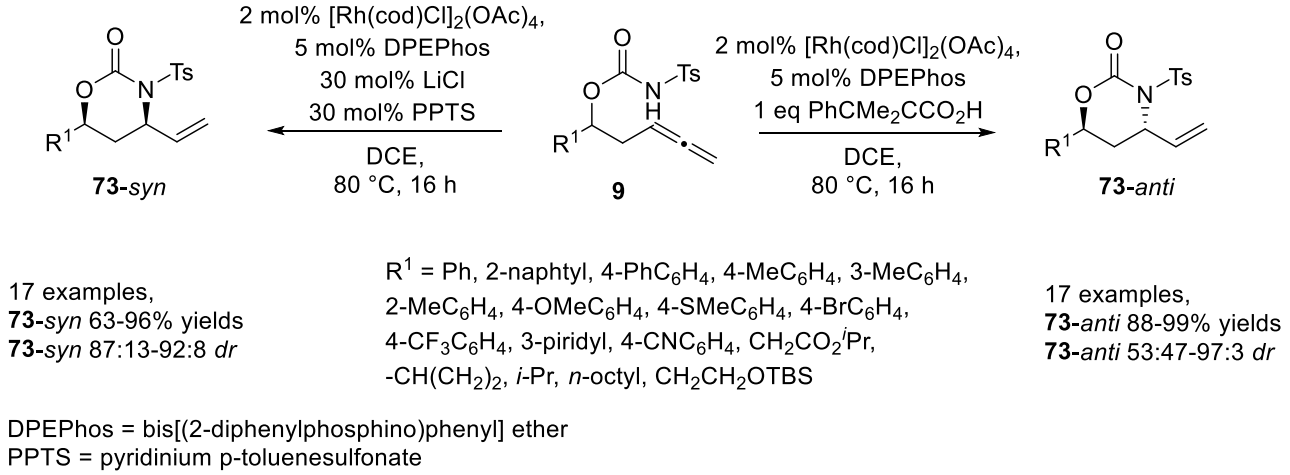
[Scheme 38. Cyclization of β-allenyl sulfamates]

Studying the reactivity of buta-2,3-dienyl carbamates **70**, the same authors obtained different results with the same catalytic system. Through a mechanism involving the intramolecular aziridination of the allene, a bicyclic oxazolidinone-aziridine system **71** was isolated.[48] The low stability of **71** allowed the ring-opening in the presence of nucleophile such as organolithium or Grignard reagents, affording 4-alkenyl-oxazolidin-2-ones **72** (Scheme 39).



[Scheme 39. Cyclization of allenyl carbamates]

Intramolecular addition of N-tosylcarbamates **9** to terminal allene moiety afforded *N*-allylated cyclic carbamates **73** selectively. The reaction was performed in the presence of $[Rh(cod)Cl]_2$ (2.0 mol%) and DPEphos (5.0 mol%) in DCE as solvent at 80 °C. In the absence of additive, or in the presence of LiCl and PPTS, the *syn*-configuration product was obtained, with high d.r. value. Using benzoic or phenyl isobutyric acid additives, a complete inversion of the diastereoselectivity was observed, obtaining the *anti*-configuration in high yield and high d.r. value. A broad range of substituents were tolerated giving access, after removal of both the tosyl and carbamate groups, to the corresponding 1,3-aminoalcohols (Scheme 40).[49]

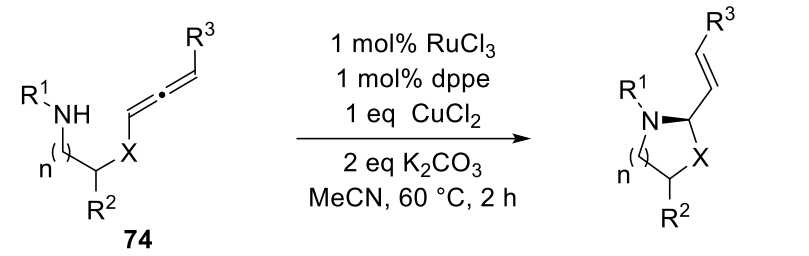


DPEPhos = bis[(2-diphenylphosphino)phenyl] ether
PPTS = pyridinium p-toluenesulfonate

[Scheme 40. Cyclization of β-allenyl *N*-tosylcarbamates]

A valuable alternative, to known transition metal catalytic systems in obtaining 2-vinyl substituted five-, six- and seven-membered 1,3-diaza- or 1,3-oxaza-heterocyclic structures was represented by the ruthenium-catalyzed hydroamination of amino-heterosubstituted allenes **74** and anthranilic allenamides **75**. The transformation proceeded through the complexation of the unsaturated system with ruthenium affording zwitterionic intermediate **A**, followed by the addition of the nitrogen atom onto the proposed oxycarbenium specie producing the heterocycle **B**.[50] The proton transfer from the heterocycle **B** could take place through

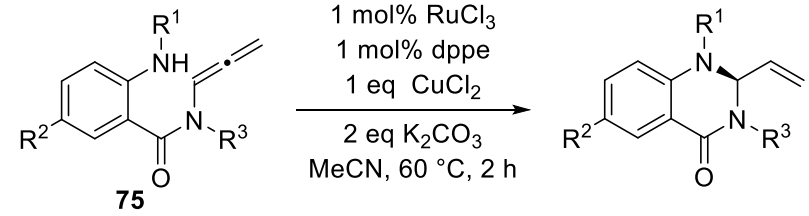
the formation of Ru^{IV} hydride **C** and subsequent reductive elimination or through the Ru carbenoid species **D** followed by 1,2-hydrogen shift and final decomplexation (Schemes 41 and 42).



74

X = NMe, NTs, O
R^1 = Boc, Ts; R^2 = H, C=O
R^3 = H, Ph
n = 1, 2, 3

7 examples,
61-90% yields



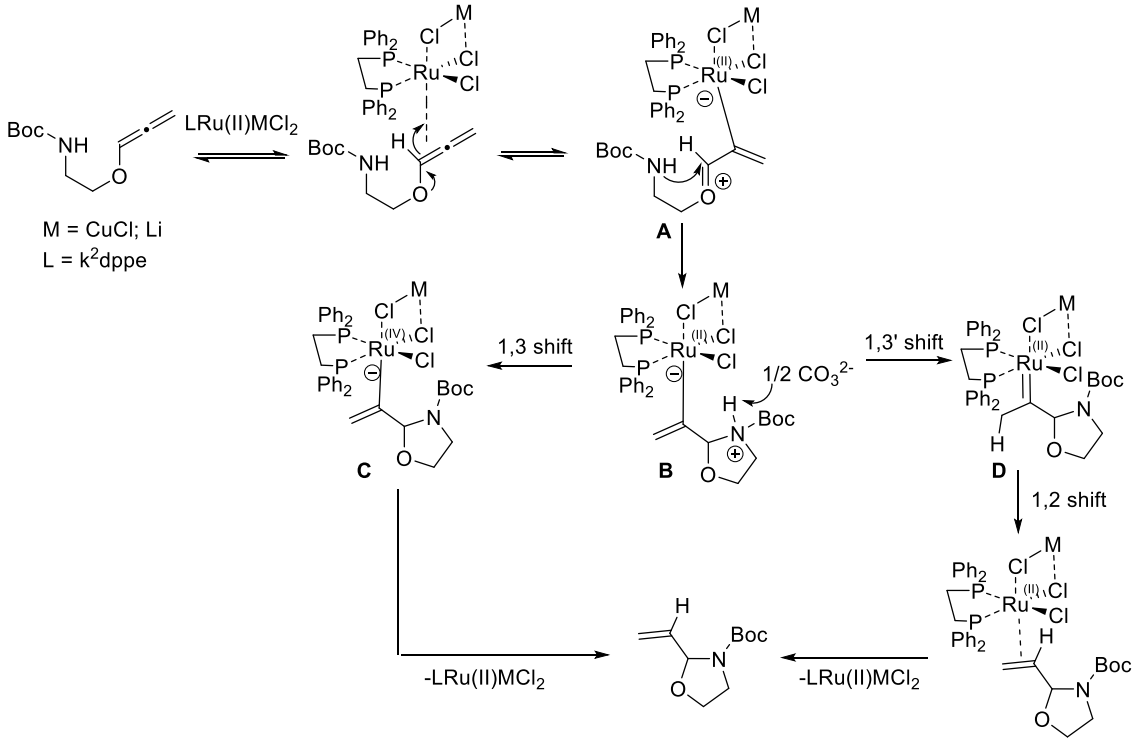
75

X = NMe, NBn
R^1 = Boc, Ts; R^2 = H, Cl
R^3 = NMe, NBn

4 examples,
61-90% yields

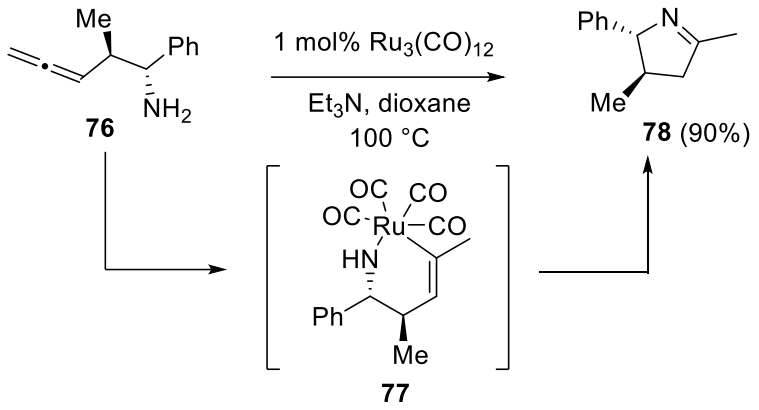
dppe = bis(diphenylphosphino)ethane

[Scheme 41. Ru-catalyzed cyclization of γ-, δ-, ε–aminoallenes and anthranilic allenamides]



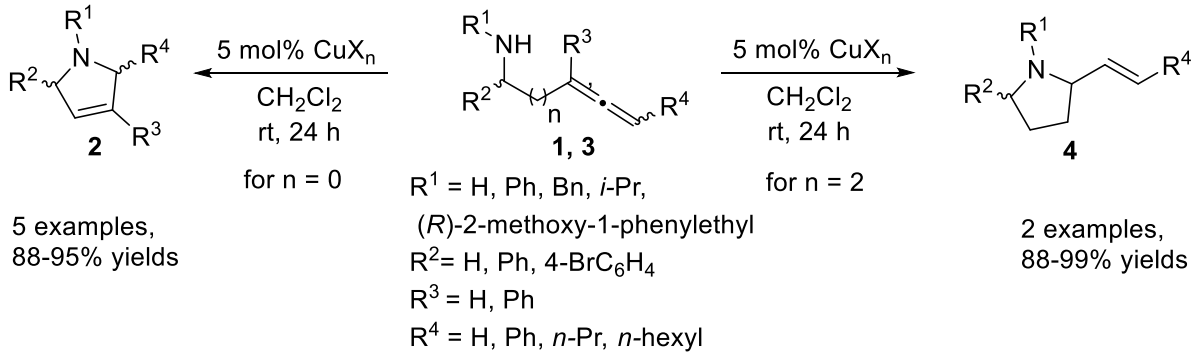
[Scheme 42. Mechanism of the cyclization]

Hydroamination of 1-phenyl-2-methyl-3,4-pentadienylamine **76**, using $Ru_3(CO)_{12}$ resulted in the diastereomerically pure *trans*-4-methyl-5-phenyl-pyrrolidine **78**. The proposed mechanism involved the formation of the intermediate oxaruthenacycle **77** and the subsequent ring formation through the elimination of the metal (Scheme 43).[51]



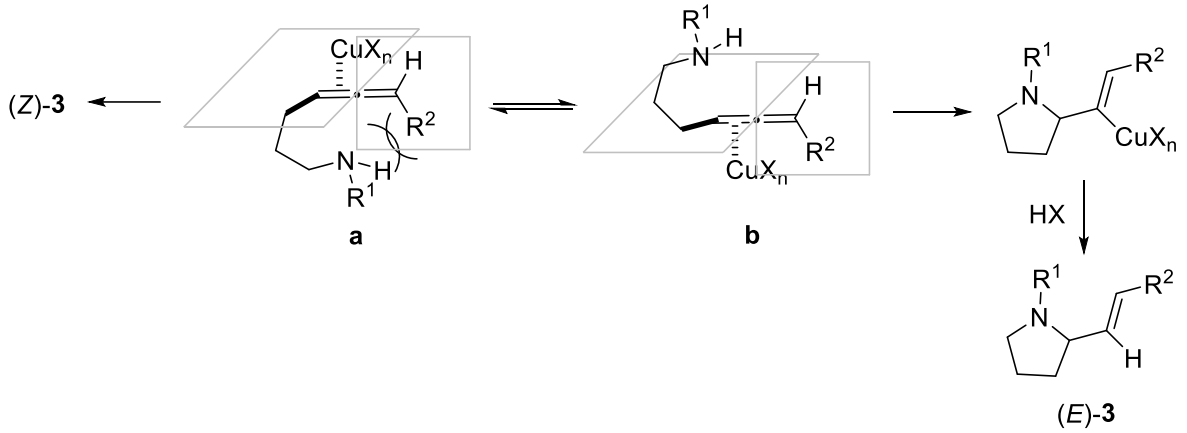
[Scheme 43. Cyclization of 1-phenyl-2-methyl-3,4-pentadienylamine]

Secondary γ-allenylamines **3** are the substrates for the intramolecular hydroamination with different inexpensive Cu(I) and Cu(II) salts (as CuCl or CuOTf but also $CuCl_2$ and $Cu(OTf)_2$), in catalytic amount, in DCM at r.t. providing 2-alkenylpyrrolidines **4** through an *exo*-cyclization process.[52] In contrast α-allenylamines **1** cyclized in an *endo*-cyclization fashion afforded 3-pyrrolines **2** in excellent yields (Scheme 44). The reaction was faster than that with $AuCl_3$ but slower than that with AgOTf under the same conditions. Under these conditions no results were reported with allenamides.



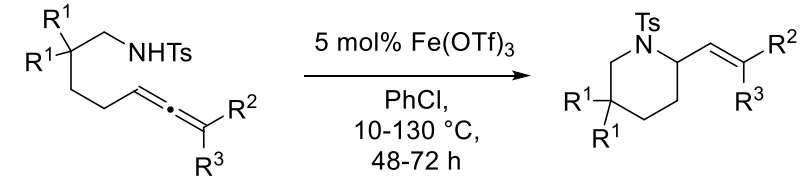
[Scheme 44. Regioselective Cu-catalyzed cyclization of allenylamines]

Based on the alkene geometry of the product, where the *E*-olefin was formed with high selectivity, the reaction mechanism for the *exo*-cyclization involved an *anti*-aminometallation pathway favoring the less sterically hindered side of the allene (Scheme 45).



[Scheme 45. Mechanism of the *exo*-cyclization]

An alternative to the use of the traditional transition metals was represented by the iron salts, showing advantages due to the nontoxicity and low costs. Despite much research into reactivity of Fe catalysts toward alkenes and alkynes, the allenes remain less studied. Various Fe(III) catalysts with different counterions were tested in hydroamination (and hydroalkoxylation) reactions.[53] Their activity toward allenes were dependent on the counterion and reaction conditions. $Fe(OTf)_3$ in chlorobenzene at different temperature, depending on the substrate, gave the best results affording piperidines. Also, in this case the mechanism suggested involve the traditional metal allene complexation, nucleophilic addition and protodemetalation, similar to other metals described (Scheme 46).



R^1 = H, Ph
R^2, R^3 = H, Me, Ph, *n*-pentyl,
$-(CH_2)_5-$, $-(CH_2)_6-$

6 examples,
31-83% yields

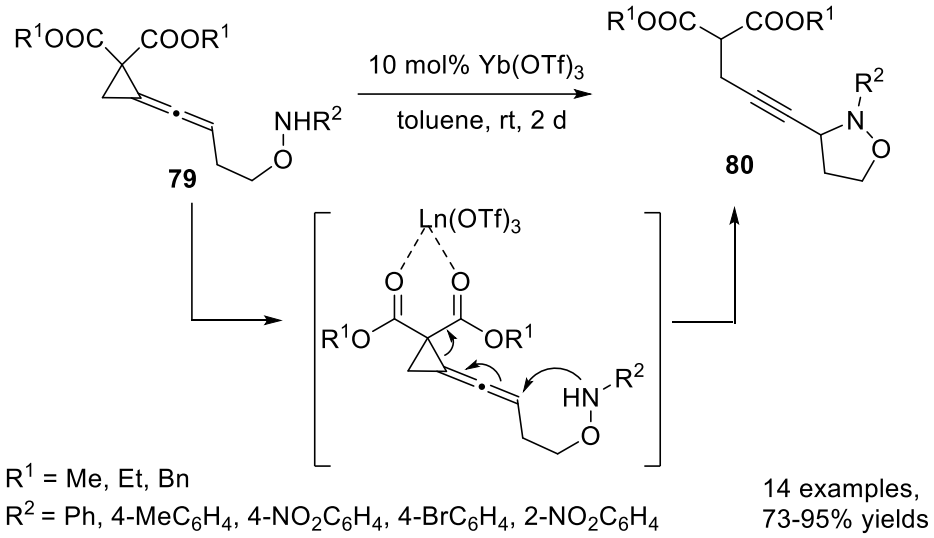
[Scheme 46. Fe-catalyzed cyclization of *N*-Ts allenamides]

Intramolecular hydroamination of γ- and δ-aminoallenes has been performed also using organolanthanide complexes ($Cp'_2LnCH(TMS)_2$ Cp' = η^5-Me_5C_5; Ln = La, Sm, Y, Lu) affording a mixture of two regioisomeric products: pyrrolidines and piperidines mono- and disubstituted.[54] A useful regio- and stereoselective application of this methodology was reported for the construction of mono- and bicyclic alkaloids such as (+)-xenovenine and (+)-pyrrolidine 197B.[55]

On the same time computational studies were reported to investigate in depth the detailed mechanism for the cyclization process under organolanthanide catalysis and zirconocene catalysis, in particular to elucidate the factors effective in controlling the regio- and diastereoselectivity.[56]

After that, the use of lanthanide triflates $Ln(OTf)_3$ has been explored owing to their efficacy as Lewis acid catalysts and to their low environmental impact. Among the synthesis of five-membered *N,O*-containing cycles, the hydroamination of particular substrate 1,1-vinylidenecyclopropanediesters **79** bearing sulfonamide as substituent, afforded the isoxazoline rings **80** in the presence of $Yb(OTf)_3$. The catalyst, in which the strong electron-withdrawing trifluoromethanesulfonate anion enhanced the acidic character,

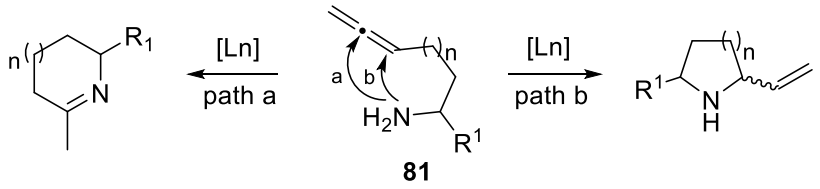
mainly acted as hard Lewis acid through the coordination with polar functional groups such as carbonyls (Scheme 47).[57] The intramolecular nucleophilic attack can trigger a domino reaction with formation of a triple bond and ring-opening of the cyclopropane ring followed by proton transfer.



