Metal-Catalyzed Intermolecular Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C–N, C–C, and C–O Bonds

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Metal-catalyzed Hydrofunctionalization of Allenes: Easy Access to Allylic Structures via the Selective Formation of C-N, C-C and C-O Bonds.

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Dedicated to Pierre H. Dixneuf for his outstanding contribution to catalysis and organometallic chemistry.

Abstract

This review aims to present the methods allowing the metal-catalyzed hydrofunctionalization of allenes.

Following a strong regain of interest over the past 20 years in the chemistry of allenes, this "forgotten" family of unsaturated molecules is undergoing a renaissance.

In this context, the metal-catalyzed hydrofunctionalization of allenes is nowadays one of the most studied transformations. The latter is of great interest because it opens a way to produce selectively functionalized allylic structures. These motifs are particularly important in synthesis, particularly for the formation of asymmetric centers.

Hydrofunctionalization of allenes is also a totally atom economical strategy, avoiding generation of any waste, to produce allylic functionalized structures. Compared to the main pathway to obtain the latter (aka Tsuji-Trost allylic substitution), metal-catalyzed hydrofunctionalization does not require the prefunctionalization of starting material with a leaving group.

This review presents a state of the art on all existing metal-catalyzed methods allowing the selective intermolecular hydrofunctionalization of allenes with N-H, C-H and O-H nucleophiles or electrophiles.

Contents

1. Introduction

Despite a first synthesis described 133 years ago,[1,2] allenes are still the least studied all-carbon unsaturated functional group. The first efficient methodologies to obtain this structure were only described in the 60's surely because the structural originality of allene with a linear 3-carbon skeleton built with 2 cumulative π-bonds had lowered its development. Starting in the 60's, a burgeoning interest in allene chemistry has triggered a multiplication of synthetic methods for accessing a wide variety of these unsaturated molecules, particularly in the last 20 years.[3–9] Consequently, allene reactivity studies get more and more interest in organic community and beyond.[10–15]

In this field, hydrofunctionalization has emerged as an atom efficient tool to exploit the reactivity of allenes, meanwhile avoiding the generation of any wastes. While this type of transformation has been accomplished with organocatalysis in some seminal works, the use of metal catalysts remains the most developed strategy for obtaining both selectivity and efficiency.[16–20]

The aim of this review is to highlight the potential of hydrofunctionalization of allenes for the formation of C-N, C-C and C-O bonds and to give an exhaustive overview of the current knowledge in this field. The need of a comprehensive review is strengthened by the rate at which new catalytic systems and new conditions have been described in this area in the past few years. Note that the methods presented herein will be restricted to intermolecular reactions and will not cover reactions where allenes are considered as intermediate substrates generated in-situ. Moreover, only mono-hydrofunctionalizations will be covered, also excluding dimerization or cyclization processes. Gathering all the known examples, this review will illustrate how, thanks to metal-catalyzed reactions, allenes became unavoidable and valuable synthetic building blocks to selectively afford both linear and branched allylic molecules.

2. C-N Bond Formation

Hydroamination of unsaturated molecules and related reactions catalyzed by transition metal complexes were extensively studied in the past few decades. Despite their high reactivity, allenes remain the less studied unsaturated compounds toward this kind of addition. However, this reaction could give an easy access to various allylic moieties of high interest for organic synthesis (Figure 1). Starting in the beginning of the 90's, the intermolecular catalytic addition of aliphatic and aromatic amines to allenes were performed especially with palladium, gold and rhodium catalysts. These metals have been also used to perform the hydroamination of allenes with amide nucleophiles, and currently gold-based catalysts remain unique in their ability to catalyze the addition of ammonia. Gold and iron catalysts were

able to perform hydroazidation. Hydrohydrazination of allenes was also described under rhodium and gold catalysis.

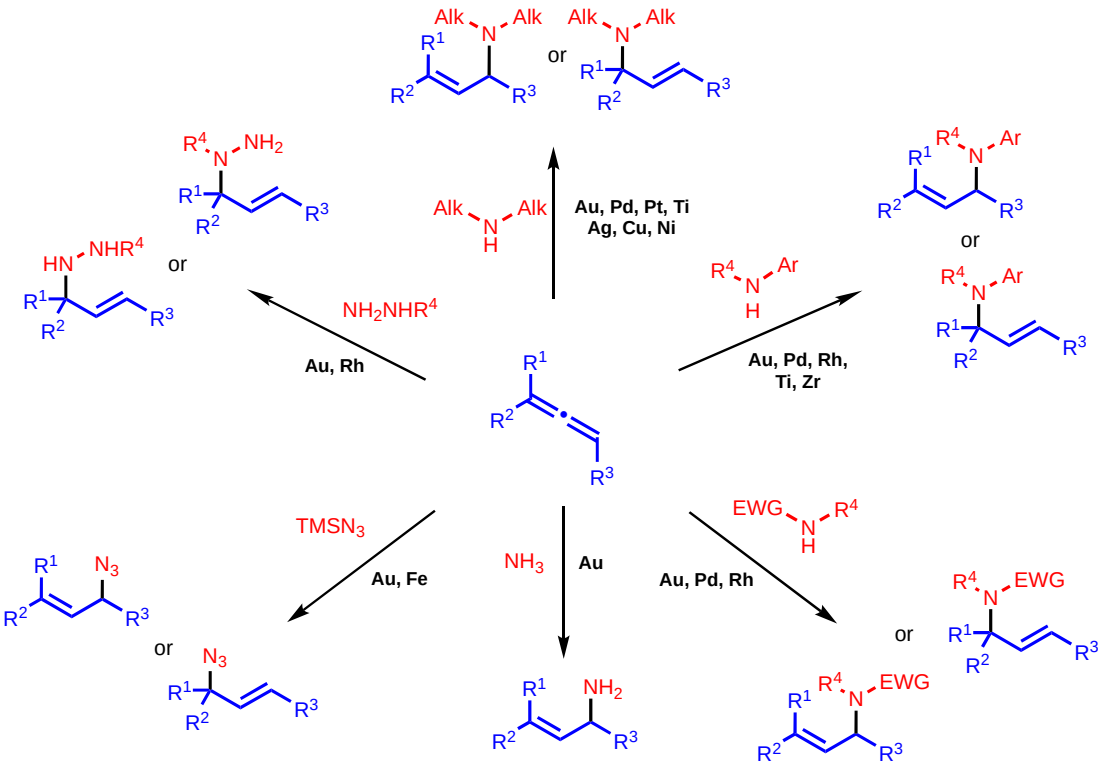
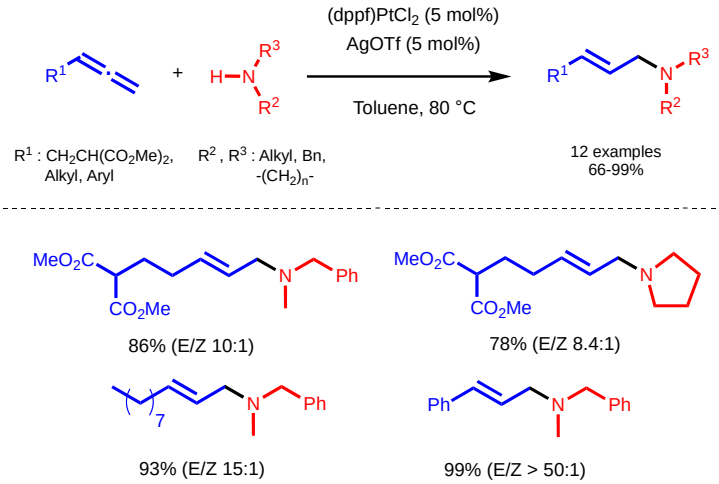


Figure 1: transition-metal catalyzed hydrofunctionalization of allenes for C-N bond formation.

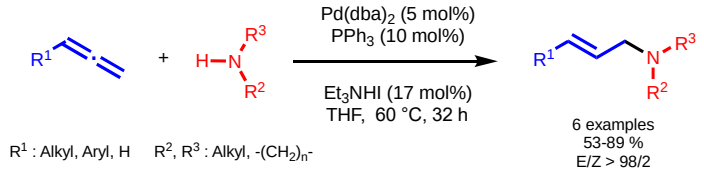
2.1. Hydroamination with aliphatic amines

The first hydroamination of an allene was observed in 1978 by Panunzi and Vitagliano.[21] This group focused on the preparation of allene-platinum complexes and reported their reaction with the nucleophilic addition of aliphatic and aromatic amines. This process was not catalytic as it used an equimolar amount of platinum. Based on this work and their previous results on hydroamination of alkenes,[22] Widenhoefer reported in 2010 the platinum(II)-silver co-catalyzed hydroamination of mono-substituted terminal allenes with aliphatic cyclic and acyclic amines (Scheme 1).[23] This method, currently the only example using a platinum system, afforded the corresponding *E* allylic amines with complete regioselectivity and excellent stereoselectivity. The Ag-based co-catalyst is proposed to generate the catalytically active cationic Pt(I) complex by extracting a chloride to the neutral (dppf)$PtCl_2$ complex.



Scheme 1: Pt/Ag co-catalyzed hydroamination of terminal allenes.

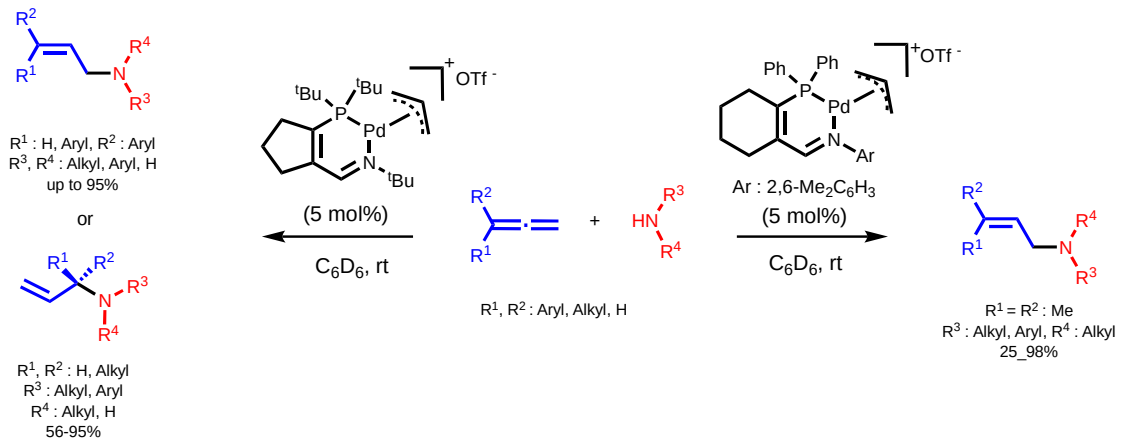
In the middle of the 90's, the group of Cazes described a Pd-catalyzed regio- and stereoselective hydroamination of terminal allenes with secondary aliphatic amines.[24] The reaction was performed with $Pd(dba)_2/PPh_3$ and triethylammonium iodide, giving a hydropalladium iodide species able to form a π-allyl palladium key intermediate in presence of allenes. While allenes are known to telomerize in presence of a palladium catalyst, this reaction occurred with only traces of telomerization with the selective formation of (*E*)-allylic amines resulting from an addition of the amine on the terminal carbon of the allene (Scheme 2).



Scheme 2: Pd-catalyzed regio- and stereoselective hydroamination of terminal allenes.

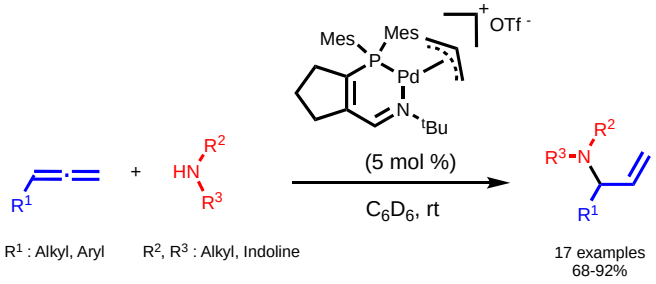
A few year later, in 1997, Yamamoto and co-workers described a related method involving the formation of a hydropalladium(II) intermediate by oxidative addition of acetic acid to a Pd(0) complex.[25] With this catalyst in hand they performed the hydroamination of mono-substituted allenes with various amines such as diethyl iminoacetate or tosylamine.

In 2011 Schmidt and co-workers reported the use of a palladium(II)-3-iminophosphine (3IP) complex to perform the hydroamination of mono- and 1,1-di-substituted allenes with secondary amines and anilines derivatives. The reaction with 1,1-dimethylallene and the $[(3IP^{Ar})Pd(allyl)]OTf$ catalyst gave access to linear allylic amines,[26] while using $[(3IP^{tBu})Pd(allyl)]OTf$ gave access to branched or linear allylic amines from mono-substituted allenes (Scheme 3).[27] In another study, they further explored the role of the 3-iminophoshine ligand and of the palladium complexes in the selectivity of the reaction.[28]



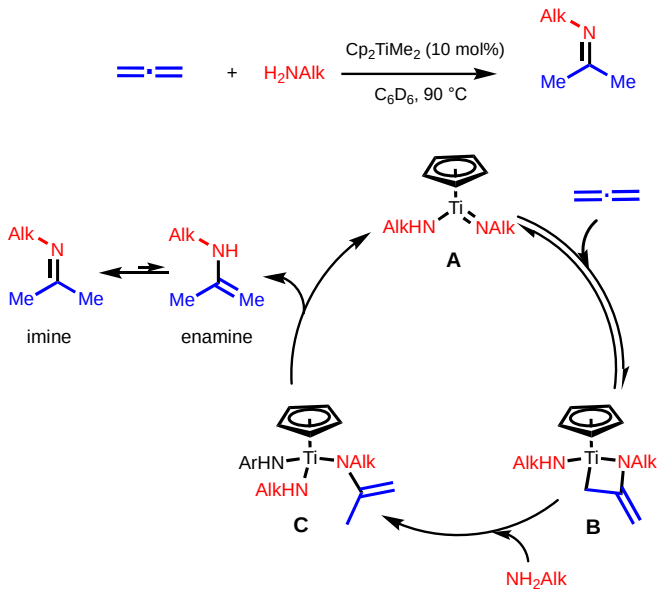
Scheme 3: Pd(iminophosphine) catalyzed addition of amines to terminal allenes.

In 2019, the same group developed an original allylpalladium triflate catalyst able to completely inhibit the isomerization process leading to the linear allylic amine.[29] This novel catalyst, composed by a bulky phosphine bearing mesitylene groups, allows the production and isolation of unprecedented branched allylamines without traces of the undesired linear allylamines starting from mono-substituted allenes (Scheme 4). The authors postulated that the greatly increased steric hindrance of the phosphine is responsible for the inhibition of product isomerization.



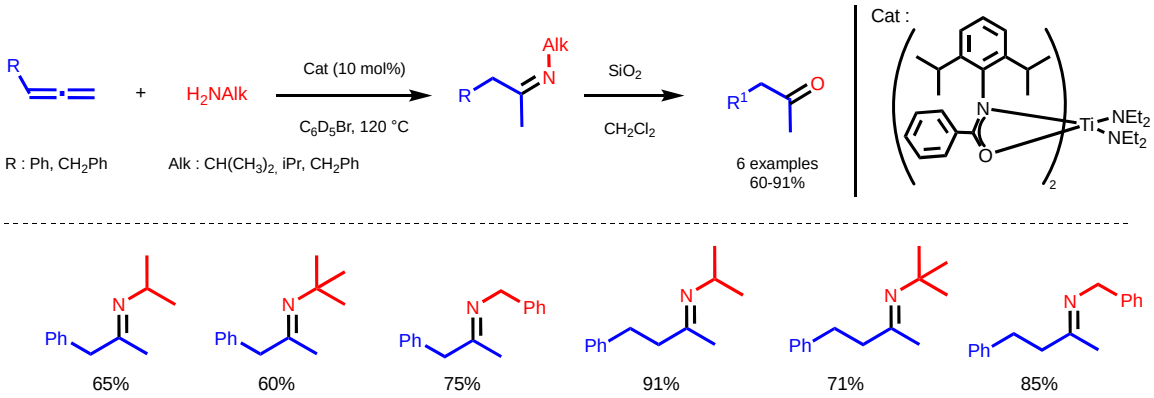
Scheme 4: Selective branched allylamines synthesis by Pd(iminophosphine)-catalyzed hydroamination of mono-substituted allenes.

Titanium complexes were also used to catalyze hydroamination reactions. Noteworthy, the group of Bergman reported in 2001 an in-situ formed imidotitanium complex **A** (Scheme 5) able to catalyze the hydroamination of the propadiene and alkynes with primary aliphatic amines, anilines or hydrazines to obtain the corresponding imine molecules.[30] The complete observed regioselectivity of the addition of amine on the central carbon was explained by intermediate formation of an azametallacyclobutane **B**, the latter is protonated by the amine and then eliminate the enamine compound which tautomerize in more stable imine. The mechanism was studied by DFT calculation for the hydroamination of allene, alkenes and alkynes with cyclopentadienyltitanium-imido complexes.[31]



Scheme 5: Proposed mechanism for the Ti-catalyzed hydroamination of propadiene.

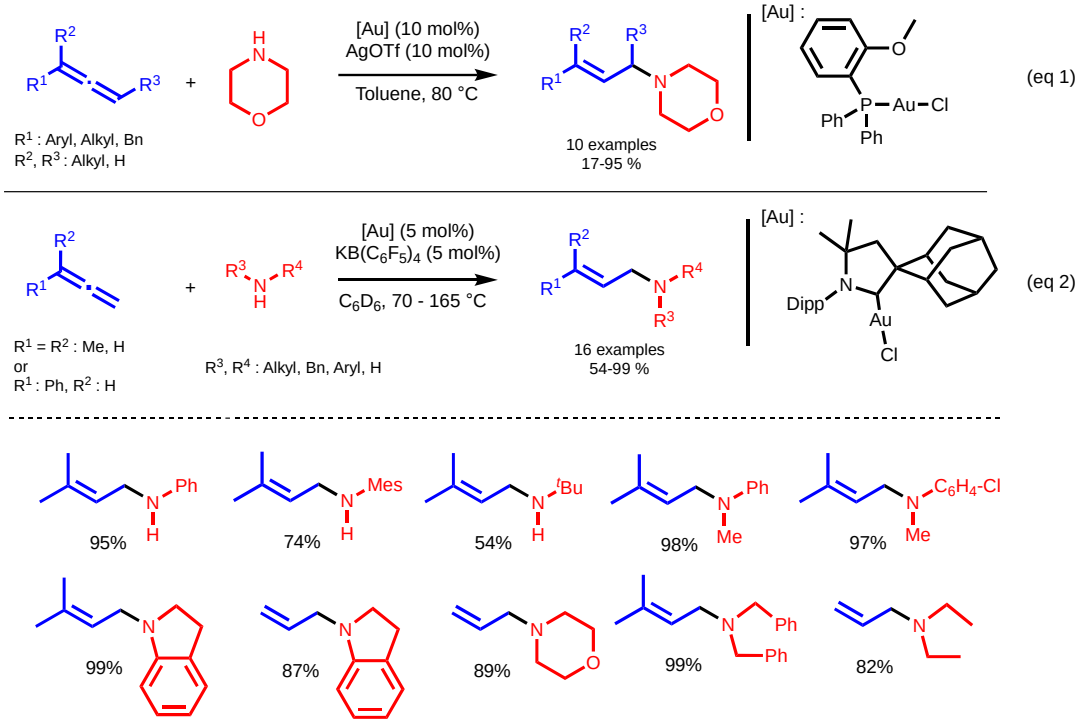
By using a bis(amidate)-bis(amido) titanium precatalyst, Schafer and co-workers performed the reaction of primary aliphatic or aromatic amines with mono-substituted allenes and obtained regioselectively the corresponding imines (Scheme 6).[32] The latter were not stable, and hydrolyzed to the corresponding ketones during purification over silica gel.



Scheme 6: Ti(imido) complexes as catalyst for hydroamination of terminal allenes.

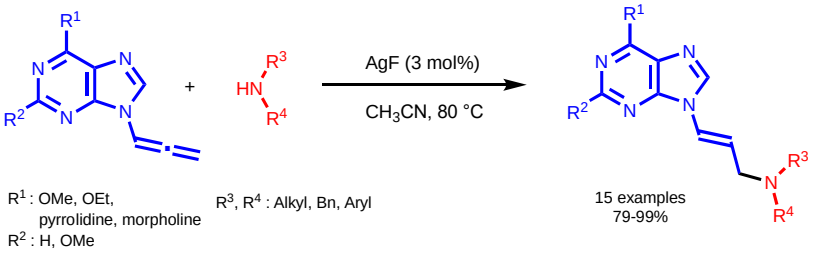
Gold-catalyzed systems have been also described for the hydroamination of allenes with aliphatic amines. The first example was reported in 2007 by Yamamoto and co-workers.[33] Using (PAr_3) AuCl or PPh_2(*o*-tolyl)AuCl as precatalyst with AgOTf (10 mol%) at 80 °C, the addition was performed on mono- and 1,1-di- and tri-substituted allenes with morpholine (Scheme 7, eq. 1).[34] In 2009 Bertrand and co-workers described a cationic gold(I) based catalyst bearing a bulky cyclic carbene ligand (CAAC-type ligand) enabling the reaction of phenylallene or 1,1-dimethylallene with various secondary aliphatic and

aromatic amines (Scheme 7, eq. 2).[35] For both systems, reactions occurred with total regio- and stereoselectivity, excepted for some substrates as tri-substituted allenes.



Scheme 7: Au(I)/Ag co-catalyzed and Au(I)-catalyzed hydroamination of di- and tri-substituted allenes with aliphatic amines.

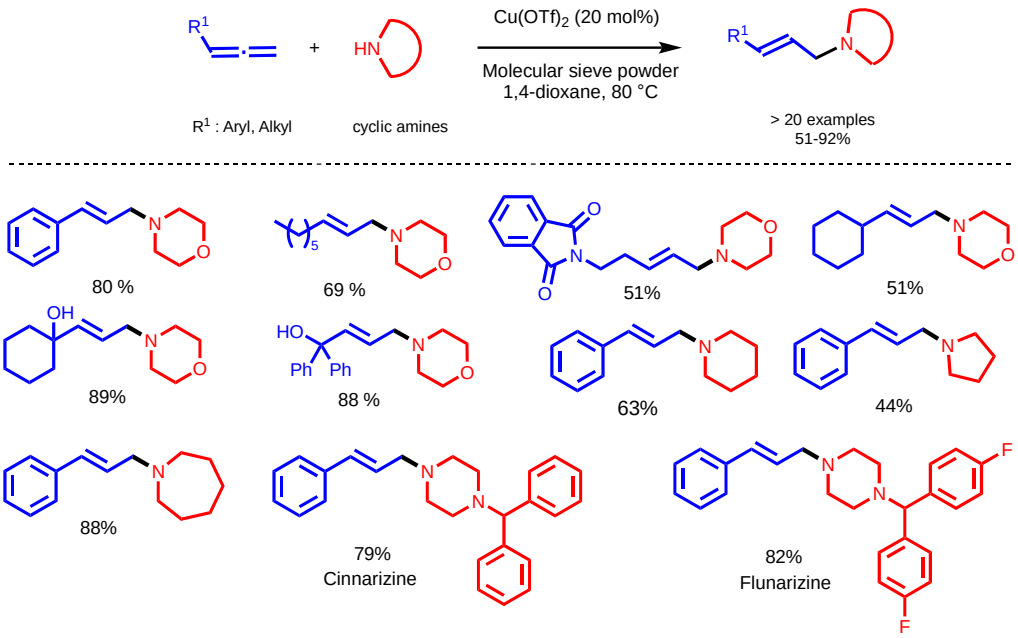
In 2014, the group of Guo reported the functionalization of 9-allenyl-*9H*-purines with various nucleophiles, including secondary aliphatic amines thanks to a very simple ligand-free silver-based catalytic system (Scheme 8).[36] The method was only described with purine nucleoside derivatives.



Scheme 8: Ag(I)-catalyzed hydroamination of allenylpurines.

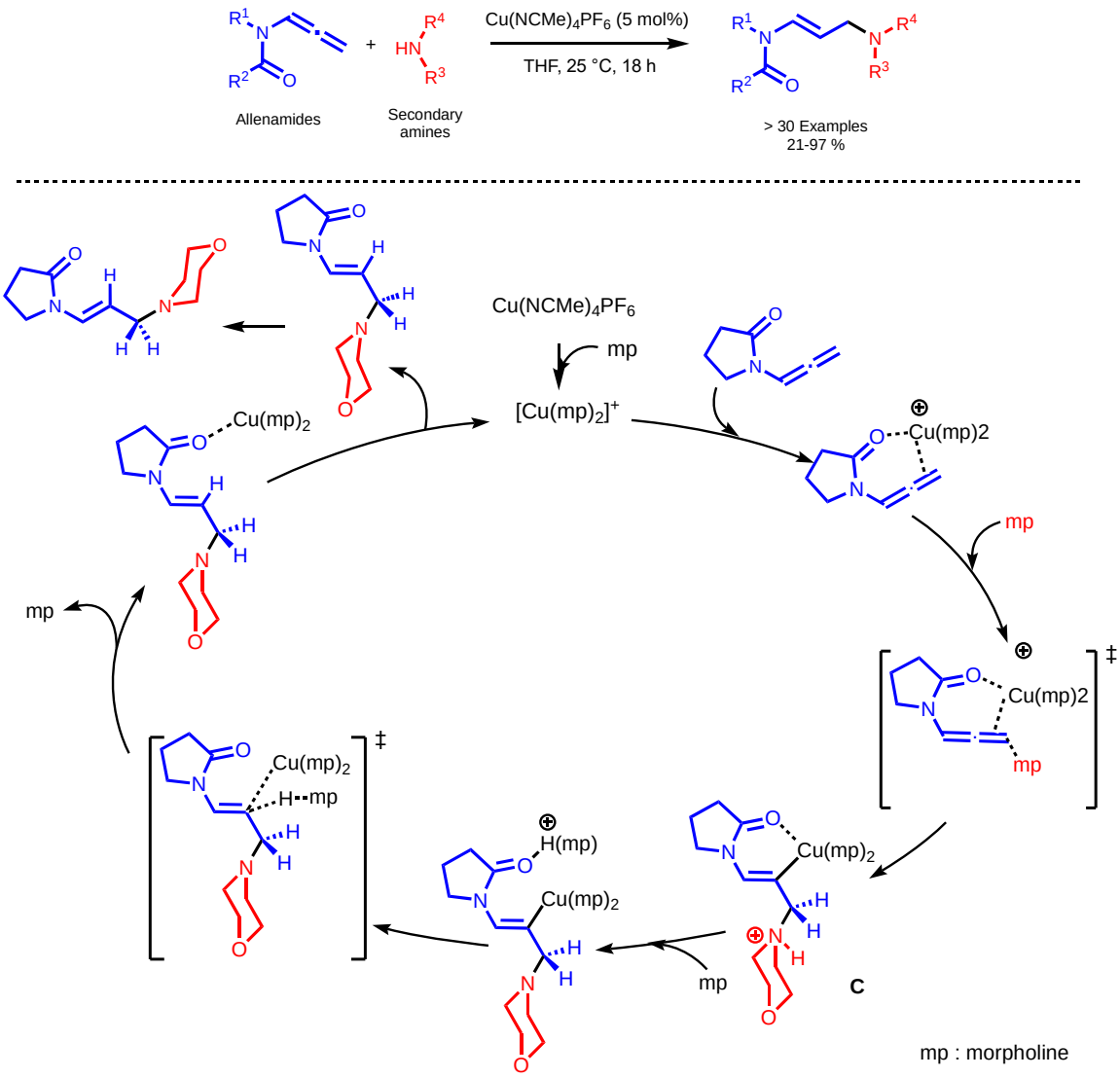
In 2016, our group reported the first use of a copper-based catalyst for the catalytic hydroamination of terminal allenes with cyclic secondary amines thus affording (*E*)-allylamines with complete regio- and stereoselectivity (Scheme 9).[37] This meaning system, which proceeds at 80 °C, is also efficient with aromatic amines and presents the advantage of using only commercial copper source ($Cu(OTf)_2$) without

any additional ligand. Noteworthy, straightforward synthesis of two drugs, Cinnarizine and Flunarizine, were achieved with excellent yields under a total control of regio- and stereoselectivity.



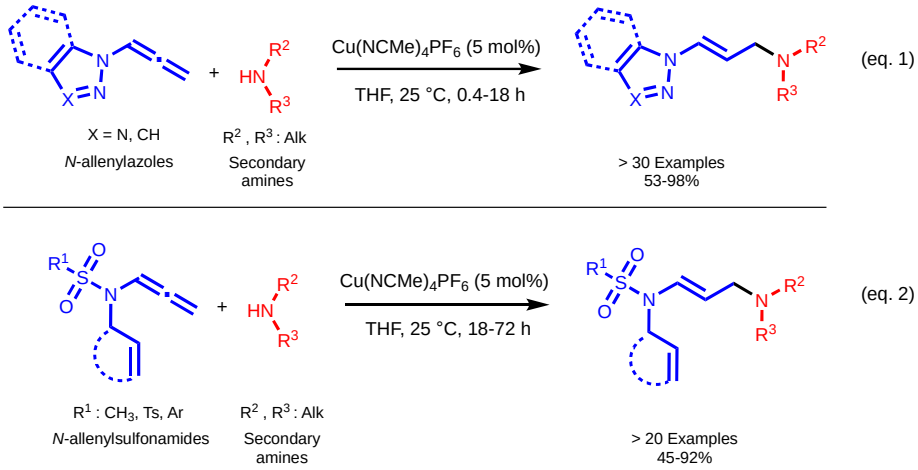
Scheme 9: Copper-catalyzed hydroamination of terminal allenes with cyclic secondary amines.

We then discovered that an enhanced reactivity (5 mol% of $[Cu(NCMe)_4]PF_6$, 25 °C) could be obtained using allenamides instead of classical allenes (Scheme 10). Mechanistic study revealed that coordination of the metal center assisted by the carbonyl group had a crucial role on the reactivity.[38] A mechanism involving the initial formation of a complex $[Cu(mp)_2]^+$ with allenamides was proposed. Subsequent attack of the amine nucleophile onto the copper-allene complex afford an alkenyl-copper intermediate prone to give the hydroamination product after protodemetalation. Using a cationic Cu(I) precatalyst, the hydroamination of allenamides has been reported under mild conditions for a large scope of secondary amines.



Scheme 10: Mechanism for the Cu-catalyzed hydroamination of allenamides with secondary amines.

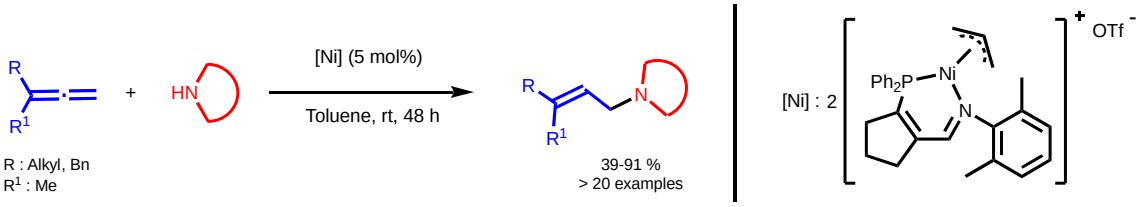
Exploring the potential of this assistive coordination effect, we subsequently reported the hydroamination of *N*-allenyl azoles[39] and *N*-allenyl sulfonamides[40] with secondary amines using the same catalytic system (Scheme 11). In the first case the coordination with copper was achieved via nitrogen,[39] and total conversion into the corresponding allylic amines could be achieved in some case in less than 15 min (Scheme 11, eq. 1). In the second case, the presence of an unsaturation or an aromatic cycle was necessary to obtain a satisfying conversion (Scheme 11, eq. 2).[40] In each case, linear allylamines were obtained with complete control of the regio- and stereoselectivity.



Scheme 11: Cu-catalyzed hydroamination of N-allenylazoles and N-allenylsulfonamides with secondary amines.

This approach has been applied to the synthesis of α-CF_3-substituted ornithine derivatives and to their phosphorus containing analogues with primary and secondary amines.[41] The same Cu(I) precatalyst was efficient for the selective hydroamination of CF_3-containing α-allenyl-α-aminocarboxylates and their phophonates derivatives and has kept the same excellent regioselectivity.

In 2017, Schmidt et al. reported the currently unique example of nickel catalyzed hydroamination of allenes. Using a cationic [(iminophosphine)nickel(allyl)] complex the method was applied to the addition to mono-substituted allenes or dimethylallene, with secondary cyclic amines (Scheme 12).[42] Using a sophisticated preformed Ni-catalyst, structurally similar to the one they used with palladium (Scheme 3), this method gave also access selectively to linear allylic amines.

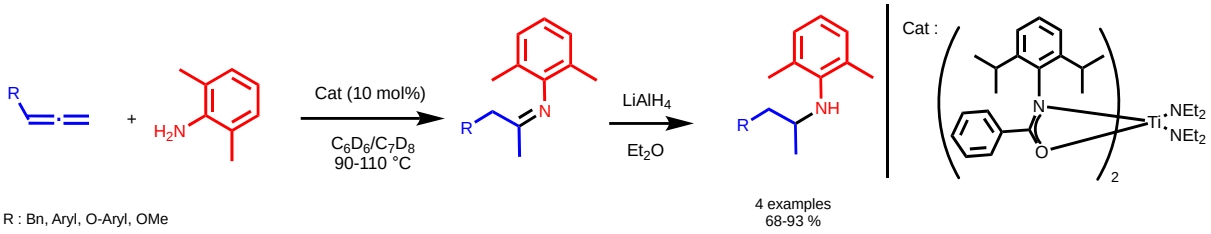


Scheme 12: Ni(I)-catalyzed hydroamination of allenes with secondary cyclic amines.

2.2. Hydroamination with Aromatic Amines and N-heteroaromatics

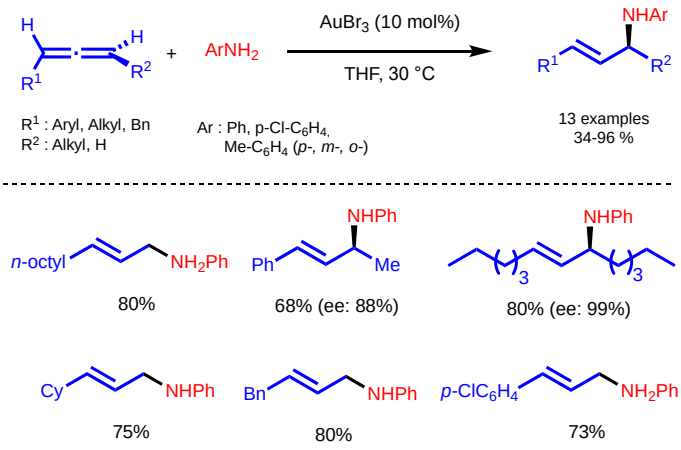
Number of previously cited examples reporting the hydroamination of allenes with aliphatic amines included the use of aromatic amines like indolines or anilines derivatives.[21,25–27,30,32,34–37,40,42] Some other articles reported the exclusive use of aromatic amines such as the one of Vitagliano and Panunzi, with the addition of anilines on an allene, initially coordinated to a stoechiometric amount of platinum(II).[43] In 1992, Bergman used zirconium bisamides $Cp_2Zr(NHR)_2$ in catalytic amount to perform in 6 days the selective addition of anilines, on the central carbon of mono-substituted allenes.[44] The same selectivity

was observed by Schafer in 2011 with catalytic amount of zirconium and titanium amido complexes (Scheme 13).[45] Due to low stability of the formed imines, the latter were reduced with $LiAlH_4$ to afford the corresponding amines.



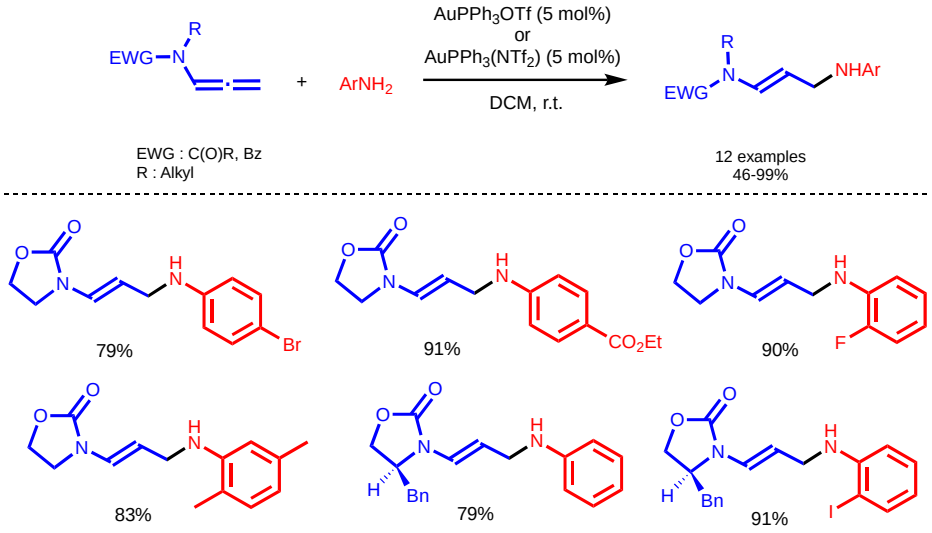
Scheme 13: Ti- and Zr-catalyzed hydroamination of terminal allenes with 2,6-dimethylaniline.

Using catalytic amount of $AuBr_3$, Yamamoto reported in 2006 the first use of gold for the addition of various anilines to mono- and 1,3-di-subsituted allenes.[46] This reaction occurred under mild conditions at room temperature, and with an excellent transfer of chirality when performing the reaction with chiral allene (Scheme 14). The authors suggested an inner-sphere nucleophilic addition, excluding the formation of a π-allyl complex, to explain the observed selectivity.



Scheme 14: Au-catalyzed hydroamination of allenes with anilines with chirality transfer.

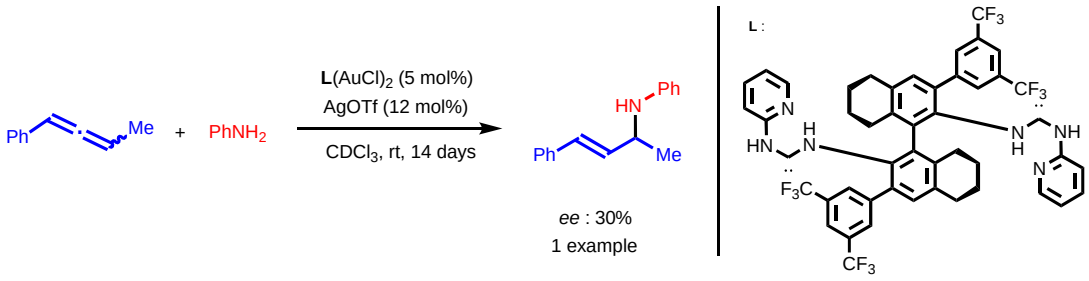
In 2010 Kimber used a cationic gold catalyst to realize the regioselective hydroamination of allenamides with differently substituted anilines[47] and latter with tetrahydrocarbazole.[48] This protocol took advantage of the propensity of allenamides to afford allylamino enamides, presented as potential valuable building blocks for various post-functionalization (Scheme 15).



Scheme 15: Au-catalyzed hydroamination of allenamides with anilines.

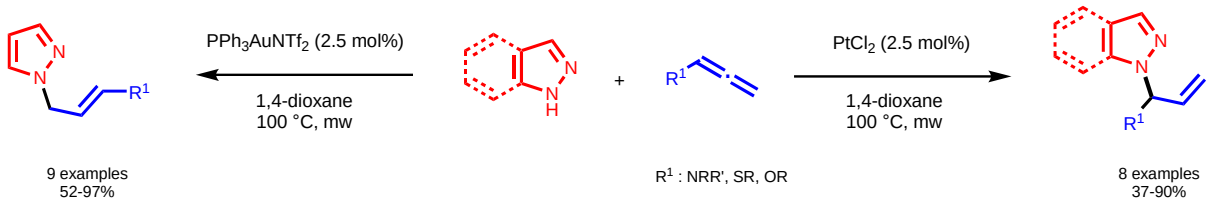
The same year, Widenhoefer and co-workers reported a gold(I)-NHC complex for the catalytic transformation of mono-, 1,1- and 1,3-disubsituted allenes with anilines and their alkylated derivatives.[49]

The regio and enantioselective addition of aniline on 1,3-disbustituted allene (buta-1,2-dien-1-ylbenzene) was first described with a poor enantiomeric excess by Toste in 2016, employing a sophisticated chiral bis-NHC ligand with a BINAM scaffold (Scheme 16).[50]



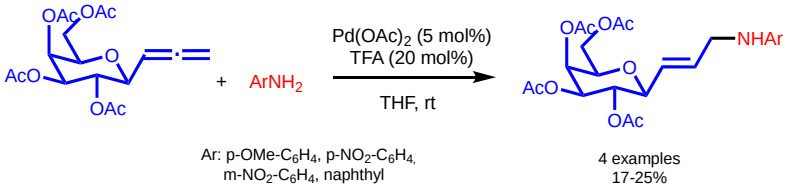
Scheme 16: Au/Ag co-catalyzed hydroamination of di-substituted allenes with anilines.

Another example of the use of gold for the hydroamination of allenes with aromatic amines was described by the group of Paz Muñoz in 2019, as they described the reactivity of activated allenes with azoles using gold- and platinum-based catalysts.[51] Interestingly, using the gold catalyst lead to the formation of linear allylic amines while platinum lead to the formation of the branched product (Scheme 17). Noteworthy, a bimetallic system using both gold and platinum promoted efficiently a 1,3-double addition.



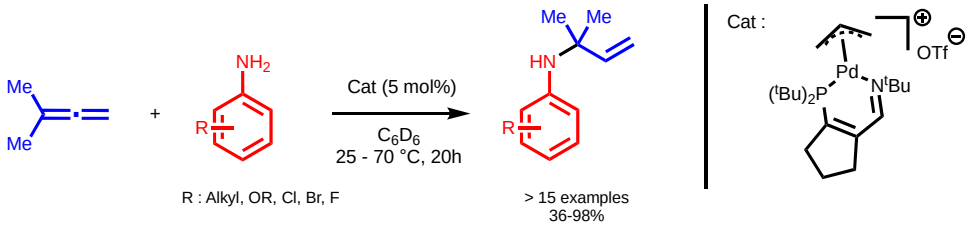
Scheme 17: Au- and Pt-catalyzed hydroamination of activated allenes.

Palladium-based catalytic systems were also efficient for the addition of arylamines on allenes. Thus, a $Pd(OAc)_2$/TFA complex was employed for the selective hydroamination of allenosugars with various anilines at room temperature and allowed the formation of the corresponding allylamines with low yields (Scheme 18).[52]



Scheme 18: Pd-catalyzed hydroamination of allenosugars with anilines.

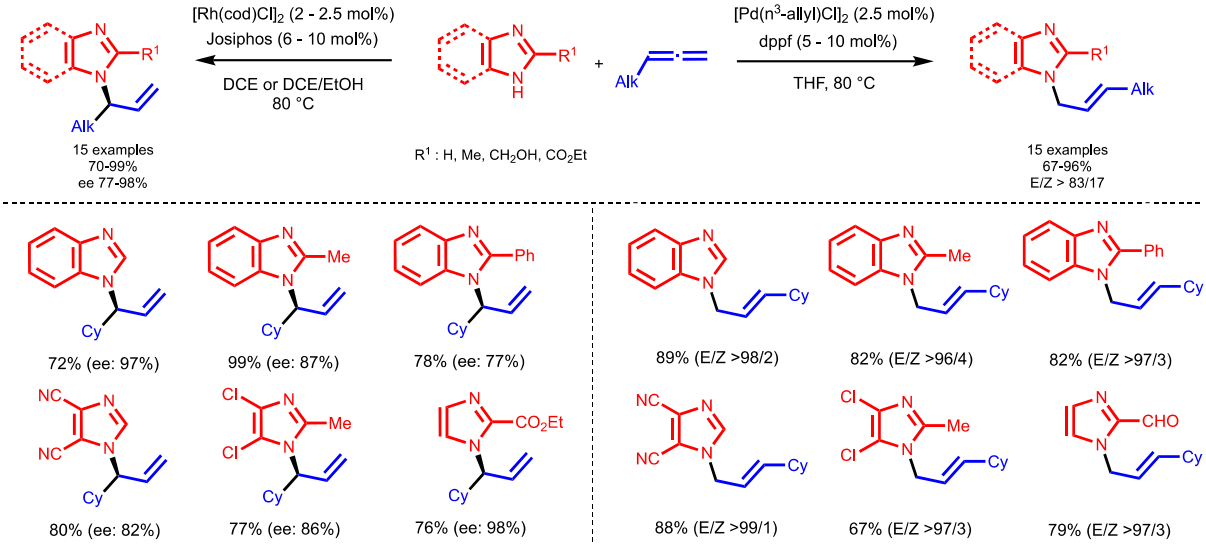
As briefly mentioned previously, the palladium-catalyzed system developed by the group of Schmidt was efficient with arylamines.[26–28] First developed with the 1,1-dimethylallene, this system allowed a complete addition on the more hindered carbon (Scheme 19).[53] The study of the steric and electronic role of the ligand showed that electron-donating substituent placed on the phosphine or the imine function induced enhanced catalytic activities.[54]



Scheme 19: Palladium catalyzed hydroamination of 1,1-dimethylallene with anilines.

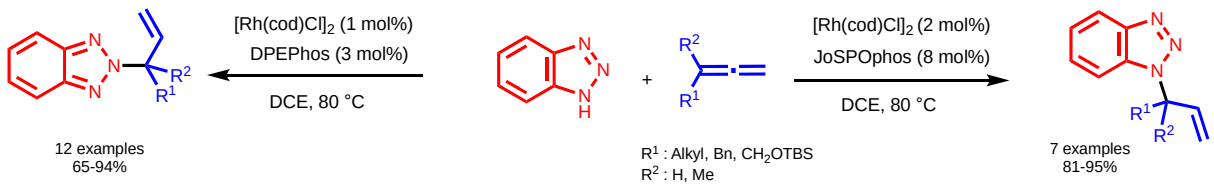
The groups of Rutjes and Gómez-Bengoa reported the palladium catalyzed hydroamination of alkoxyallenes with *N*-containing heterocycles.[55] Breit and co-workers used a palladium(II) catalytic species for the hydroamination of terminal allenes with imidazole and benzimidazole (Scheme 20).[56] In the presence of $[Pd(\eta^3\text{-allyl})Cl]_2$ the reaction was totally regio- and stereoselective, giving access to the linear allylic amines while using a rhodium catalyst $[Rh(cod)Cl]_2$ associated with chiral Josiphos ligand

gave total inversion of the regioselectivity with a chiral control. This regiodivergence could be explained by the nature of the catalyst that allows a difference of reductive elimination process: Pd-based catalysis leads to the reductive elimination on the less hindered position to generate the linear product. The same regiodivergence phenomenon was also observed in the addition of purines derivates[57] and 4-pyridones.[58]



Scheme 20: Regiodivergent hydroamination of allenes with benzimidazoles with enantio-, stereo and regioselective Rhodium catalyst and with regio- and stereoselective Pd-catalyst.

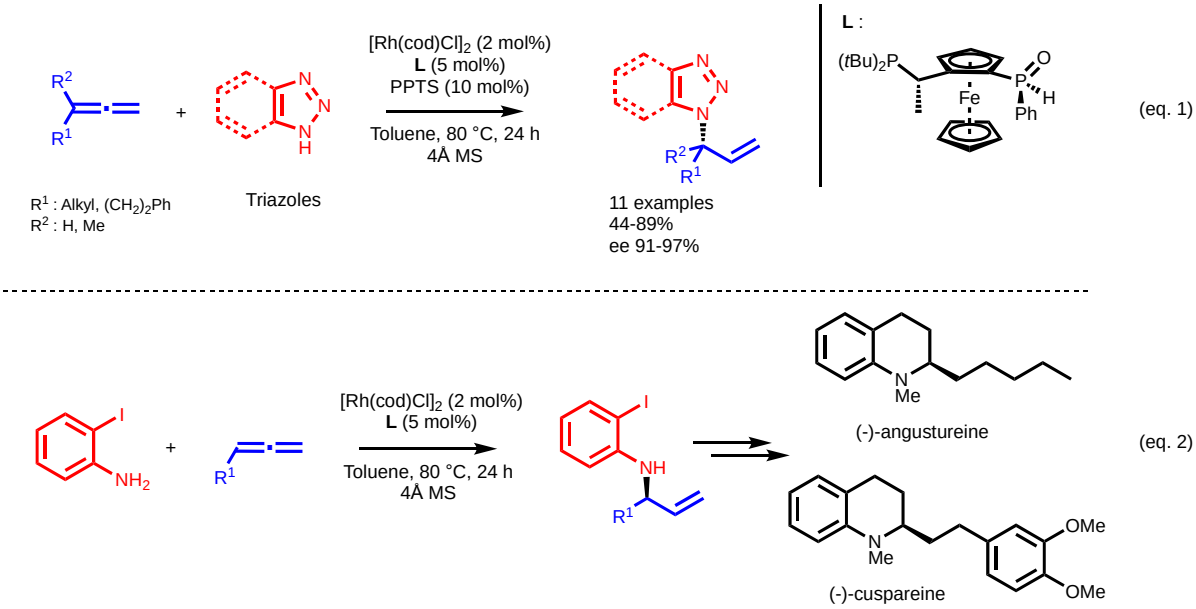
The exclusive rhodium catalyzed hydroamination of terminal allenes leading to the branched allylic amines with a chiral control was actually published by the same group since 2012, with anilines.[59] The method was also successfully applied to a large scope of nitrogen containing heterocycles, including pyrazoles,[60] 2-pyridone,[61] tetrazoles[62] and pyridazinones.[63] Notably, when using 1,1-di-substituted allenes and benzotriazoles as nitrogen-containing partner the selectivity of the reaction, occurrence on the N^1 or N^2 of the benzotriazole core was found to be ligand dependent (Scheme 21).[64] The mechanism of this ligand-controlled regioselectivity has been studied by DFT calculations, pointing the crucial influence of electrostatic interaction during the rate-determining oxidative addition step.[65]



Scheme 21: Rh-catalyzed regiodivergent hydroamination of di-substituted terminal allenes with benzotriazoles.

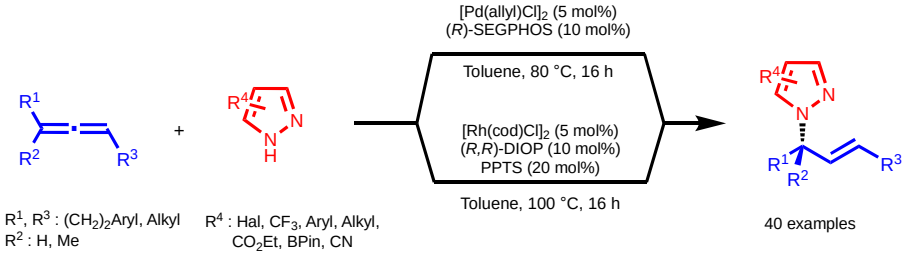
Dong and co-workers reported in 2015 the enantioselective rhodium catalyzed hydroamination of alkynes with indoline.[66] During their study-and based on the work of Breit, they suggested the formation of allene type intermediates resulting β-hydride elimination from Rh-vinyl intermediate. To support this hypothesis, they showed that the reaction occurs identically starting from the corresponding allenes.

In 2018, Breit and co-workers described the enantioselective hydroamination of terminal allenes with various triazoles, catalyzed by a rhodium/chiral ferrocene-diphosphine ligand based system (Scheme 22, eq. 1).[67] One year later, a similar method was applied to anilines and derivatives, giving a straightforward access to (-)-Angustureine and (-)-Cuspareine, two natural molecules with antiplasmodial and cytotoxic activities (Scheme 22, eq. 2).[68]



Scheme 22: Rh-catalyzed hyroamination of allenes with triazoles and anilines.

The same group developed other efficient catalytic systems based on palladium or rhodium catalysts, for the hydroamination of di- or trisubstituted allenes with pyrazoles (Scheme 23).[69] In both cases, the hydroamination occurred with the dynamic kinetic resolution of racemic internal allenes and allowed the addition of pyrazole on N^1 for the selective formation of branched *N*-allylated pyrazoles.



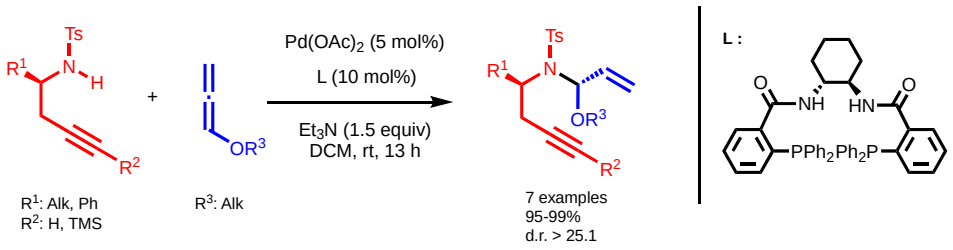
Scheme 23: Rh- and Pd-catalyzed hydroamination of internal allenes with pyrazoles.

The mechanism of the palladium-catalyzed dynamic kinetic resolution was later computationally studied by the group of Huang.[70] They suggested the formation of a Pd(0) intermediate, catalytically active in the reaction and able to form a η^3-allyl Pd(II) complex. The racemization was then explained by a plausible η^3-η^1-η^3 allylic isomerization of this η^3-allyl Pd(II) complex.

2.3. Hydroamidation with amides, sulfonamides and carbamates

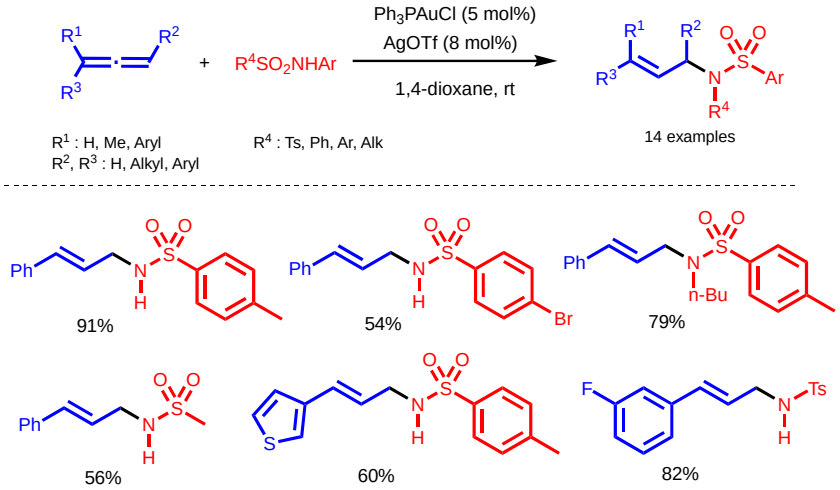
Beyond amines, hydroamidation reactions involving amides, sulfonamides and carbamates have been also widely described in recent literature.

Yamamoto in his seminal investigation in 1997 showed the efficiency of a palladium/dppf system for the addition of a tosylamine on aryl allenes.[25] Later, the group of Rutjes performed hydroamidation on allenyl ethers with secondary sulfonamides catalyzed by a palladium-based system. They focused of the obtention of N,O-acetals, used for ring-closing metathesis or tin-catalyzed cyclization.[71–74] This approach was also used by Donohoe et al. to generate aromatic heterocycles such as furans and pyrroles.[75,76] Employing a chiral sulfonamide as starting material and a chiral ligand, Rhee and co-workers published in 2012 the first synthesis of stereodefinded N,O-acetals thanks to a Pd/chiral PNNP ligand-catalyzed hydroamination of allenyl-ethers where the addition of the sulfonyl-protected homopropargylic amines occurred on the α-carbon of the allene (Scheme 24).[77] Worth noting that using the *ent*-L chiral ligand, the stereocontrol could be totally inverted. The enantiomeric control was also performed few month later with achiral nitrogen-containing partner, using the same catalytic system.[78,79]



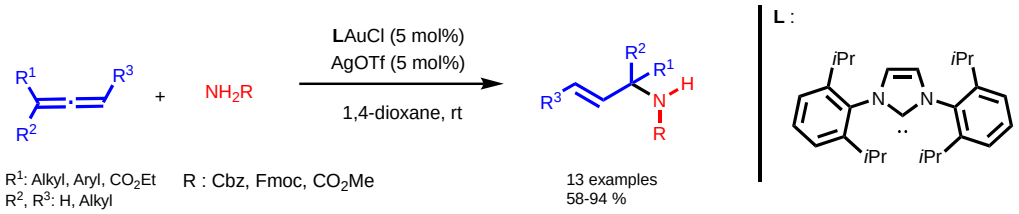
Scheme 24: Stereoselective hydroamidation of allenyl ethers with sulfonamides catalyzed by Pd.

The regio- and stereoselective hydroamination of various mono-, 1,1- and 1,3-disubstituted aromatic allenes, using primary and secondary sulfonamides like $TsNH_2$ and its derivatives, was also reported with a gold-silver co-catalysis (Scheme 25).[80] The addition of sulfonamides occurred on the terminal carbon of mono-substituted allenes or on the less-hindered carbon of 1,3-disubstituted allene.



Scheme 25: Hydroamidation of di- and trisubstituted allenes with sulfonamide co-catalyzed by Au/Ag.

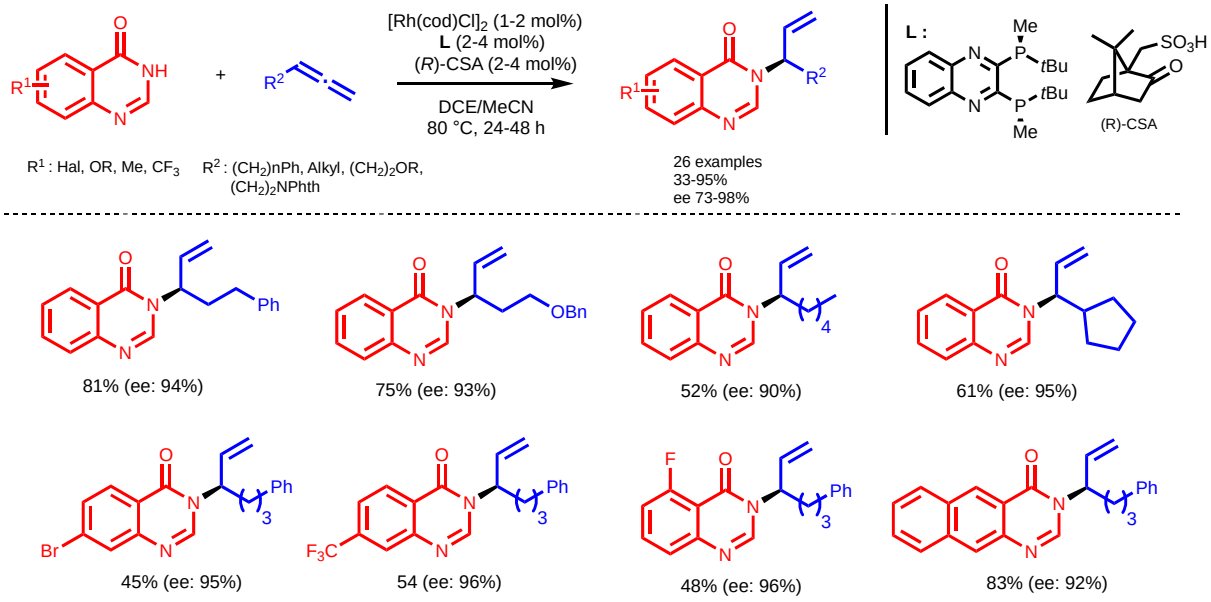
Using a gold-NHC complex, the group of Widenhoefer extended the method to primary carbamates, amides and lactams with 1,3-disubstituted and trisubstituted allenes (Scheme 26).[81] The reaction took place with high stereoselectivity and in the case of 1,3-di-substituted allenes, on the more electro-rich carbon.



Scheme 26: Au/Ag co-catalyzed hydroamidation of 1,3-di- and trisubsituted allenes with amides and lactams.

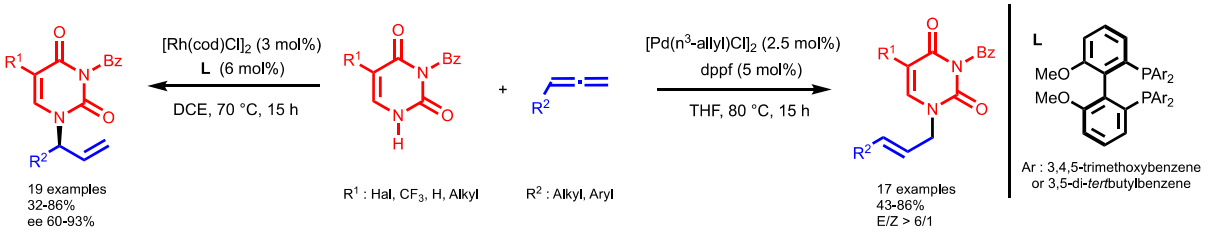
A slight change of the catalytic system, using non-coordinating anion from $AgBF_4$ and a chiral version of the NHC-ligand, made possible the enantioselective addition of carbamates on 1,3-disbustituted allenes.[82] N-carbamates were also successfully tested by Toste with an enantioselective gold-based catalytic system hydroamination of 1,3-disbustituted allenes.[50]

Noteworthy, the team of Breit reported in 2017 the rhodium catalyzed enantioselective hydroamidation of terminal allenes with quinazolones (Scheme 27).[83] The addition of the nucleophile was observed on the α-carbon of the allene in the presence of a rhodium/diphosphine system combined with (*R*)-camphorsulfonic acid.



Scheme 27: Enantioselective Rh-catalyzed hydroamination of terminal allenes with quinazolones.

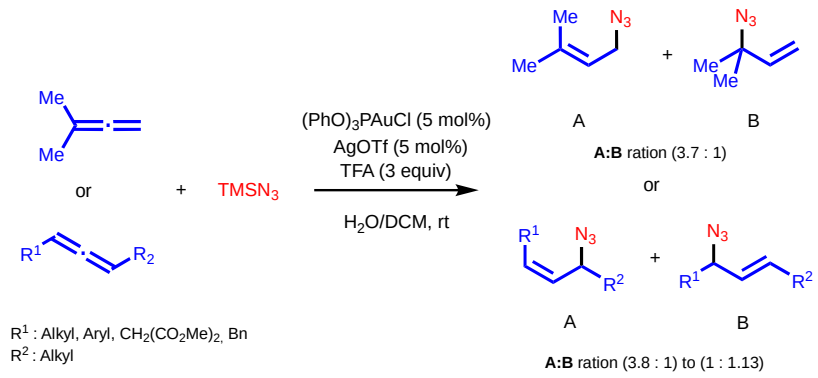
In 2018, thanks to the use of a rhodium/diphosphine-based catalytic system, Guo and co-workers reported the hydroamidation of terminal allenes with pyrimidines. The authors obtained exclusively the branched allylic amines in an enantioselective manner. In the same study they disclosed an efficient palladium/diphosphine catalytic system for the regioselective formation of the linear allylic molecules[84] (Scheme 28) and applied the method for the synthesis of acyclic phosphonate nucleoside analogs.



Scheme 28: Regiodivergent Rh- or Pd-catalyzed hydroamination with pyrimidines.