[Scheme 47. Yb-catalyzed cyclization of 1,1-vinylidenecyclopropanediesters]

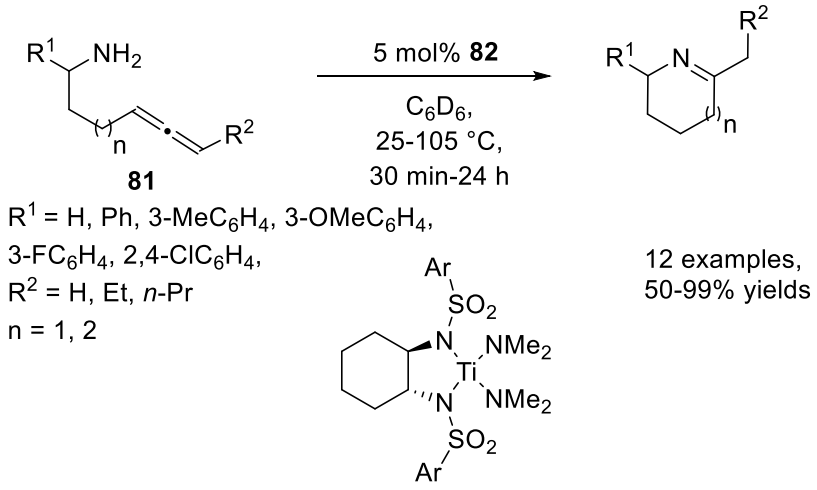
The intramolecular hydroamination of aminoallenes was studied also exploiting the titanium complexes and zirconium complexes.

Comparing the reactivity of the 2-aryl-4,5-esadienylamines **81** by using different transition-metals, the Ag- or Pd-precatalysts provided exclusively 2-vinylpyrrolidines through 5-*exo* cyclization, where the lanthanide complexes converted the substrate into the mixture of two possible regioisomers. Lanthanide complexes in the presence of titanium pre-catalysts formed the cyclic imines through the exclusive 6-*endo* cyclization (Scheme 48). [58]



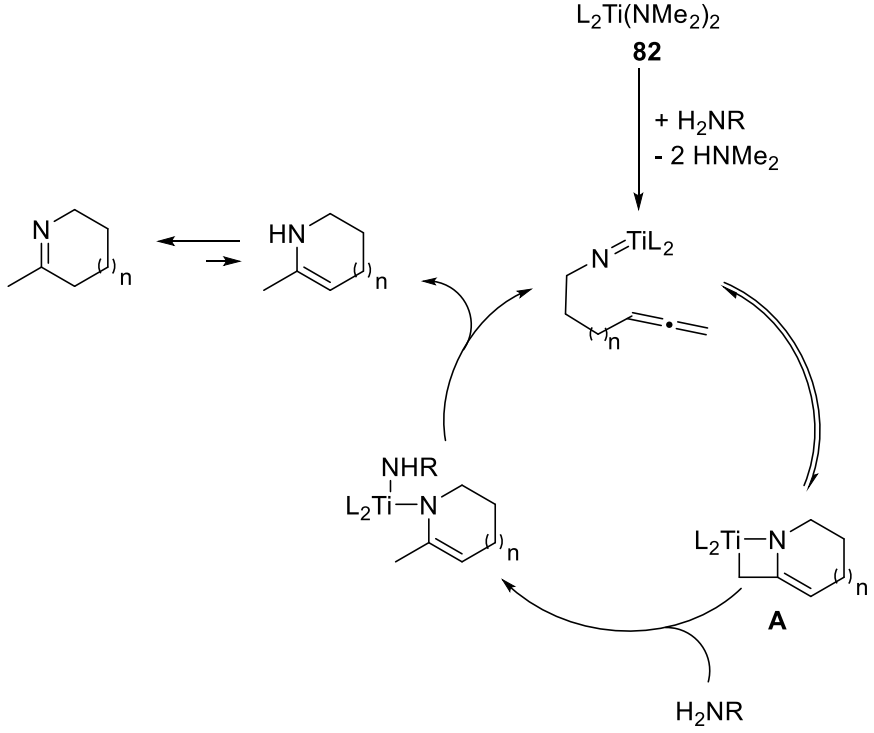
[Scheme 48. Ln-catalyzed regioselective cyclization of 2-aryl-4,5-esadienylamines]

Among different titanium complexes, the regioselectivity in the cyclization step depended on the nature of the precatalyst, where the most selective was the bis(sulfonamide)titanium complex **82** (Scheme 49).



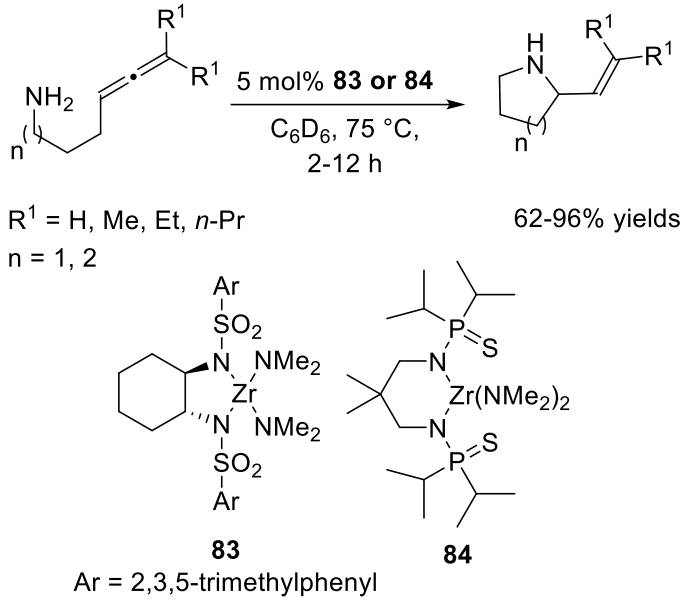
[Scheme 49. Ti-catalyzed cyclization of γ-, δ-allenylamines]

The proposed mechanism postulated the intermediate formation of an azametallacyclobutane **A** arising from a formal [2+2] cycloaddition of the titanium-imido species on the allene. Then, the subsequent protonation regenerated the catalyst and released the product (Scheme 50). The enhanced regioselectivity may be due to the sterically demanding bis(sulfonamide)ligand, which disfavors the cycloaddition of the titanium imido species with the internal double bond of the allene. A particular study with different chiral aminoalcohols prepared to be used as ligands for titanium catalyst confirmed the influence of the ligands in the selectivity towards the formation of the pyrrolidine regioisomer.[59]



[Scheme 50. Mechanism of the Ti-catalyzed cyclization]

In contrast to the titanium complexes **82**, the zirconium analogue complexes **83** or **84**, gave an inverted regioselectivity, providing the substituted pyrrolidines. The introduction of one substituent at the terminal position of the allene moiety afforded the *Z*-isomers exclusively. Also in the case of disubstituted allene the regioselectivity favoured the formation of the 5-membered ring (Scheme 51).[59,60]



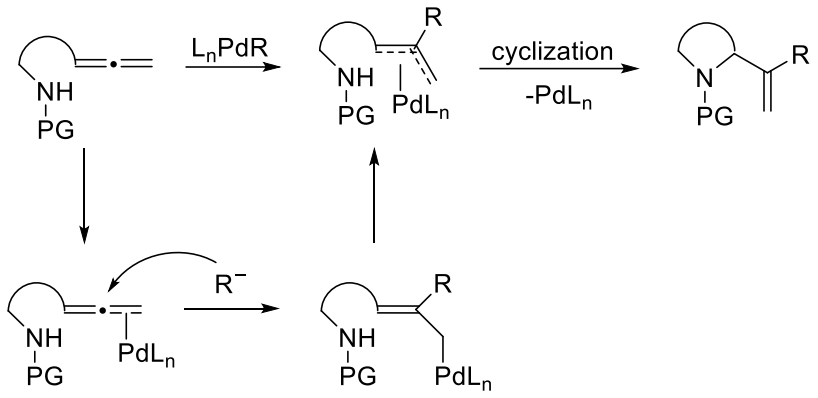
[Scheme 51. Zr-catalyzed cyclization of γ-, δ-allenylamines]

CARBOAMINATION OF ALLENES

Intramolecular transition metal-catalyzed reactions involving nitrogen nucleophiles and allenes, via formation of two bonds, are important tools in organic synthesis, providing a large variety of three to ten-membered heterocycles. Palladium-catalyzed coupling reactions of unsaturated 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 groups. The Pd-catalyzed reactions performed in the presence of chiral ligands result in a complete stereoselective cyclization processes. Compared to palladium, few examples of copper, gold and rhodium catalyzed reactions are reported.

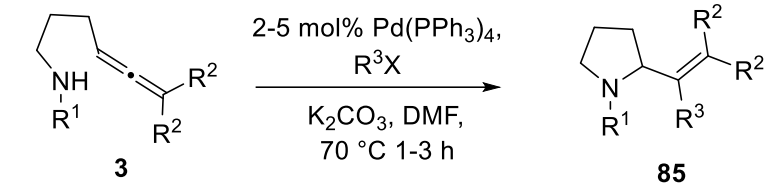
Palladium-catalyzed intermolecular coupling/intramolecular amination processes

The cyclization of an allene tethered to nitrogen nucleophiles, such as secondary amines, amides sulfonamides, and carbamates following a carboamination pathway can be fruitfully promoted by Pd(0)-catalysts in the presence of an aryl, allyl or vinyl halide. The formation of an intermolecular carbon-carbon bond, is followed by an intramolecular nucleophilic attack from the NH group on the π-allyl-complex which determines the kind of heterocycle (Scheme 52). 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.



[Scheme 52. General mechanism of the carboamination]

In 1993, Gallagher and co-workers reported the cyclization of γ-amino-substituted allenes (**3**) to access to 2-vinyl-substituted pyrrolidines (**85**) (Scheme 53).[61] The reaction was performed with $Pd(PPh_3)_4$ as the catalyst, using a wide range of aryl or vinyl halides to trigger the formation of the electrophilic species determinant for the generation of the organopalladium(II) intermediate.

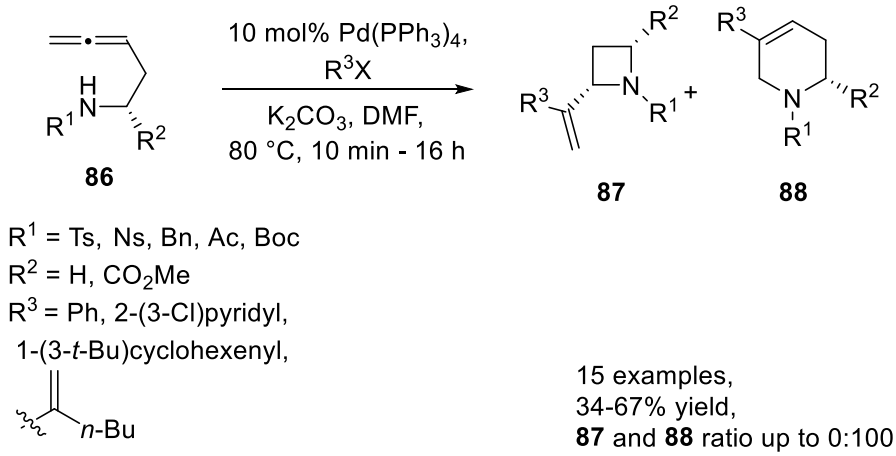


R^1 = Bn, Ts, Boc; R^2 = H, Me
R^3 = Ph, 4-MeC$_6$H$_4$, 3-MeOC$_6$H$_4$,
1-naphtyl, 2-thienyl, 1-styryl, 2-styryl

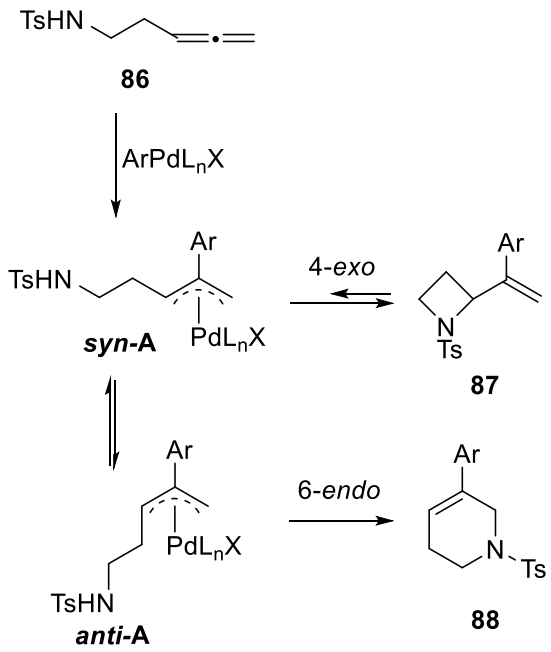
16 examples,
66-84% yields

[Scheme 53. Carboamination of γ-aminoallenes]

The regioselectivity of the cyclization could depend on the substituents of the starting material, as shown with β-aminoallenes **86**, which furnished four- or six-membered nitrogen-containing heterocycles **87** and **88** by treatment with catalytic $Pd(PPh_3)_4$ and K_2CO_3 in the presence of aryl and heteroaryl halides or triflates (Scheme 54).[62] Four- or six-membered ring formation resulted from the attack of the nitrogen onto one of the *sp*^{2}-allene carbon atoms depending on the mechanistic pathways that diverge according to the geometry of an π-allyl intermediate. 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*-**A**, which could be converted into the more hindered isomer *anti*-**A** (Scheme 55). The kinetic product azetidine **87,** obtained by 4-*exo* cyclization of the *syn*-intermediate, could undergo $Pd(PPh_3)_4$-mediated ring opening and through the *anti*-**A** the preferred 6-*endo* cyclization provided the thermodynamically more stable six-membered ring **88**. 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.



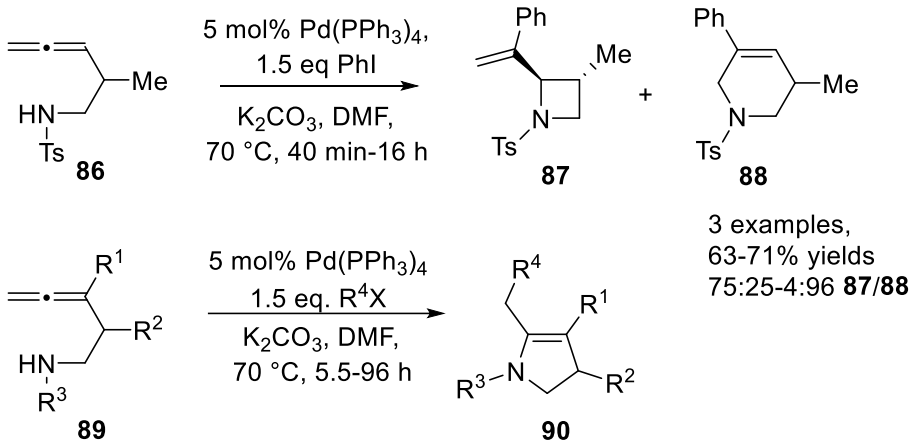
[Scheme 54. Regioselective carboamination of β-aminoallenes]



[Scheme 55. Regioselective carboamination mechanism of β-aminoallenes]

A similar Pd-catalyzed reaction starting from *N*-arylsulfonyl-substituted β-aminoallenes afforded 2,4-*cis*-disubstituted azetidines.[63]

The pivotal role of the substituents on β-aminoallenes in determining their reaction path in Pd-catalyzed coupling-cyclization process in the presence of aryl halides was confirmed by the studies of Ma and co-workers.[64] Starting from 3,4-allenamides **86,** substituted or unsubstituted in position 5, azetidines **87** and/or 1,2,5,6-tetrahydropyridines **88** 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 **90** were proven to be the cyclization products when 3-substituted-5-unsubstituted-3,4-allenamides **89** were treated with aryl halides in the presence of $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 in DMF at 70°C (Scheme 56). 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.