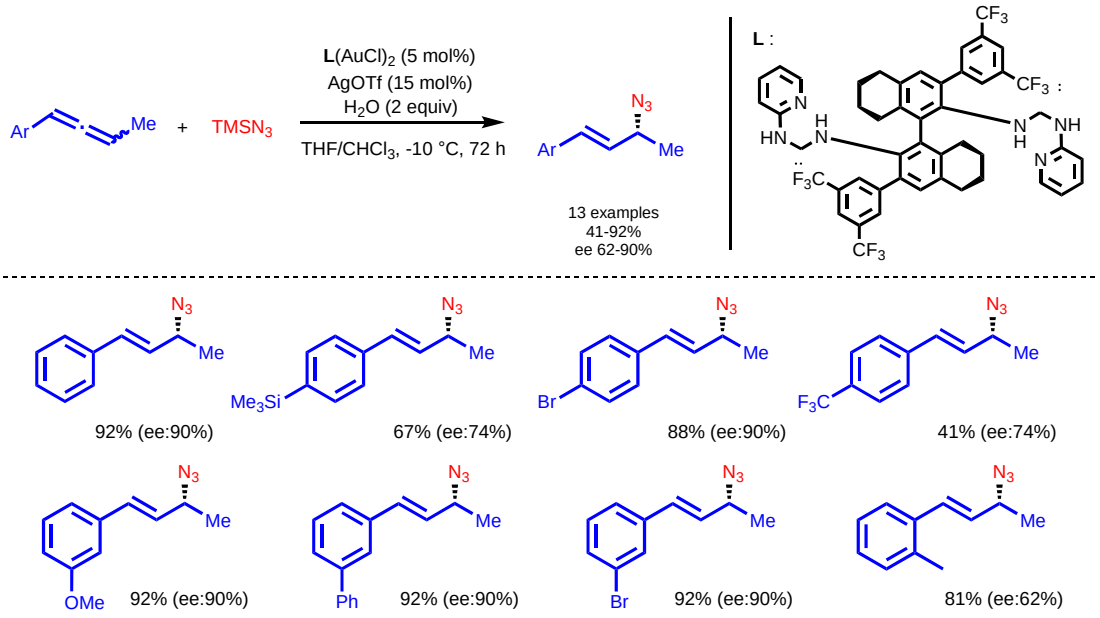
2.4. Hydroazidation

Very few examples of hydroazidation of allenes have been reported in the literature. The first method published by the group of Paz Muñoz in 2014 used a catalytic amount of $(PhO)_3PAuCl$ and AgOTf with trimethylsilyl azide ($TMSN_3$) as azido source (Scheme 29). It was applied to mono- and di-substituted allenes but with low regioselectivity as both linear and branched products were obtained.[85]



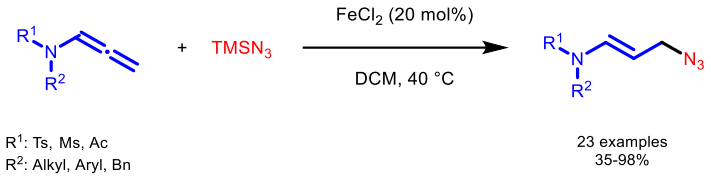
Scheme 29: Au/Ag co-catalyzed hydroazidation of disubsituted allenes with $TMSN_3$

The enantioselective gold-catalyzed process for the hydroamination with anilines described by Toste[50] (Scheme 16) was also applied for the hydroazidation of internal 1,3-disubstituted allenes using $TMSN_3$ at -10 °C. In this case, the yield and enantiomeric excess of the obtained chiral allylic azides were very good and the addition was totally regioselective on the carbon bearing the methyl group (Scheme 30).



Scheme 30: Hydroazidation of disubstituted allenes with azides derivatives catalyzed by Au.

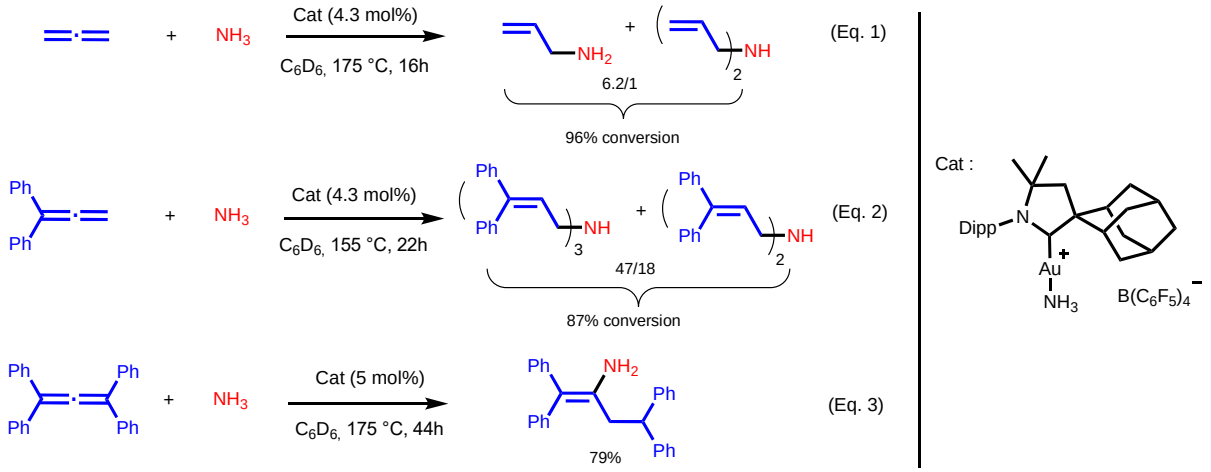
In 2020, an alternative to gold has been reported, with the publication by the group of Li and Zhao describing the catalytic use of $FeCl_2$.[86] Restricted to allenamides, this additional ligand-free catalytic system lead to the selective formation of the linear product with a good stereoselectivity (Scheme 31). This reaction constitutes the only example of hydroazidation of allenes catalyzed by iron, the latter has the advantage to be a cheap, low-toxic and abundant transition metal.



Scheme 31: Fe-catalyzed hydroazidation of allenamides.

2.5. Hydroamination with Ammonia

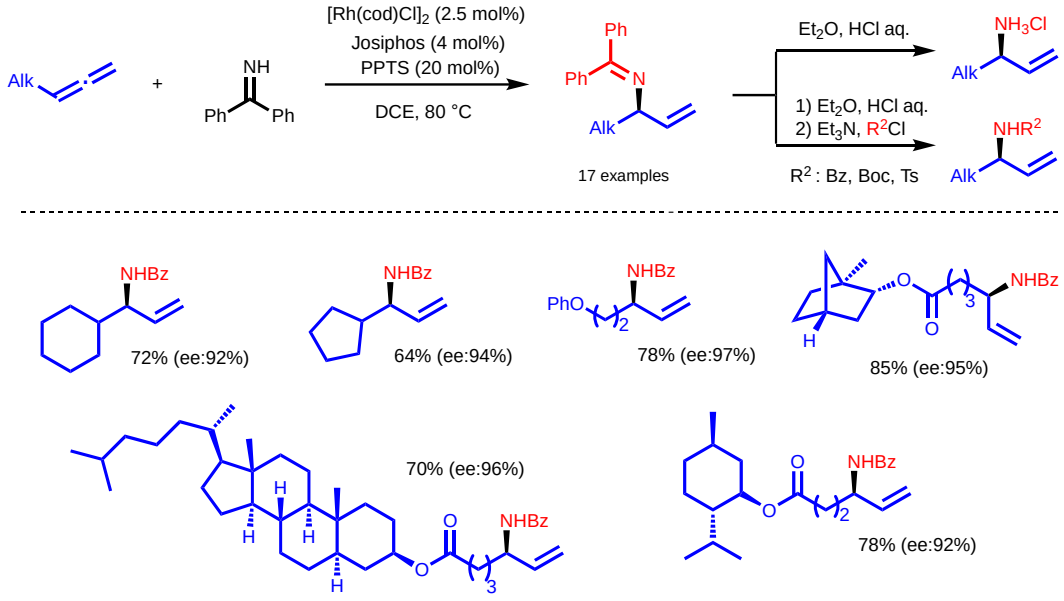
Due to its abundance and low price, ammonia is an attractive source of nitrogen. However, hydroamination reaction using ammonia is particularly challenging due to a possible poisoning of the metal catalyst through the formation of inert Werner complexes. So far, only one example has been described with allenes. Using a cationic gold(I) complex with cyclic (alkyl)(amino)carbene ligand (CAAC), Bertrand and co-workers described the only example of a catalytic addition of ammonia to allenes.[87] Starting from 1,2-propadiene, a mixture of mono-, di- and triallylamine was obtained, the proportion of which could be tuned by a variation of the ammonia/allene ratio or a modification of the catalytic charge (Scheme 32, eq. 1). The reaction was also applied to 1,1-disubstituted allenes (Scheme 32, eq. 2) and to tetra-substituted allenes (Scheme 32, eq. 3) , with a selective mono-addition of the central carbon for this last case (Scheme 32).



Scheme 32: Au(CAAC)-catalyzed hydroamination of 1,2-propandiene, di- and tetrasubsituted allenes with ammonia.

To find an alternative to ammonia and its poisoning effect, the group of Breit showed that ammonia surrogates such as imines could undergo the hydroamination of allenes (Scheme 33). Notably benzophenone imine was found to be an ideal partner with a chiral rhodium-catalytic system, giving an

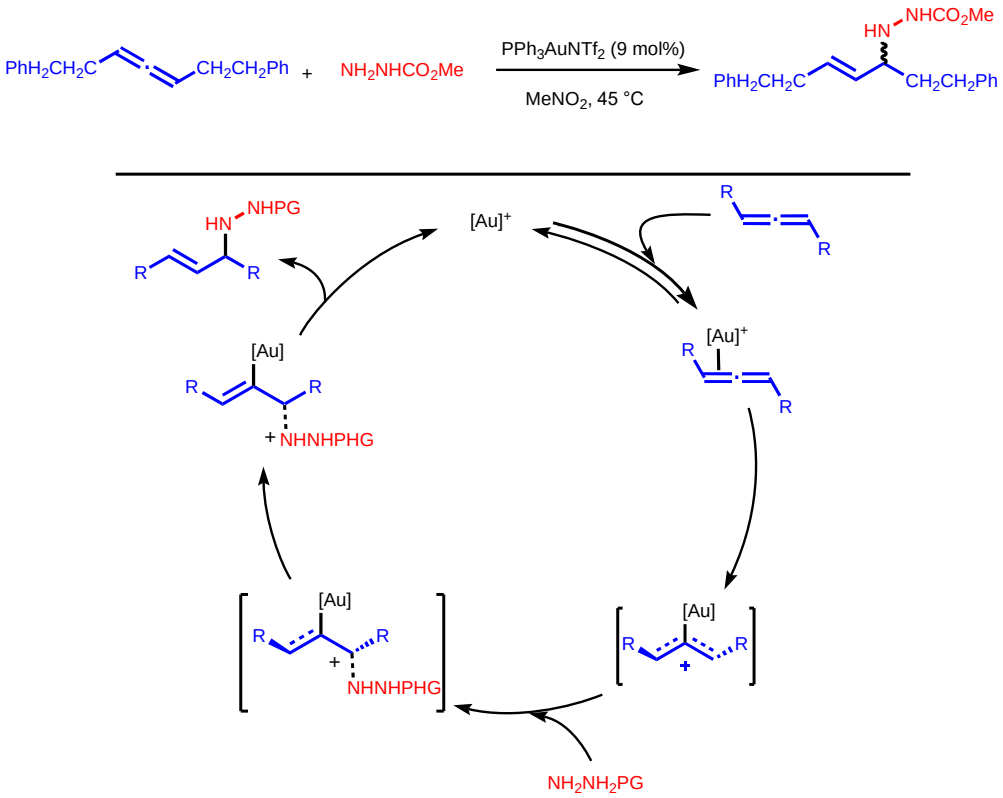
easy access to the chiral allylic ammonium salt after a simple deprotection of the imine moiety.[88] A simple acylation could also be realized to give access to the chiral allylic amide. Interestingly, several bioactive molecules bearing an allene function have been successfully engaged under these conditions and afforded enantioselectively the hydroaminated product in good yields.



Scheme 33 : Enantioselective Rh- catalyzed hydroamination of terminal allenes with benzophenonimine.

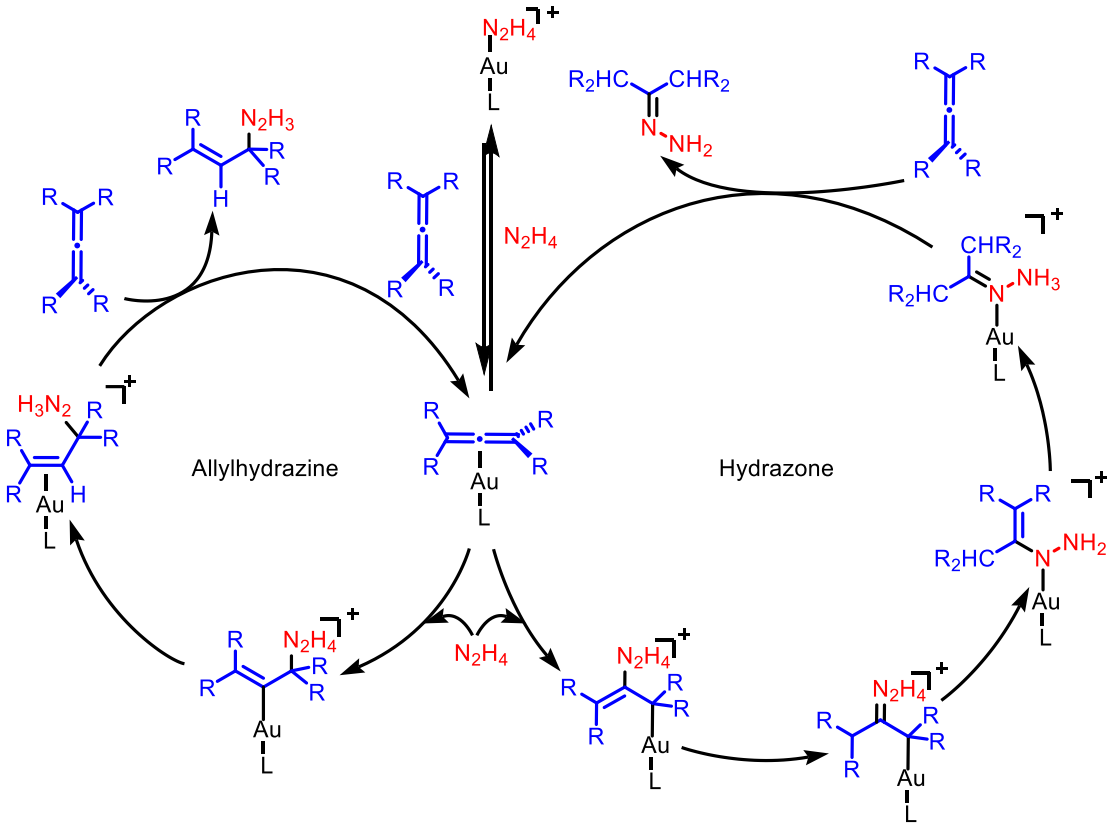
2.6. By Hydrohydrazination/Hydrohydrazidation

In 2010, Toste and co-workers reported the first addition of hydrazide to allenes using $Ph_3PAuNTf_2$ as catalyst, and methyl carbazate as a nucleophile (Scheme 34).[89] Mechanistic investigation performed with 1,7-diphenylhepta-3,4-diene, supported an outer-sphere mechanism, through a two-step no-intermediate pathway. Indeed, this mechanism would initially go through a bent allene – gold complex transition state directly involved in the outer-sphere nucleophilic addition. Using an enantioenriched allene, they also investigated the occurrence of chirality transfer process, and disclosed its highly dependency on the concentration of methyl carbazate. This shifting degree of chirality transfer suggested that even if calculations shown that the reaction proceeds through a two-step no-intermediate mechanism, a more classical two-step mechanism involving a planar intermediate is also possible. Note that the reaction was later extended to hydroazidation[50] with $H_2NNHBoc$.



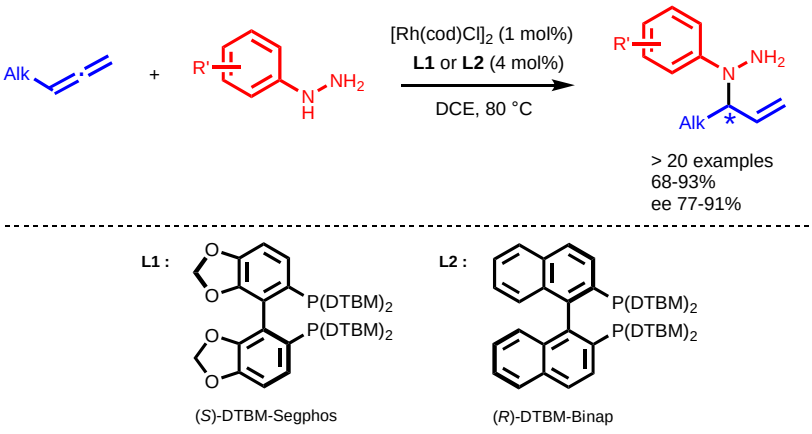
Scheme 34: Au-catalyzed hydrohydrazination of disubsituted 1,7-diphenylhepta-3,4-diene with methyl carbazate.

Using a (CAAC)Au catalyst, the group of Bertrand successfully extended the hydroamination of alkynes and allenes with ammonia[87] to the hydrohydrazination of alkynes, diynes and allenes.[90] It was shown that the outcome of the reaction catalyzed by a CAAC-Au complex was highly dependent of the substrate, giving a mixture of hydrazone and allylhydrazine with 1,2-propadiene, whereas only hydrazone was obtained with tetraphenyl-1,2-propadiene. The mechanism of this reaction was later elucidated by Ujaque and Lledós.[91] These authors emphasized that the regioselectivity of the reaction is dictated by the nucleophilic addition occurring in through an outer-sphere pathway, following coordination of the allene by the gold complex. Moreover, this attack occurring either on a terminal or central carbon of the allene, leading respectively to the formation of the allylhydrazine or the hydrazone, was shown to be highly dependent on the substitution pattern of the allene. In the case of the allyhydrazone, proton transfer, following nucleophilic addition is necessary to generate the product. On the other hand, for the hydrazone formation, a sequence of proton transfer, gold migration and a second proton transfer is necessary (Scheme 35).



Scheme 35: Suggested mechanism for the Au-catalyzed hydrohydrazination.

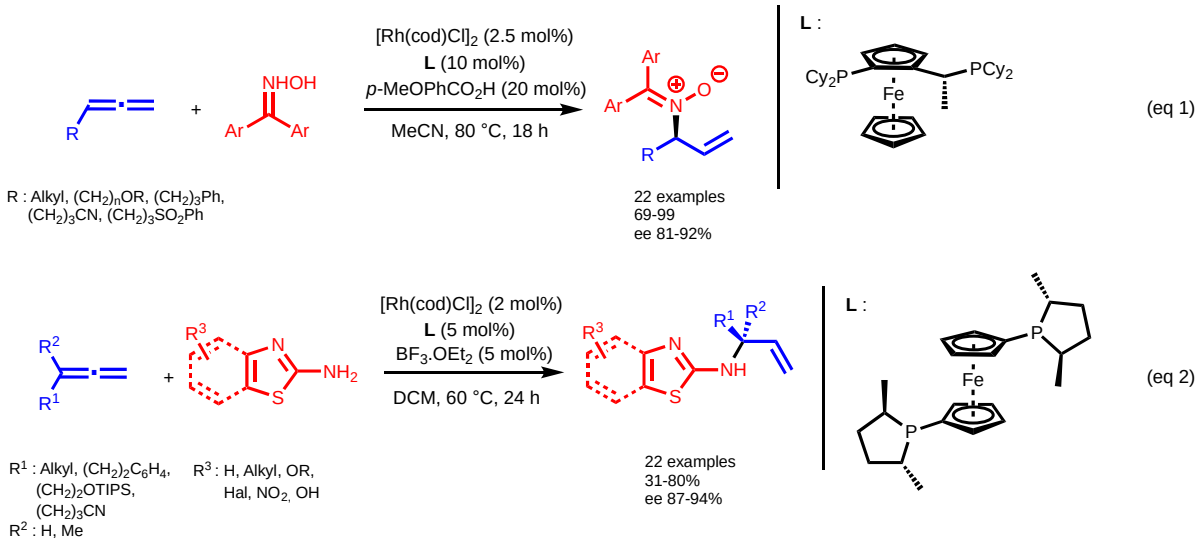
The catalytic system using dimer $[Rh(cod)Cl]_2$ combined with chiral diphosphines developed by Breit and co-workers for the hydroamination of allenes with amines also allowed the efficient addition of arylhydrazines on mono-substituted allenes.[92] This reaction proceed with good enantioselectivity, and regioselectively on the substituted α-carbon of the allene. (Scheme 36).



Scheme 36: Enantio- and regioselective Rh-catalyzed hydrohydrazination of terminal alkyl allenes with arylhydrazine derivatives.

2.7. Miscellaneous

In 2019 the group of Breit expended the scope of nucleophiles compatible with rhodium/chiral diphosphine ligand system. Thus, the addition of oximes[93] or aminothiazoles[94] occurred on the α carbon of respectively terminal mono and disubstituted allenes with excellent enantioselectivities. (Scheme 37). In these studies, chiral bisphosphine-ferrocene type ligands appeared to be the most efficient one among various bis-phosphine-type ligands.



Scheme 37: Enatioselective Rh-catalyzed addition of oximes and aminothiazoles on terminal allenes.

3. C-C Bond Formation

During the past few decades, allenes were widely used to generate C-C bonds through metal-catalyzed hydrofunctionalization processes. Starting in the end of the 80's with rare examples, this functionalization gained interest over time with the discovery of various catalytic systems usually occurring under mild conditions and with low amount of waste (Figure 2). The hydroarylation reaction was the first performed, mostly with gold-, platinum- and palladium-based catalysts. The latter was also used to add carbonated pronucleophiles, alkynes, carbon monoxide and carbon dioxide to allenes. The uses of rhodium and iridium were more specifically described for the addition of aldehydes and alcohols. Finally, hydrocyanation was exclusively reported with a nickel catalyst.

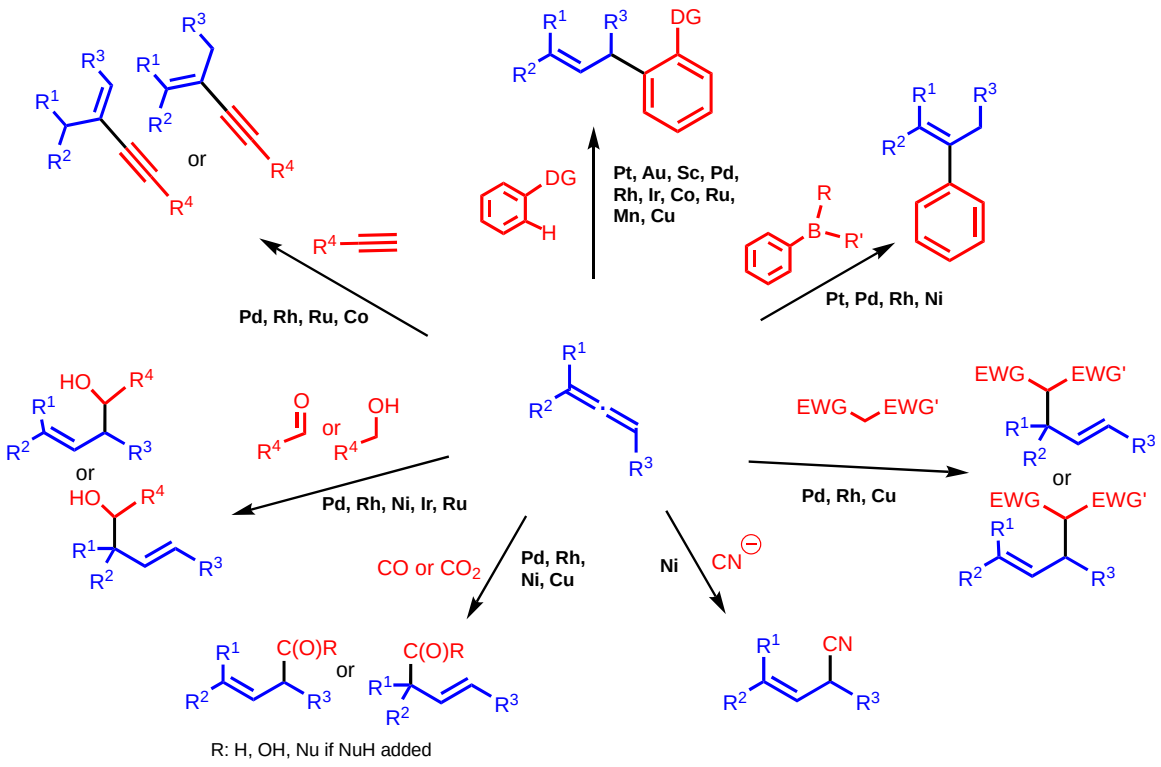
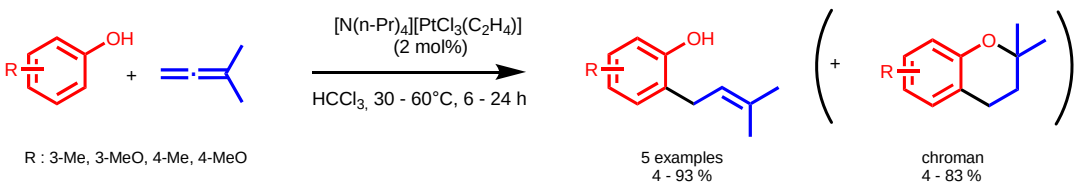


Figure 2 : Transition-metal catalyzed hydrofunctionalization of allenes for C-C bond formation.

3.1. Hydroarylation with Arenes, Aryl Boronic Acids and Aryl Halides

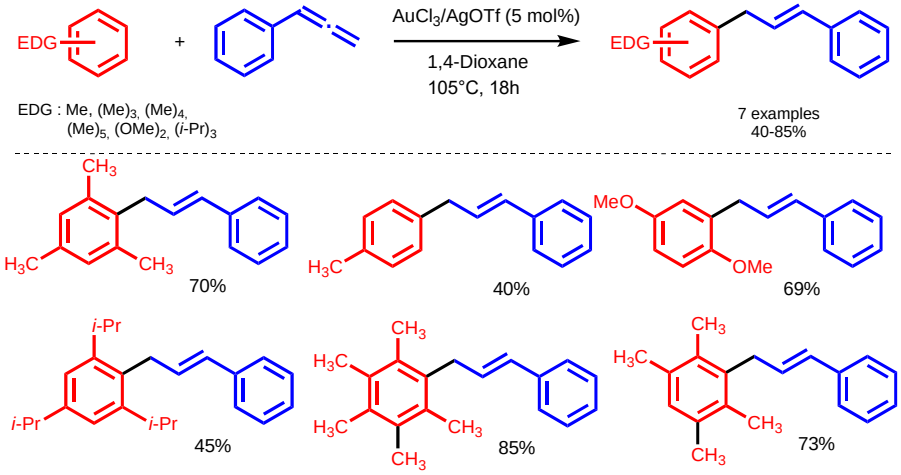
- C-H functionalization

One of the most straightforward method to generate C-C bonds via hydroarylation of allenes is the metal-catalyzed C-H functionalization of aromatic compounds. Pioneered by the group of Panunzi in 1983, performing C-H functionalization of 1,1-dimethylallene with electron enriched phenols, this reaction was performed using a platinum(II) catalyst.[95] While the regioselective *C*-alkenylation on the terminal carbon of the allene was demonstrated, a side reaction leading to chroman derivatives resulting from the cyclization of the main product was observed (Scheme 38).



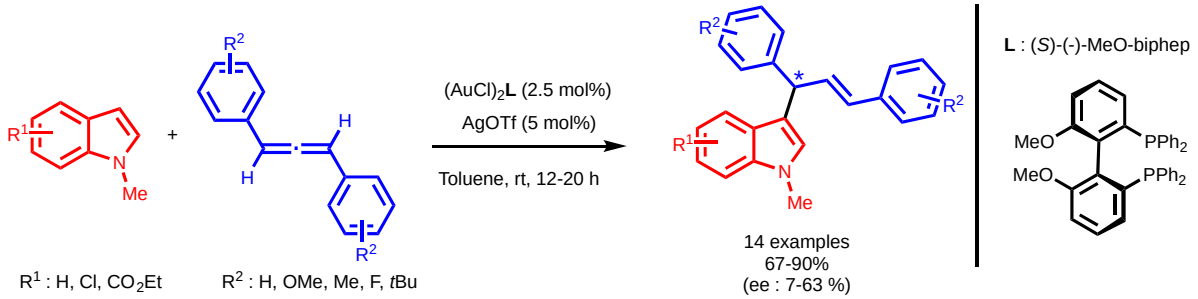
Scheme 38: Pt-catalyzed hydroarylation of 1,1-dimethylallene with electron enriched phenol derivatives.

In 2008, the group of Li reported the gold-silver co-catalyzed regioselective hydroarylation of phenylallene with electron-donating substituted benzene reagents (Scheme 39).[96]



Scheme 39: Au/Ag co-catalyzed hydroarylation of phenylallene with aryl electron enriched aryl derivatives.

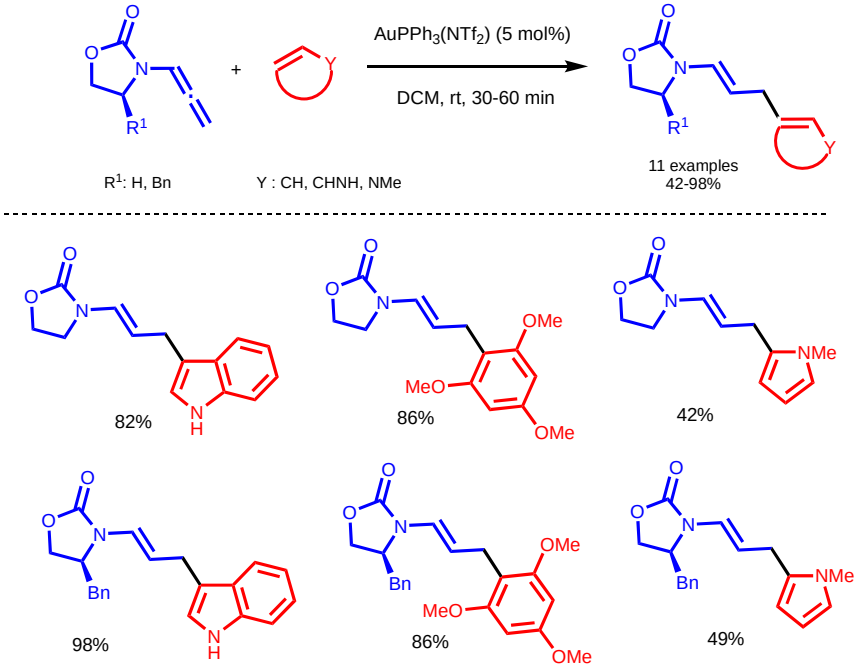
While rich heterocycles like indole did not react under the above described conditions, the group of Widenhoefer overcame this limitation with a similar Au/Ag co-catalytic system associated to NHC-ligand.[97] Their method allowed the *C*2-carbon addition of *N*-substituted indole on 1,3-disubtituted and tetra-substituted allenes with good yields. An enantioselective Au/Ag co-catalyzed hydroarylation of disubstituted allenes with N-methyl indoles was also reported by Che and co-workers but with poor enantiomeric excess (Scheme 40).[98] A mechanistic study including DFT calculations, deuterium-labelling experiments and NMR suggested that the activation of the allene by the gold catalyst was sufficient to induce a direct nucleophilic addition of the indole.



Scheme 40: Au/Ag co-catalyzed hydroarylation of disubsituted allenes with indol derivatives.

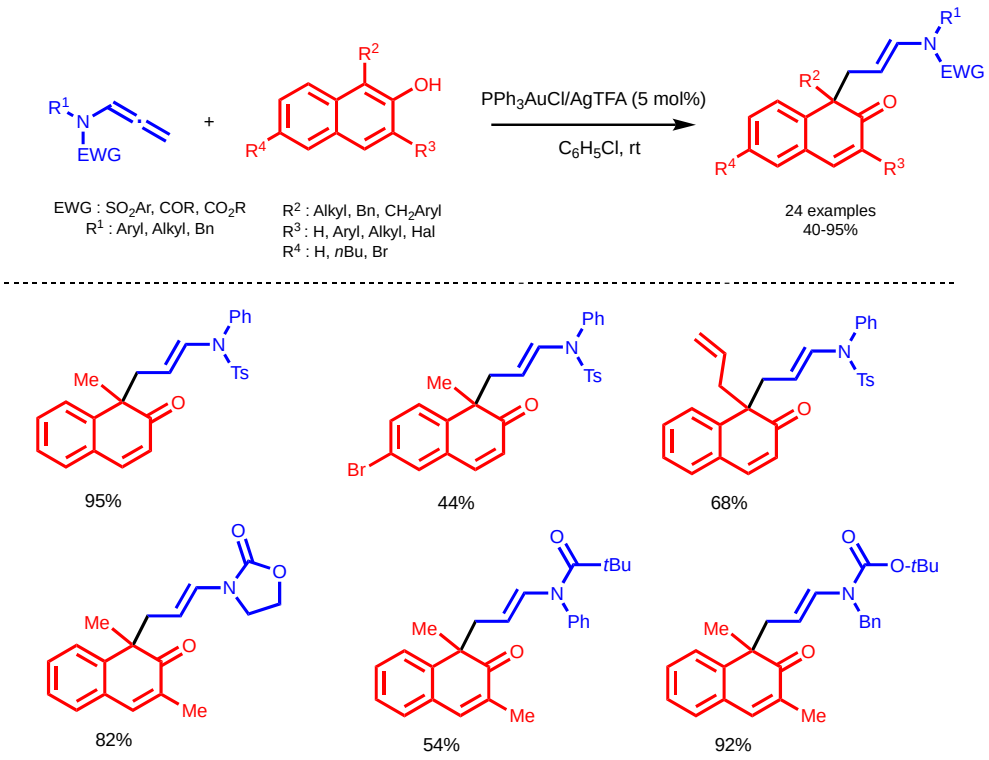
The gold-catalyzed hydroarylation of allenyl ethers with *N*-methyl indole[99] and terminal allenes with trimethoxybenzene were then reported,[100] while Kimber and co-workers applied this gold catalytic

system to cyclic allenamides, giving access to enamides at room temperature under mild conditions (Scheme 41).[48]



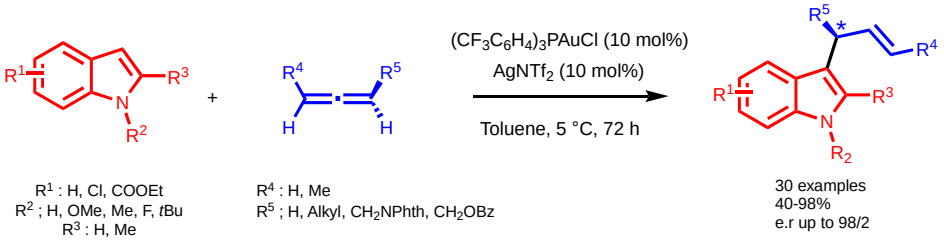
Scheme 41: Au-catalyzed hydroarylation of cyclic allenamides with electron rich (hetero)aryl derivatives.

The reactivity of allenamides towards 2,3-disubstituted indoles was successfully tested by Bandini, in a gold-catalyzed de-aromatization process.[101] The latter was strongly dependent of the counterion present on the catalyst, as later observed by NMR studies.[102] In 2018 the same group reported a de-aromatization of naphthol by addition of allenamides under gold-silver co-catalysis (Scheme 42).[103] A similar de-aromatization of naphthol with mono-substituted alkoxyallenes has been reported by the group of Zeng.[104] Using a catalytic system based on $Pd_2(dba)_3$ and chiral (R,R)-DACH-naphthyl Trost-type ligand, the reaction took place selectively on the terminal carbon of the allene, with good enantioselectivity.



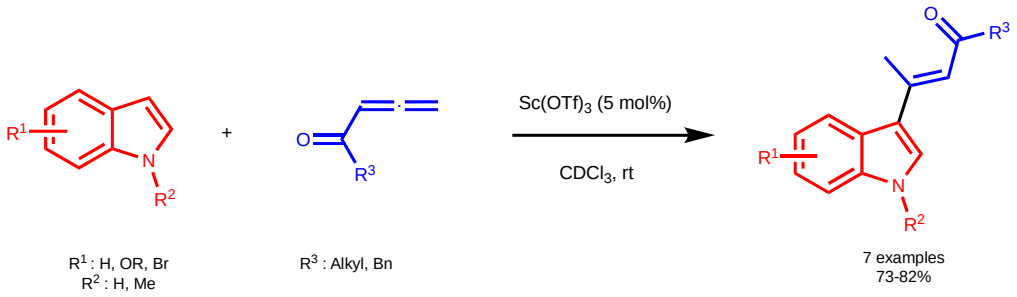
Scheme 42: Au-Ag co-catalyzed hydroarylation of allenamides via dearomatization of naphthol.

In 2018, under gold-silver co-catalysis, Lee and co-workers extended the hydroarylation of enantioenriched 1,3 disubstituted allenes with indoles derivatives with high chirality transfer (Scheme 43).[105] High enantioselectivity was achieved and use of highly nucleophilic (hetero)aryl favoured hydroarylation rather than racemization, contributing to the efficient chirality transfer.



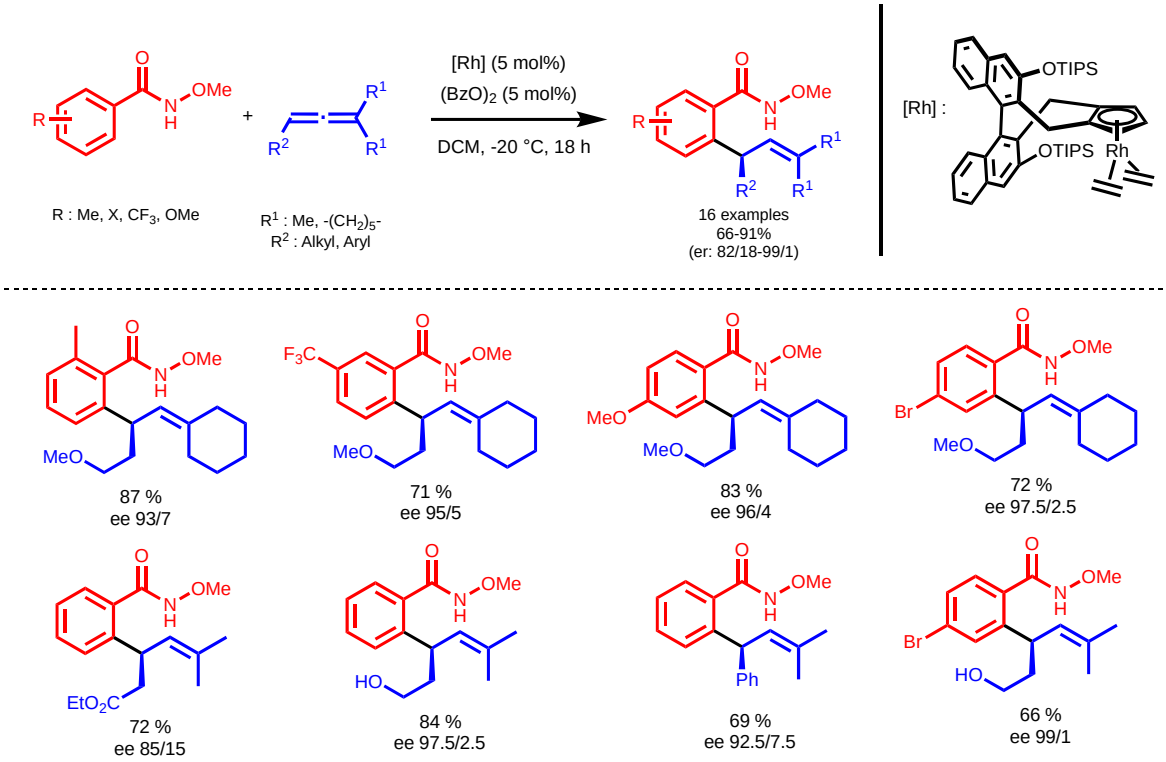
Scheme 43: Au-Ag co-catalyzed hydroarylation of enantioenriched disubstiuted allenes with indoles derivatives.

In addition to the use of gold associated to silver, other metals also proved to be able to perform hydroarylation of allenes by C-H activation. In 2005, the group of Ma reported a very simple hydroarylation of allenic ketones with indoles, catalyzed at room temperature by 5 mol% of $Sc(OTf)_3$ (Scheme 44).[106] In 2015, another scandium-catalyzed system was reported for the hydroarylation of allenes with pyridines.[107]



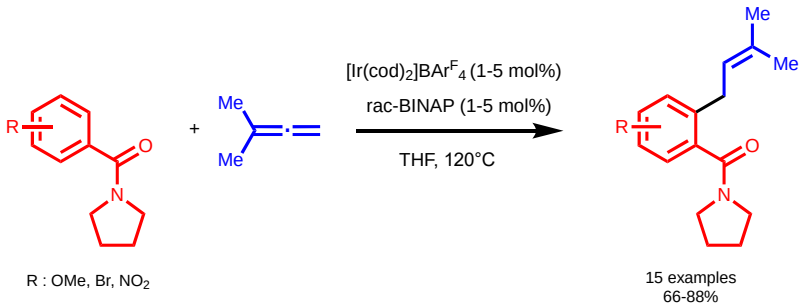
Scheme 44: Sc-catalyzed hydroarylation of 1,2-allenic ketones with indoles.

Ma et al. also published the first example involving a palladium catalyst, used for allylation of electron-rich aromatic compounds with 2,3-allenaotes,[108] and the first method with a rhodium catalyst, for the allylation of N-methoxybenzamides with allenes.[109] The use of rhodium was improved by Cramer in 2013 with the development of a specific class of a chiral cyclopentadienyl (Cp) type ligand, allowing the enantioselective hydroarylation of substituted allenes with *N*-methoxybenzamides, acting as directing group (Scheme 45).[110] The enantioselective rhodium-based system was also reported in 2017 by the group of Antonchick and Waldmann with a hydroxamate directing group and another original chiral Cp type ligand.[111]



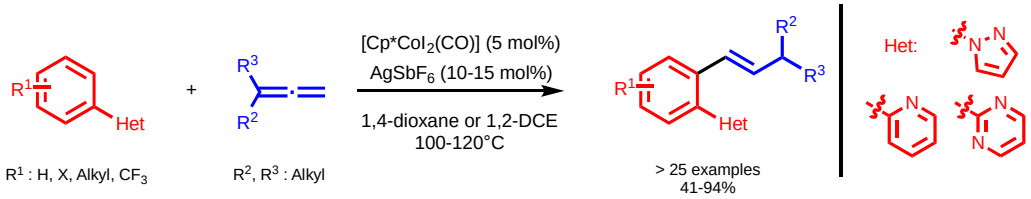
Scheme 45: Rh-catalyzed hydroarylation of allenes with benzamides.

The group of Krische reported the addition of 1,1-dimethylallene on aromatic and heteroaromatic carboxamides with an iridium catalyst (Scheme 46).[112] Proceeding at high temperature, this reaction took place through an oxidative addition/allene hydrometallation mechanism, as supported by deuterated studies.



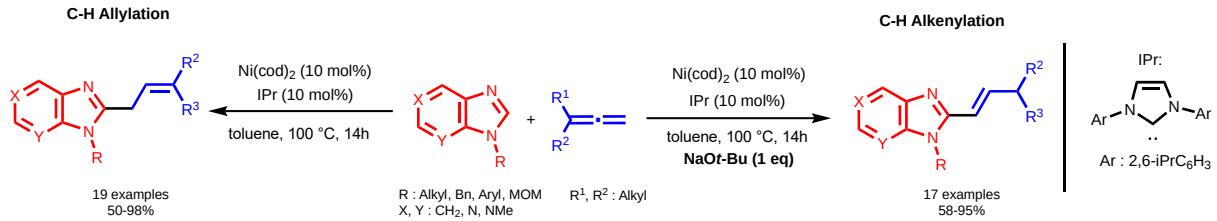
Scheme 46: Ir-catalyzed hydroarylation of 1,1-dimethylallene with aromatic carboxamides.

Ackermann and co-workers were the first to published the use of a cobalt-catalyzed system able to promote the reaction of various 1,1-disubstituted allenes with aromatic compounds.[113] These latter are substituted with nitrogen containing heterocycles (het) which played the role of directing groups (Scheme 47). Worth noting that the position of the double bond (α–β) after completion of the hydroarylation is different than the one observed (β–γ) if the catalytic system is based on iridium or rhodium.



Scheme 47: Co/Ag co-catalyzed hydroarylation of 1,1-disubstituted allenes.

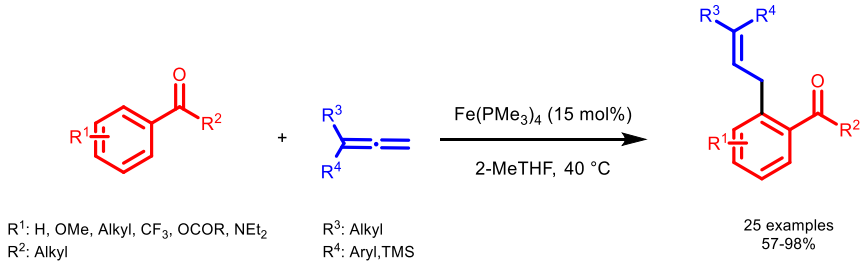
The same group reported the use of a ruthenium catalytic system mainly designed for allenylation of aromatics by a C-H functionalization, which included one example of hydroarylation of allene.[114] In 2017 they also published a nickel-based catalytic system enabled to performed C-H allylation, alkenylation and dienylation of heteroarenes, such as imidazole and purine derivatives, with terminal allenes.[115] The control of the selectivity in order to install allyl or alkenyl groups has been obtained simply by the presence or absence of a base (NaO*t*Bu) in the medium (Scheme 48).



Scheme 48: Nickel-catalyzed allene hydroarylations via C-H allylation or C-H alkenylation.

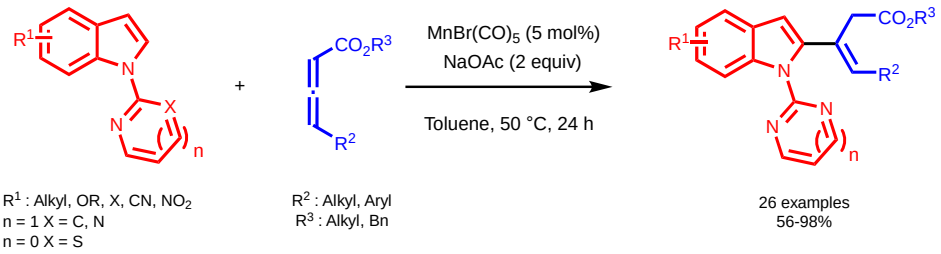
A mechanistic investigation of this C-H allylation or alkenylation was reported in 2020 by the group of Liu and Bi in order to understand its highly switchable selectivity.[116] In presence of base, this study highlighted an original Ni/NaO*t*Bu co-promoted mechanism and disclosed the crucial role of the base in the hydrogen abstraction but also in an isomerization step of the allylated product leading to the formation of the alkenylated one.

In 2020, Ackermann et al. extended their studies of hydroarylation of allenes using directing groups with the publication of an iron-catalyzed process directed by a weak O-coordination.[117] The addition occurred selectively on the *ortho*-position with high efficiency, using simple ketones as directing group (Scheme 49). During their investigations they were even able to isolate an intermediate ferracycle complex.



Scheme 49: Fe-catalyzed hydroarylation of 1,1-disubstituted allenes.

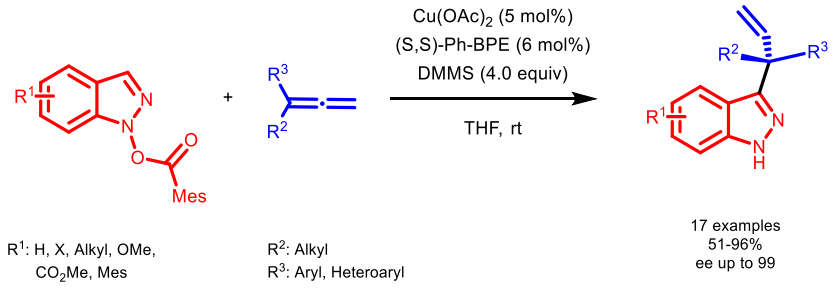
In addition to these methods, Rueping and co-workers reported the first hydroarylation of allenes catalyzed by manganese.[118] This method was applied to indole derivatives with 1,3-disubstituted allenic esters by using a catalytic amount of $MnBr(CO)_5$ (Scheme 50). A very similar system has been published for the diheteroarylation of trisubstituted allenes affording the synthesis of several bicyclic and tricyclic heterocycles.[119]



Scheme 50: Mn-catalyzed hydroarylation of allenic ester with indoles derivatives.

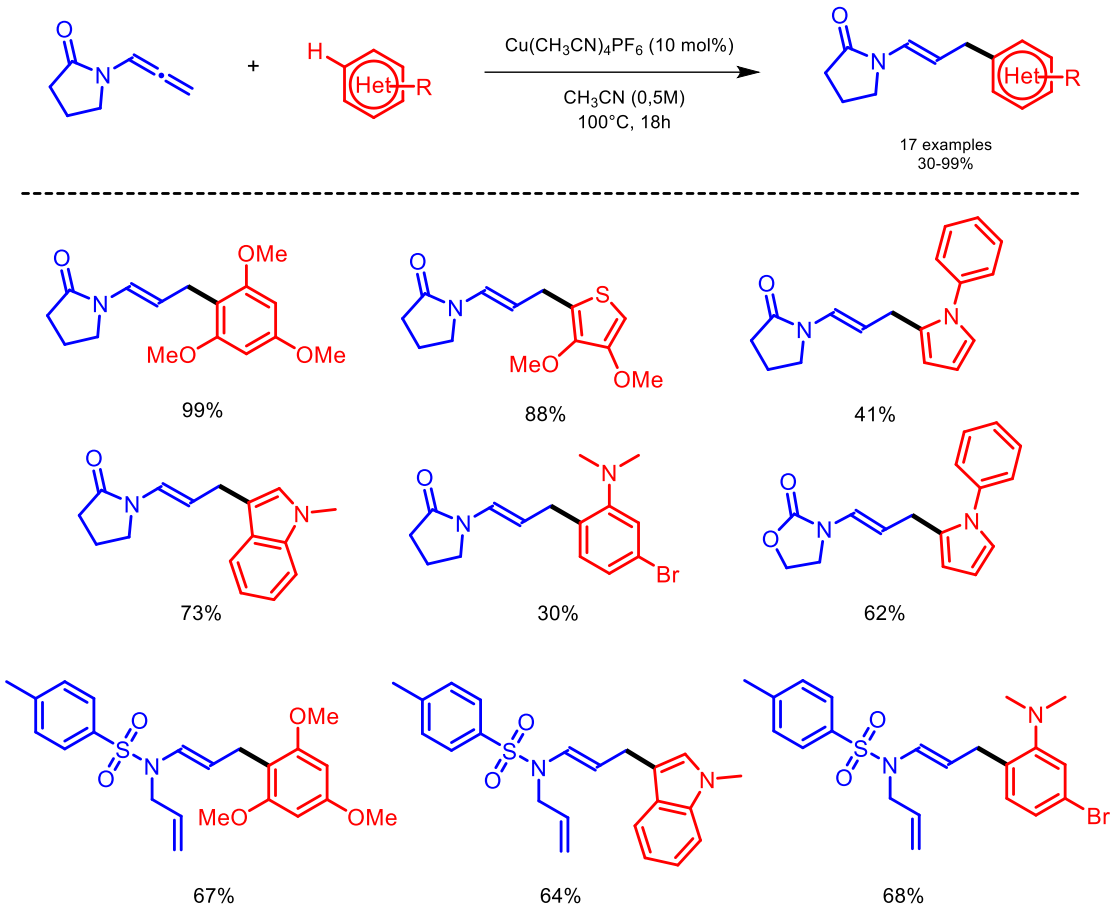
Few month later, a similar catalytic system was reported by Wang and co-workers for the allylation of indoles with various 1,1-disubstituted terminal allenes.[120]

In 2020, the groups of Liu and Buchwald reported a C-H activation process involving a copper-hydride catalyst for the hydroarylation of 1,1-disubstituted allenes with an original electrophilic indazole reagent.[121] The reaction took place on the α-position of the allene, and the use of a chiral diphosphine ligand has made possible the direct formation of *C3*-allyl indazoles bearing quaternary center with excellent enantioselectivity (Scheme 51).



Scheme 51: Cu-catalyzed hydroarylation of allenes with indazole.

In the meantime, our group described a copper-catalyzed arylation of terminal allenes.[122] Starting from electron-rich arenes, this method allowed the regio- and stereoselective C-H functionalization of mono-substituted N-allenyl derivatives for the synthesis of poly-substituted arene and heteroarenes such as thiophene, pyrrole, indole and anilines (Scheme 52).



Scheme 52: Cu-catalyzed hydroamination of allenamides.

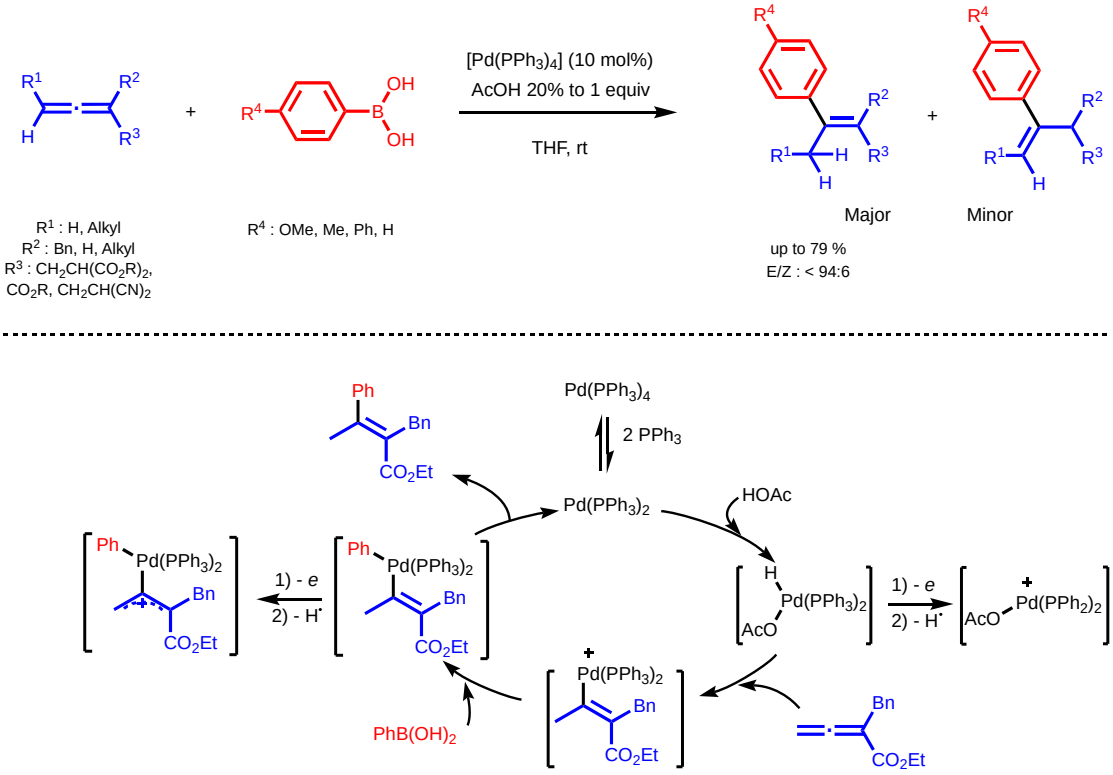
- Addition of Boronic acid

As an alternative to hydroarylation by C-H functionalization, several metal-catalyzed methods using organoboronic compounds as nucleophile were reported.

The most common catalyst used for this reaction is based on palladium. The pioneering work was reported by Ma, using 10% of $Pd(PPh_3)_4$ and acetic acid to perform the regio- and stereoselective addition of various phenylboronic acid to mono-, di- and tri-substituted allenes (Scheme 53).[123] On the same period, the group of Oh reported a quite similar catalytic system using 3% of $Pd(PPh_3)_4$, in presence of 10% of acetic acid applied to mono- and di-substituted allenes.[124]

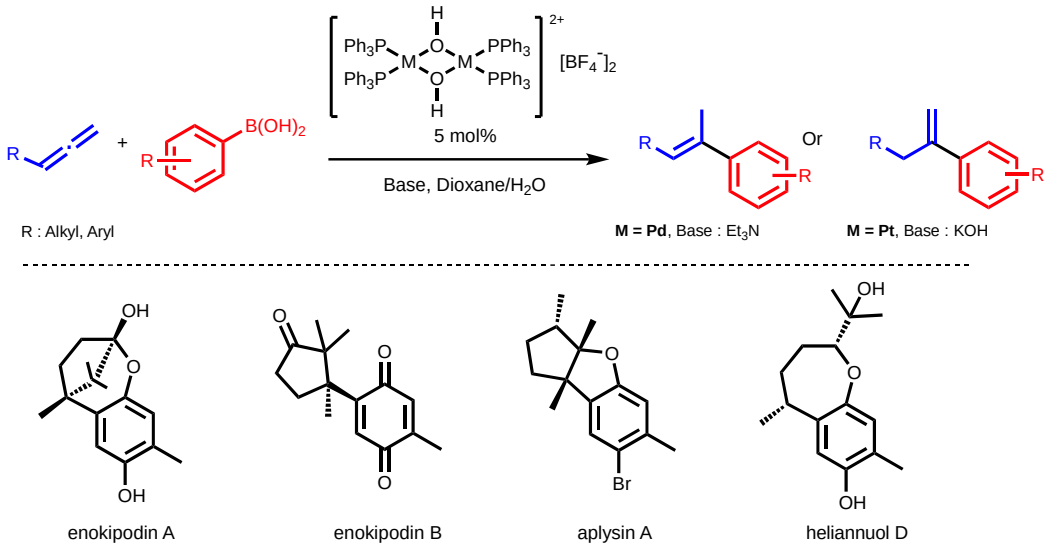
In order to investigate the mechanism of the reaction, Ma published a study based on mass spectrometry.[125] This work, performed with the group of Guo, postulated the generation of a palladium hydride species by the oxidative addition of organoboronic acid and Pd(0) as the first step of the mechanism, then they showed the formation of key cationic π-allyl intermediate, probably formed by

oxidation and elimination of a hydrogen of a (η^3-allyl)palladium complex, during the analysis process (Scheme 53). They also extended the method to 1,2-allenylphosphonates, 1,2-allenic sulfones and sulfoxides.[126]



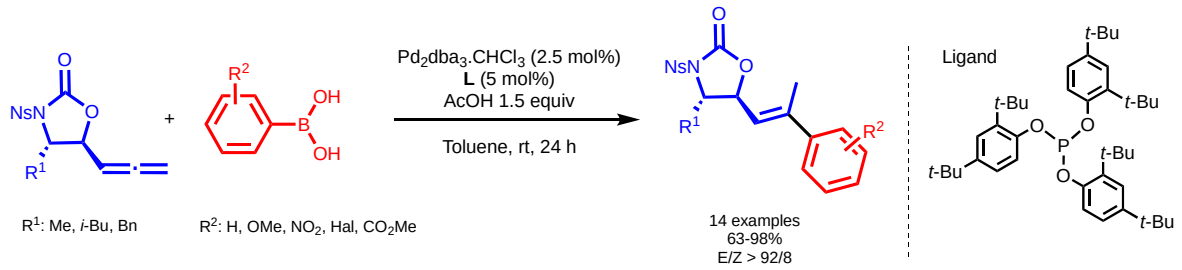
Scheme 53: Hydroarylation of allenes with aryl boronic acids and mechanistic studies.

Alternatively, the group of Yoshida and Shishido reported the use of hydroxyplatinum and hydroxypalladium complexes for the arylation of terminal allenes with various aryl boronic acids, giving the opportunity to control the position of the formed double bond on the final product (Scheme 54).[127] Pd-based catalysts enable the formation of the internal insaturation while platinum dimer catalyst allowed preferentially the terminal double bond. The same authors applied these conditions for the total synthesis of bioactive compounds: Enokipodins A and B,[128] Aplysin A,[129] and Heliannuol D (Scheme 54).[130]



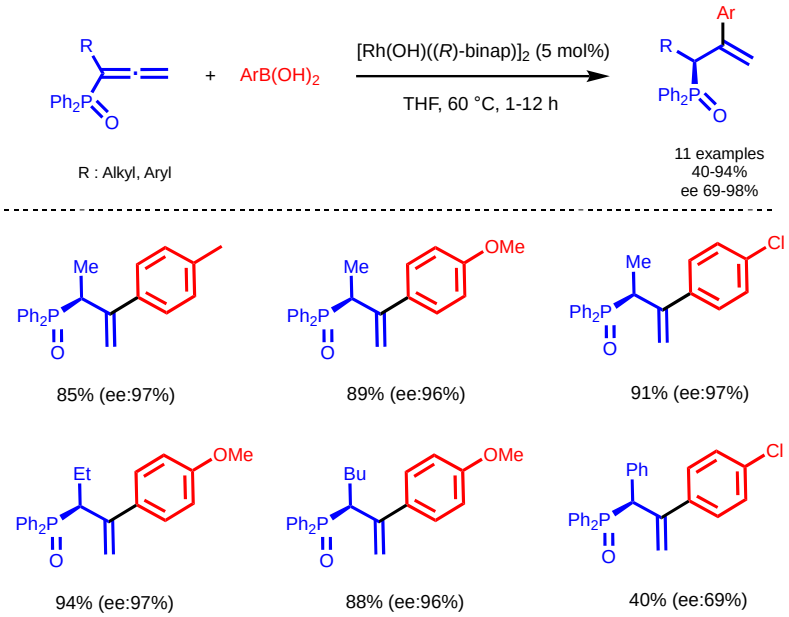
Scheme 54: Hydroarylation of allenes with aryl boronic acids by Pt- and Pd-catalysis assistance.

In 2019, investigating the reactivity of enantioenriched 5-allenyloazolidinones, the group of Hyland reported their palladium(0)/phosphite-catalyzed coupling with boronic acid derivatives.[131] This reaction gave a direct access to 5-vinyloxazolidinones which are valuable building block to construct bioactive scaffolds (Scheme 55).



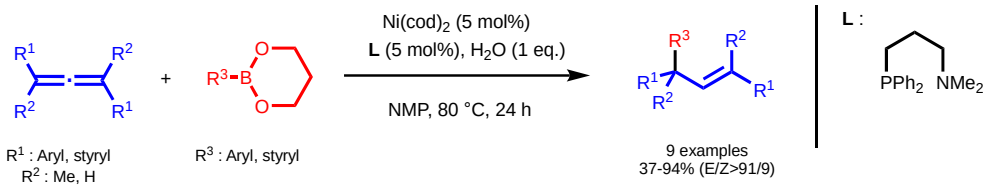
Scheme 55: Pd(0)-catalyzed hydroarylation of allenyloxazolidinones with arylboronic acids.

Using a palladium precatalyst and sodium hydroxide as additive under an atmosphere of oxygen, the hydroarylation with arylboronic acids was extended to di- and trisubstituted diphenylphosphorylallenes by Zhou.[132] The reactivity of phosphorus containing allenes with arylboronic acids has also been described by the group of Hayashi in an asymmetric way with a rhodium/BINAP-based catalytic system (Scheme 56).[133] Chiral allylic phosphine oxide which are interesting potential ligands were obtained with good yields.



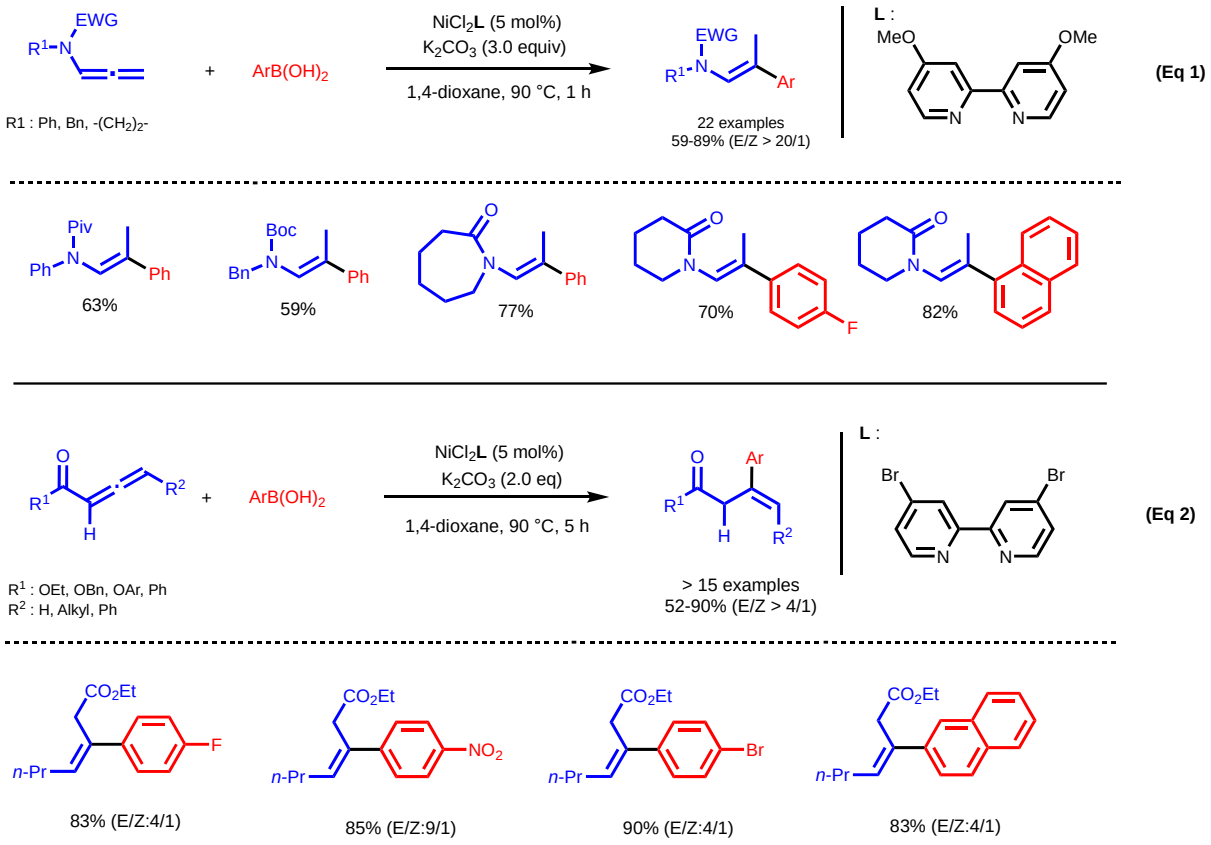
Scheme 56: Asymmetric hydroarylation of (P)-allenes with aryl boronic acids by Rh-catalysis.