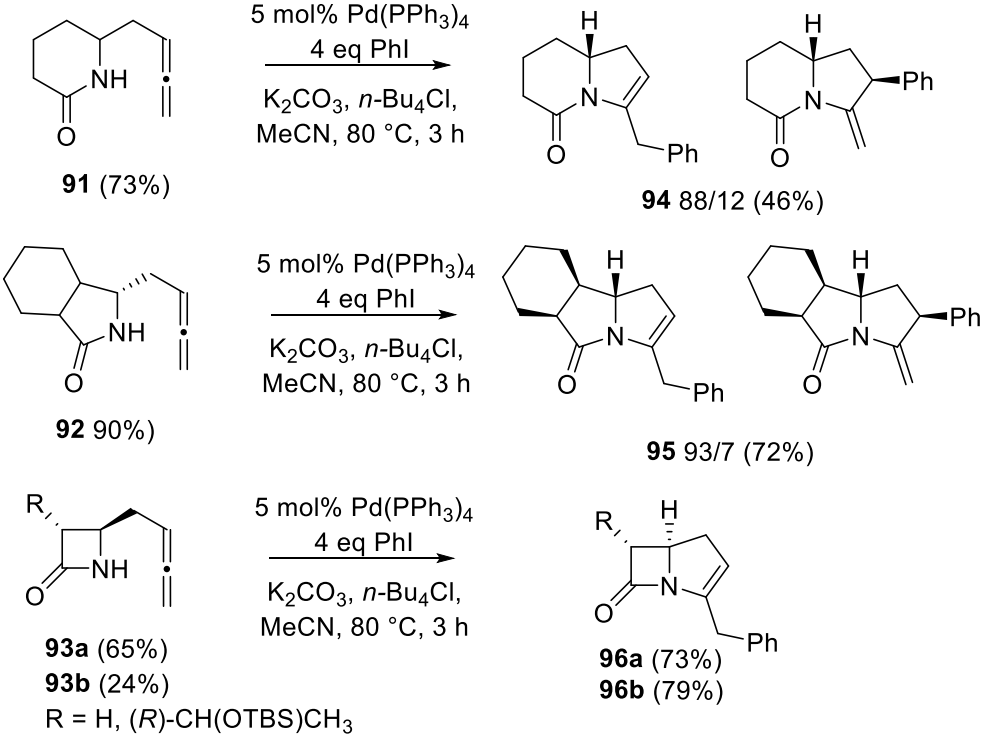


R^1 = Me, *n*-Pr, *n*-Bu, *t*-Bu, *n*-heptyl
R^2 = H, CH_3, *n*-Pr; R^3 = Ts, Ns
R^4 = Ph, 4-$OMeC_6H_4$, 4-$CO_2MeC_6H_4$, 4-BrC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 2-thienyl, 2-pyridyl, 1-naphtyl

15 examples,
45-78% yields

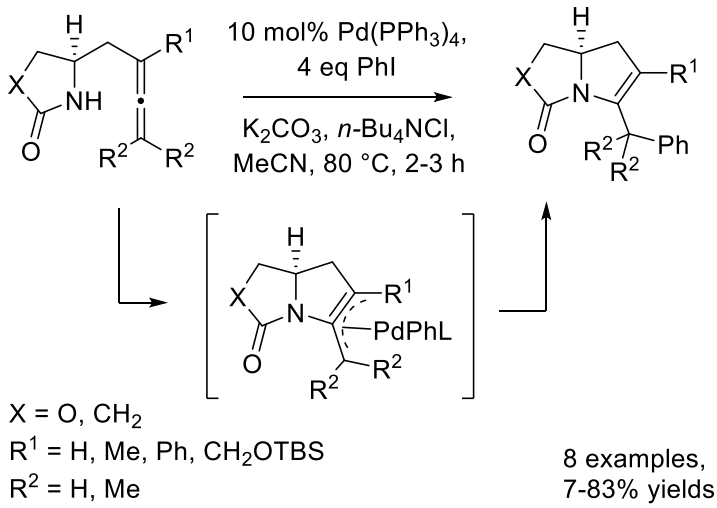
[Scheme 56. Role of the substituents in the β-aminoallenes carboamination]

The unusual cyclization involving the central allene carbon was previously observed by Hiemstra and co-workers. Their investigation on allenyl lactams **91-93** allowed to define fruitful conditions based on $Pd(PPh_3)_4$ as catalyst, K_2CO_3 as the base, Bu_4NCl as the additive and iodobenzene, to access five-membered fused-rings, leading to carbapenem (**94**), pyrrolizines (**95**), and indolizines (**96**) structures (Scheme 57).[65] Reasonably, due to the uncommon tendency of a π-allyl-complex to undergo attack on the central carbon, especially with soft phosphine ligands, a π-olefin-complex should be the key intermediate of the reaction.



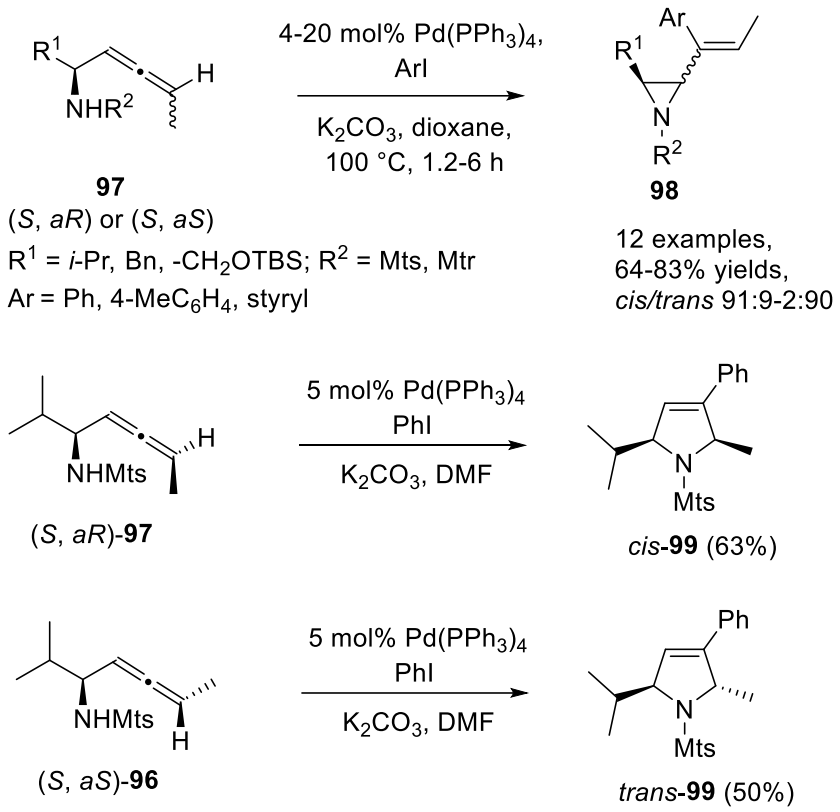
[Scheme 57. Carboamination of allenyl lactams]

Using the same conditions, enantiopure bicyclic enamides were achieved starting from enantiopure allenyl lactams (Scheme 58).[66]



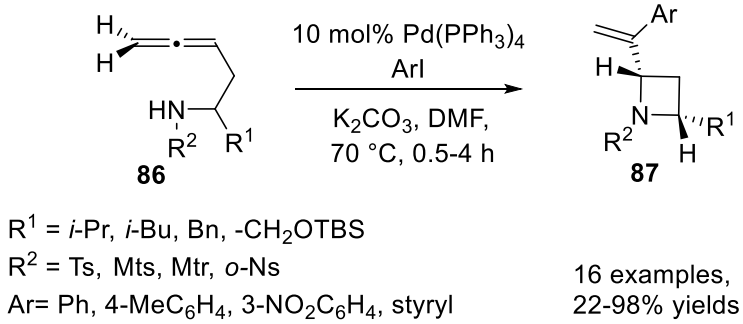
[Scheme 58. Enantioselective carboamination of allenyl lactams]

In 1999, Ibuka, Tanaka, Ohno and co-workers described the first Pd-catalyzed aziridination reaction starting from α-aminoallenes. Substrates **97** were converted to aziridine derivatives **98** in the presence of iodobenzene, Pd(0)-catalyst, K_2CO_3 and 1,4-dioxane as solvent (Scheme 59).[67] The careful choice of the solvent was proven to be crucial for the divergent outcome of the cyclization by 3-*exo*- or 5-*endo-allylic* reaction. Thus, a different reaction pathway was observed using the same conditions in DMF as the solvent, affording 2,5-dihydropyrrole derivatives **99** as the sole products. The expected aziridine products were achieved in good yield in 1,4-dioxane, also replacing iodobenzene with either 4-iodotoluene or β-bromostyrene. In the case of chiral **97**, the products were obtained with *cis* selectivity.



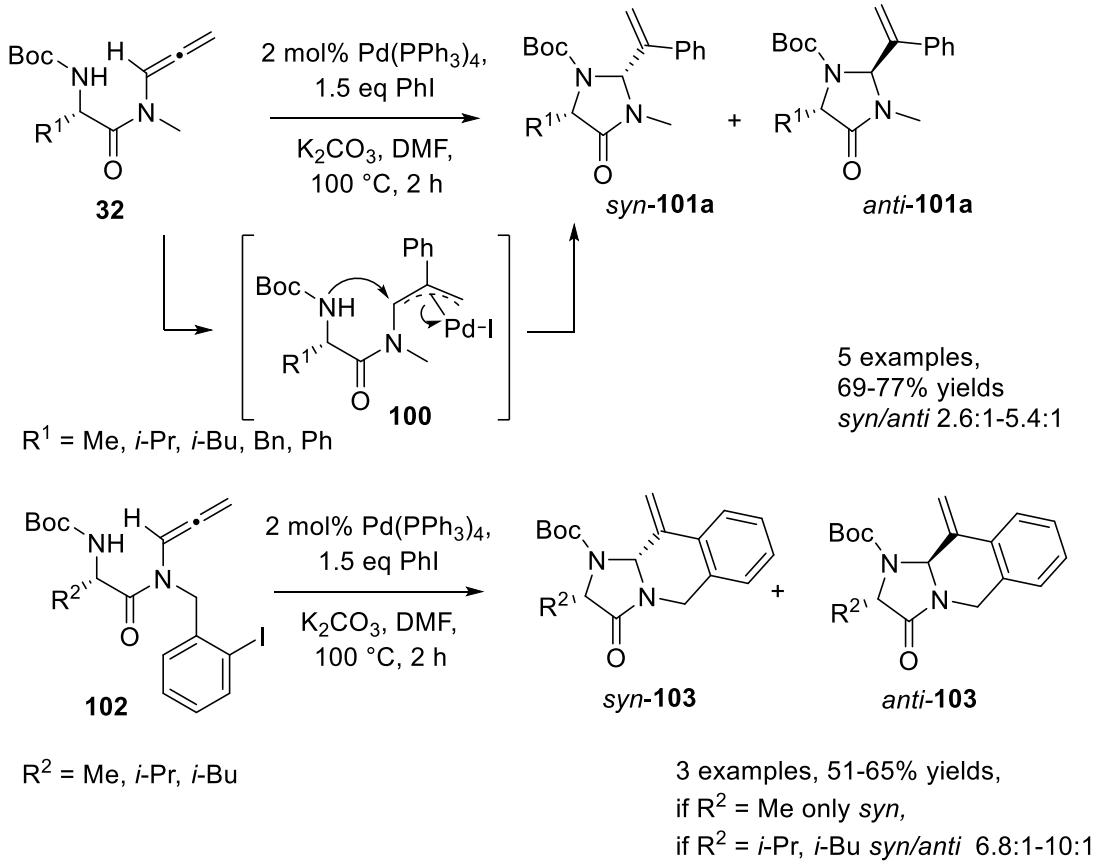
[Scheme 59. Regioselective carboamination of α-aminoallenes]

Analogously, in the same reaction conditions, the treatment of β-aminoallenes **86** and iodobenzene in 1,4-dioxane afforded the 2,4-*cis*-4-alkyl-2-alkenylazetidines **87** as exclusive product. No formation of the possible regioisomeric six-membered ring was observed unless a strong electron-withdrawing *p*-nitrophenylsulfonyl group was introduced at the nitrogen atom (Scheme 60).



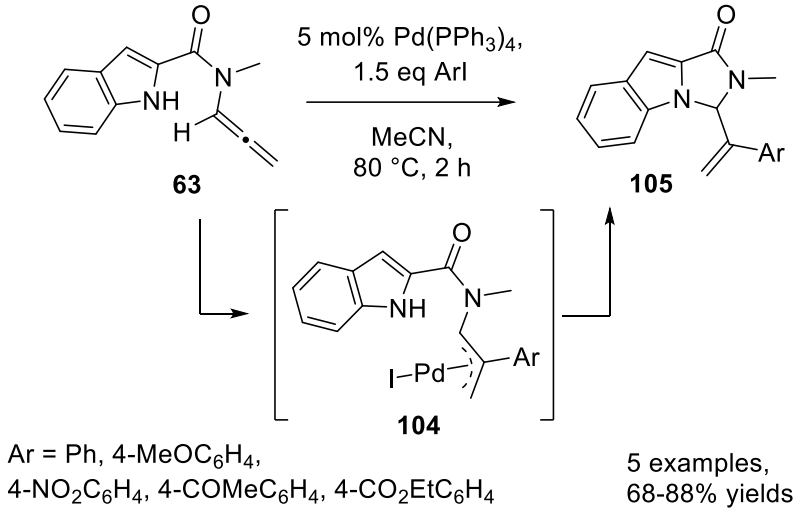
[Scheme 60. Regioselective carboamination of β-aminoallenes]

The carboamination of optically active α-amino allenamides **32** was performed with a catalytic amount of $Pd(PPh_3)_4$, an excess of K_2CO_3 in DMF at 100 °C affording the enantiopure 4-imidazolidinones **101** (Scheme 61).[68] The reaction proceeds through a carbopalladation/5-*exo*-allylic amination sequence with the π-allyl intermediate **100**. The intramolecular carbopalladation instead of the intermolecular alternative worked successfully providing the tricyclic fused-ring imidazolidinones **103**. The styryl derivatives **101,** after deprotection and suitable functionalization, were conveniently used as intermediates for the preparation of a new class of tetracyclic benzodiazepine derivatives.[69]



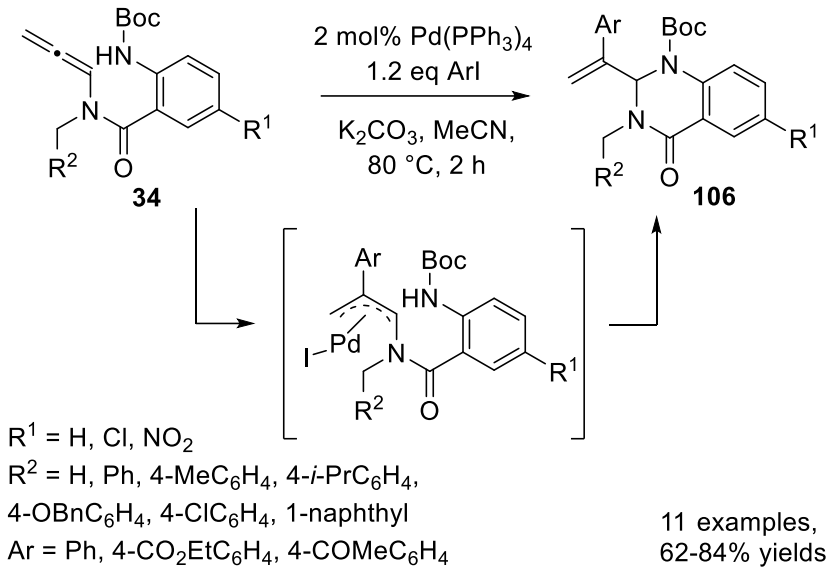
[Scheme 61. Carboamination of optically active α-amino allenamides]

This carboamination procedure was further developed exploiting the indole nitrogen of the *N*-allenyl amides **63** (Scheme 62).[46] The use of classical reaction conditions in acetonitrile as the solvent at reflux, furnished the styryl-substituted indoloimidazole derivatives **105**. The reaction proceeded through the π-allyl-complex **104** 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 ring was never observed.



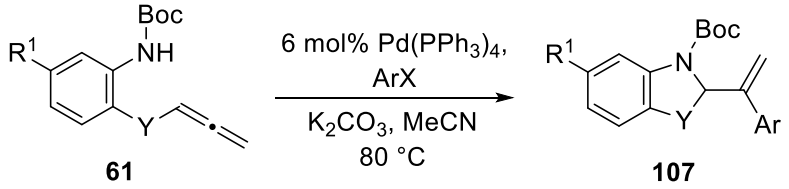
[Scheme 62. Carboamination of indole 2-carboxylic acid allenamides]

The Pd(0)-catalyzed reaction of the anthranilic allenamides **34** with aryl iodides was proved as an efficient tool for the preparation of 2-(α-styryl)quinazolin-4-one derivatives **106** (Scheme 63).[34]



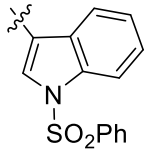
[Scheme 63. Carboamination of anthranilic allenamides]

Working once again at reflux with acetonitrile as the solvent, Boc-protected allenyl derivatives of the 2-aminophenols and 1,2-phenylenediamine **61** reacted with (hetero)aryl iodides providing the 2-substituted dihydrobenzoxazoles and dihydrobenzimidazole **107** by treatment with a catalytic amount of $Pd(PPh_3)_4$ and K_2CO_3 (Scheme 64).[45] In terms of regioselectivity, the cyclization of *N*-allyl-1,2-phenylenediamine was strongly depended on the protecting group tethered to the nitrogen atoms, switching the reaction toward the seven-membered ring product **108**.

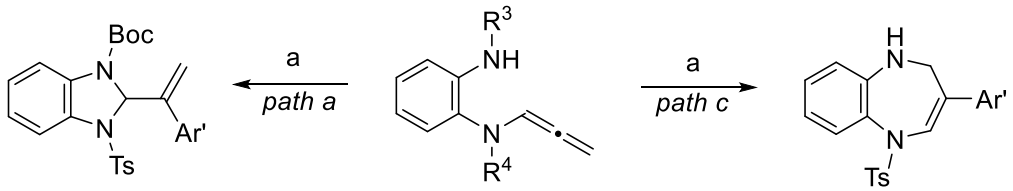


61 **107**

Y = O, NTs; R^1 = H, NO_2, Cl, Me
Ar = Ph, 3-$CF_3C_6H_4$, 4-$CO_2EtC_6H_4$,
4-$NO_2C_6H_4$, 4-$OMeC_6H_4$, 2-thienyl, 2-pyridyl, $CH_2CH{=}CH_2$,



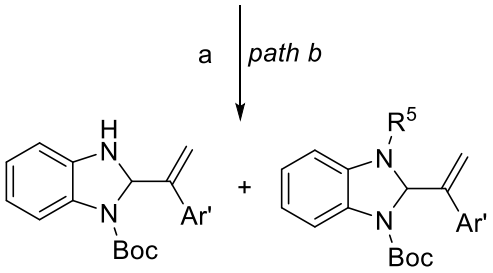
17 examples,
46-86% yields



(46-86%)

R^3= $COCF_3$; R^4 = Ts, Boc
Ar' = *p*-$NO_2C_6H_4$

108
(78%)

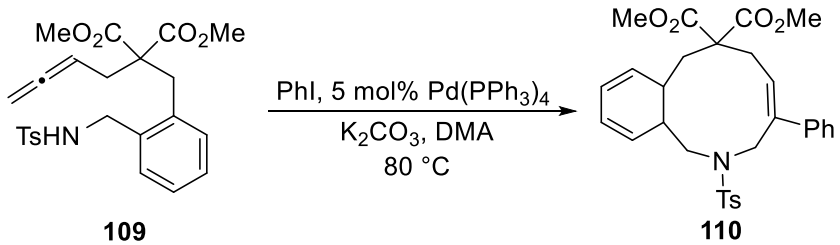


(50%)

a: 6 mol% $Pd(PPh_3)_4$, Ar'I, K_2CO_3, MeCN, 80 °C

[Scheme 64. Carboamination of allenyl 2-aminophenols and 2-phenylendiamine]

The same catalytic system could promote the cyclization of ω-aminoallenes to ten-membered azacycle products. Indeed, the Pd(0)-catalyzed reaction of compound **109** with iodobenzene in dimethylacetamide gave the benzo[*c*]azecine derivative **110** as the sole product (Scheme 65).[70]

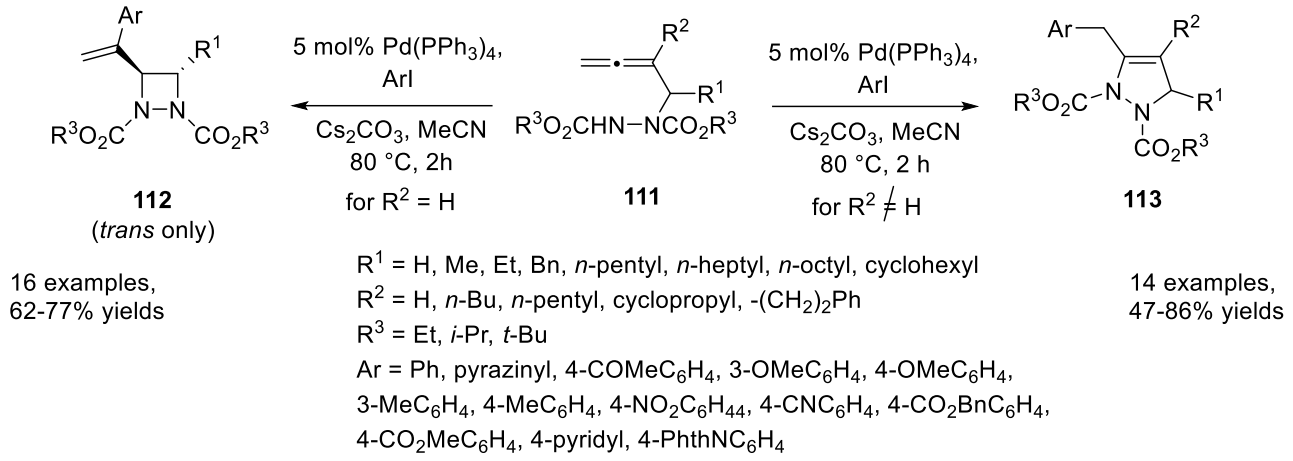


109 **110**

[Scheme 65. Carboamination of ω-aminoallenes]

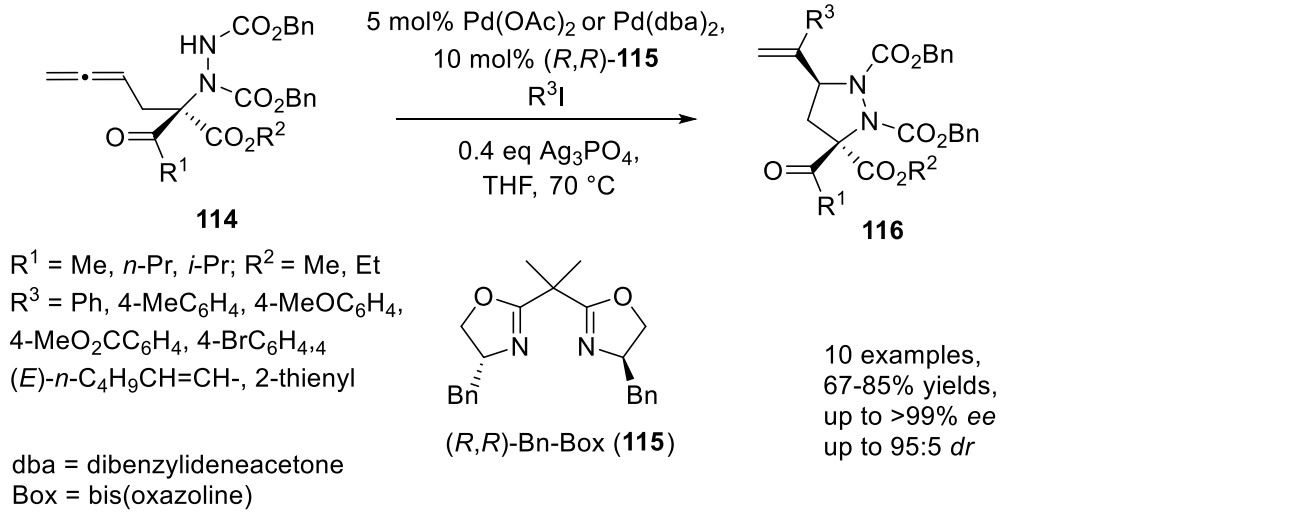
In 2008, Ma and co-workers reported the regio- and *trans*-diastereoselective intermolecular coupling/intramolecular amination of 2,4-unsubstituted 2,3-allenyl-hydrazines **111** with aryl iodides providing the *trans*-1,2-diazetidines **112** (Scheme 66).[71] Conversely, carrying out the reaction in the same

conditions on substrates bearing a substituent in 2-position, a different regioselectivity was observed with formation of the 2,3-dihydro-1*H*-pyrazoles **113**.[72]



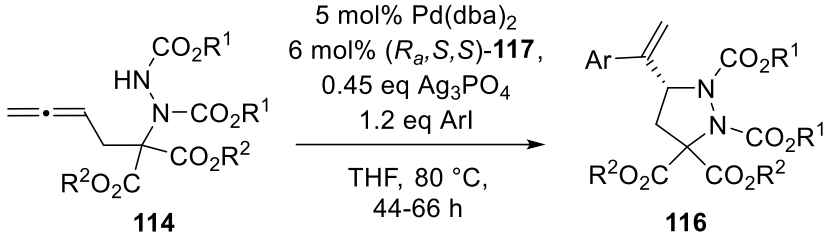
[Scheme 66. Regioselective carboamination of α-allenyl-hydrazines]

Highly diastereoselective synthesis of pyrazolidines was performed by Ma and co-workers. The asymmetric synthetic protocol was based on a Pd(0)-catalyzed carboamination between the optically active allenyl hydrazines **114** and (hetero)aryl halides in the presence of Ag_3PO_4 as the base and a chiral ligand in THF as the solvent (Scheme 67).[73] (*R,R*)-Bn-Box (**115**) was proven the most efficient ligand, giving (3*R*,5*S*)-pyrazolidines **116** 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 **114**, 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.

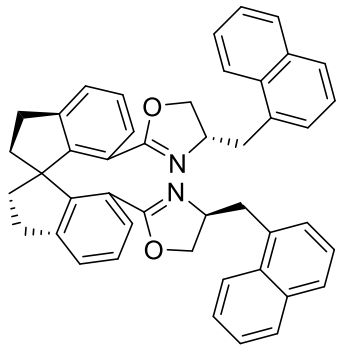


[Scheme 67. Stereoselective carboamination of β-allenyl-hydrazines]

A spirooxazolidine chiral ligand (R_a,*S,S*)-**117** was conveniently applied to the enantioselective cyclization of allenyl hydrazines **114** with (hetero)aryl iodides, affording pyrazolidines **116** in high yields and enantiomeric excess (Scheme 68).[74] Control experiment revealed that the high enantioselectivity strongly depended on the spiro skeleton and the α-naphthylmethyl group.



R^1, R^2 = Et, Bn; Ar = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-BrC_6H_4, 4-$CO_2MeC_6H_4$, 4-$COMeC_6H_4$, 4-CNC_6H_4, 4-PhC_6H_4). 4-(4'-BrC_6H_4)C_6H_4, 3,4-$Me_2C_6H_3$, 3,5-$Me_2C_6H_3$, 3,4-$(OCH_2)_2C_6H_3$, 3-thienyl

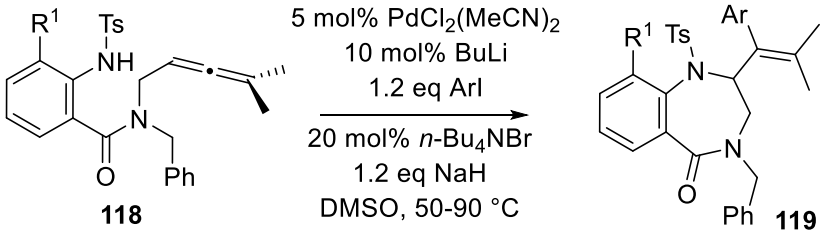


(R_a,S,S)-**117**

15 examples,
71-90 % yields
up to 95% *ee*

[Scheme 68. Enantioselective carboamination of β-allenyl-hydrazines]

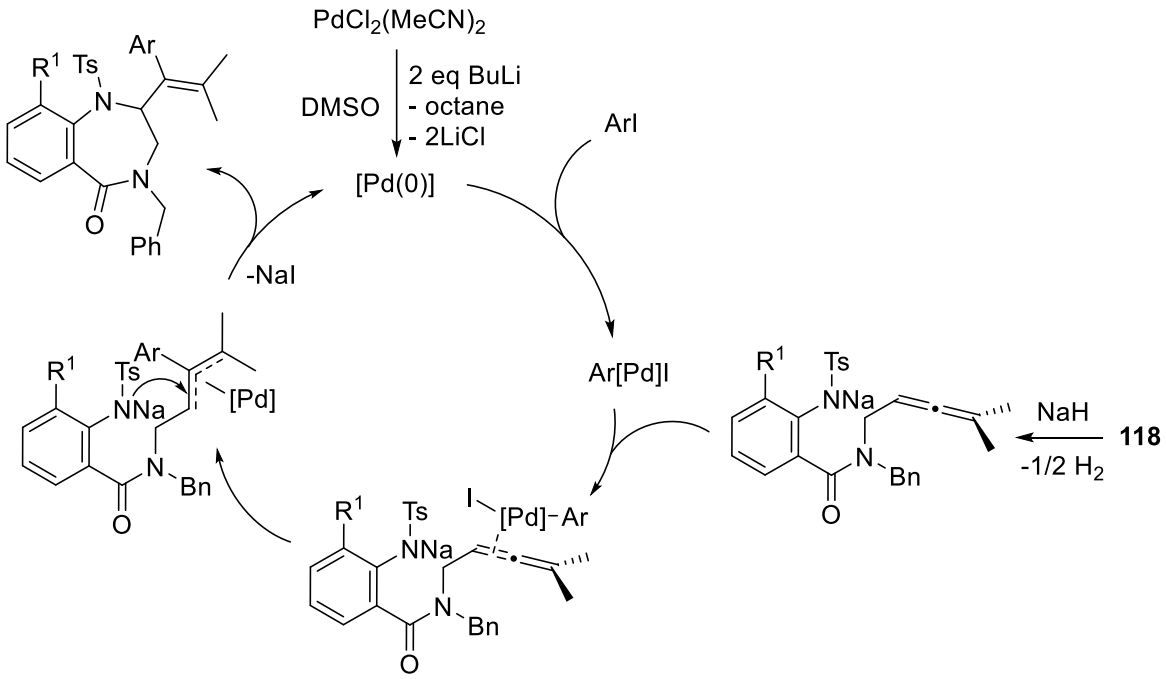
A phosphine-free Pd(0)-catalyzed carbopalladation/allylic amination domino sequence performed on allenyl anthranyl amides **118** in the presence of aryl iodides was proven an efficient way to yield vinyl-substituted 1,4-benzodiazepinones **119** (Scheme 69).[75] The active Pd(0)-species was generated from $PdCl_2(MeCN)_2$ in DMSO using 2 equiv. of BuLi as *in situ* reducing agent. This pure domino reaction run 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 70). This procedure could be satisfactorily carried out with tosyl, nosyl, and terbutoxycarbonyl *N*-protecting groups.



R^1 = H, Me; Ar = Ph, 4-MeC_6H_4, 4-$CO_2MeC_6H_4$, 2-$OMeC_6H_4$, 3-$OMeC_6H_4$, 4-$OMeC_6H_4$, 4-$COMeC_6H_4$, 4-$NO_2C_6H_4$, 3-pyridyl

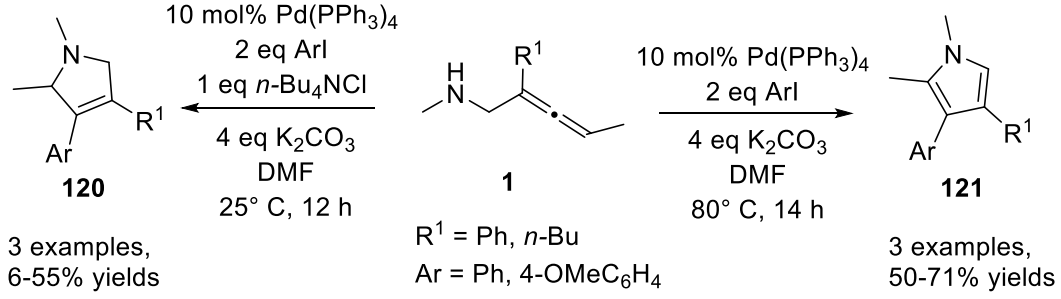
10 examples,
61-82 % yields

[Scheme 69. Carboamination of α-allenyl anthranylamides]



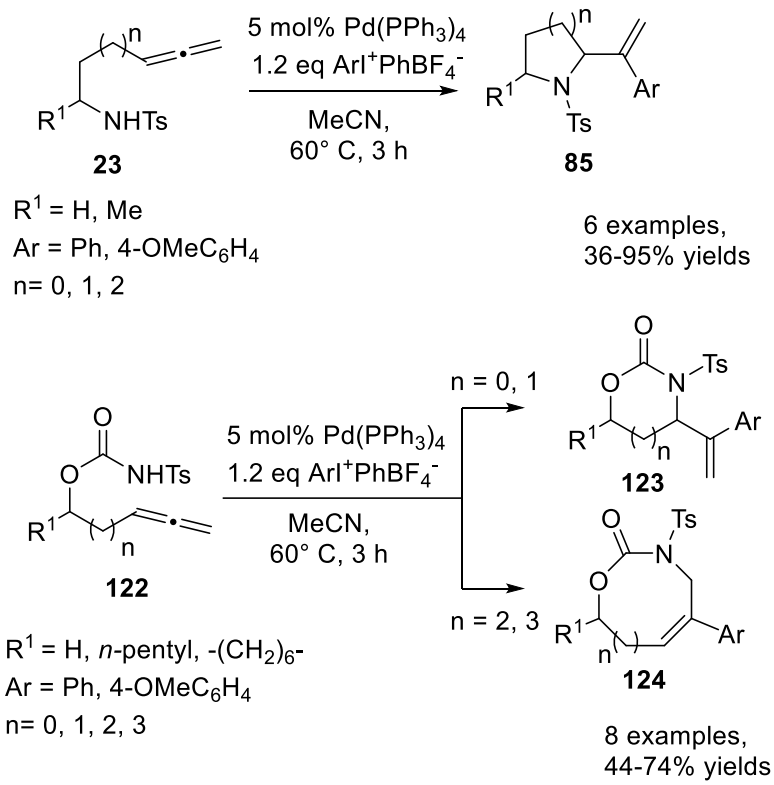
[Scheme 70. α-Allenyl anthranylamides carboamination mechanism]

α-Aminoallenes **1**, after coupling with aryl iodides, can react intramolecularly giving either 3-pyrrolines or pyrroles (Scheme 71).[3a] Working with catalytic $Pd(PPh_3)_4$, K_2CO_3, and Bu_4NCl in DMF at 25°C, the hydroamination afforded 3-aryl-3-pyrrolines **120**. Conversely, the use of the same conditions at higher reaction temperatures gave the corresponding pyrroles **121**, bearing an aryl group at the C-3 position.



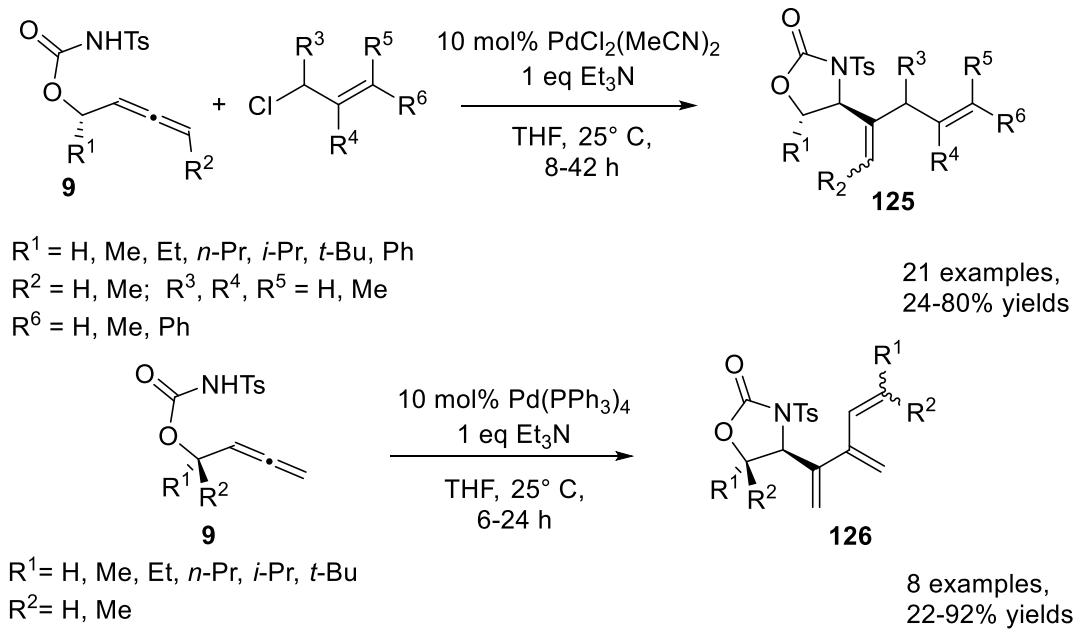
[Scheme 71. Carboamination of α-Aminoallenes]

An alternative version of the palladium-catalyzed intermolecular coupling-intramolecular amination reaction, based on the use of hypervalent iodonium salts instead of aryl halides, was developed by Kang and co-workers.[76] Diphenyl iodonium tetrafluoborate has been used with *N*-tosyl aminoallenes **23** in the presence of catalytic amount of $Pd(PPh_3)_4$ in acetonitrile, affording the styryl-substituted heterocyclic products **85** (Scheme 72). Application of these conditions to allenyl carbamates **122**, led to *exo*- or *endo*-cyclizations providing oxazolidinones and 1,3-oxazin-2-ones **123** as well as higher membered 1,3-*N,O*-heterocycles **124**. 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. Although this method showed some advantages, the application of hypervalent iodonium salts was restricted to aromatic substrates.