Finally, nickel-based catalytic system also demonstrated their efficiency for hydroarylation of allenes with boronic acids and esters. The first nickel-catalyzed addition of aryl- and styryl-boronic esters to allenes was reported by the group of Shirakawa.[134] This system was efficient and highly stereoselective on multi-substituted allenes and occurred with $Ni(cod)_2$ as catalyst and a simple bidentate P-N ligand (Scheme 57).



Scheme 57: Ni-catalyzed hydroarylation of allenes with aryl- and styryl boronic esters.

The group of Bandini also used a nickel catalyst with bipyridine-type ligand to perform the arylation of allenamides with aryl boronic acids (Scheme 58, Eq. 1).[135] The mechanism of this reaction has been further investigated and the reactivity was extended to methylation and three-component reactions.[136] Same authors also adapted these conditions in order to use allenoates and prepare β,γ-unsaturated β-arylated esters with excellent yields (Scheme 58, Eq. 2).[137]

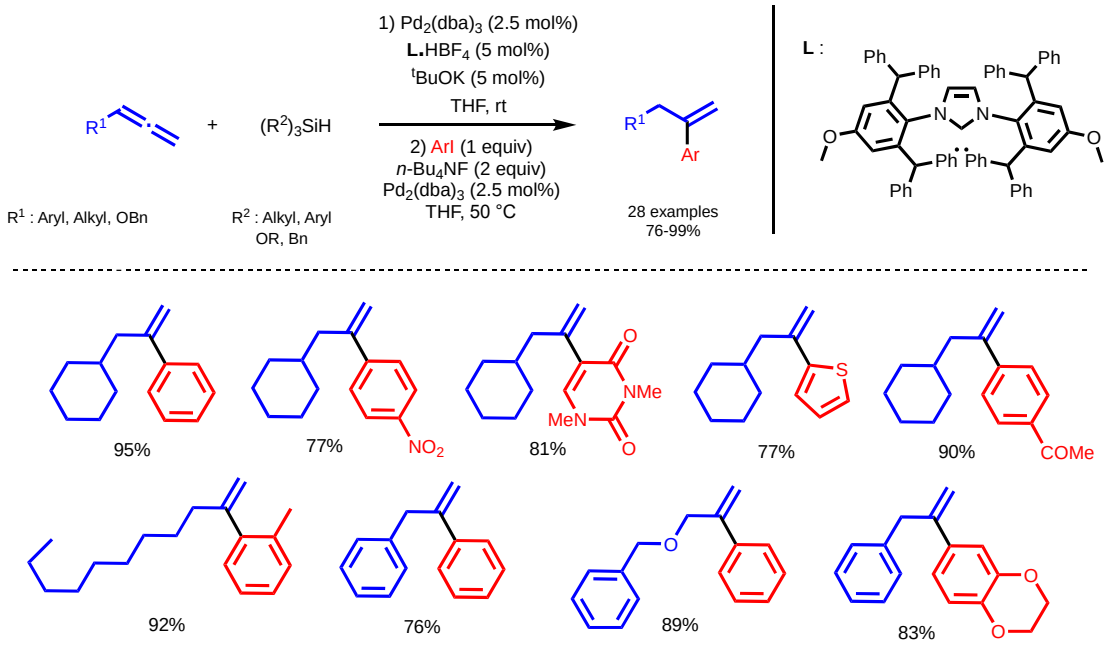


Scheme 58: Ni-catalyzed hydroarylation of allenamides and allenoates with boronic acids.

- Addition of aromatic halides

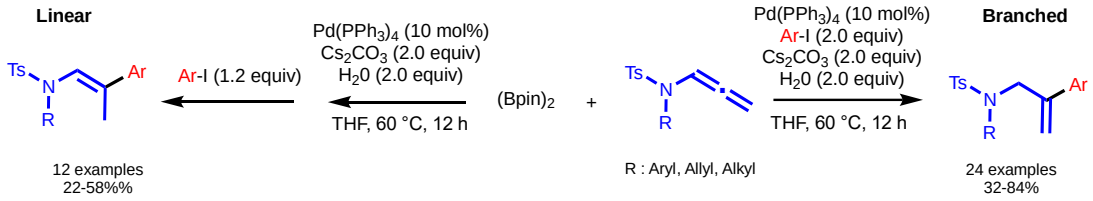
In addition to the hydroarylation of allenes by C-H activation or with organoboronic compounds, some examples involving aryl halides as aromatic coupling partners were also reported.

The first one was presented by the group of Tsuji, describing the palladium-catalyzed addition of aryl halides (I or Br) or alkenyl bromides on allenes, with a double bond migration or a subsequent amination.[138] The use of aryl halides was also reported by Larock in a reaction catalyzed by $Pd(OAc)_2$ or $Pd(dba)_2$ and involving a carboannulation[139] or a heteroannulation.[140] The hydroarylation of allenes was also reported by Montgomery. In a one-pot procedure, a palladium-catalyzed hydrosilylation of mono-substituted allenes was performed regioselectively in the presence of a bulbky NHC-type ligand, followed by a cross-coupling reaction between the obtained silane and aryl iodide derivatives.[141] This tandem reaction allowed the addition of the silane on the central carbon of the allene and gave the formation of 1,1-disubstituted alkenes in excellent yields (Scheme 59).



Scheme 59: Pd-Catalyzed hydroarylation of allenes via the intermediate formation of silanes.

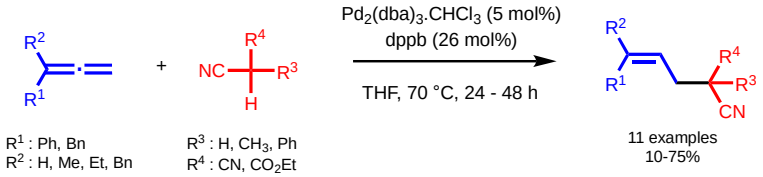
In 2019, another use of palladium as catalyst was reported for the hydroarylation of *N*-allenyl sulfonamides with aryl iodides.[142] This catalytic system was relying on a borylation-arylation strategy, and interestingly, the position of the obtained double bond can be modified using a one-pot or a sequential procedure (Scheme 60) giving access to both linear vinylic and branched allylic amines.



Scheme 60: Pd-catalyzed hydroarylation of N-allenyl sulfonamides: Access to linear vinylic amines and branched allylic amines.

3.2. By hydrocarbonation with carbon pronucleophile

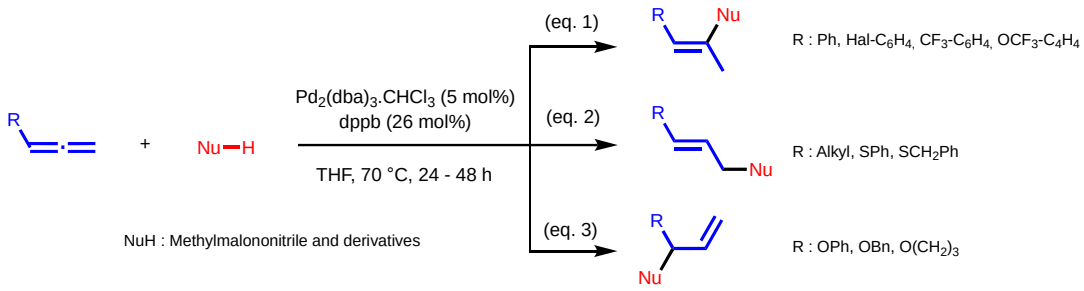
Parallel to the addition of aromatic moieties, the addition of carbon pronucleophiles such as dicarbonyls compounds and derivatives has been widely described. The first example was published by Yamamoto in 1994.[143] Using $Pd_2(dba)_3.CHCl_3$ and dppb as ligand, the addition of activated methylene and methyne compounds to mono- and 1,1-disubstituted allenes was performed with a regiodivergentselectivity (Scheme 61).



Scheme 61: Pd-catalyzed addition of methyne and methylene derivatives with allenes.

Later, the group of Trost used an allylpalladium chloride dimer as catalyst associated to diverse bidentate ligands to perform a similar reaction with mono- or 1,3-di-subsituted allenes and bis(benzenesulfonyl)methane or methylated Meldrum's acid.[144] Simultaneously, Cazes reported the addition of malonates and β-ketoesters to monosubstituted allenes by a palladium-catalyzed process.[145]

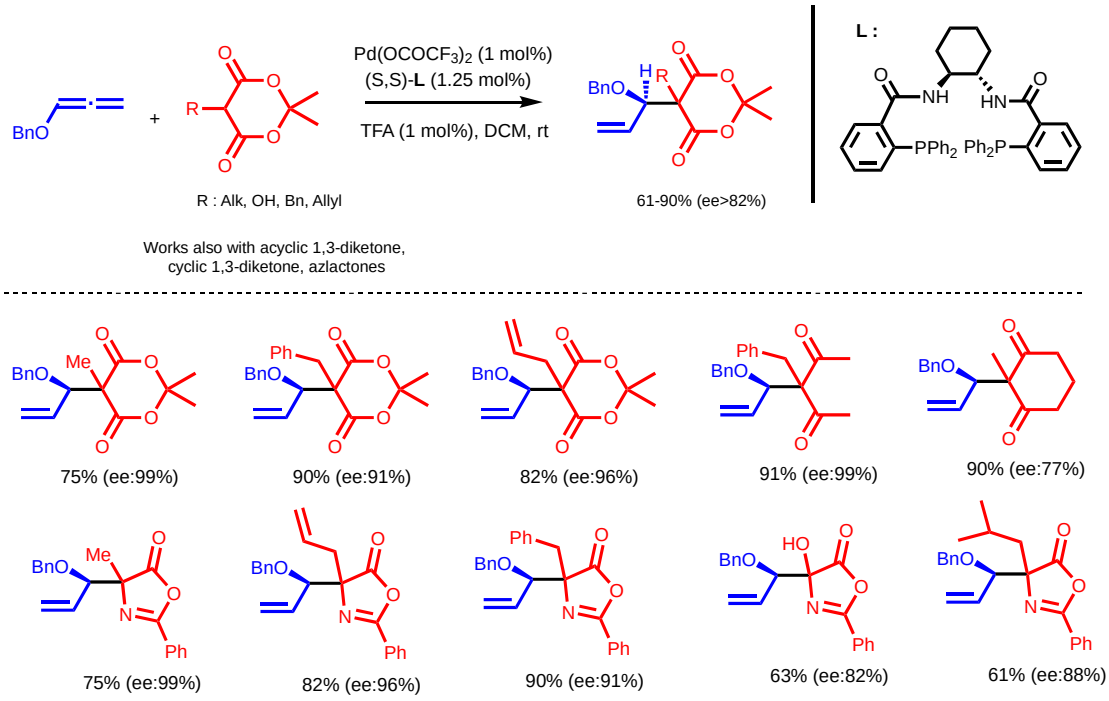
Pursuing their investigations on the hydrofunctionalization of allenes with methylmalononitrile and derivatives, the group of Yamamoto noticed that aliphatic carbon-based allenes and allenyl sulfides underwent addition of the pronucleophile on the γ carbon (Scheme 62, eq. 2), while the reaction with alkoxyallenes occurred exclusively on the α carbon (Scheme 62, eq. 3).[146–148] Besides, when arylallene derivates were used, both additions on the carbon β and γ were observed (Scheme 62, eq. 1).



Scheme 62: Influence of the nature of the allene for the regioselectivity of the addition.

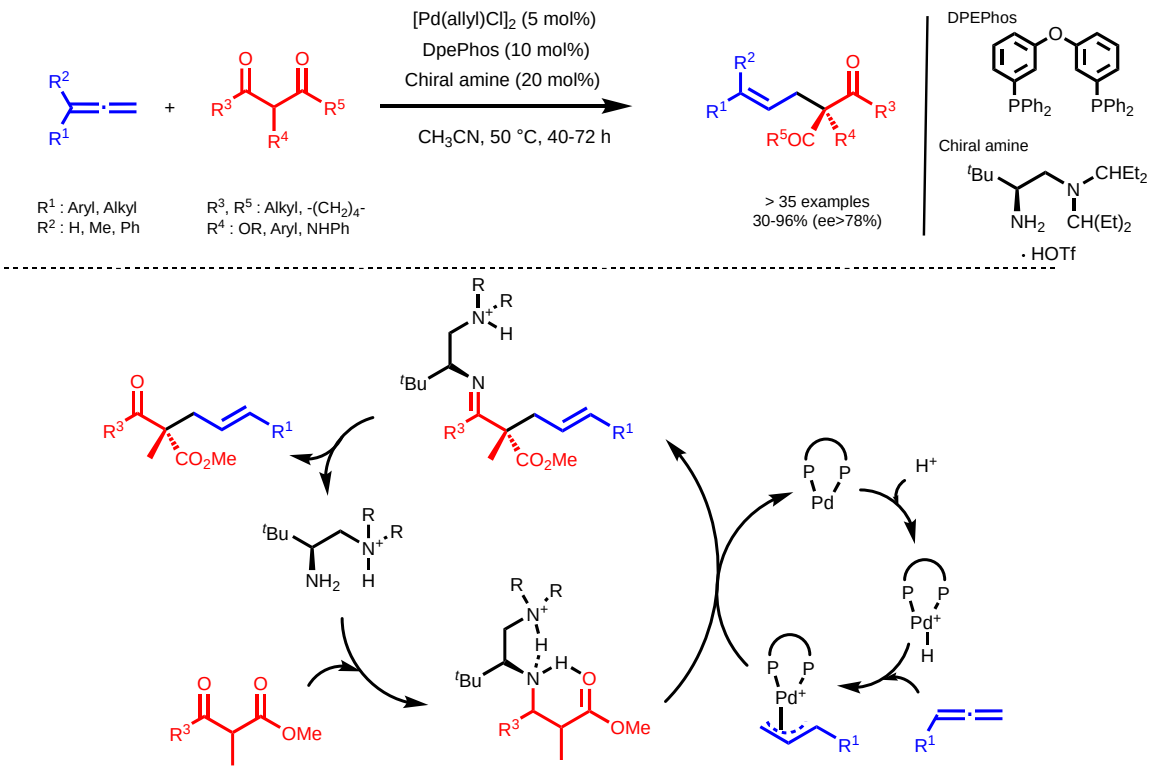
The authors suggested that in the case of alkoxyallenes, the alkoxy group stabilizes positive charge formed at the α-position, thereby enhancing the electrophilicity of this carbon α. On the other hand, a sulfur containing substituent may destabilizes such a positive charge and promotes addition on the γ-position. Finally, regarding allenes bearing an aromatic group, a cumulative influence of electronic effect of the substituents on the aromatic rings and a steric effect due to the structure of the methylmalononitrile derivative may dictate the regioselectivity. These studies also led to the publication of a novel system, using $Pd(PPh_3)_4$, and adapted for the addition of malonate-type pronucleophiles.[149]

Trost and co-workers reported the first enantioselective addition of pronucleophile on terminal alkoxyallenes, performed in presence of a palladium/DACH-phenyl ligand system. The method, regioselective on the α carbon, was first limited to Meldrum's acid (Scheme 63) and was later extended to more general 1,3-dicarbonyl compounds such as acyclic and cyclic 1,3-diketone and azalactones.[150,151]



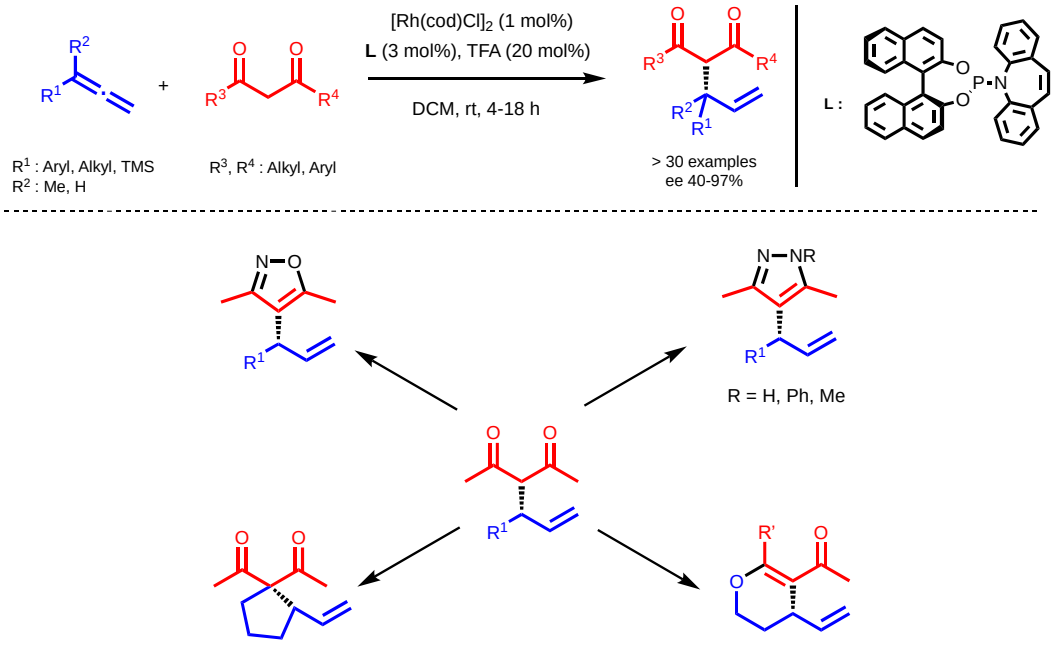
Scheme 63: Pd-catalyzed regio- and enantioselective addition of alkoxyallenes with 1,3-dicarbonyl compounds.

In 2017, the group of Luo described the enantioselective terminal addition of β-ketocarbonyls and aldehydes to 1,1-disubstituted allenes, performed in the presence palladium precatalyst coupled with a chiral amine and a diphosphine type ligand (Scheme 64).[152] In terms of mechanism, palladium is supposed to activate the allene to allow the formation of an allyl-palladium species. The latter is able to couple with the enamine intermediate, resulting from the condensation of the ketoester and the chiral amine, and then liberate the product after hydrolysis.



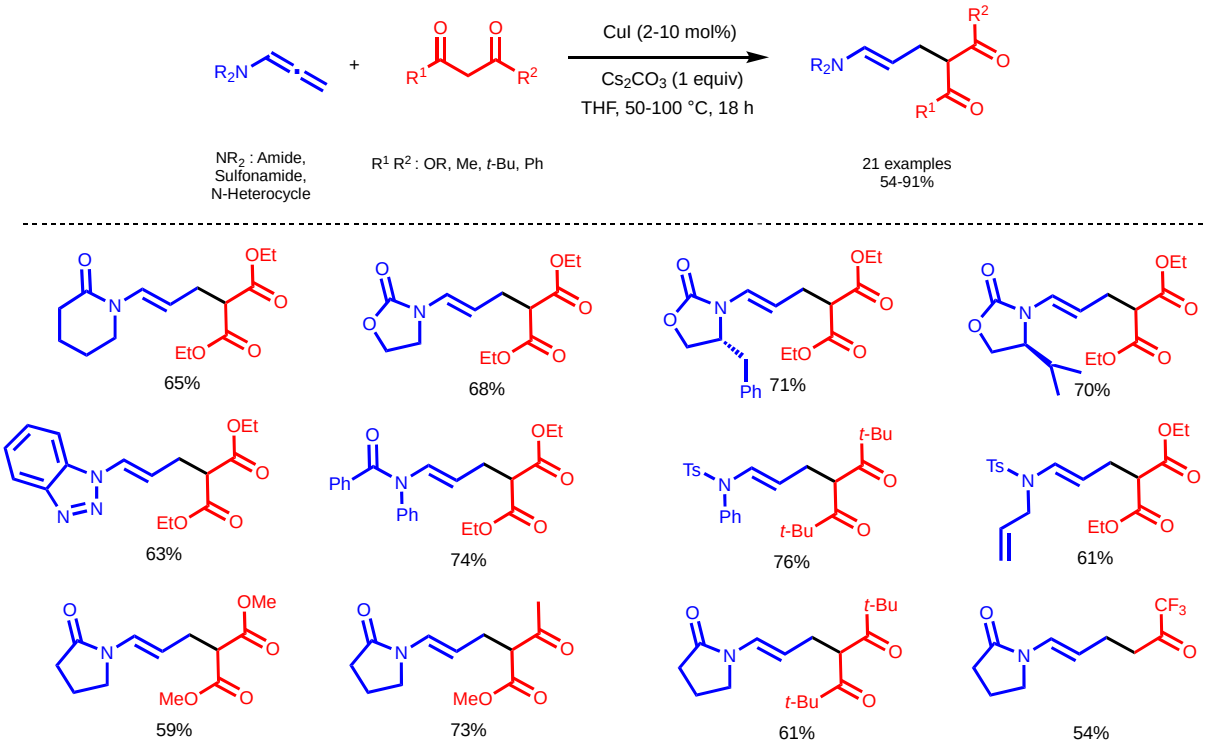
Scheme 64: Pd(chiral amine)-catalyzed enantioselective addition of mono and 1,2-disubstituted allenes with 1,3-dicarbonyl compounds.

As an alternative to palladium, the group of Breit developed a rhodium/phosphine based catalytic system. The method involves β-ketoacids and mono- and disubstituted terminal allenes to produce γ,δ-unsaturated ketones via a regioselective C-C bond formation occurring with a decarboxylative process.[153] The same catalytic system associated with a chiral phosphorous ligand was also used to performed the enantioselective addition of 1,3-diketones on terminal allenes with moderate to excellent enantioselectivity (Scheme 65).[154] The authors showed that obtained chiral 1,3-diketones could be useful for the synthesis of various heterocycles or others carbocycles without loss of the enantiomeric excess.



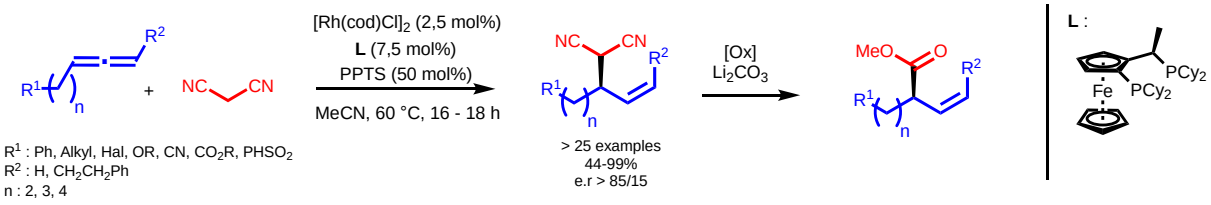
Scheme 65: Enantioselective addition of allenes with 1,3-dicarbonyl compounds catalyzed by rhodium.

In 2018 our group developed for the first time the use of a copper-based catalytic system for the allylation of 1,3-dicarbonyl compounds starting from terminal allenamides. As low Cu(I) loading allows the regio- and stereoselective formation of the desired product, the method offers an efficient and cheap alternative to the systems based on precious metals such as palladium and rhodium. (Scheme 66).[155] Noteworthy, malonitriles derivatives did not react under these conditions.



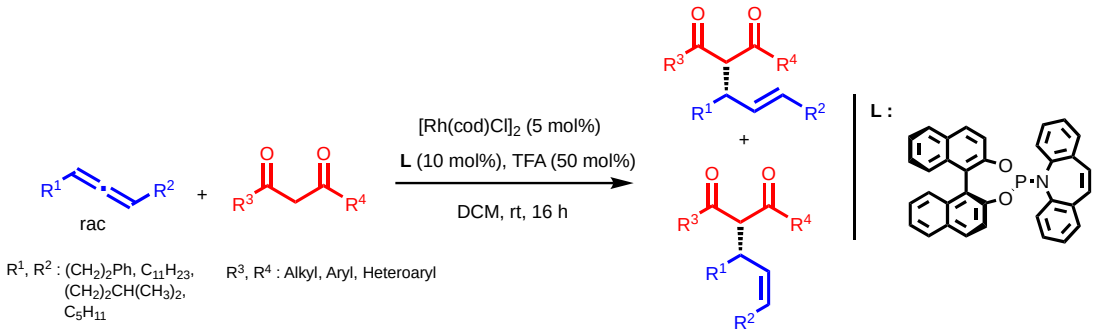
Scheme 66: Cu-catalyzed allylation of 1,3-dicarbonyl compounds with allenamides.

The same year, the group of Breit employed malonitrile as dicarbonyl compounds, and performed allylation with a rhodium/Josiphos-type ligand catalyst with excellent enantioselectivity (Scheme 67).[156] The reaction scope was quite large and tolerated many functionalities on the starting 1,3- disubstituted allenes. Furthermore, authors performed oxidative cleavage of the synthetized substituted malonitriles to obtain β-γ-unsaturated methyl esters.



Scheme 67: Rh-catalyzed enantio allylation of malonitriles.

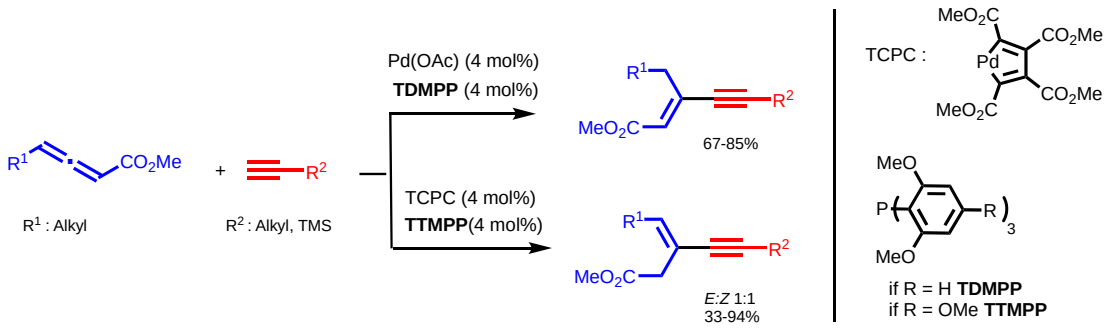
The same group proposed in 2019 an efficient kinetic resolution of racemic internal allenes for synthesis of enantiopure allylic diketones thanks to a combination of rhodium precatalyst and chiral phosphine of phosporamidite type. (Scheme 68).[157]



Scheme 68: Rhodium-catalyzed synthesis of enantiopure allylic diketones by kinetic resolution from 1,3-disubstituted allenes.

3.3. By Addition of Alkynes, Alkenes and Alkanes

The hydroalkynylation of allenes to give the corresponding enynes is rather rare in the literature. This reaction has been described firstly by the team of Trost in 1990 with a palladium catalytic system and 1,1-di- and 1,1,3-trisubstituted allenes.[158] Using palladium acetate with tris(2,6-dimethoxyphenyl)phosphine (TDMPP) or alternatively tetrakis(carbomethoxy)-palladacyclopentadiene (TCPC) with tris(2,4,6-trimethoxyphenyl)phosphine (TTMPP) selectively allowed the synthesis of enynes with a total inversion of the double bond position (Scheme 69).

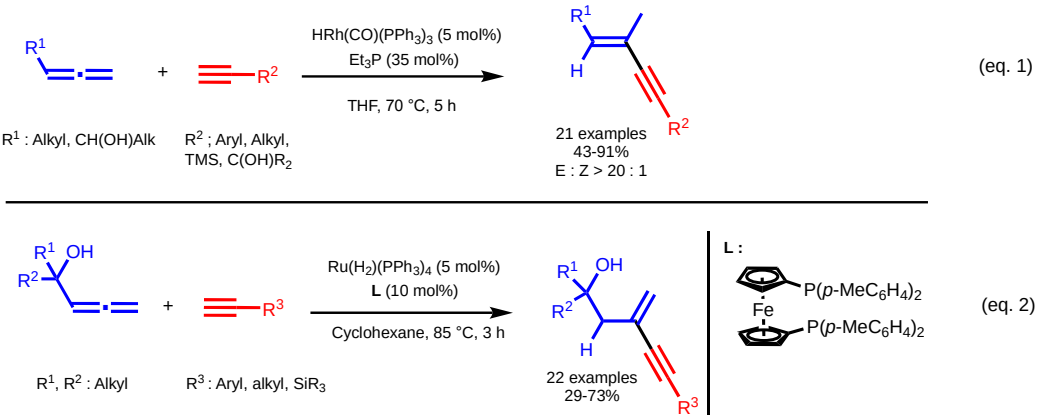


Scheme 69: Pd-catalyzed addition of alkynes to allenyl esters.

This selectivity was also observed in 2003 by Gevorgyan when he extended this reaction to allenylphosphine oxides and obtained enynephosphine oxydes.[159] At the same time Grigg published a regioselective addition of alkynes to allenes by a palladium and copper co-catalytic system.[160]

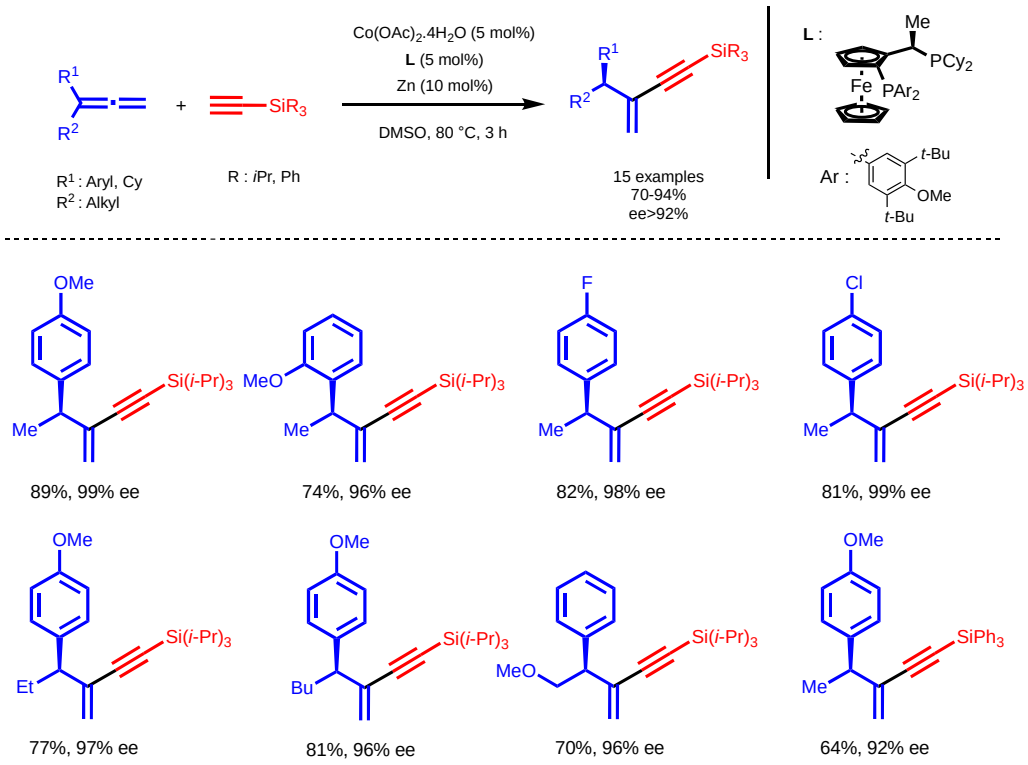
Parallel to the use of palladium, rhodium-catalyzed condensation of mono-substituted allenes and alkynes has been reported by Yamaguchi in 1994. Using $HRh(CO)(PPh_3)_3$ and triethylphosphine, the enyne obtained is almost exclusively the endo-(*E*) one (Scheme 70, eq. 1).[161] Inspiring by the latter, a catalytic system based on $Ru(H_2)(PPh_3)_4$/diphosphine catalytic was used for the generation of enyne

with an exo-selectivity (Scheme 70, eq. 2).[162] In this case, the use of a hydroxyl group is necessary for this condensation, the exo-selectivity being probably due to steric hindrance.