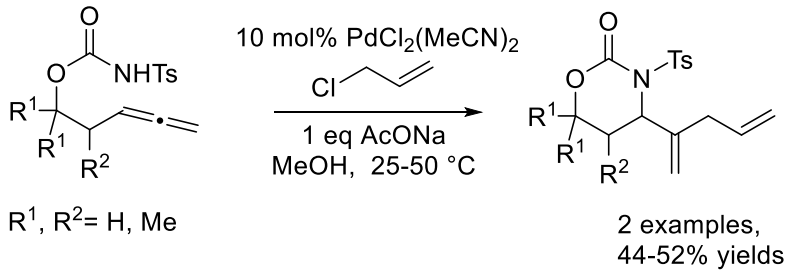
[Scheme 72. Carboamination of *N*-Ts-aminoallenes and *N*-Ts-allenyl carbamates]

A palladium-catalyzed intermolecular coupling combined with an intramolecular amination could, also, be obtained treating the aminoallenes with allyl halides. Seminal work on this procedure was reported by Tamaru and co-workers for the cyclization of the allenyl tosylcarbamates **9** to the 4-pentadienyl-substituted oxazolidinones **125** (Scheme 73).[77] The reaction was carried out using catalytic $PdCl_2(PhCN)_2$, triethylamine in THF with an excess of allylic chlorides and the tosyl-protection was proven to be essential for the cyclization. If the final oxazolidinones were 4,5-disubstituted, high *trans*-stereoselectivity was obtained. 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 rarely 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 **126**.



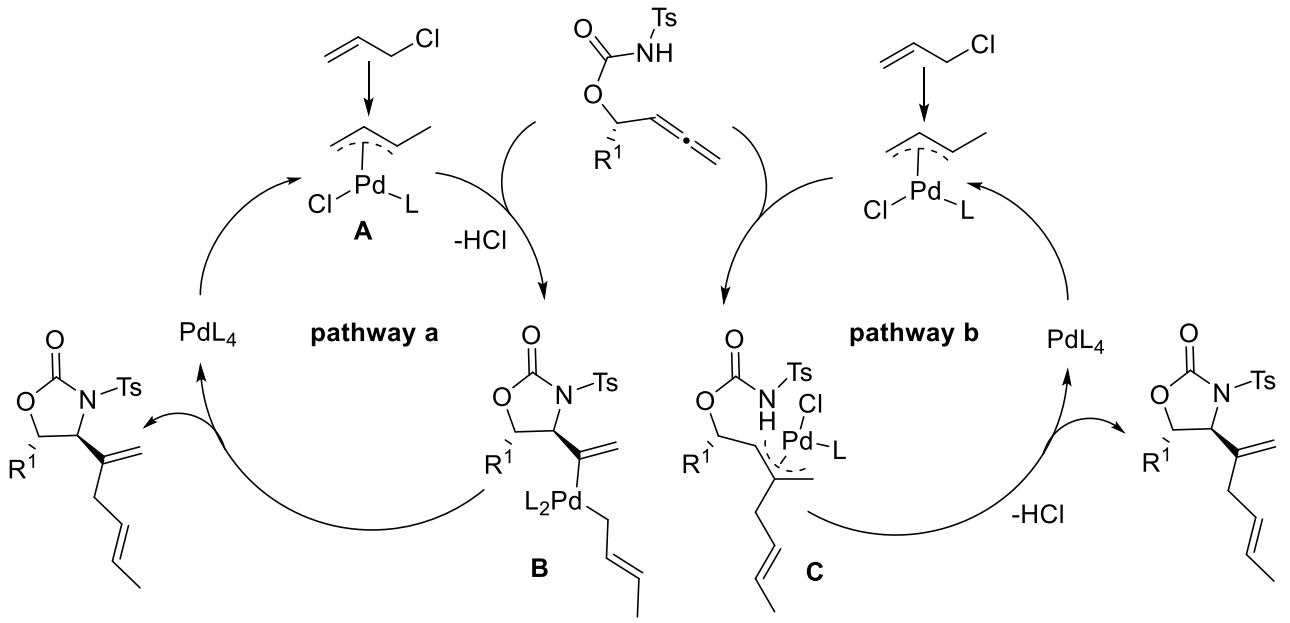
[Scheme 73. Carboamination of *N*-Ts α-allenyl carbamates with allyl halides]

The reaction could not be extended to the synthesis of the six-membered ring analogs. Only in the case of *N*-Ts-1,1-dimethyl-3,4-pentadienylcarbamates, in the presence of AcONa as base, the expected substituted *N*-Ts-4-(1-allylvinyl)-tetrahydro-1,3-oxazin-2-ones were obtained (Scheme 74).[77b]



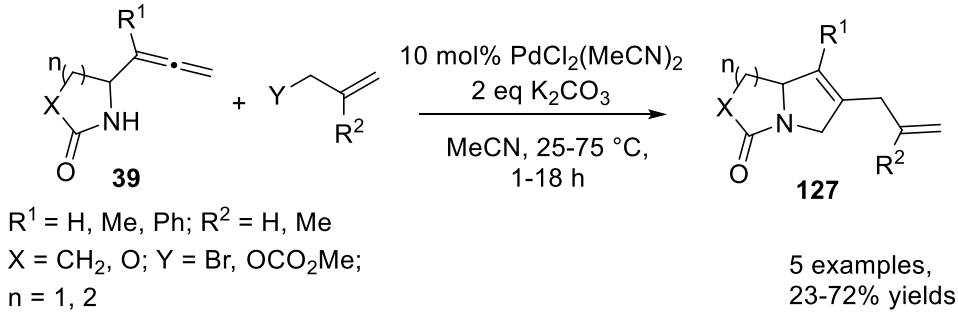
[Scheme 74. Carboamination of *N*-Ts β-allenyl carbamates with allyl halides]

The reaction mechanism plausibly involved the intervention of the π-allyl intermediate **A**, which proceeded following two possible pathways (Scheme 75). **A** 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 **B**, which was converted into the final product by reductive elimination of the metal (path a). Otherwise, **A** could generate the π-allyl-palladium complex **C**, which underwent nucleophilic substitution by the carbamate anion furnishing the oxazolidinone product and a Pd(0)-species (path b). Between these pathways, the former seemed to be preferable due to speculative considerations, although the latter could not be ruled out.



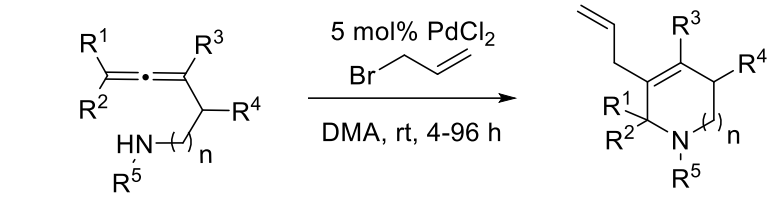
[Scheme 75. Mechanism for *N*-Ts-allenyl carbamates carboamination with allyl halides]

The same behavior was observed when cyclic allenamides **39** were treated with allyl halides in the presence of $PdCl_2(MeCN)_2$ as the catalyst and K_2CO_3 in acetonitrile to give the allyl-substituted bicyclic heterocycles **127** (Scheme 76).[78]



[Scheme 76. Carboamination of cyclic allenamides with allyl halides]

The application of this procedure to α- or β-aminoallenes allowed to fine-tune an efficient synthesis of the 3-allyl-3-pyrrolines and 3-allyl-1,2,3,6-tetrahydropyridines **128**, performing the reaction in the presence of allyl bromides, in DMA as solvent at r.t. (Scheme 77).[79] Both five- and six-membered rings were isolated in very high yields.



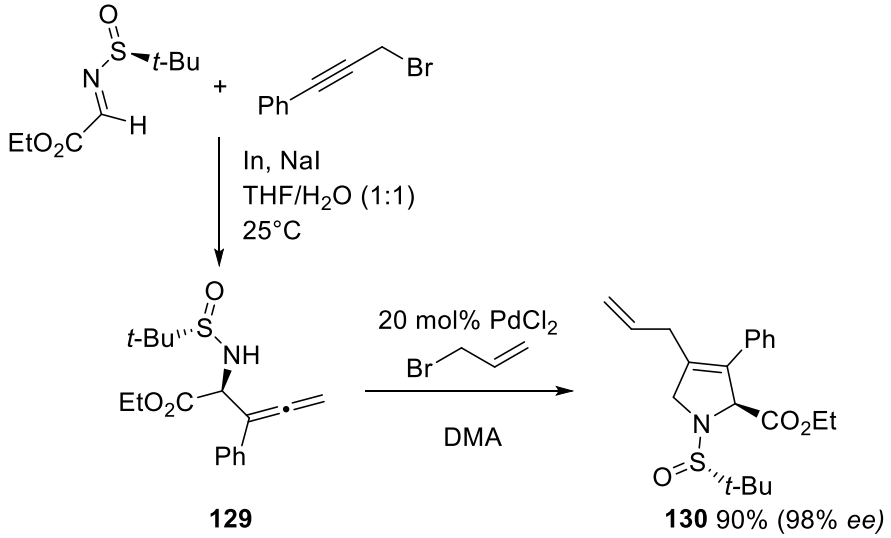
128

R^1 = H, Me, *i*-Pr, *n*-Bu, -$(CH_2)_5$-, *n*-hexyl
R^2 = H; R^3 = H, Me, *n*-Bu, *t*-Bu, allyl
R^4 = H, Me, *n*-Pr, *n*-Bu, *n*-pentyl, *n*-hexyl, Ph, Bn, CO_2Me; R^5 = Ts, Ns, Ac, Bz
n= 0, 1

27 examples,
32-96% yields

[Scheme 77. Carboamination of aminoallenes with allyl halides]

Enantiomerically enriched *cis*-substituted proline derivative **130** was available by aminocyclization of the optically active α-allenylglycine **129**, in turn achieved by indium-mediated allenylation of chiral *N*-*tert*-butanesulfinyl imino ester with propargylic halide (Scheme 78).[80]

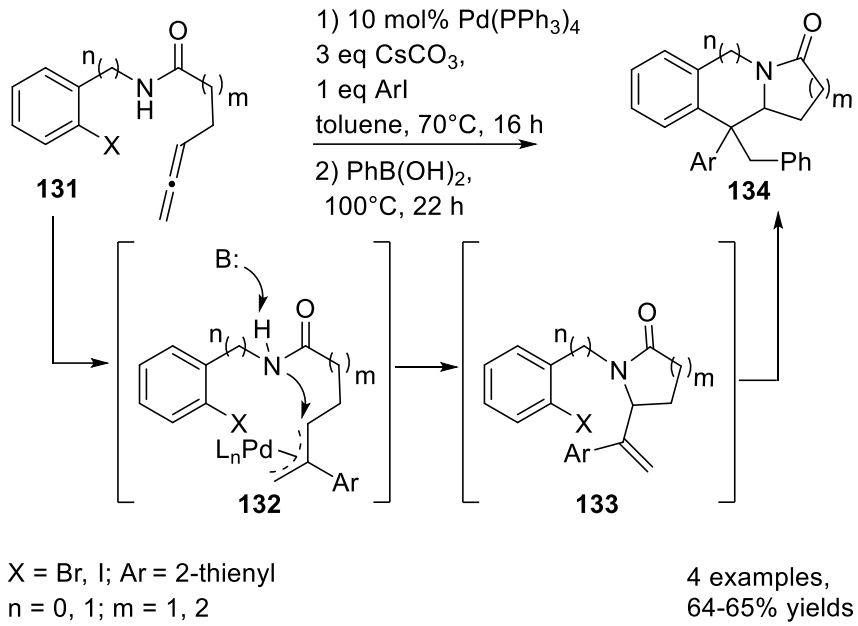


129

130 90% (98% *ee)*

[Scheme 78. Enantioselective carboamination of α-allenylglycine with allyl bromide]

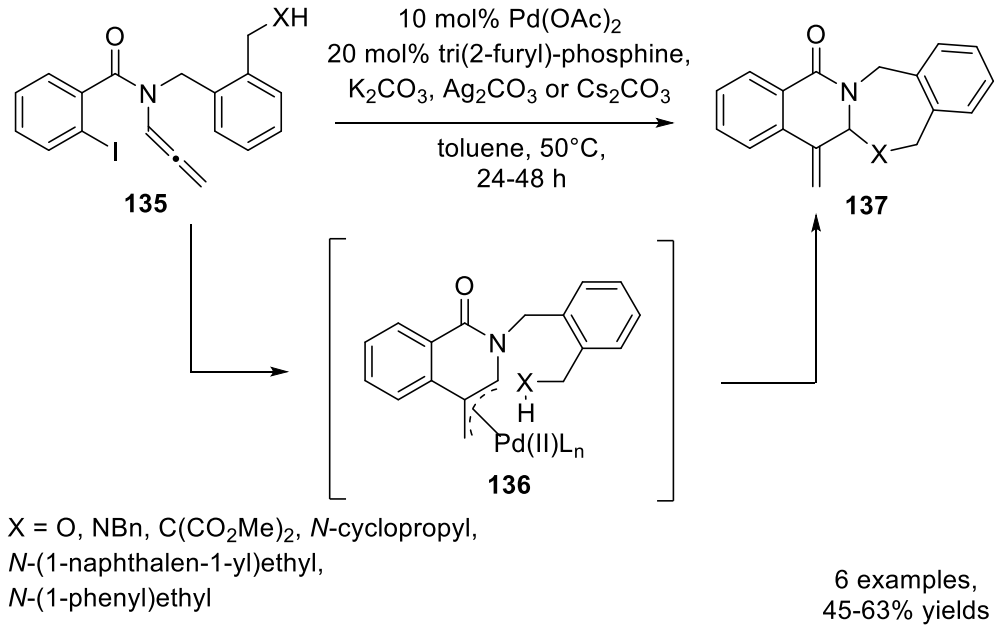
The intramolecular amination on the π-allyl-palladium complexes **132** generated from allenamides **131** and aryl iodides in the presence of $Pd(PPh_3)_4$ and K_2CO_3 first led to cyclized products **133** (Scheme 79).[81] The latter evolved again by a Pd-catalyzed cyclization involving phenylboronic acid to yield the tricyclic systems **134**.



[Scheme 79. Sequential double carboamination of allenamides]

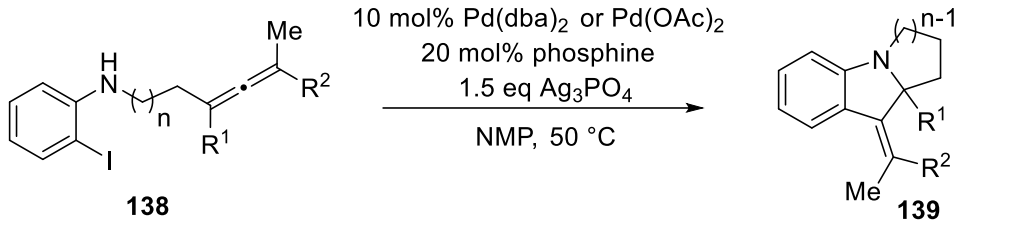
Palladium-catalyzed intramolecular coupling/intramolecular amination processes

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 cyclization capture intramolecular process was performed starting from substrates **135** in the presence of K_2CO_3 or Ag_2CO_3 with formation of the tetracyclic isoquinolinone derivatives **137** (Scheme 80).[82] After oxidative addition of Pd(0) to the aryl iodide, a selective carbopalladation/cyclization onto the central allenic carbon would first generate the Pd-π-allyl complex **136** which would be further intramolecularly captured by a nucleophile giving the final product.



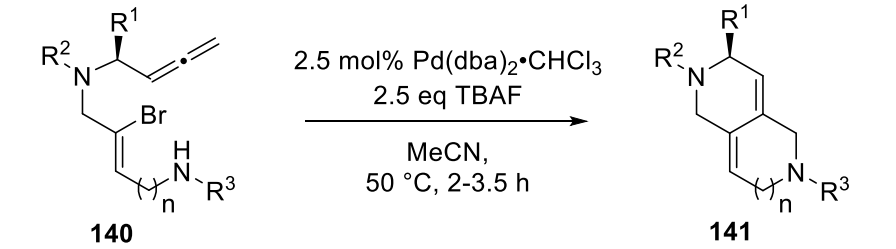
[Scheme 80. Double intramolecular processes of *N*-allenyl o-iodobenzamides leading to tetracyclic systems]

Treatment of the *o*-iodoanilines bearing an allenyl moiety **138** with Pd(0)-catalyst, a phosphine ligand and triethylamine in acetonitrile afforded indole derivatives **139** by intramolecular carbopalladation of allenes followed by intramolecular amination of π-allylpalladium complexes (Scheme 81).[83] An asymmetric version of this procedure has been developed using a chiral phosphine ligand.[84] The enantioselectivity was found to be dependent of the chiral ligand and the solvent used. (*S*)-(-)-BINAP or (*S*)-Tol-BINAP resulted the most useful chiral ligands examined, using *N*-methylpiridone as solvent.



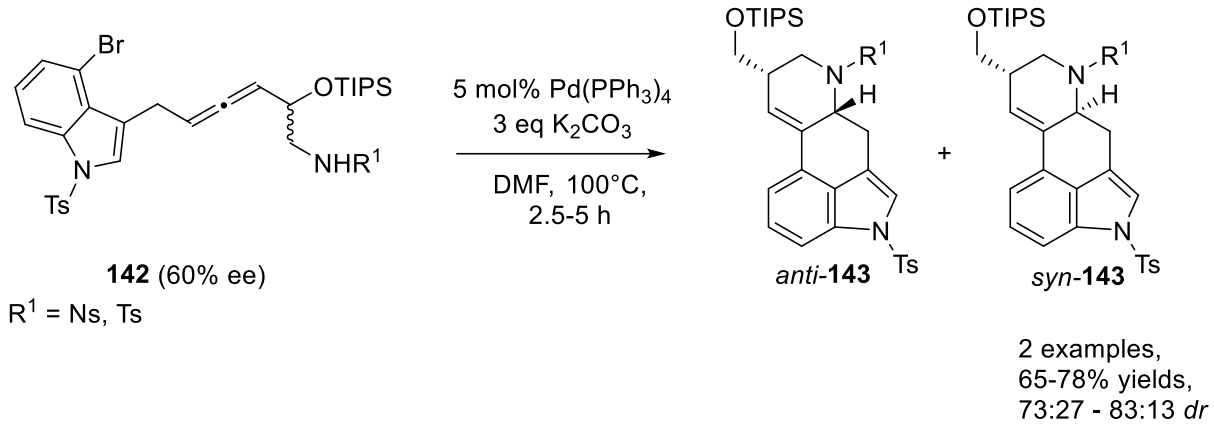
[Scheme 81. Double intramolecular carboamination of allenyl *o*-iodoanilines leading to tricyclic systems]

Allenyl bromoalkenylamines were suitable starting materials for domino Pd(0)-catalyzed cyclization which afforded bicyclic heterocycles in good to high yields.[85] Using a catalytic amount of palladium(0) in the presence of TBAF or Cs_2CO_3 in acetonitrile, substrates **140** were converted into the fused six-six-, six-seven-, or six-eight-membered bicyclic products **141** (Scheme 82).



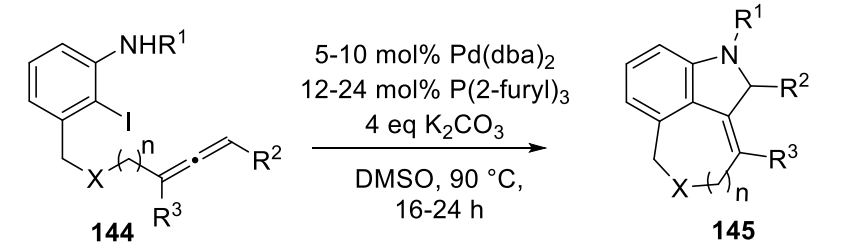
[Scheme 82. Double intramolecular carboamination of allenyl bromoalkenylamines]

The application of this strategy to 4-bromo indoles bearing an allenyl group inserted in a chain at the 3-position allowed the access to a tetracyclic structure, precursor of the biologically relevant ergot alkaloids.[86] One of the key features of this total synthesis that leads to lysergol, isolysergol, and lysergic acid, is the Pd(0)-catalyzed domino cyclization of the bromoindolyl allenes **142** which enabled the direct construction of the C/D ring system of the ergot alkaloids skeleton **143** (Scheme 83). This procedure could be performed in an enantioselective manner using optically active substrates prepared from a chiral 1,3-aminoalcohol.[87] The C5 stereogenic center was generated with transfer of the allenyl axial chirality to the central chirality.



[Scheme 83. Carboamination of bromoindolyl allene leading to ergot alkaloids skeleton]

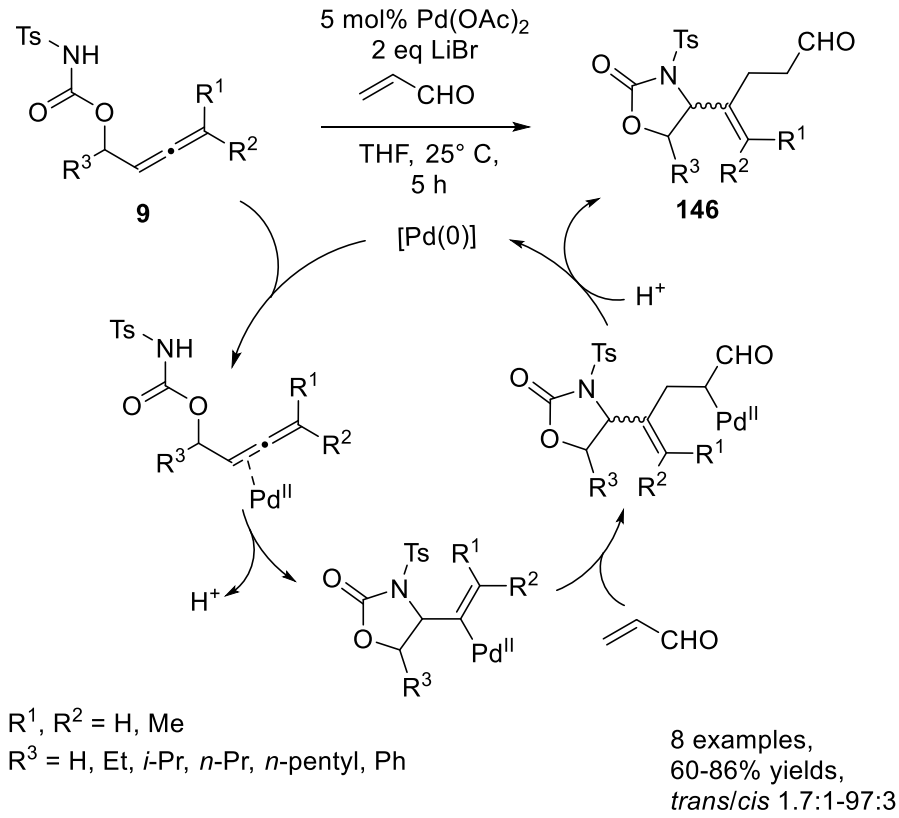
An intriguing Pd-catalyzed domino cyclization by a dual intramolecular coupling/amination sequence was developed by Nemoto and co-workers.[88] Allenes tethered at the *meta-position* of 2-iodoaniline derivatives **144** reacted with Pd(0)-catalyst in the presence of K_2CO_3 in DMSO providing 3,4-fused tricyclic indoline derivatives **145**, which were divergently transformed into three types of indole derivatives (Scheme 84).



[Scheme 84. Double intramolecular carboamination of allenyl 2-iodoanilines leading to tricyclic indoline derivatives]

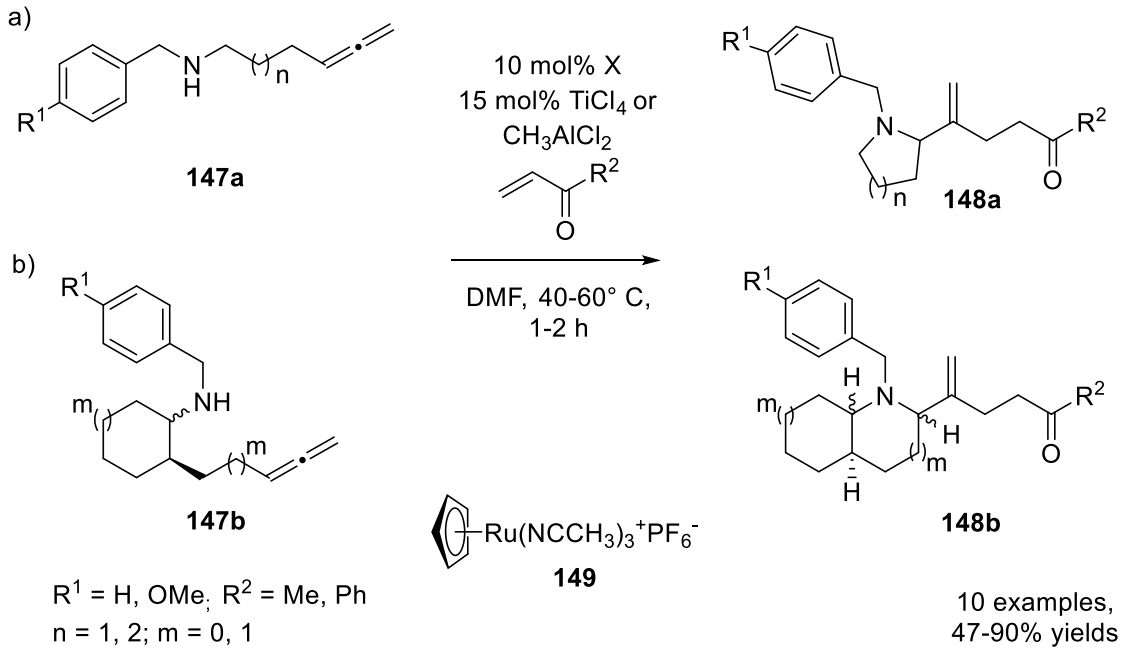
Transition metal-catalyzed miscellaneous carboaminations

Among the Pd-catalyzed intramolecular amination processes involving aminoallene derivatives, a significant example was given by the Pd(II)-catalyzed cyclization-coupling reaction of allenyl *N*-tosyl-carbamates with acrolein (Scheme 85).[89] Substrates **9** treated with $Pd(OAc)_2$ as catalyst, lithium bromide and acrolein in THF, were regioselectively converted into the functionalized 2-oxazolidinones **146**. Same conditions were valuable for the conversion of *N*-tosyl-allenamides into lactams. The reaction involved the intramolecular aminopalladation of the allenyl group, followed by acrolein insertion and halide-assisted protonolysis to generate a Pd(II)-species without the need of oxidants.



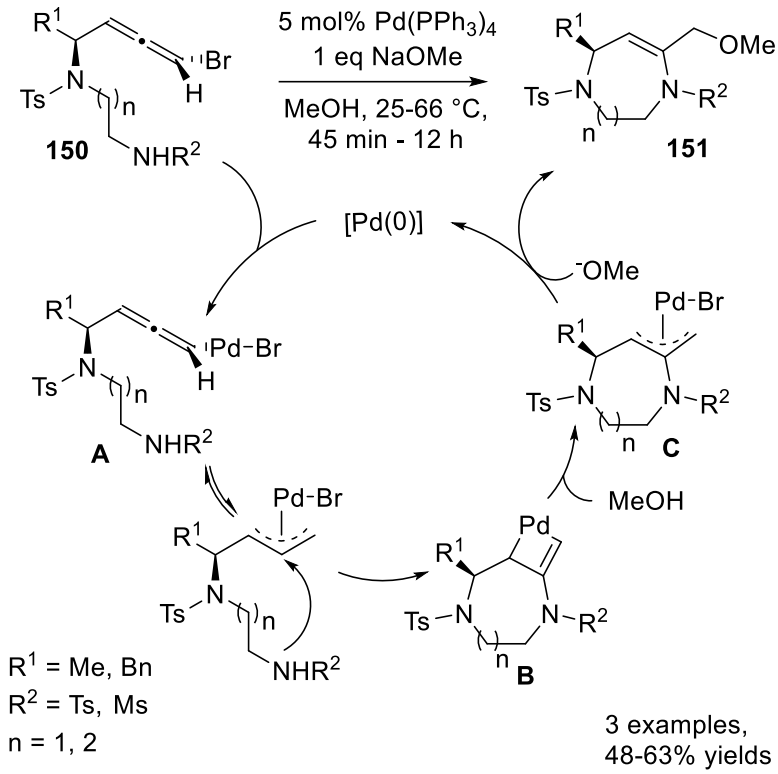
[Scheme 85. Carboamination of allenyl *N*-tosyl-carbamates with acrolein]

The cyclization of aminoallenes in the presence of an α,β-unsaturated carbonyl compounds could be performed also by ruthenium catalysis.[90] The reaction between aminoallenes **147** and methyl vinyl ketone in the presence of catalyst **149** and a strong Lewis acid as cocatalyst in DMF was proved as a fruitful procedure to access to the pyrrolidine and piperidine derivatives **148** (Scheme 86).



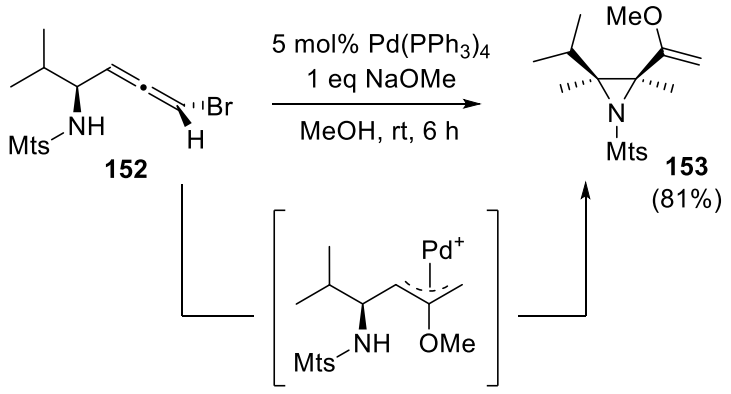
[Scheme 86. Ru-catalyzed carboamination of aminoallenes with vinyl ketones]

Ohno and co-workers have developed a highly regio- and stereoselective Pd-catalyzed approach for the synthesis of medium-sized heterocycles containing two nitrogen atoms by cyclization of bromoallene derivatives, providing the access to seven- and eight-membered heterocycles without the use of high dilution conditions.[91] The treatment of compounds **150** in the presence of a palladium(0) catalyst and sodium methoxide in methanol provided the products **151** (Scheme 87). Bromoallenes acted as an allyl dication equivalent through the initial generation of the complex **A** that underwent selectively an intramolecular nucleophilic attack at the central carbon atom. The so-formed palladacyclobutene **B** was protonated by methanol to generate the π-allylpalladium complex **C**. The final attack of the methoxide was preferred at the terminal carbon due to the steric repulsion with the R group, giving products **151**.



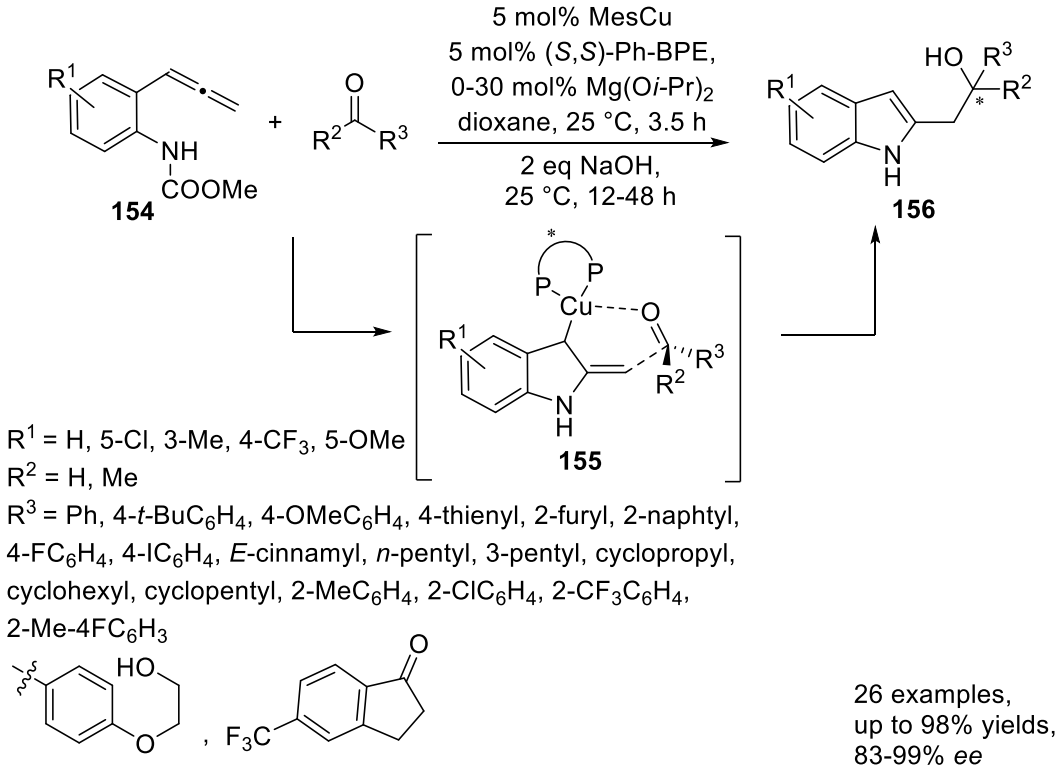
[Scheme 87. Cyclization of amino bromoallenes in the presence of NaOMe]

Analogously, a reaction started from *N*-Mts-4-bromo-1-isopropyl-2,3-butadiene (**152**) provided 2,3-*cis*-2-(1-methoxy)vinylaziridine (**153**) following an *exo*-trig-cyclization on the π-allyl cationic Pd intermediate (Scheme 88).[92]



[Scheme 88. Cyclization of *N*-Mts-4-bromo-1-isopropyl-2,3-butadiene in the presence of NaOMe]

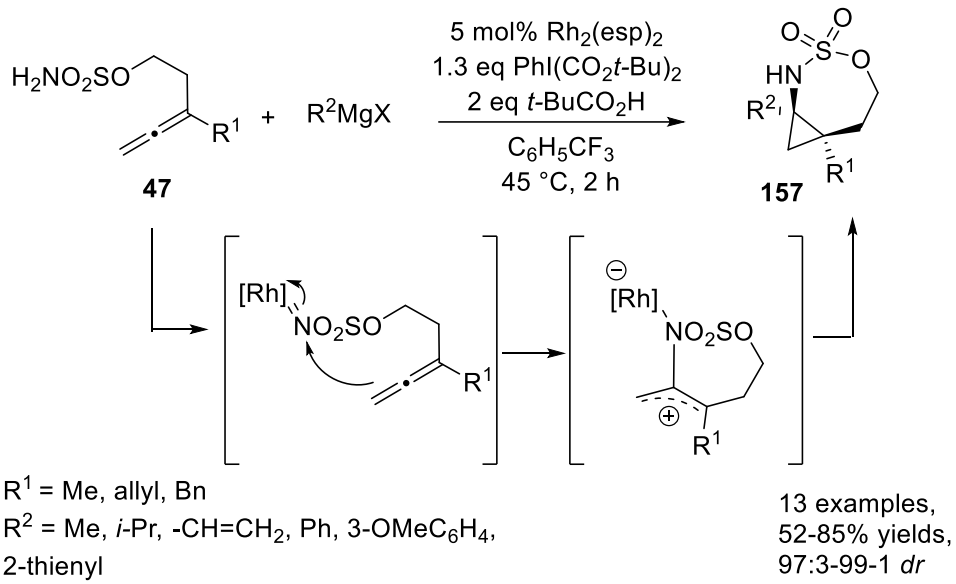
An enantioselective synthesis of 2-(2-hydroxyethyl)indole derivatives **156** was developed starting from *o*-allenylanilines **154** in the presence of a copper catalyst and chiral phosphines.[93] The reaction started by a catalytic intramolecular amido-cupration of the allene giving a relatively stable chiral allylcopper species **155**, which acted as nucleophile in an asymmetric addition to aldehydes and ketones (Scheme 89).