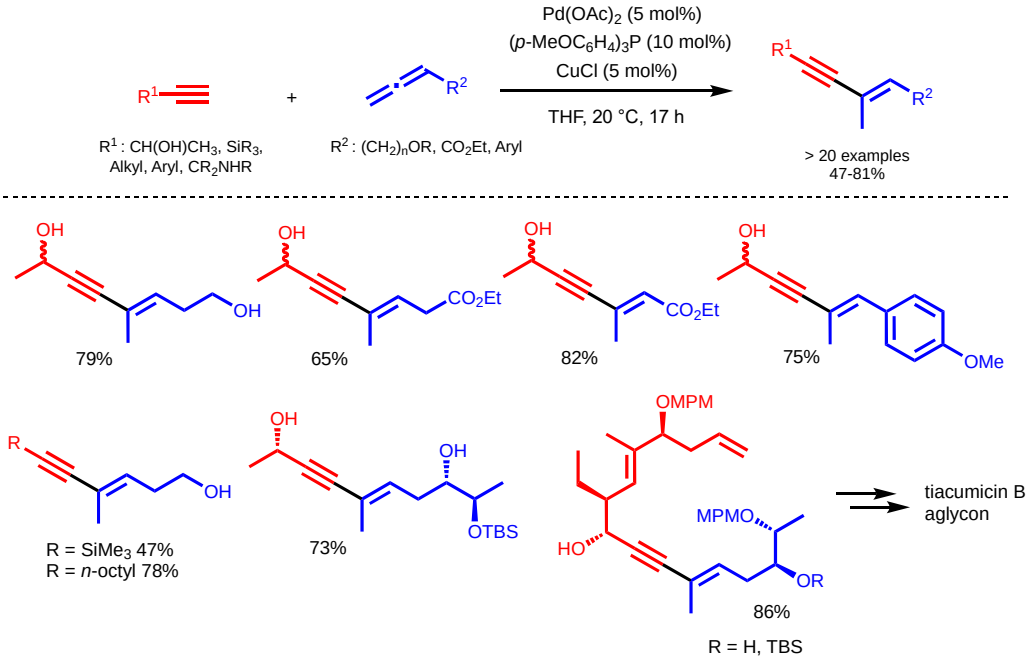
Scheme 70: Addition of alkynes with terminal allenes for C-C bond formation catalyzed by Ru or by Rh.

The rhodium-catalyzed asymmetric addition of terminal alkynes to diarylphosphinylallenes was reported by Nishimura and Hayashi, using [Rh(acac)(C_2H_4)$_2$] and (*R*)-binap as ligand.[163] From 1,1-di-substituted allenes, the addition gave selectively the corresponding exo-phosphinoenyne with good enantioselectivity. The same group performed the cobalt-catalyzed asymmetric addition of silylacetylenes to 1,1- disubstituted allenes, and the corresponding enynes were obtained with high enantiomeric excess (Scheme 71).[164]



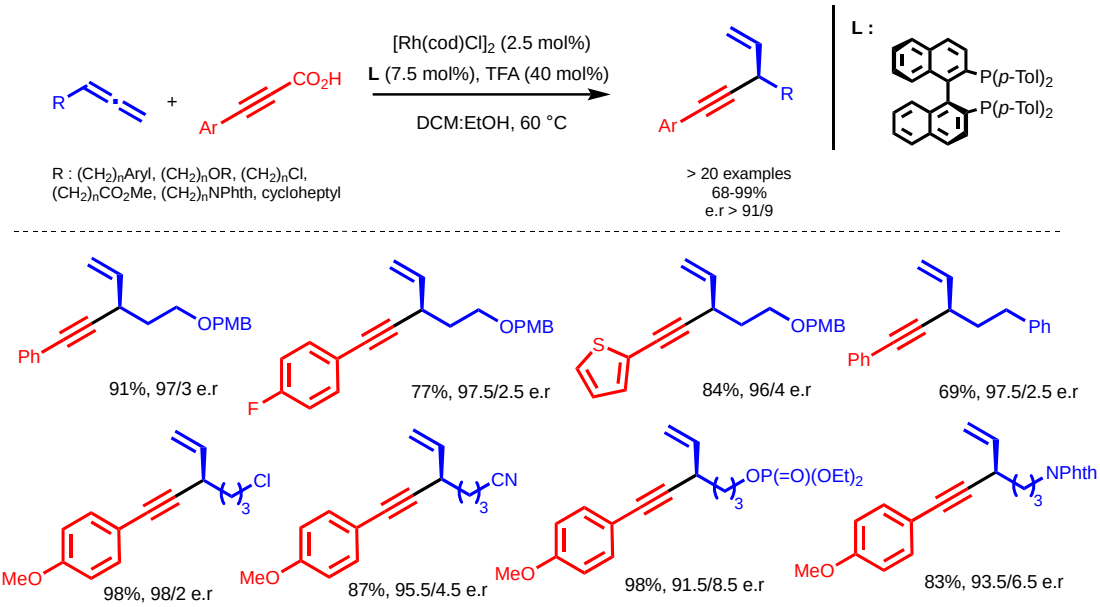
Scheme 71: Enantioselective addition of silylacetylenes to terminal allenes for C-C bond formation catalyzed by Co.

In 2019, Roulland and co-workers developed a simple Pd/Cu co-catalytic system able to stereoselectively produce 1,3-enynes starting from alkynes and terminal allenes (Scheme 72). [165] Among many examples, this simple method was applied to the formation of two key intermediates for the synthesis of tiacumicin B aglycon, a natural antiobiotic drug.



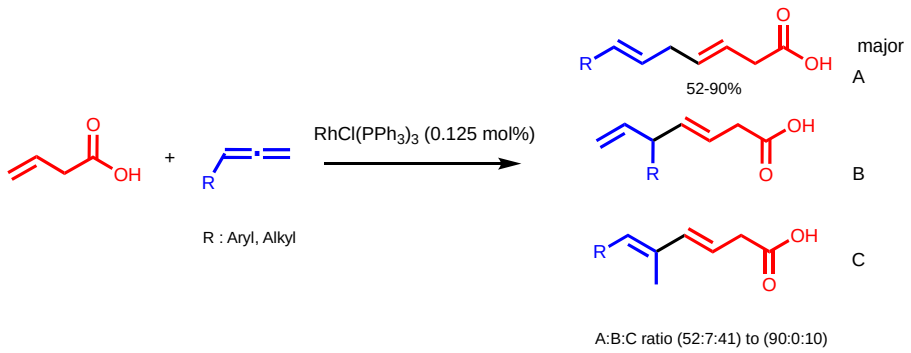
Scheme 72: Pd/Cu-catalyzed hydroalkynylation of terminal allenes.

Another strategy was reported in 2018 by the group of Breit, using a decarboxylative hydroalkynylation reaction with terminal allenes and aryl propiolic acids under rhodium/diphosphine catalysis (Scheme 73).[166] The reaction scope is quite large and the system allows the synthesis of the corresponding enantiopure enynes with excellent regio- and enantioselectivity.



Scheme 73: Rh-catalyzed enantioselective decarboxylative hydroalkynylation of terminal allenes.

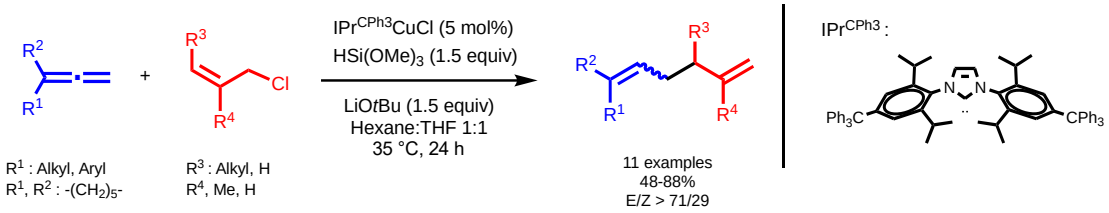
The reaction of allenes with alkenes has been reported only in few cases. The first one described the condensation of mono-substituted terminal allenes with 3-butenoic acid using the Wilkinson rhodium-based catalyst.[167] The reaction, which favored the addition on the terminal carbon of the allene, was reported with moderate to good yields due to polymerization of the later (Scheme 74).



Scheme 74: Rh catalyzed addition of 3-butenoic acid with allenes for C-C bond formation.

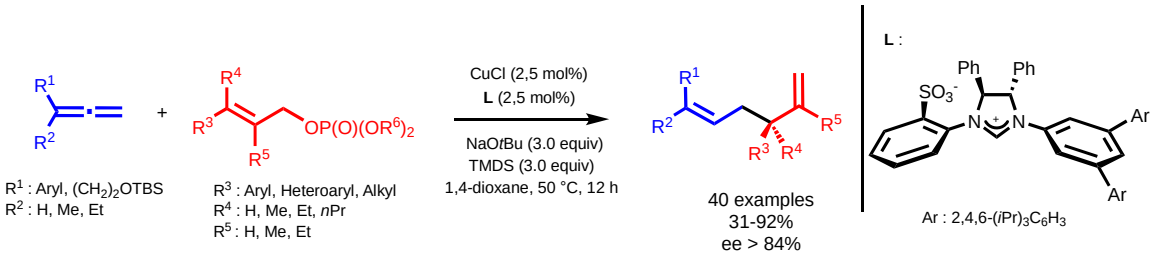
The second example was described by the group of Tsuji and Fujihara, who reported a copper-catalyzed system able to perform the hydroallylation of allenes with allyl chlorides (Scheme 75).[168] The

precatalyst is a complex of copper coordinated to a NHC ligand (N-Heterocyclic Carbene). This reaction provided access to (*E*)-1,5-dienes with excellent stereoselectivity.



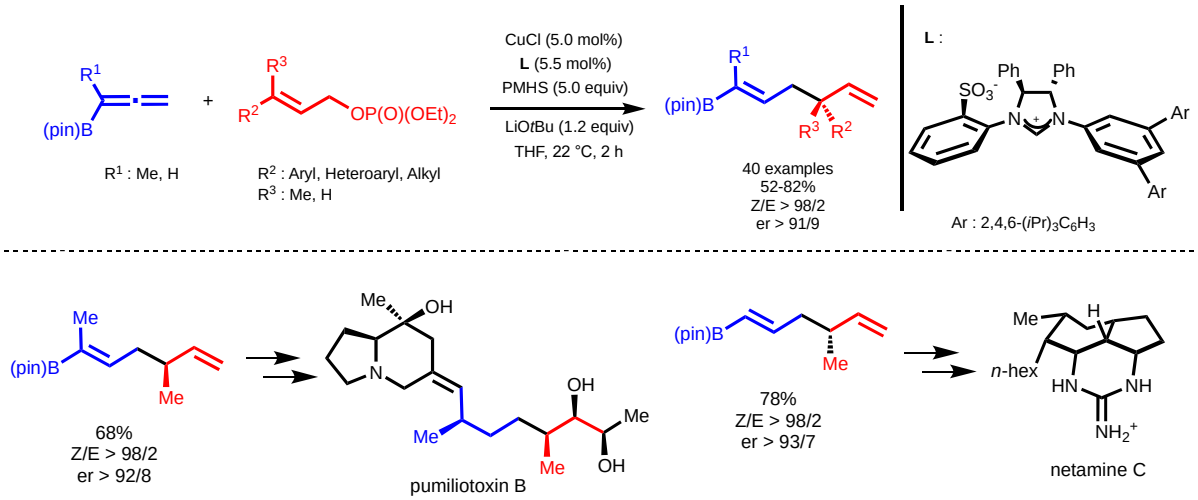
Scheme 75: Hydroallylation of allenes with allyl chlorides catalyzed by Cu/NHC ligand.

Copper/NHC systems were also used to catalyze the reductive allyl-allyl cross-coupling of allenes in an efficient manner. Starting from allylic phosphates and terminal allenes, they were able to obtain optically active 1,5-dienes in a highly enantioselective and site-specific fashion (Scheme 76).[169] The versatility of the reaction was successfully showed on more than 40 substrates given the corresponding dienes with excellent yields and selectivity.



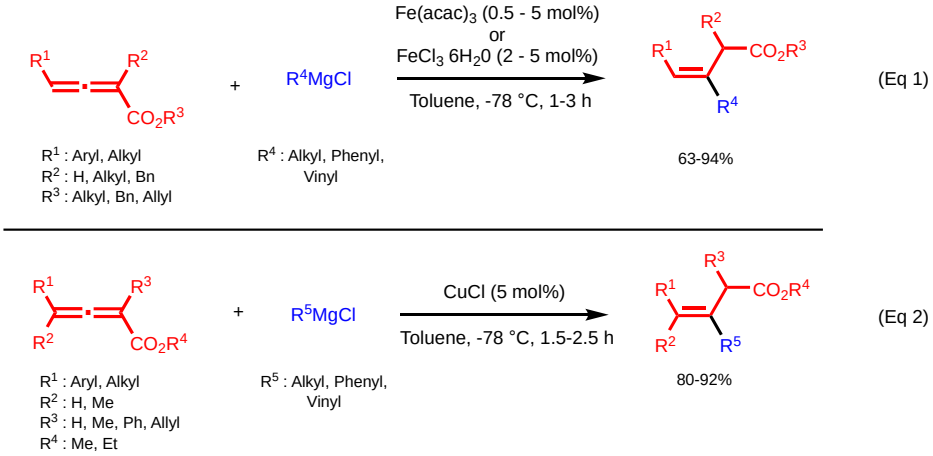
Scheme 76: Cu-catalyzed enantioselective allyl-allyl cross-coupling.

A third copper/NHC-catalyzed enantioselective reaction has been reported the same year by Hoveyda and co-workers.[170] In this study, they succeed to use allenyl boronates with allylic phosphates, in order to give a direct and selective access to organoboronic species (Scheme 77). The method was efficient with lot of substrates, and the interest of the obtained class of compounds was then demonstrated by the total synthesis of bioactive molecules: pumiliotoxin B (myotonic, cardiotonic) and netamine C (anti-tumor and anti-malarial).



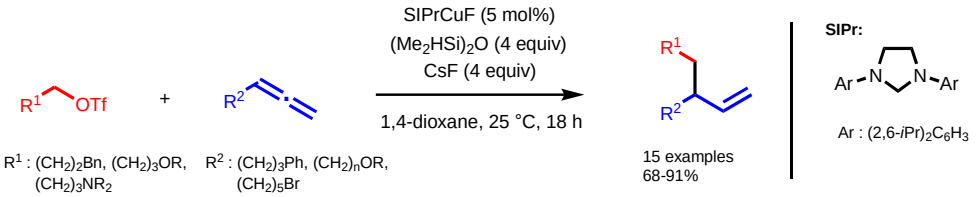
Scheme 77: Enantioselective Cu-catalyzed reaction of terminale allenes with allenyl boronates.

Iron-based catalysts are also able to allow the formation of C-C bonds by allene hydrofunctionalization, as shown by the team of Ma who reported an iron-catalyzed conjugate addition of 2,3-allenoates with Grignard Reagents, with good regio- and stereoselectivities (Scheme 78, eq. 1).[171,172] Five years after, the same team developed a reaction catalyzed by CuCl with tetrasubstituted allenes (Scheme 78, eq. 2).[173]



Scheme 78: Fe- and Cu-catalyzed addition of Grignard reagents to allenoates.

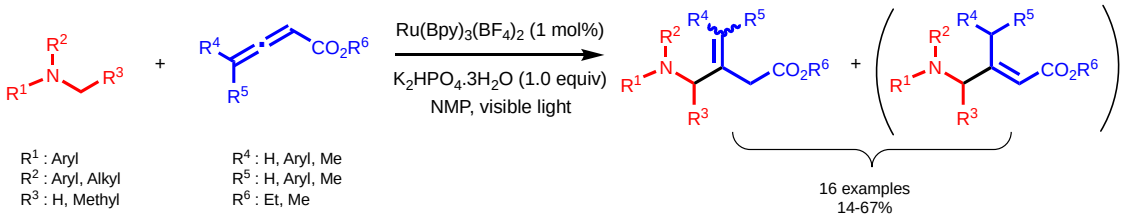
In 2017, the group of Lalic used an in-situ-generated Cu-H catalytic system to perform the hydroalkylation of mono-substituted allenes, using alkyl triflates as electrophile.[174] This reaction, which was performed with a copper(I)/NHC precatalyst, led to the formation of branched allylic compounds (Scheme 79).



Scheme 79: Copper catalyzed hydroalkylation of mono-substituted allenes with alkyltriflates.

3.4. Aminoalkylation

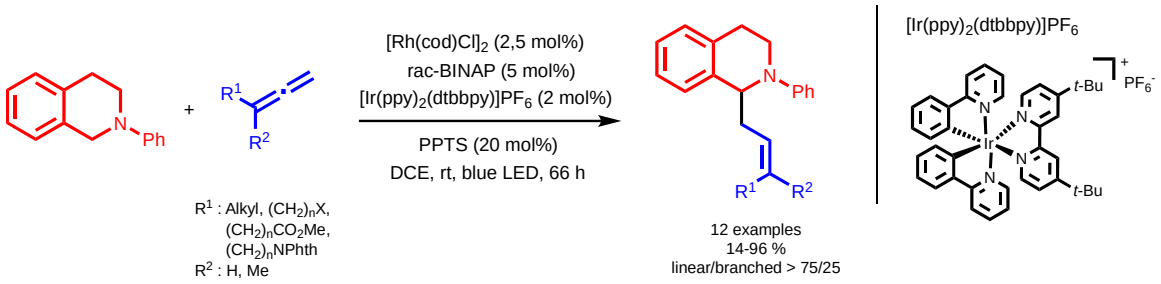
The radical aminoalkylation of allenes has been performed in 2015 by the group of Li and Xu, using visible light photoredox catalysis with 1 mol% of $[Ru(Bpy)_3](BF_4)_2$. With mono-, di- and tri-substituted allenes, this regioselective addition on the central sp-hybridized carbon led to the formation of unsaturated γ-aminobutyric ester derivatives (Scheme 80). A mixture of *E/Z* (up to 91/9) compounds and a variation of position of the final double bond has generally been obtained.[175]



Scheme 80: Ru-based photocatalyzed aminoalkylation of mono-, di- and trisubstituted allenoates.

In the meantime, the group of Krische developed an original aminomethylation reaction between allenes and hexahydro-1,3,5-triazine branched products of hydroaminomethylation bearing all-carbon quaternary centers under ruthenium/diphosphine catalysis.[176]

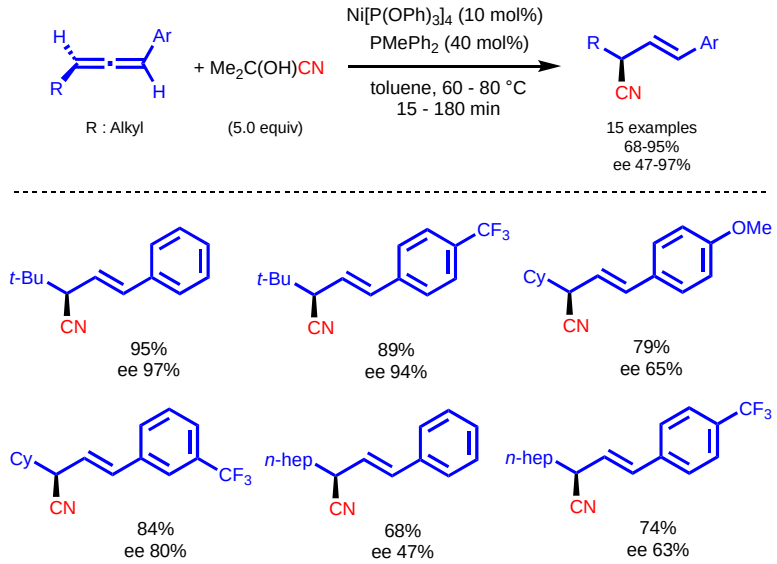
In 2019 Breit and co-workers extended the use of the rhodium/diphosphine toolbox for the functionalization of allenes to hydroaminoalkylations.[177] Photoredox catalysis based on rhodium- or iridium systems was able under blue LED activation and in the presence of rac-BINAP ligand, to allow the selective linear allylation of N-Phenyl tetrahydroisoquinoline (Scheme 81).



Scheme 81: Combined photoredox- and Rh- or Ir-catalyzed hydroaminoalkylation of disubstituted terminal allenes.

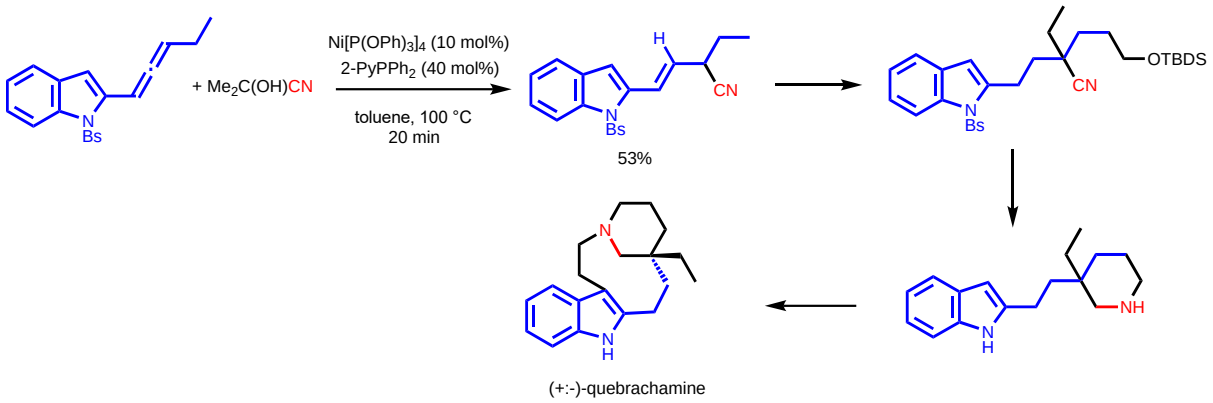
3.5. Hydrocyanation

The metal-catalyzed hydrocyanation of allenes did not received much attention in the past. The first example was reported in 1985 and catalyzed by a nickel complex.[178] However this process suffered for a lack of selectivity, giving addition of the nitrile on the three different carbons of the allene (*C1*, *C2* and *C3*). An hydrocyanation resulting product was observed by Arai during the study of a cyclization process or with the cleavage of a cyclopropane ring.[179,180] However the regio- and stereoselective hydrocyanation was only reported with 1,3-disubstituted allenes bearing an aryl group and acetone cyanohydrine as cyano surrogate. The catalytic system is based on Ni(0) and $PMePh_2$ acting as ligand.[181] The use of enantioenriched allenes allowed to perform the reaction with good to excellent chirality transfer (Scheme 82).[182]



Scheme 82: Ni-catalyzed enantioselective hydrocyanation of chiral allenes with acetonecyanohydrin.

Recently, the authors applied their catalytic system to the formal synthesis of (±) quebrachamine, acting as α-adrenergic blocking behavior in uro- genital tissue (Scheme 83).[183]

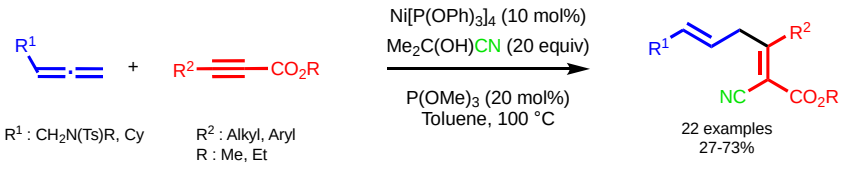


Scheme 83: Synthesis of Quebrachamine by nickel-catalyzed allene hydrocyanation.

An extension of this asymmetric system has been reported later by Fang and co-workers, using a (*R*,*R*)-Ph-BPE-Ni(0) complex catalyst.[184] Various enantiomerically enriched allylic nitriles were obtained with good enantiomeric excess in good yields.

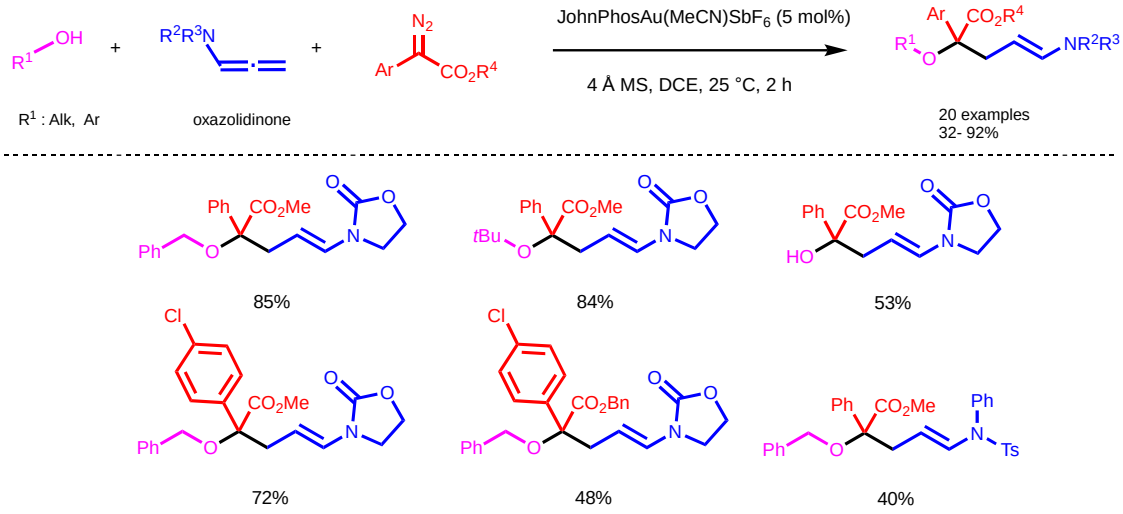
3.6. Miscellaneous

In order to further gain in molecular complexity, some studies reported original hydrofunctionalizations of allenes involving three-component reactions. In 2013, as part of their work on hydrocyanation of allenes, Arai and co-workers reported a nickel-catalyzed procedure for the cyanative hydroalkynylation of terminal allenes, efficient in an intra- and inter-molecular manner (Scheme 84).[185] This 3-component reaction allows the selective formation 1,4-cyano dienes in good yields.



Scheme 84: Ni catalyzed triconponent cyanative hydroalkynylation of terminal allenes with acetonecyanohydrin.

A second example of 3-component method has been published in 2019, with the gold-catalyzed reaction between alcohols, α-aryl-α-diazoesters and terminal allenamides, giving a selective access to *tert*-allylic ethers with excellent stereoselectivity (E/Z > 20/1).[186] This system was also efficient with water, making possible the synthesis of *tert*-allylic alcohols (Scheme 85).

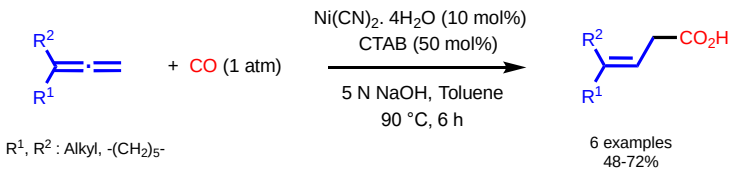


Scheme 85: Au-catalyzed stereoselective three-component reaction with allenamides alcohols and diazoesters.

3.7. Umpoled reaction with carbon dioxide and carbon monoxide (and surrogates)

The development of metal-catalyzed hydrofunctionalization of allenes is not only described with nucleophilic coupling partner but is also possible with electrophilic species. Allenes are then considered as pronucleophilic species. Several electrophiles have been used with this strategy, such as carbone dioxide CO_2 and carbon monoxide CO. This strategy constitutes umpoled reactions compared to all the others described in this review.

In 1990 Alper reported the first use of carbon monoxide for the functionalization of allenes.[187] The catalytic system is based on nickel cyanide, used in a two-phases system with cetyltrimethylammonium bromide (CTAB) as phase-transfer agent. With one atmosphere of carbon monoxide, it gave regioselectively the β,γ-unsaturated acid (Scheme 86).

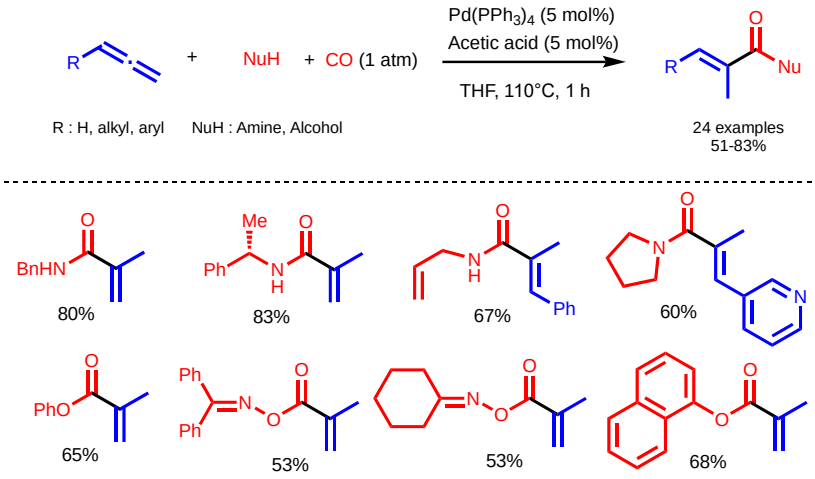


Scheme 86: Hydrocarbonylation of allenes catalyzed by Ni.

In parallel, the addition of carbon dioxide to mono-substituted and 1,3-disubstituted allenes was performed and catalyzed with an electrogenerated nickel(0) complex.[188] Proceeding with smooth conditions, this system unfortunately lead to the formation of mixture of different regioisomers, with addition of the carbon dioxide on the three different carbons of the allene. The ratio of regioisomers was

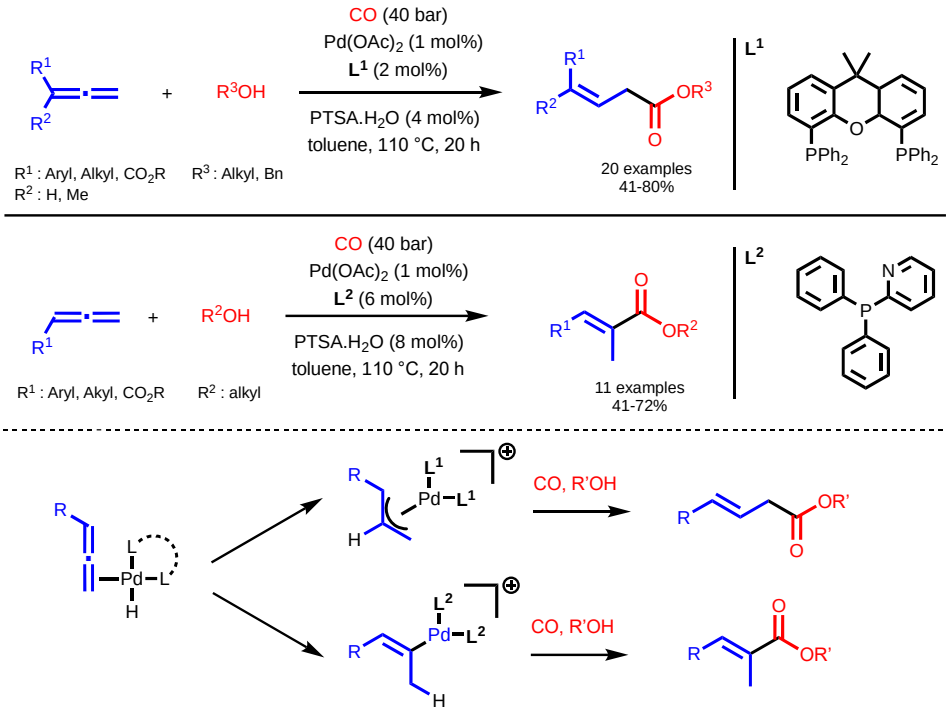
highly dependent to the substitution of the allene. Currently the regio- and stereoselectivity for the nickel-mediated hydrocarboxylation of mono- and 1,3-disubstituted allene with carbon dioxide is only available with a stoechiometric amount of metal.[189–191]

Palladium-based catalyst is well known to perform carbonylation reactions, and this is also true in presence of allenes. In 1998, Grigg used 5 mol% of $Pd(PPh_3)_4$ under one atmosphere of carbon monoxide for the addition on terminal allenes of a of amine or alcohol nucleophiles, to give the corresponding allylic amides or esters (Scheme 87).[192] The broad reaction scope of this method gives access to allyl molecules *via* insertion of CO on the central carbon of the starting allene.