(*S*,*S*)-Ph-BPE = (+)-1,2-bis[(2*S*,5*S*)-2,5-diphenylphospholano]ethane

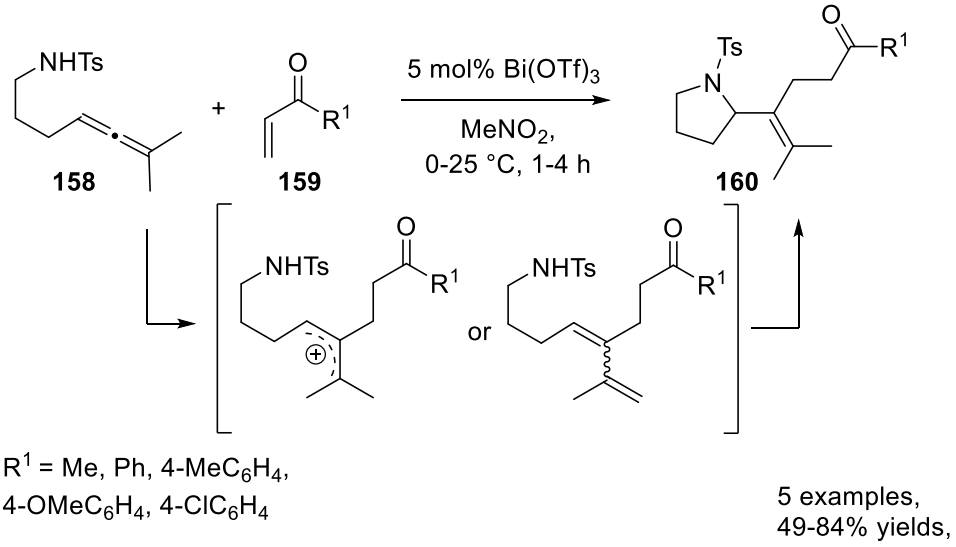
[Scheme 89. Cu-catalyzed carboamination of o-allenylanilines with ketones]

An implementation of the allene amination strategy was achieved exploiting the rhodium catalysis applied to the reaction of the allenyl sulfamates **47** in oxidative conditions, obtaining highly substituted aza-bicycles **157** (Scheme 90).[94] The conversion was promoted by intramolecular interaction between a metallonitrene, generated from the sulfamate ester, with the allene moiety which afforded a versatile intermediate having a 2-amidoallylcation-like reactivity. The latter underwent oxidative rearrangement to give cyclopropylimine that could add an external dipolarophile such as a Grignard reagent, providing substituted aminocyclopropanes with excellent diastereoselectivity.



[Scheme 90. Rh-catalyzed carboamination of allenyl sulfamates with Grignard reagents]

A bismuth catalyzed ene-reaction/hydroamination process starting from aminoallene compounds with vinyl ketones led to highly functionalized pyrrolidine derivatives.[95] Thus, $Bi(OTf)_3$ was proven to act as an effective catalyst to convert allene **158** and vinyl ketones **159** to the products **160** (Scheme 91).



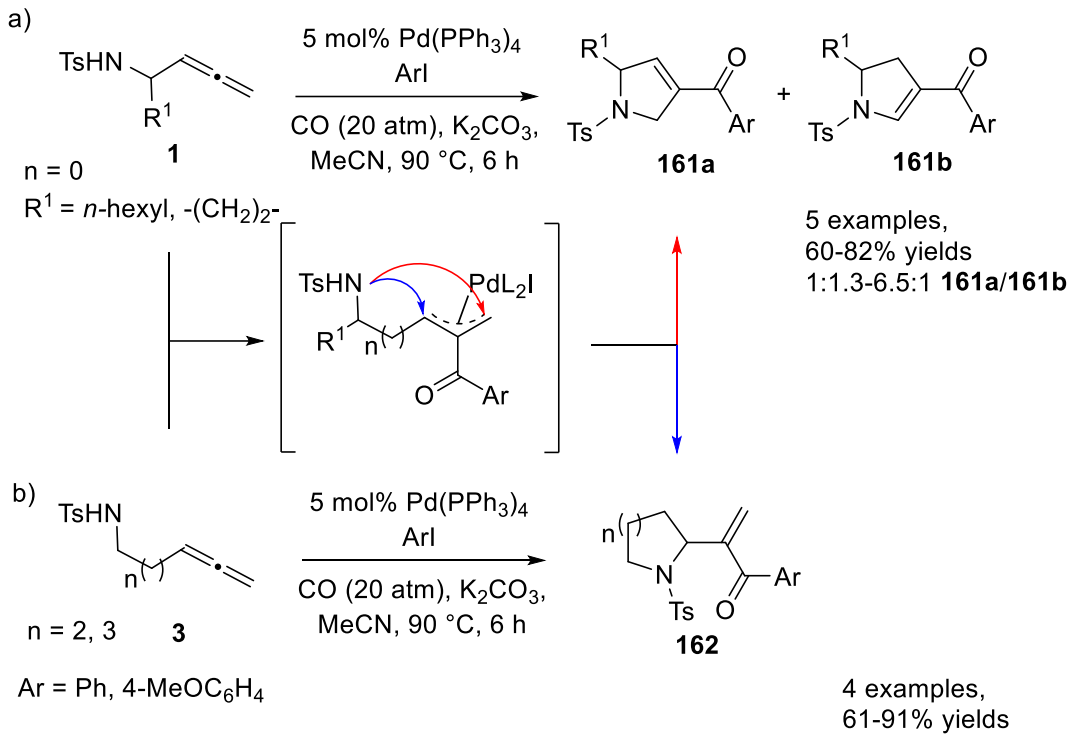
[Scheme 91. Bi-catalyzed carboamination of *N*-Ts-6-methylhepta-4,5-dienamine with vinyl ketones]

AMINOCARBONYLATION OF ALLENES

The intramolecular reaction of aminoallenes, carried out in the presence of carbon monoxide, could intercept 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 an ester functional group was obtained.

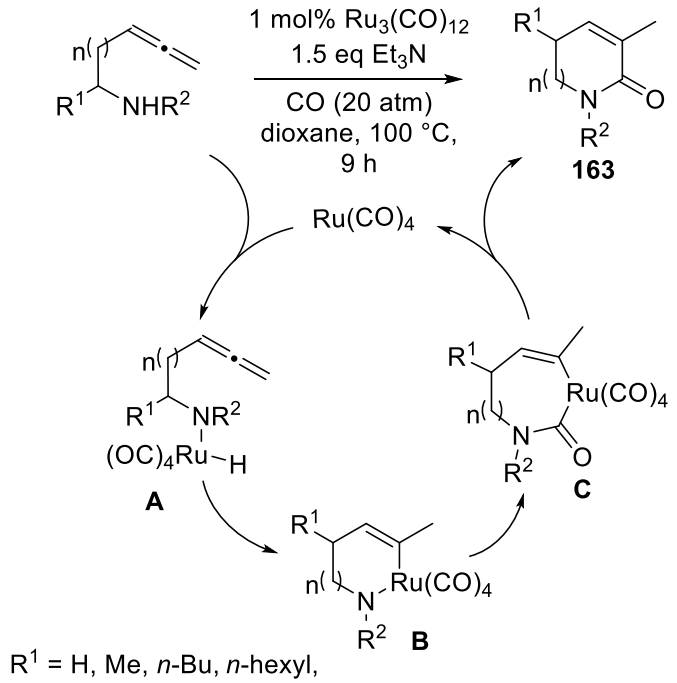
Cyclization of *N*-tosyl α-, γ- and δ-aminoallenes **1** and **3**, performed in the presence of ArI with catalytic $Pd(PPh_3)_4$ and K_2CO_3 in acetonitrile and CO atmosphere, arose in *exo*- or *endo*-manner depending on the length of the chain between the allene and amine moieties (Scheme 92).[96] The oxidative addition to generate

the organopalladium(II) species involved carbon monoxide giving 3-acyl- or 2-vinylpyrrolines (**161** or **162**, respectively).



[Scheme 92. Pd-catalyzed aminocarbonylation of *N*-tosyl α-, γ- and δ-aminoallenes]

The intramolecular amination of the aminoallenes with insertion of carbon monoxide could be achieved using catalytic $Ru_3(CO)_{12}$ and triethylamine in dioxane under CO atmosphere (Scheme 93).[97] The reaction, resulted in the formation of lactams **163**, involved an oxidative addition of ruthenium to the N-H bond (**A**), followed by insertion of the allene into the Ru-H bond (**B**) to generate a vinyl organometallic species **C**. Finally, carbon monoxide insertion and reductive elimination completed the sequence.

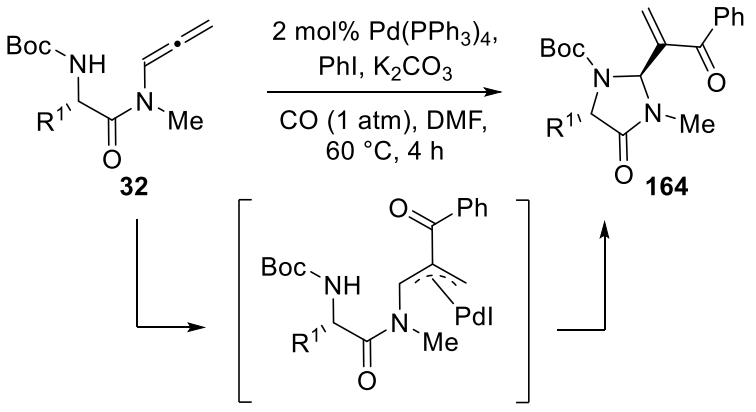


R^1 = H, Me, *n*-Bu, *n*-hexyl,
-$(CH_2)_6$-, Ph, 2-furyl, 2-thienyl
R^2 = Ts, Mts, Bn
n = 0, 1

10 examples,
54-95% yields

[Scheme 93. Ru-catalyzed aminocarbonylation of α- and β-aminoallenes]

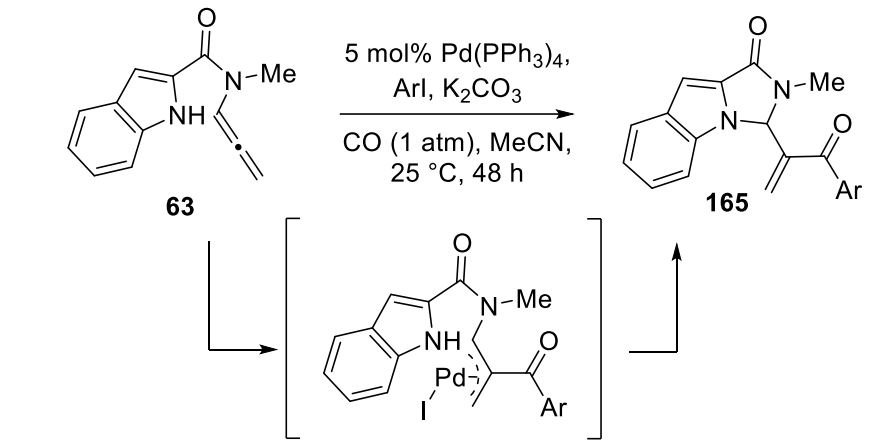
Using the conditions which successfully promoted the intermolecular coupling/intramolecular amination reaction of allenamides **32** and **63** under CO, imidazolidines **164** and indoloimidazoles **165** bearing an enone moiety were obtained (Schemes 94 and 95, respectively).[68] These reactions occurred selectively by carbopalladation-5-*exo*-*dig* amination with variously substituted aryl iodides through aryl palladium π-allyl intermediates, depicted for the reaction with **63**.



R^1 = Me, *i*-Pr, *i*-Bu, Bn, Ph

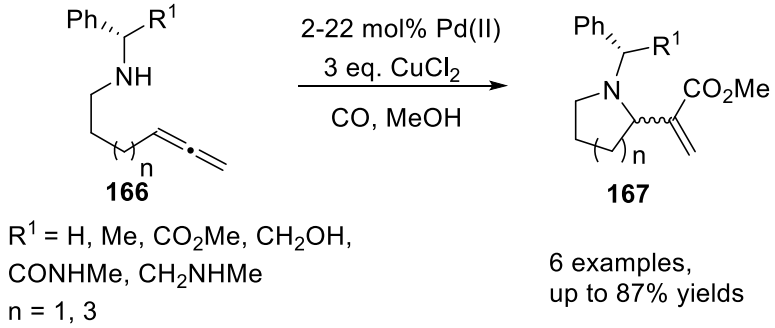
5 examples,
38-67% yields

[Scheme 94. Aminocarbonylation of α-aminoacid allenamides]



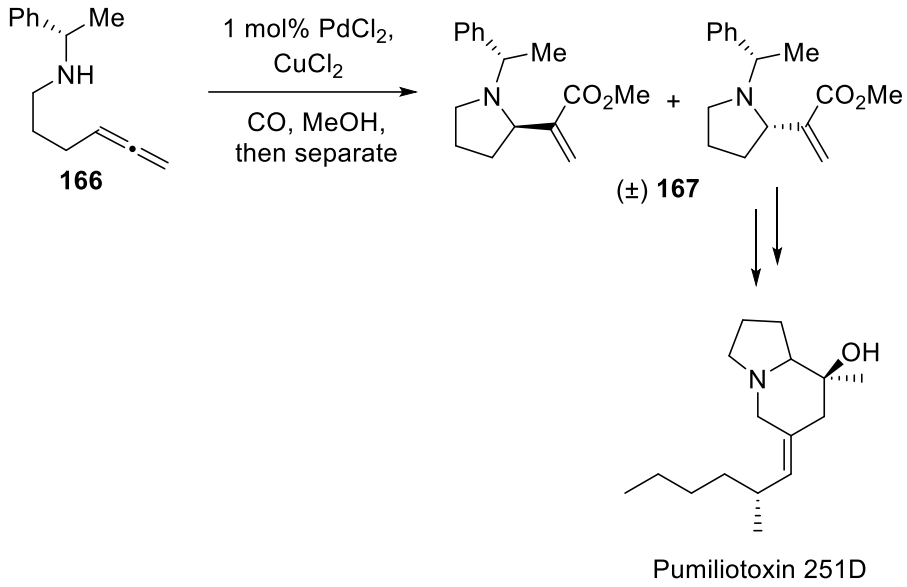
[Scheme 95. Aminocarbonylation of indole 2-carboxylic acid allenamides]

The Pd-catalyzed cyclization in oxidative conditions of aminoallenes **166** occurred with formation of the α-(heterocyclic) acrylates **167** (Scheme 96).[98] $PdCl_2$ as catalyst, $CuCl_2$ as oxidant in methanol under CO were used as the best conditions to achieve acrylate substituted five-, six- and seven-membered ring products, through an aminocarboxylation process.