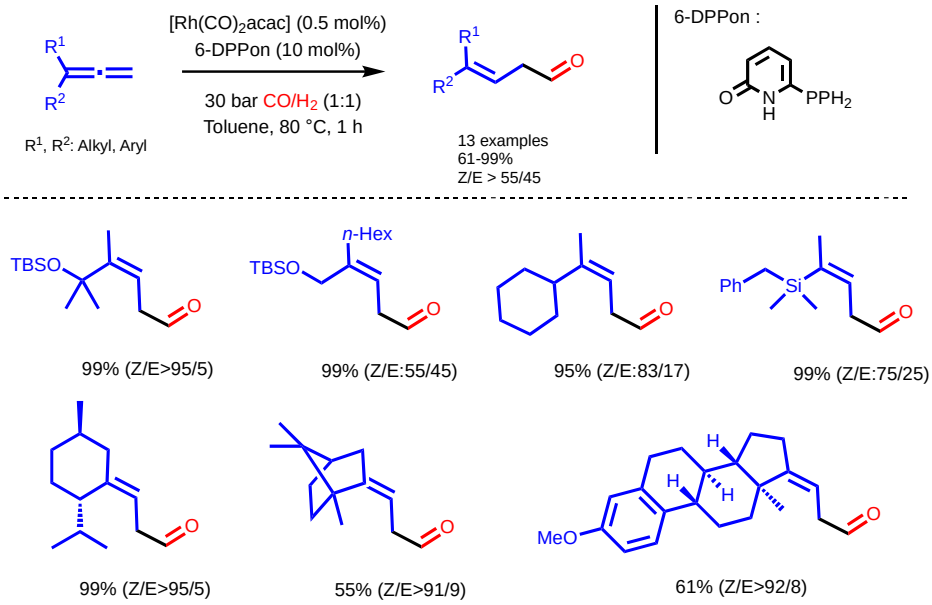
Scheme 87: Hydrocarbonylation of terminal allenes in presence of amine or alcohol nucleophiles catalyzed by Pd.

As an extension of this work, Beller studied the hydroalkoxycarbonylation of allenes in the presence of alcohols under 40 atmosphere of CO for the synthesis of α,β- and β,γ-unsaturated esters. The regioselectivity of this palladium-catalyzed system could be inverted by a simple change of ligand (Scheme 88).[193] The authors suggested that Xantphos **L¹** favors the intermediate formation of a π-allyl-Pd complex and then affords the corresponding β,γ-unsaturated esters (Scheme 88, eq. 1). On the other hand, when diphenylphosphinopyridine **L²** is employed as ligand, an alkenyl-Pd complex is generated that allows the formation of α,β-unsaturated esters (Scheme 88, eq. 2). Same authors associated with Jioa also studied the mechanism of a similar cobalt-catalyzed hydroformylation of allenes by DFT and proposed that the anti-Markovnikov product is favored by both kinetic and thermodynamic effects.[194]



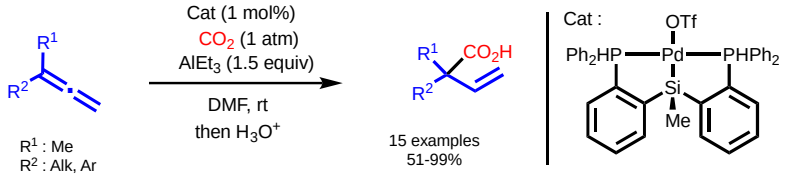
Scheme 88: Ligand-controlled the regioselectivity of hydroalkoxycarbonylation of allenes catalyzed by Pd.

The employ of rhodium-based catalytic system was also described for the addition of carbon monoxide coupled with hydrogen. The group of Ma reported the use of this mixture at a pressure of 4.8 bars to perform the hydroformylation-hydrogenation of 1,2-allenyl-phosphine oxides and phosphonates catalyzed by $RhH(CO)PPh_3)_3$.[195] Breit and co-workers reported a method proceeding under 30 bar of CO/H_2, in which the regioselective hydroformylation of 1,1-di-substituted allenes was accomplished using [Rh(CO)2(acac)] catalyst associated to the 6-DPP ligand (Scheme 89). It was applied to the synthesis of substrates of interest such as (-)-menthone, (+)-camphor and estrone derivatives.[196] The rhodium-catalyzed hydroformylation was also extended to 1,1,3-trisubstituted allenes by Schomaker and co-workers in 2017. Using BisDiazaphos ligand, the reaction was performed regioselectively on the terminal carbon of the allene under 10 bars of CO/H_2 (1:1).[197]



Scheme 89: Rh-catalyzed hydroformylation of disubstituted terminal allenes.

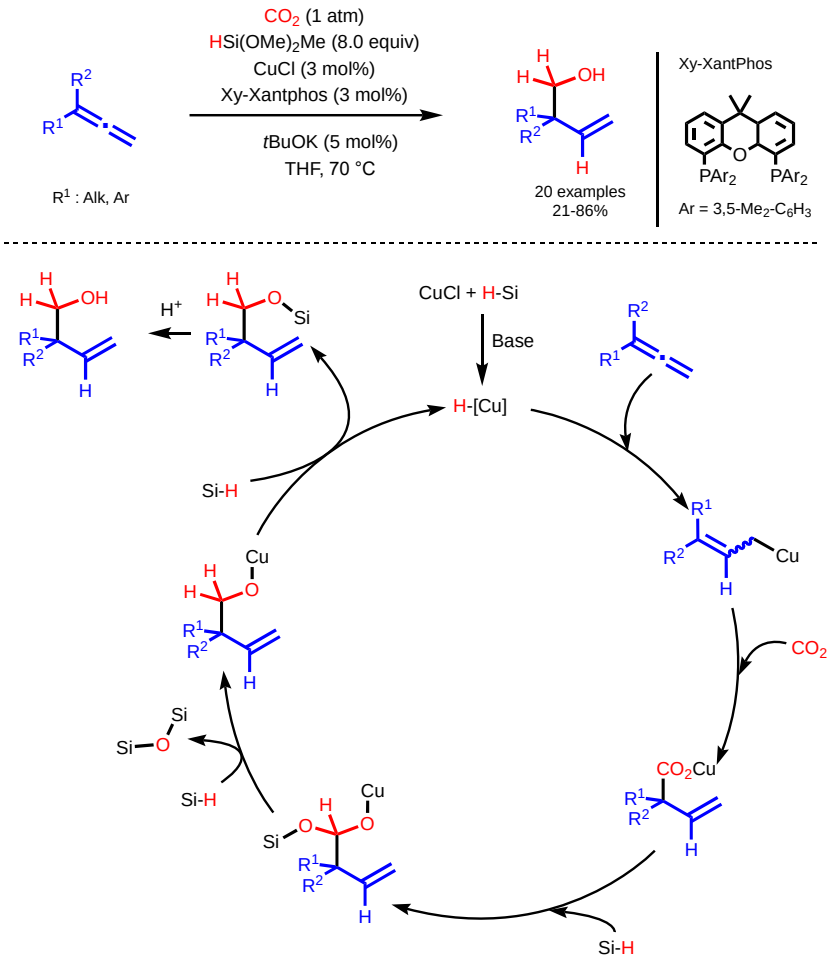
Carbon dioxide was also used as an electrophile with palladium catalysts. Thus, Iwasawa published the hydrocarboxylation on the more substituted carbon of 1.2 disubstituted terminal allenes with a silyl pincer-type palladium complex (Scheme 90).[198] This reaction, which was the model for the study of original PSiP pincer ligands, was also applied to mono-substituted and 1,1- or 1,3-disubstituted allenes.[199]



Scheme 90: Hydrocarboxylation of terminal allenes with a Pd/PSiP system.

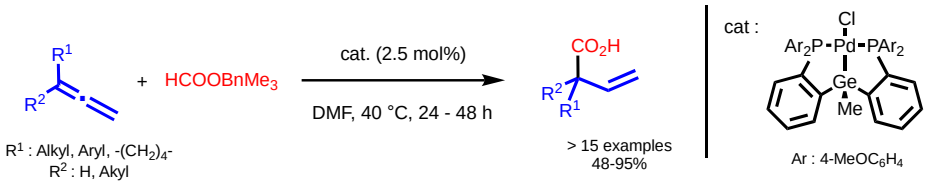
In 2015, Tsuji and Fujihara also reported the use of carbon dioxide for the synthesis of homoallylic alcohols from allenes, using a catalytic system based on a copper/diphosphine ligand system associated to a hydrosilane (Scheme 91).[200] Authors proposed a mechanism starting from the generation of a copper-hydride complex, then an allylcopper intermediate reacts with CO_2 at the γ carbon to afford a copper carboxylate. The latter is then reduced by hydrosilane to form a copper alkoxide intermediate that provide the final homoallylic alcohol.

These methods of hydrocarboxylation[198,200] are of high interest because they could allow the fixation of CO_2 but also create high valuable molecules such unsaturated carboxylic acids.[199]



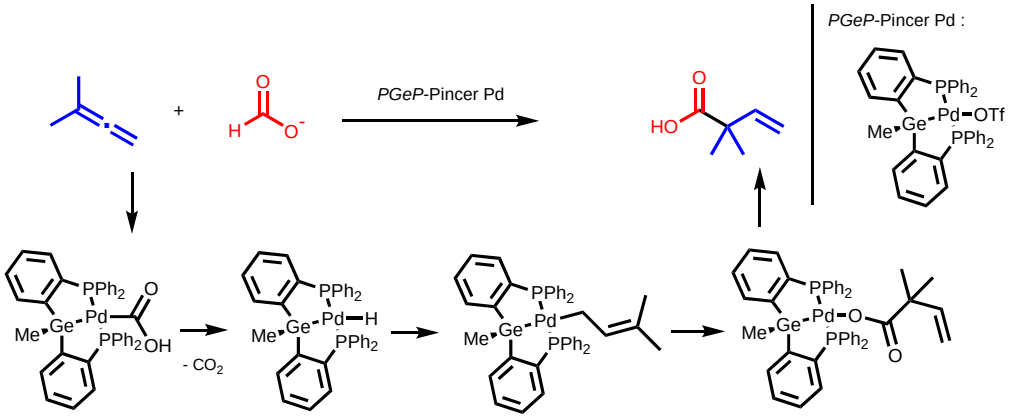
Scheme 91: Mechanism of the synthesis of homoallylic alcohols from allenes and CO_2 catalyzed by Cu.

Exploring the use of carbon dioxide surrogate for the hydrocarboxylation of allenes, the group of Iwasawa reported the reaction of formate salts (benzyltrimethylammonium formate) to generate in-situ CO_2 and a hydride. Occurring with a PGeP-palladium catalyst, the regioselective hydrocarboxylation was observed on the more hindered extremity of 1,1-di-substituted allenes (Scheme 92).[201] A good tolerance to various functional groups was observed and extension to mono-substituted and 1,3-subsituted allenes was also possible. Additionally, benzyltrimethylammonium formate can be successfully replaced by the commercially available and much more atom-economical potassium formate HCO_2K in the particular case of 1,1-dimethylallene.



Scheme 92: PGeP-Pd complex catalyzed hydrocarboxylation of allenes with formate salts as CO_2 surrogate (benzyltrimethylammonium formate).

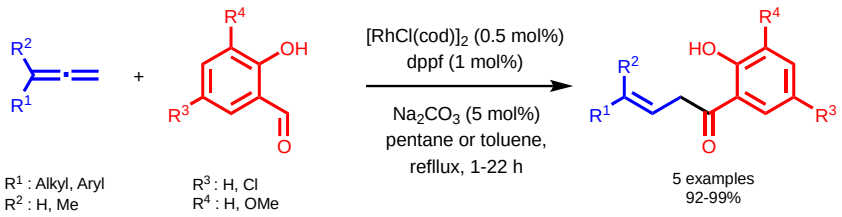
The group of Lu published in 2018 a DFT study on hydrocarboxylation of dimethylallene catalyzed by PGeP-palladium (Scheme 93).[202] After an initial coordination of the palladium with the formate (in excess), a new palladium hydride intermediate would be formed via releasing of CO_2. The hydride formed could react with dimethylallene to afford to an allyl palladium complex. The latter would undergo an insertion of CO_2 and would then release the expected product.



Scheme 93: DFT studies of the palladium catalyzed hydrocarboxylation of dimethylallene with formate salts.

3.8. Umpoled Reaction with Aldehyde

Another possibility for the use of allenes as pronucleophile is their hydrofunctionalization with readily accessible aldehydes.[203] Thus, during their investigations about the aldehyde C-H bond cleavage involving a rhodium catalyst, the group of Miura observed in 1999 the addition of aldehydes (2-hydroxybenzaldehyde) on γ carbon of terminal allenes (Scheme 94).[204] This reaction was performed with 1,1-dimethylallene or mono-substituted allenes with a good regioselectivity on the terminal carbon, except for the phenylallene which underwent addition on both last and central carbons.

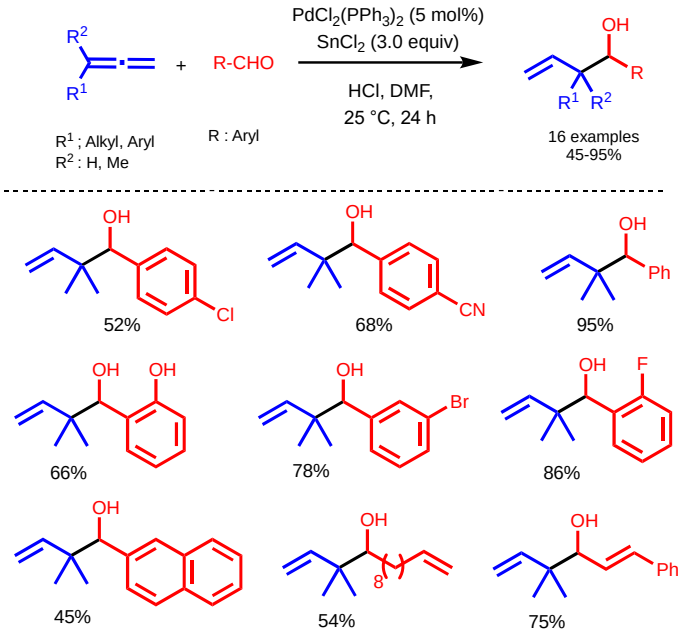


Scheme 94: Rh-catalyzed addition of aldehydes with mono- and disubstituted terminal allenes.

The rhodium-catalyzed hydroacylation of allenes was then described by Willis in an enantioselective manner in 2008, with *ee* up to 96% thanks to the use of chiral P-P ligand (DuPhos type ligand).[205] Very efficient on 1,3-di-substituted allenes, this reaction was limited to β-S-aldehydes (Scheme 95). An extension of the scope without chirality was also published with tri-substituted allenes.[206]

Scheme 95: Rh-catalyzed hydroacylation of 1,3-disubstituted allenes with aryl aldehydes.

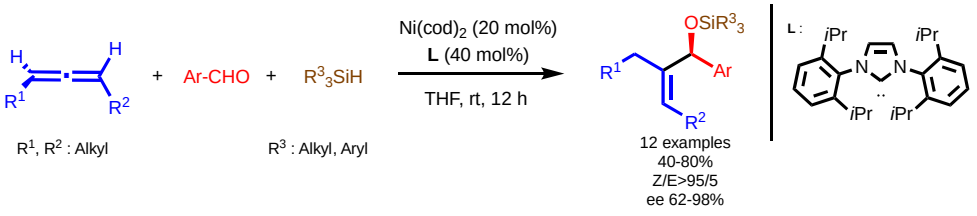
The addition of benzaldehyde derivatives to 1,1-di-substituted allenes was also described using a palladium catalyst, by formal reductive coupling. Thus, Cheng and co-workers reported that $PdCl_2(PPh_3)_2$ in presence of $SnCl_2$ was able to catalyse the *in-situ* hydrostannylation of allenes, which was followed by the addition an aldehyde to give homoallylic alcohols (Scheme 96).[207]



Scheme 96: Pd-catalyzed hydroacylation of allenes *via in-situ* hydrostannylation.

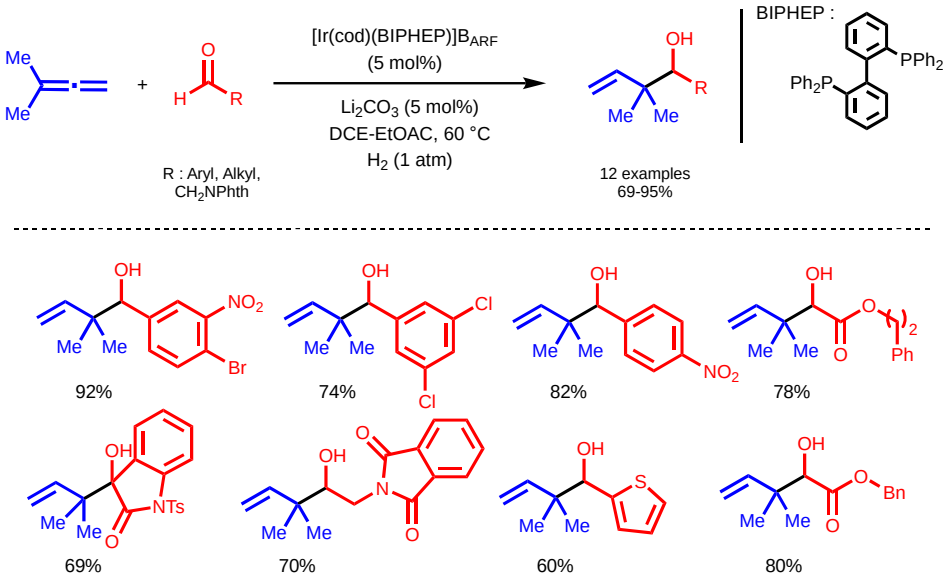
Noteworthy, the [Pd(allyl)Cl]$_2$/DPEPhos/chiral amine system described by Luo for the enantioselective addition of dicarbonyl compounds (Scheme 64) was also applied in the same study with aldehydes.[152]

In 2005, a nickel-based catalytic system for hydroacylation has been disclosed by Jamison and co-workers. Using Ni(cod)$_2$ and an achiral NHC-ligand, an enantioselective three-component reaction was performed involving internal chiral allenes, organosilanes and aromatic aldehydes (Scheme 97). A similar system without chirality transfer was also published with aliphatic aldehydes and terminal allenes and afforded the formation of trisubstituted allylic alcohols. [208–210]



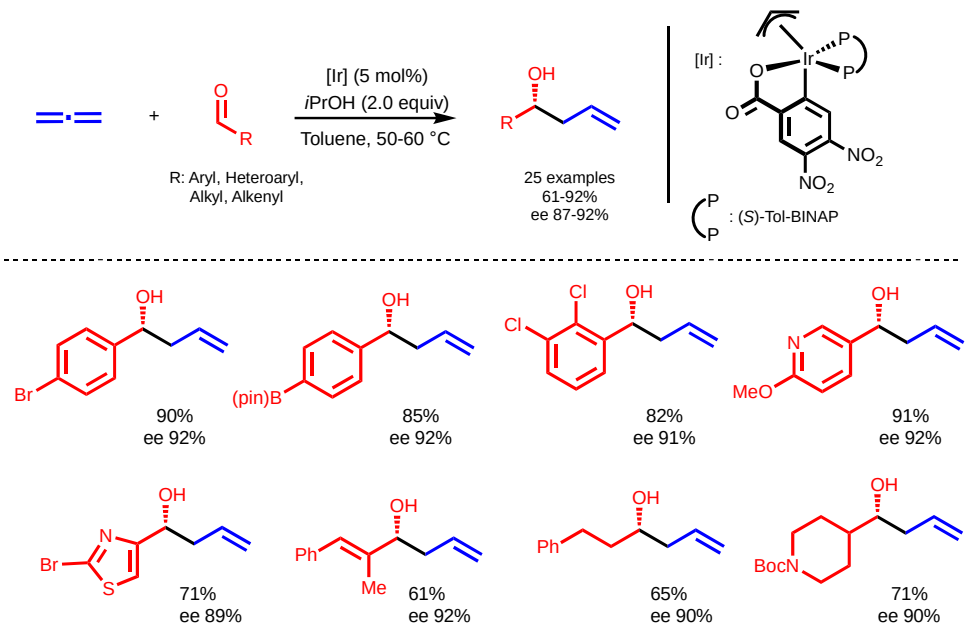
Scheme 97: Ni-catalyzed enantioselective hydroacylation of internal chiral allenes in the presence of organosilanes.

Iridium-based complexes were also efficient catalytic systems for the addition of an aldehyde to an allene. Working almost exclusively with 1,1-dimethylallene, the group of Krische reported the racemic (Scheme 98) and enantioselective iridium-catalyzed addition of various aldehydes, thus leading under atmospheric pressure of H_2 to the corresponding allylic alcohols with good to excellent yields.[211–213]



Scheme 98: Enantioselective Ir-catalyzed hydroacylation of terminal allenes.

In 2019, the same team employed gaseous allene in enantioselective aldehyde reductive coupling catalyzed by an allyl-iridium complex, giving (*R*)-homoallylic alcohols (Scheme 99).[214] In the same study, they also used the exact same catalytic system with allyl acetate instead of allene and surprisingly, an inversion of enantioselectivity has been observed leading to the formation of (*S*)-homoallylic alcohols. Computation and experimental studies suggest two different mechanisms. Using allene, a hydrometallation lead to a diastereomeric π-allyliridium-C,O-benzoate complexes, through a pentacoordinate iridium hydride. On the other hand, the use of allyl acetate involves an ionization from a square planar iridium complex. This divergence in mechanistic pathways could explain the difference of enantioselectivity.

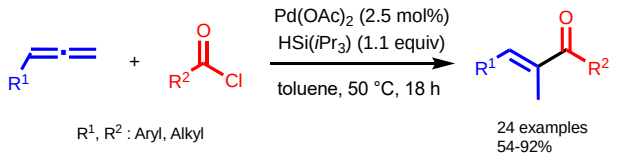


Scheme 99: Ir-catalyzed enantioselective allene-aldehyde reductive coupling.

In parallel to this development of iridium-based catalytic systems, the same group also reported the use of ruthenium catalysts for selective addition of aldehydes to allenes. They thus published the addition of paraformaldehyde on the α-position of 1,1-disubstituted allenes[215], including later trifluoromethyl-bearing allenes.[216] The diastereoselective addition of various aldehydes to sulfonamido allenes was also performed, still with a total regioselectivity on the α carbon, giving access to anti-sulfonamido alcohols.[217]

In 2016, the use of gold was disclosed simultaneously by the group of González and the group of López in collaboration with Mascareñas for the intermolecular α-functionalization of aldehydes with allenamides catalyzed by gold.[218,219] Both groups used a synergistic gold and organo- catalysis.

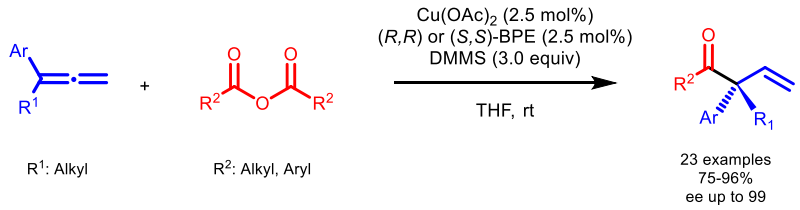
A formal hydroacylation of terminal allenes was also reported by Tsuji in 2013, employing palladium, acid chlorides and hydrosilanes (Scheme 100).[220] Performed under smooth conditions, this reaction gave an access to α,β-unsaturated ketones with regioselectivity and in favor of the formation of the *E*-product even if around 10% of *Z*-product was usually observed. A similar palladium-catalyzed system was also reported using carboxylic anhydrides and afford unsaturated ketones.[221]



Scheme 100: Regioselective Pd-catalyzed hydroacylation of terminal allenes with acyl chlorides.

In 2020, the use of copper for similar formal hydroacylation of allenes was disclosed. Two different strategies were published almost simultaneously by the group of Lee[222] and by the groups of Qian and

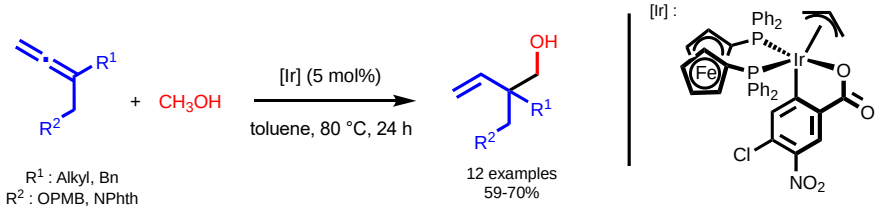
Ma,[223] both using Cu-H catalysts. In the first case, the copper-catalyst was used to perform a hydroalumination of 1,1-disubstituted allenes, whose product was then engaged with an aldehyde for the formation of β,γ-ketones. In the second case, the copper-catalyst allowed the direct addition of anhydride leading to the synthesis of similar structures and the use of a chiral biphosphine ligand made possible the enantioselective control of the obtained all-carbon-quaternary center (Scheme 101).



Scheme 101: Cu-catalyzed enantioselective hydroacylation of allenes.

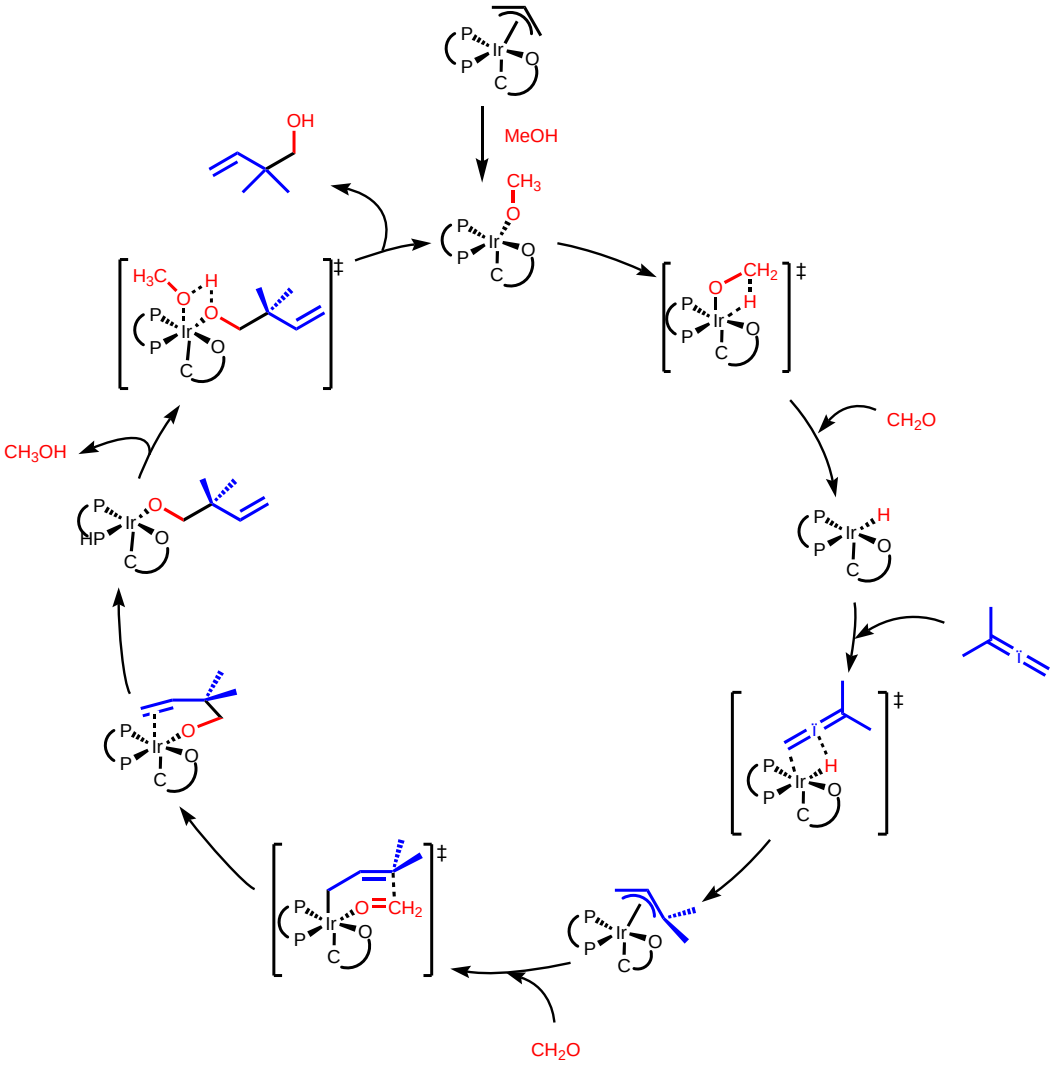
3.9. Umpoled Reaction with Alcohol

After preliminary studies using their iridium catalyst for the reaction of allenes with aldehydes but also applied to some alcohols,[211,212] Krische and co-workers reported the direct iridium-catalyzed coupling of methanol with various allenes (Scheme 102).[224]



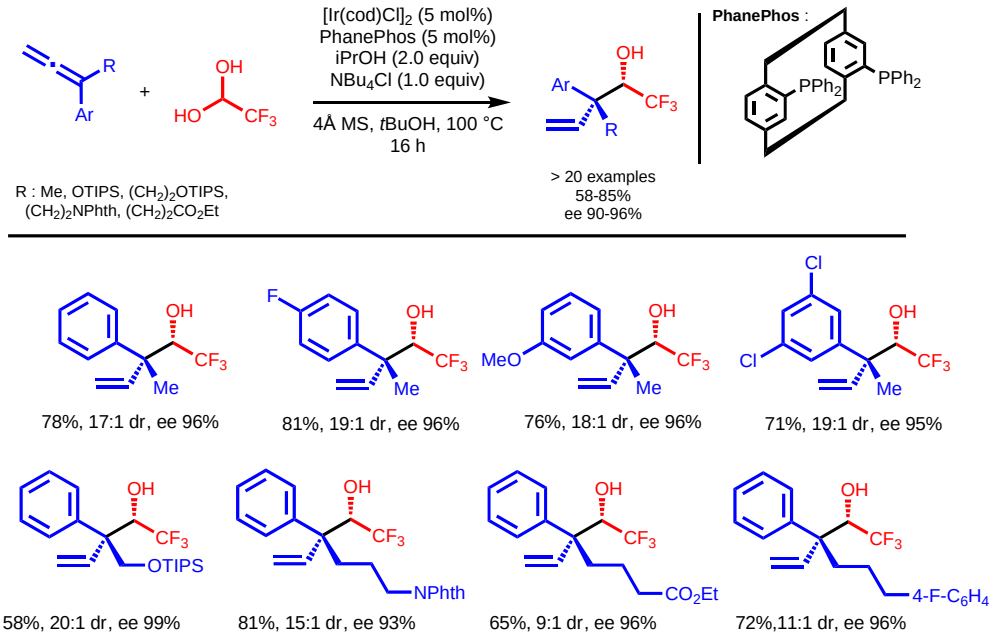
Scheme 102: Ir-catalyzed addition of methanol with allenes.

The mechanism of the reaction was studied by DFT calculations by Wang and Li (Scheme 103).[225] The first step is the addition of methanol to the precatalyst, to form the active iridium species. This step is followed by a β-elimination, to generate an iridium hydride complex and formaldehyde. Then the allene undergoes a hydrometalation to form a π-allyl complex, followed by addition of the *in situ* formed formalhyde. After rearrangement, the final product is then formed by methanolysis with regeneration of the active iridium catalyst.