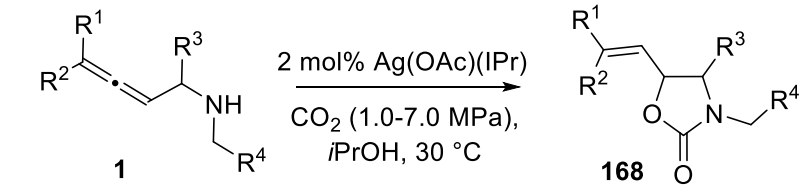
[Scheme 96. Aminocarboxylation of aminoallenes]

The possibility to achieve diastereoselective processes was studied. The use of chiral auxiliares outside of the ring as well as of chiral ligands for the palladium gave very modest diastereoselectivity, even if the diastereoisomeric mixtures of products were often easy to separate by chromatography. Thus, the allene **166** could be cyclized giving a mixture of products from which the pyrrolidine derivative **167** was separated and carried on to Pumiliotoxin 251D (Scheme 97).[99]



[Scheme 97. Aminocarboxylation of (S)-*N*-(1-phenylethyl)hexa-4,5-dienamine]

When the intramolecular reaction of *N*-alkyl-2,3-butadienylamines **1** involved CO_2, the formation of cyclic urethanes, as the 3-alkyl-5-vinyl-2-oxazolidinones **168** were reported, through the intermediate carbamic acid. The reaction performed at 50 °C in toluene as solvent was catalyzed both by Pd(0) and Pd(II).[100] More recently, the same author realized the same reaction on different substituted aminoallenes under silver catalysis with (Ag(OAc)(IPr) [IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene] in isopropanol as solvent at room temperature (Scheme 98).[101]



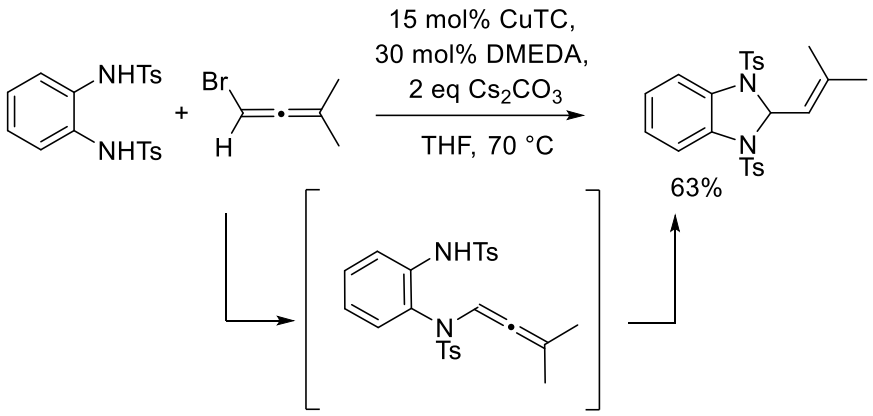
R^1, R^2 = H, *n*-Pr, -$(CH_2)_5$-
R^3 = H, Me; R^4 = H, Ph, 4-CNC_6H_4,
4-BrC_6H_4, 4-FC_6H_4, 3,4-$OCH_2OC_6H_4$

9 examples,
32-87% yields

[Scheme 98. Ag-catalyzed aminocarboxylation of *N*-alkyl-2,3-butadienylamines]

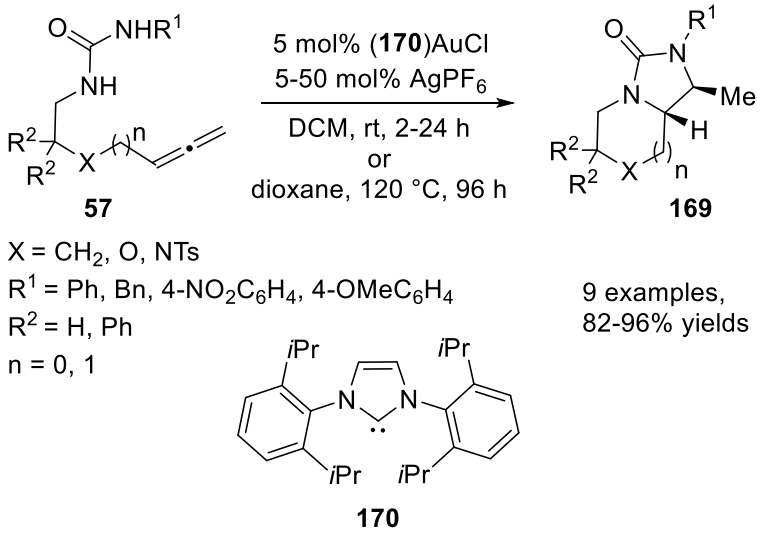
DIAMINATION OF ALLENES

The treatment of 1,2-ditosylated-1,2-diaminobenzene with 1-bromo-3-methylbuta-1,2-diene afforded directly 2-methylpropenyl-benzimidazole arising from monoallylated intermediate, which underwent cyclization under the condition employed (Scheme 99).[102]



[Scheme 99. Cu-catalyzed diamination of 1-bromo-3-methylbuta-1,2-diene]

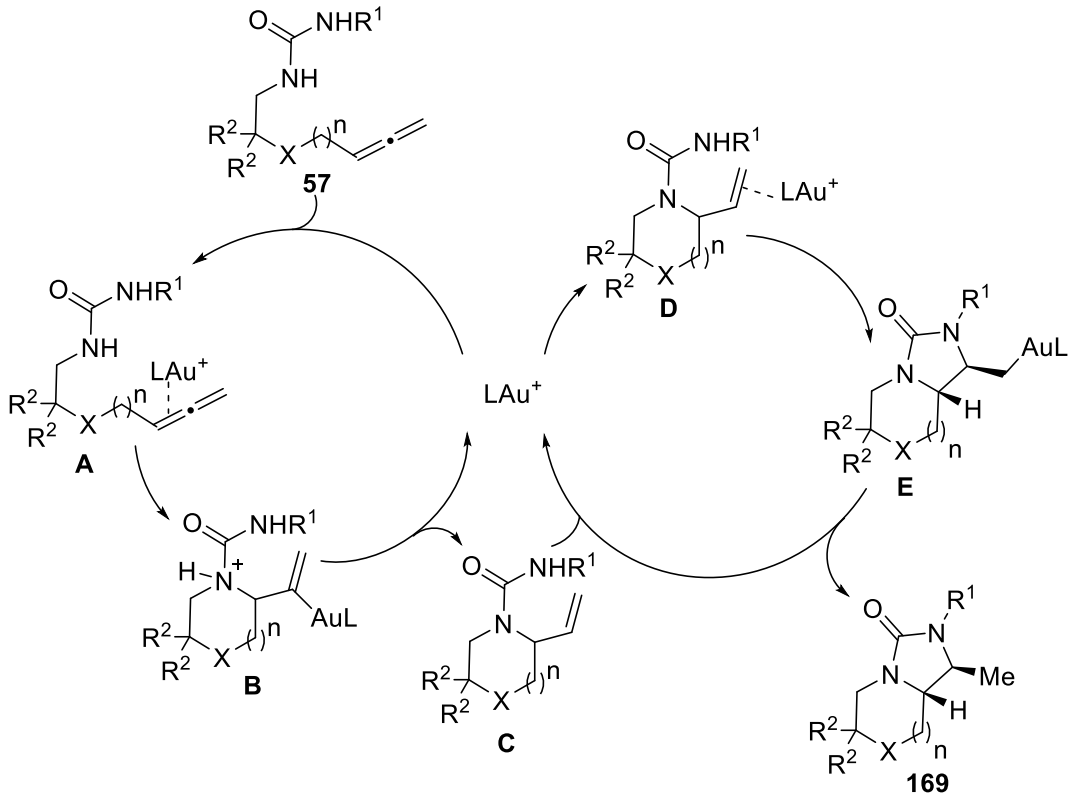
The use of substituted ureas for amination of allenes was an original method to obtain vicinal diamine derivatives. When the urea group was tethered to the allene system, the cationic gold(I)-catalyzed intramolecular dihydroamination provided the bicyclic imidazolidin-2-ones in good yield with high diastereoselectivity (Scheme 100).[103] Differently substituted *N*-δ-allenylureas **57** underwent intramolecular dihydroamination to form bicyclic imidazolidin-2-ones **169** in excellent yield as single diastereomers, with the catalytic 1:1 mixture of gold(I) *N*-heterocyclic carbene complex [**170**]AuCl [**170** = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidine] and $AgPF_6$ at room temperature. Optimization of the catalytic system revealed the pronounced effect of the silver salt. In fact, the employment of $AgSbF_6$, $AgClO_4$, AgOAc or $AgBF_4$ in combination with the complex [**170**]AuCl led only to the predominant formation of the mono-hydroamination adduct after 24 h.



[Scheme 100. Au/Ag-catalyzed diamination of allenyl ureas]

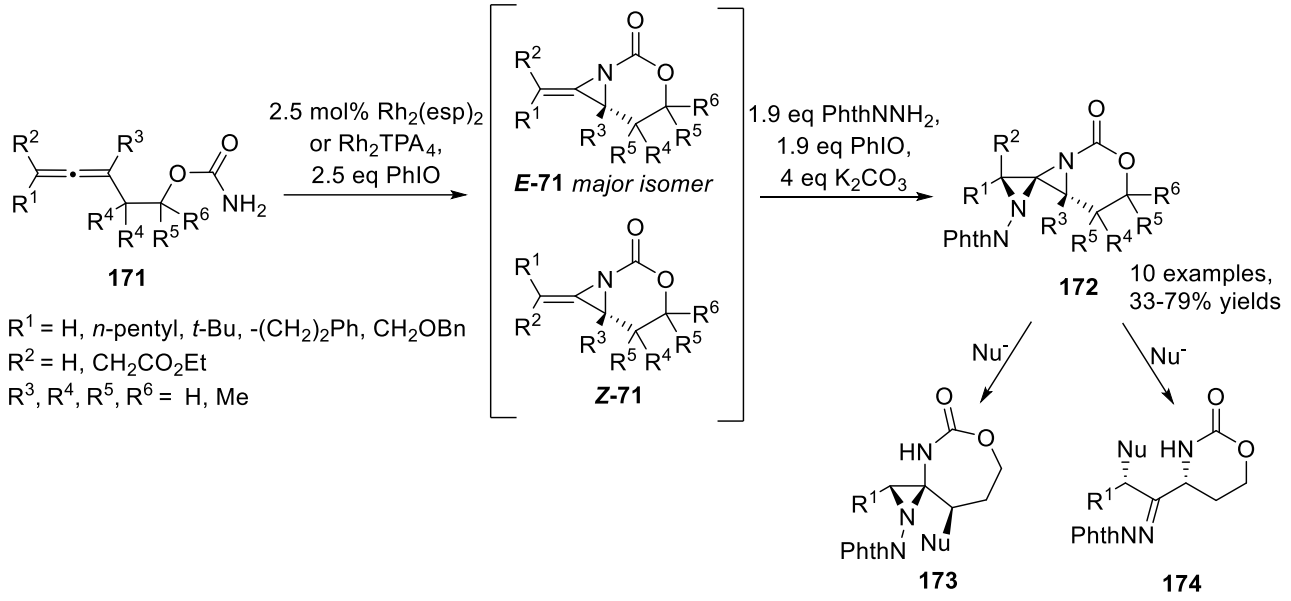
The gold catalyzed dihydroamination of *N*-allenylureas has been proposed to occur via two successive outer-sphere C-N bond forming processes. The outer-sphere attack of the internal nitrogen atom on gold π-allene complex **A** followed by proton transfer/protodeauration of the intermediate species **B** would form **C**. The second outer-sphere attack of the nitrogen atom of the gold π-alkene complex **D** followed by proton transfer/protodeauration of alkyl gold species **E** would then form **169**. The origin of the high diastereoselectivity of the process remained unclear, maybe determined during the irreversible second C-N

bond formation or by the conversion of 47 to 40 in the case of reversible C-N bond formation followed by irreversible protodeauration (Scheme 101).



[Scheme 101. Diamination of allenyl ureas mechanism]

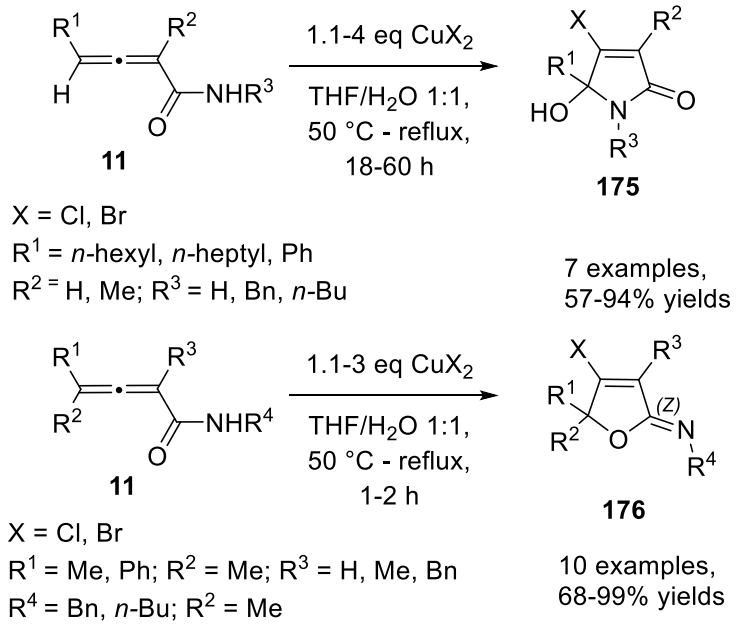
The treatment of the allenyl carbamates **171** with catalytic amount of Rh_2esp_2 (esp = α,α,α',α'--tetramethyl-1,3-benzene-dipropionic acid) or Rh_2TPA_4 (TPA = triphenylacetate) in the presence of a hypervalent iodine oxidant showed an unusual reactivity affording the bicyclic methyleneaziridines ***E*-71** and ***Z*-71.** The major isomer was generally ***E*-71**. The treatment of **71** with *N*-aminophtalimide (PhthNNH2) induced the formation of the 1,4-diazaspiro[2.2]pentane (DASP) **172** as a result of a double aziridination. This scaffold contained two electronically different aziridines able to undergo regioselective ring opening at either C1 or C3 affording spiroaminals **173** or oxazolidin-2-ones **174** respectively. The stereoselective nature of the DASP formation ensured that the axial chirality of the substrate could be transferred to the products. More interesting the allene susbstrates **171** could be converted directly to functionalized spiroaminals **173** in a one-pot reaction as a single diastereoisomer (Scheme 102). [104]



[Scheme 102. Rh-catalyzed cyclization of allenyl carbamates in the presence of N-aminophtalimide]

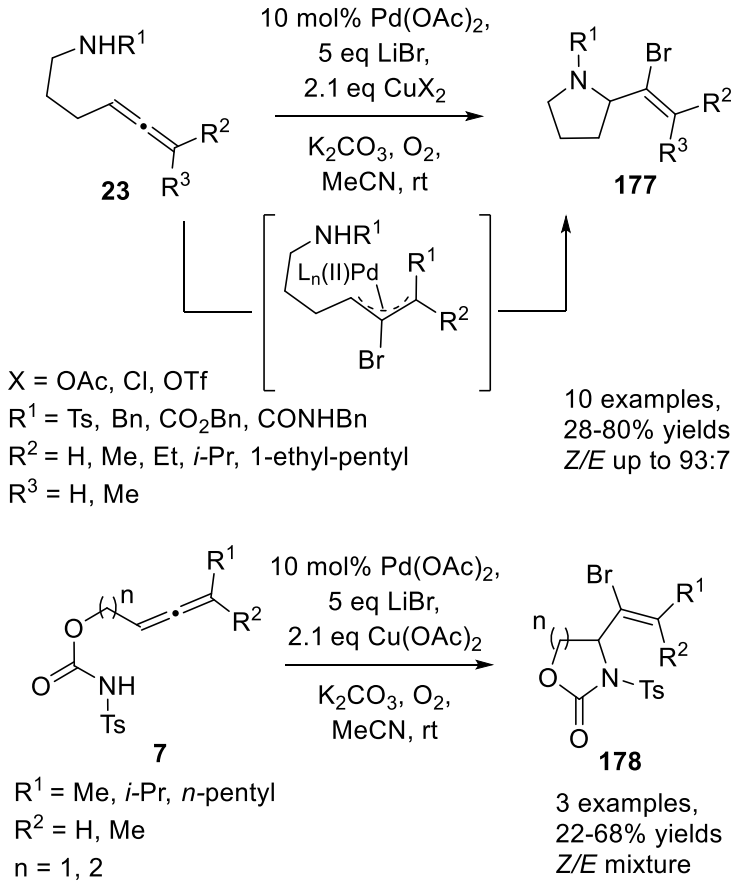
AMINOHALOGENATION OF ALLENES

4-Mono- or 4-unsubstituted 2,3-allenamides **11**, treated with CuX_2 in aqueous THF, afforded 4-halo-5-hydroxypyrrol-2-one derivatives **175** through sequential halolactamization and γ-hydroxylation processes (Scheme 103).[105] In the same reaction conditions, 4,4-disubstituted 2,3-allenamides afforded iminolactones **176** in high yields, depending on the steric hindrance of the terminal position of the allene. Moreover, electron-rich allenes afforded the corresponding chloro- or bromo-substituted products in much higher yields under milder reaction conditions.



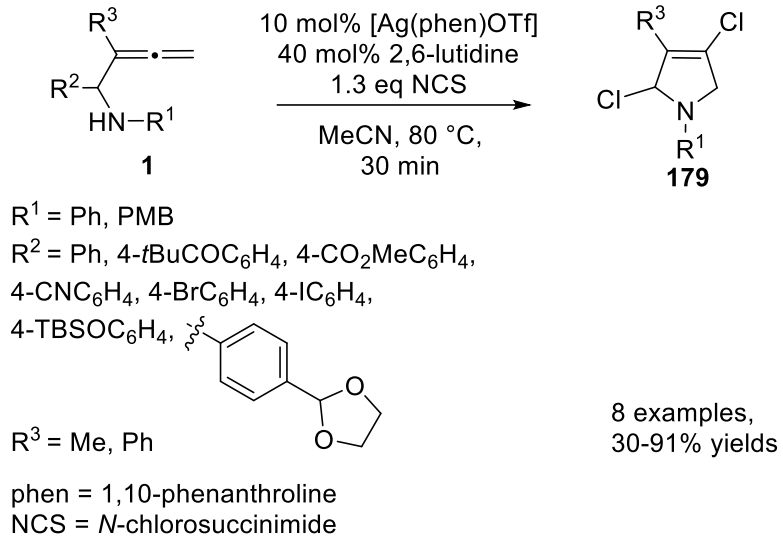
[Scheme 103. Pd-catalyzed domino reaction of α-allenamides in the presence of CuX_2]

A series of *N*-substituted allenamides **23** and *N*-tosyl allenyl carbamates **7** underwent domino process under Pd(II)-catalyzed cyclization in the presence of LiBr and $Cu(OAc)_2$ as reoxidant in acetonitrile as solvent, affording pyrrolidines **177** and oxazolidinones **178** in good yields and in short reaction times (Scheme 104). The reaction proceeded through an external nucleophilic attack of the bromine at the central allenic carbon producing a (π-allyl)palladium intermediate. Subsequently, intramolecular attack by the second nucleophile (nitrogenated moiety) gave the product.[106]



[Scheme 104. Domino reaction of γ-allenamides and *N*-tosyl allenyl carbamates in the presence of CuX_2]

The chloroamination process of α-aminoallenes **1** performed with *N*-chlorosuccinimide under silver catalysis, using 2,6-lutidine as base, in acetonitrile at 80 °C for 30 min resulted in the formation of the 3-chloro-3-pyrrolines **179**. The reaction proceeded through a 5-*endo*-cyclization followed by the insertion of chlorine on the vinyl-silver intermediate (Scheme 105).[107]



[Scheme 105. Ag-catalyzed domino reaction of α-aminoallenes in the presence of *N*-chlorosuccinimide]

CONCLUSIONS

The formation of intramolecular C-N bonds constitutes an efficient tool to synthesize nitrogen-containing rings of various sizes and polycyclic systems. The presence of three unsaturated carbons and the particular reactivity of allenes under transition-metal catalysis allow the control of the regioselectivity in the cyclization step. The cyclization step, which also depends on the transition-metal, in the presence of axial chirality gives the possibility to transfer the stereochemistry to the reaction's products. In particular, the use of new chiral ligands improves the interest due to the stereoselective synthesis, obtaining optically active compounds. Moreover, the domino processes involving amination allow inserting a variety of functional groups during the cyclization in a one-pot fashion, affording heterocycle derivatives not easily obtained by other methods. These strategies were also applied in the context of medicinal chemistry and in the total synthesis of natural products. At the same time, they will lead to further advances in the field of allene chemistry.

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