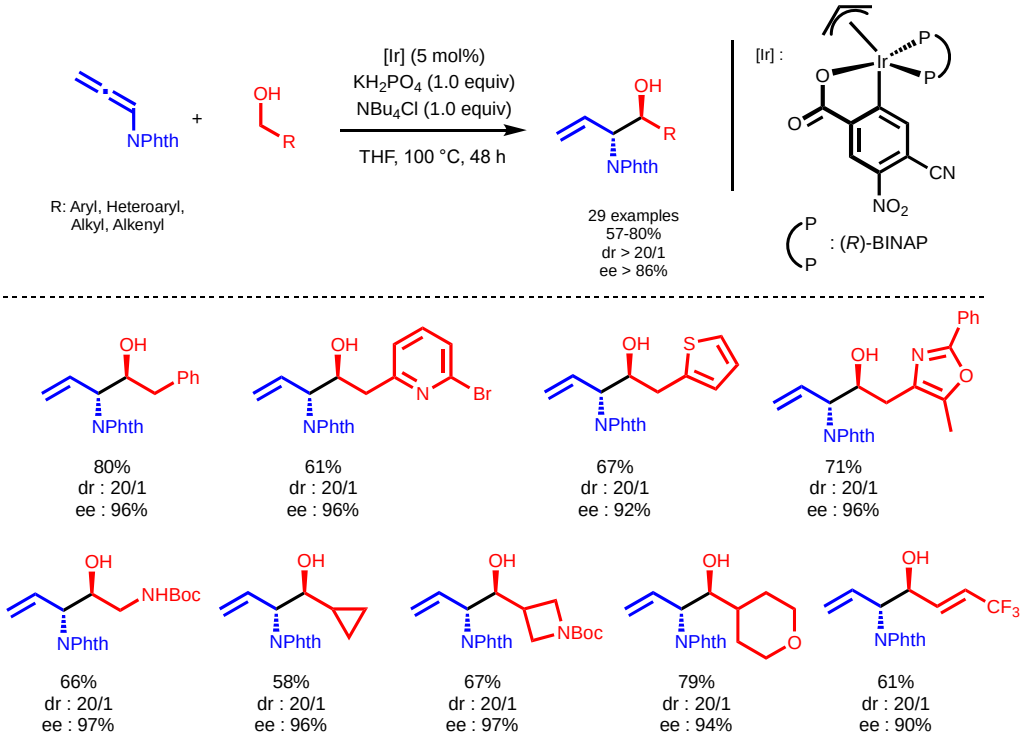
Scheme 103: Mechanism of the Ir-catalyzed addition of methanol with allenes.

An extension of this iridium-catalyzed coupling reaction of CF_3-allenes with methanol was then reported with a chiral control, for the generation of quaternary carbon bearing a CF_3 group.[226] The hydrofunctionalization of allenes in order to obtained trifluorinated patterns was also published in 2019, when Krische and co-workers described the reductive coupling between 1,1-disubstituted allenes and fluoral catalyzed by iridium combined with chiral diphosphine (PhanePhos type). This method allowed the access of CF_3-substituted secondary alcohols in excellent yields with high enantioselectivities (Scheme 104).[227]



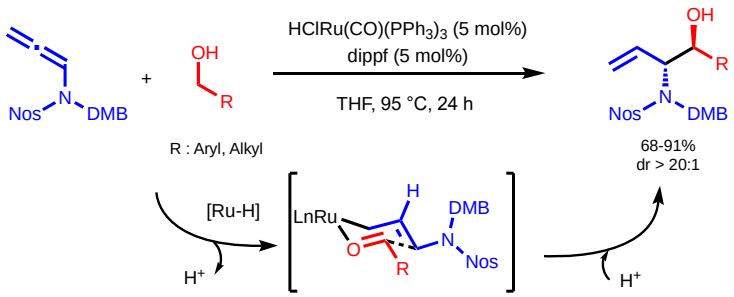
Scheme 104: Ir-catalyzed enantioselective allene-fluoral coupling.

The same year another iridium/chiral diphosphine catalytic system (cyclometalated π-allyliridium Binap complex) was applied for the hydroxyalkylation of phthalimido-allene with a large scope of primary alcohols. This enantio- and diastereoselective reaction gave a direct access to vicinal amino alcohols, which can be used for the synthesis of several valuable structure such as substituted morpholines (Scheme 105).[228]



Scheme 105: Regio- and enantioselective Ir-catalyzed reaction with phthalimido-allene.

In parallel, the same group explored the possibility to use ruthenium-based catalyzed and described the regio- and diastereoselective hydrofunctionalization of allenamides with primary alcohols (Scheme 106).[229] This reaction, supposed to proceed through a six-membered ring transition state, occurred with a total diastereoselectivity.

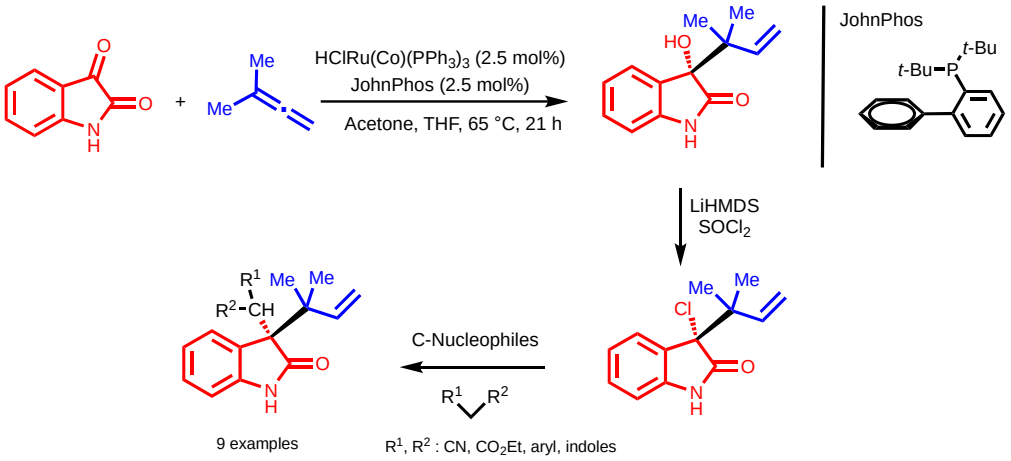


Scheme 106: Regio- and diastereoselective Ru-catalyzed addition of primary alcohols with allenamides for C-C bond formation.

The study of same reaction, performed on 1,1-di-substituted allenes, have shown that the diastereoselectivity was improved thanks to a Curtin-Hammet effect.[230] This ruthenium-catalysed system was also described with fluorinated alcohols.[231]

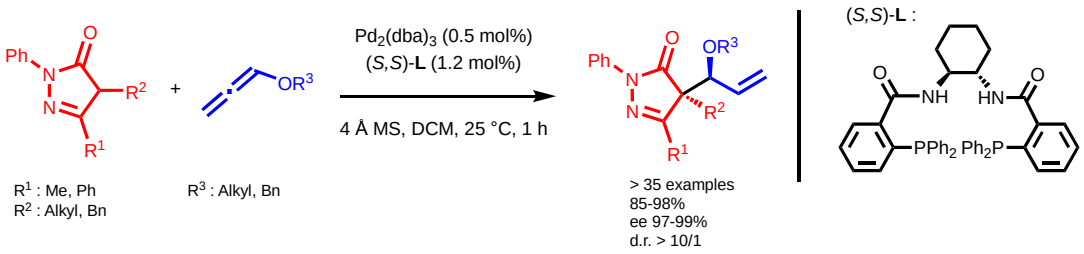
3.10. Umpoled Reaction with miscellaneous Groups

Very few examples of functionalization of allenes with ketones and derivatives were reported. Using very specific isatins as nucleophiles, Krische and co-workers reported two systems with iridium and ruthenium able to catalyze the enantioselective reaction of this natural product with dimethylallene.[232,233] With the ruthenium-based system, the method is effective with unprotected insatin, giving a concise access to 3-*tert*-prenylated oxindoles which constitute a family of interest of bioactive drugs (Scheme 107). Then authors realized the chlorination of the product in order to obtain a convenient substrate for nucleophilic substitution with various C-nucleophiles as malonates, cyanides, rich arenes and indoles.



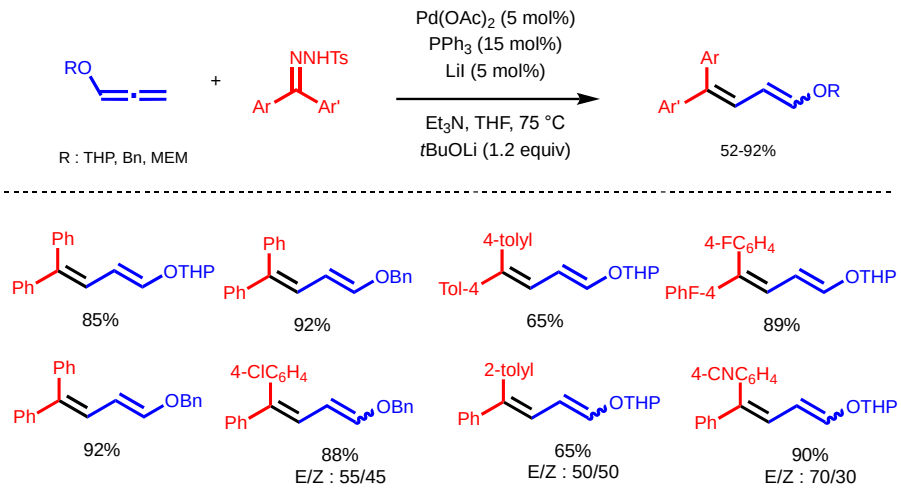
Scheme 107: Ru-catalyzed addition of isatins on 1,1-dimthylallene.

Jiang used a palladium-based catalyst to realize the addition of pyrazolones on alkoxyallenes (Scheme 108).[234] This regio- and enantioselective reaction, performed at room temperature with 0.5 mol% of palladium and a chiral P,N-ligand, occurred on the α-carbon of the allenyl ether. Its regioselectivity was inverted if the palladium-catalytic system is replaced by a chiral phosphoric acid (5 mol%). Under palladium-catalyzed conditions, branched isomer was mainly obtained (branched/linear > 11/1) with excellent diastereo- and enantioselectivities. On the other hand, the use of 5 mol % of chiral phosphoric acid afforded in the formation of the linear products. With more than 35 examples, the reaction scope of this methodology was wide and tolerant to various substitutions on pyrazolones.



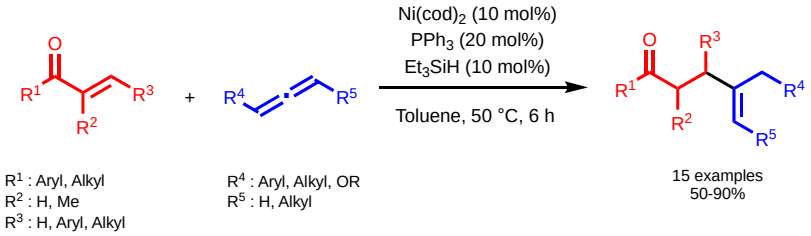
Scheme 108: Regio- and enantioselective Pd-catalyzed addition of pyrazolones with allenyl ethers.

In 2018, an addition of hydrazones on alkoxyallenes also catalysed by palladium has been reported by Deagostino and co-workers. They used a simple palladium/PPh_3 catalyst system and *t*-BuOLi as base allowing the generation of conjugated or skipped dienes (Scheme 109).[235]



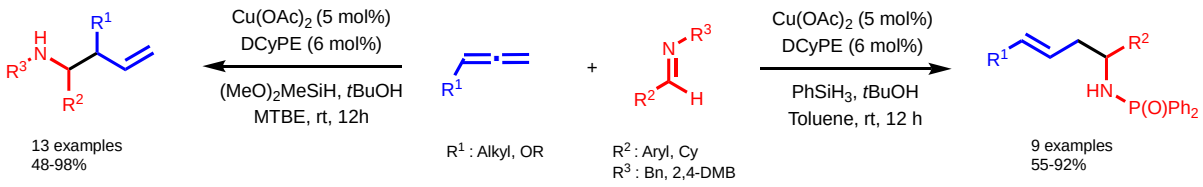
Scheme 109: Pd-catalyzed addition of hydrazones on alkoxyallenes.

The group of Montgomery published in 2010 the regioselective nickel catalyzed reductive coupling of various enones with mono- and 1,3-disubstituted allenes (Scheme 110).[236] This reaction affords the possibility to synthesize γ,δ-unsaturated carbonyl compounds with 1,1-disubstituted alkenes.



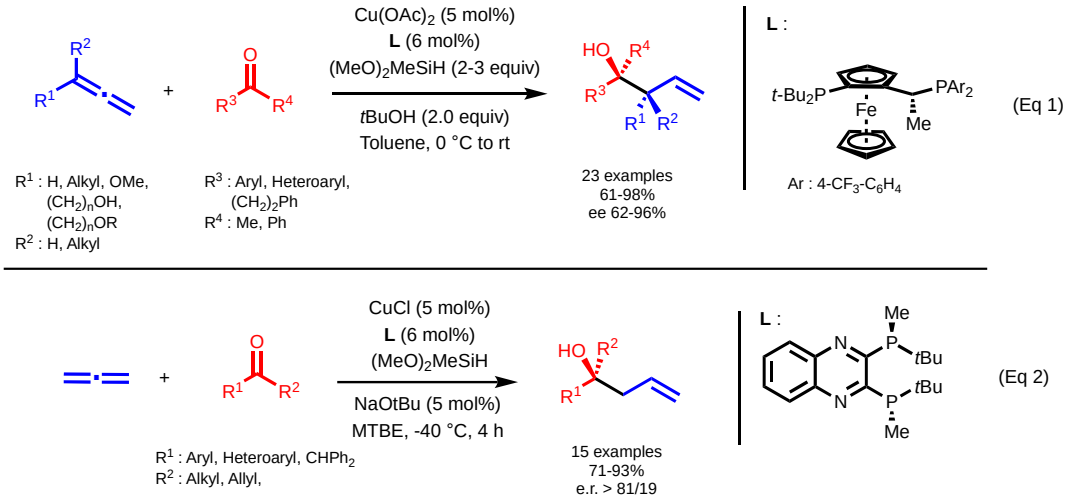
Scheme 110: Ni-catalyzed addition enones with mono- and 1,3-disubstituted allenes.

The copper-catalyzed addition of imines, as equivalent of activated carbonyl group, to allenes has been reported by the group of Buchwald using a copper-hydride catalytic system, known to be effective for the reductive addition of imines and carbonyls to unsaturated compounds (Scheme 111).[237] A variation of the functional group placed on the imine, allowed the authors to modify the regioselectivity of the addition. Classic functional groups like benzyl gave branched allylated products (homoallylic molecules) while a N-phosphinoyl imine gave access to linear products.



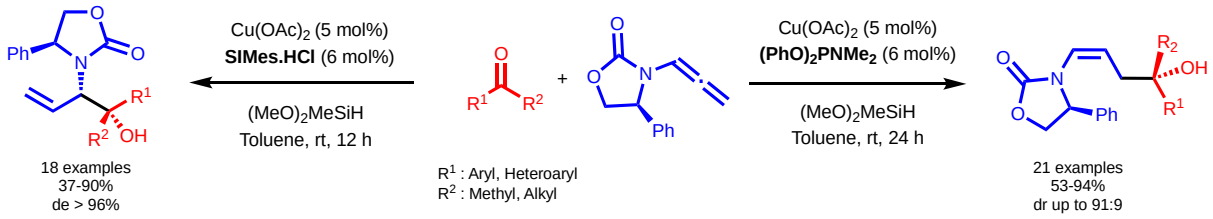
Scheme 111: Addition of terminal allenes to an imine catalyzed by a Cu-H system.

Recently the same group showed that an in-situ generated CuH-based catalyst, used in the presence of chiral diphosphine and silane, was able to perform the allylation of ketones with terminal disubstituted allenes[238] or with simple gaseous allene. (Scheme 112).[239] the corresponding chiral allylic alcohols were obtained with excellent regio- and enantioslectivities.



Scheme 112: Regio- and enatioselective Cu-catalyzed allylation of ketones.

In 2019, the team of Sieber also reported the enantioselective copper-catalyzed allylation of ketones using allenamides.[240,241] As for the copper-catalyzed functionalization of imines, an inversion of the selectivity is possible thanks to the modification of the ligand (Scheme 113). Indeed, using phosphoramidite allowed the formation of linear products (γ-hydroxyaldehyde equivalent) whereas the use of NHC-type ligands gave branched products (1,2-amino alcohol synthon).



Scheme 113: Ligand-controlled regio- and enantioselective Cu-catalyzed allylation of ketones with allenamides.

4. C-O bond formation

The use of catalytic intermolecular hydrofunctionalization of allenes to create C-O bonds is less described than it is for the formation C-N or C-C bonds. Two different routes were mainly described:

hydroalkoxylation and hydrocarbonylation (Figure 3). The first one involved allenes with aliphatic alcohols and phenols derivatives, especially with palladium and gold-based catalysts. The second one uses palladium, rhodium and copper as catalyst for the addition of allenes to various carboxylic acids.

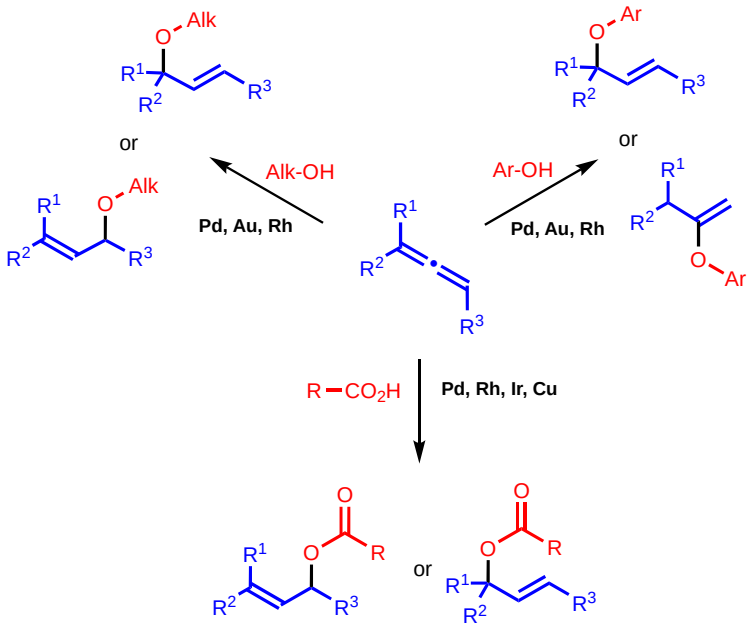
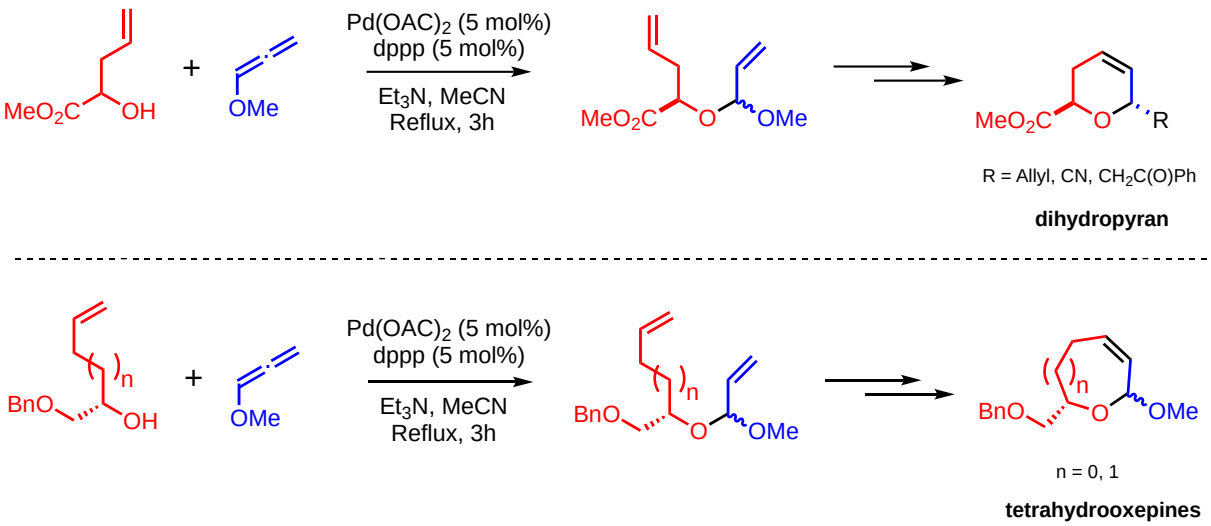


Figure 3 : Transition-metal catalyzed hydrofunctionalization of allenes for C-O bond formation.

4.1. Hydroalkoxylation

- Aliphatic alcohols

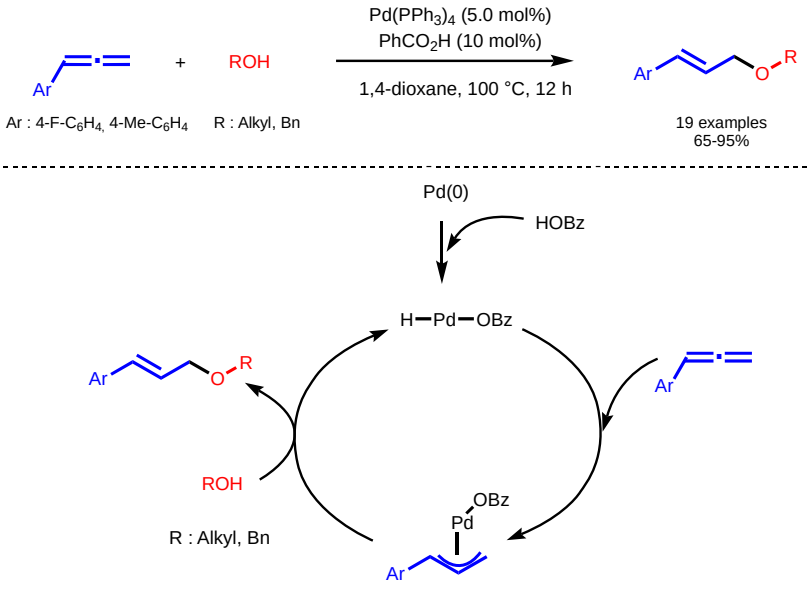
The first hydroalkoxylation of allenes with aliphatic alcohols has been described by Rutjes in 1997.[242] A palladium/diphospine (1,3-bis(diphenylphosphino)propane) catalytic system, directly inspired by a previous paper describing a carbonylation of iodophenols with allenes,[243] allowed the synthesis of functionalized dihydropyrans and tetrahydrooxepines from methoxyallene and various alcohols bearing an double bond (Scheme 114).



Scheme 114: Hydroalkoxylation of methoxyallene with aliphatic alcohols catalyzed by Pd: access to O-heterocycles.

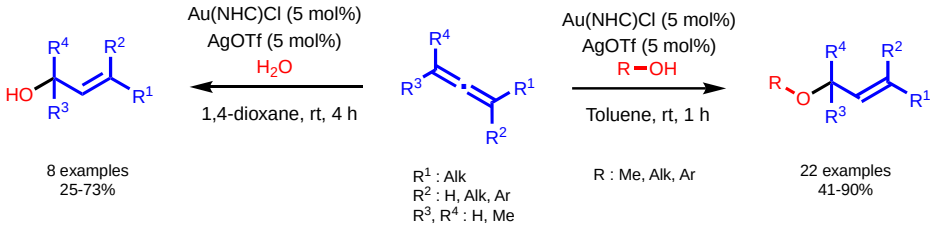
The method was used later to obtain various acetals for the synthesis of more complexes products of high interests.[244–248] This catalytic system was also enhanced by Rhee in 2014,[249] using a chiral ligand for the formation of cyclic acetals with a good enantioselectivity.

Another palladium-based system described in 2005 by Yamamoto[250] afforded an original synthesis of allyl ethers and allyl carboxylates (Scheme 115). This method, limited to mono-substituted aromatic allenes, was efficient for the addition of alcohols with a total regioselectivity on the terminal carbon, and was also used for the addition of carboxylic acids to an aryl-alkyne with an in situ generation of allenes. Authors proposed a mechanism involving a palladium-hydride complex in situ generated as the catalytic active species. The latter would be able to coordinate the terminal allene to allow the formation of a π-allylic-palladium complex that could be attacked by an alcohol and then release the corresponding allylic ether.



Scheme 115: Proposed mechanism for hydroalkoxylation of arylallenes with alcohols catalyzed by Pd.

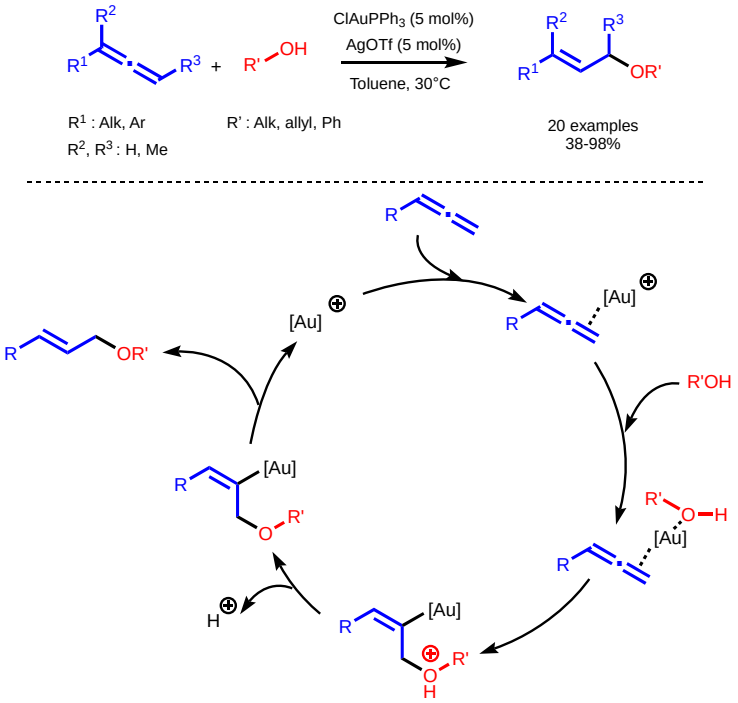
In 2008, three groups described almost simultaneously the gold/silver-catalysed hydroalkoxylation of allenes. Widenhoefer reported hydroalkoxylation of mono-substituted, 1,1- and 1,3-di-substituted, trisubstituted, and tetrasubstituted allenes with primary and secondary alcohols, methanol, phenol, and propionic acid using an NHC ligand in very soft conditions,[251] this reaction was described as fully regio- and stereoselective and was extended to the addition of water (Scheme 116).[252]



Scheme 116: Hydroalkoxylation and hydration of monosubsituted, 1,1- and 1,3-disubstituted, trisubstituted, and tetrasubstituted allenes co-catalyzed by Au and Ag.

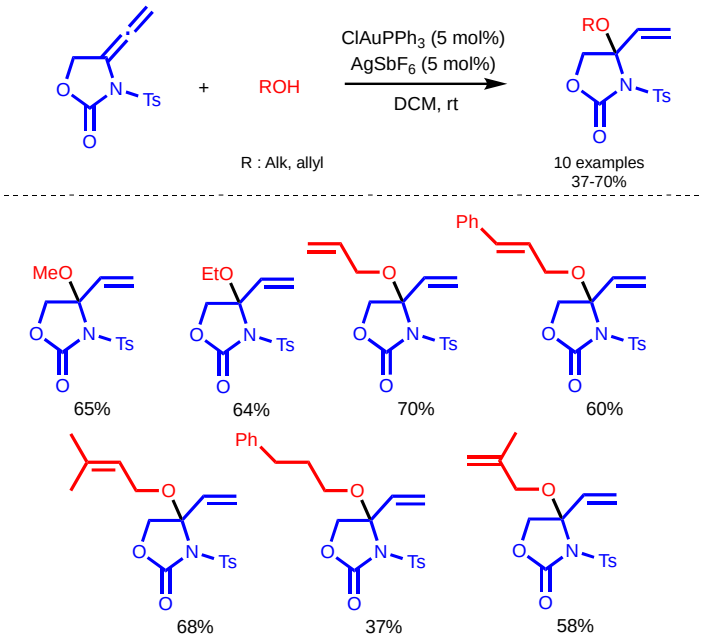
In the same time, the group of Yamamoto reported the use of a cationic gold(I) with triphenylphosphine as ligand, and focused on the mechanistic differences between hydroalkoxylation and hydroamination of allenes (Scheme 117).[34,253] Indeed, contrary to what have been observed with amines, no chirality transfer was obtained with alcohols, using a chiral allene. This information suggests that the mechanism starts with formation of a gold-allene complex, leading to racemization. Addition of the alcohol could then take place to give a gold-vinyl intermediate which allow the formation of allylic

ether and $[AuPPh_3]^+$ upon protonation of the carbon–metal bond. The cationic gold active species $[AuPPh_3]^+$ was generated by precipitation of chlorine as the silver salt.



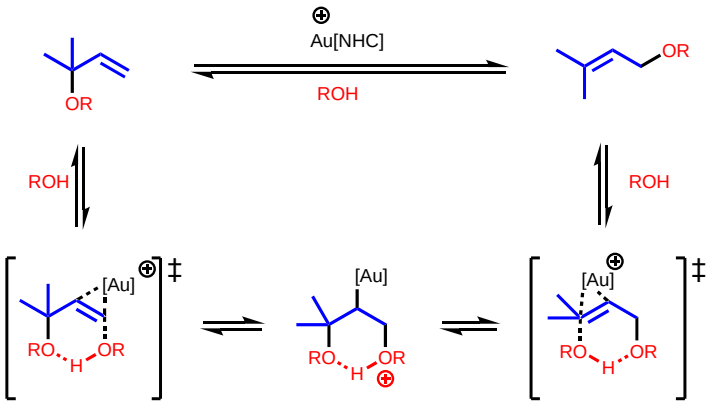
Scheme 117: Suggested mechanism for the Au/Ag-co-catalyzed hydroalkoxylation of allenes.

A related catalytic system allowed Horino to publish the addition of aliphatic alcohols on 4-vinylidene-2-oxazolidinone (Scheme 118).[254] Due to the specificity of this allene, they found out that the addition occurred on the α-carbon. The obtained 2-oxazolidione are of high interest for the synthesis of some antibacterial agents, and as chiral auxiliaries in asymmetric synthesis.



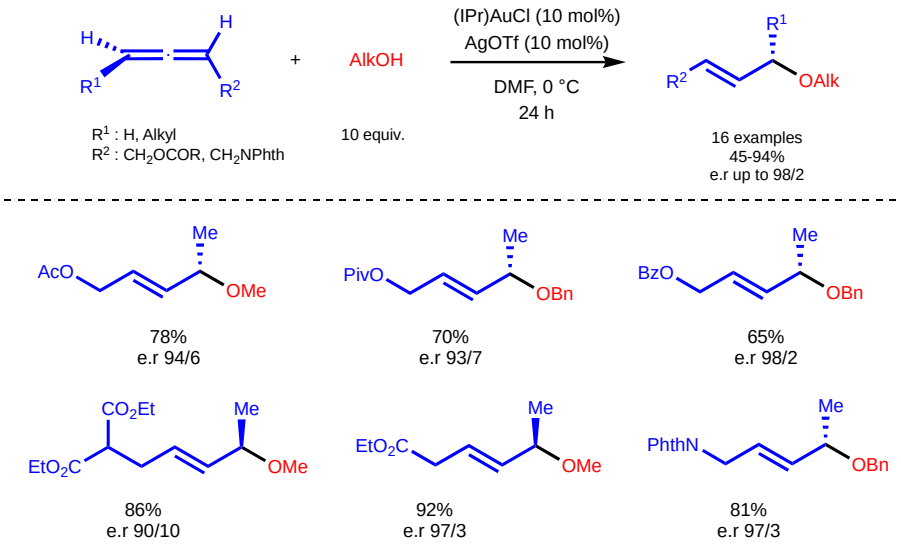
Scheme 118: Hydroalkoxylation of allenes co-catalyzed by Au/Ag.

After these first works, various strategies were developed in order to extend the application of gold-catalyzed hydroalkoxylation of allenes. Pérez-Castells observed the hydroalkoxylation of allenes as a side reaction during the synthesis of benzazepines.[255] Cui and Zhang reported two isolated examples of (Ph_3PAuNO_3)-catalyzed addition of alcohols onto aromatic allenes and alkoxyallenes.[256,257] Maseras performed in 2009 a DFT study of gold-catalyzed hydroalkoxylation of allenes,[258] suggesting that the regioselectivity observed by Widenhoefer (Scheme 116)[251,252] and Yamamoto (Scheme 117)[253] was a result of an Au(I)-catalyzed interconversion of the allylic ether product. Indeed, the catalyst used for the hydroalkoxylation was found to be able to promote the interconversion of the two different regioisomers, explaining the great selectivity for the linear product (Scheme 119).



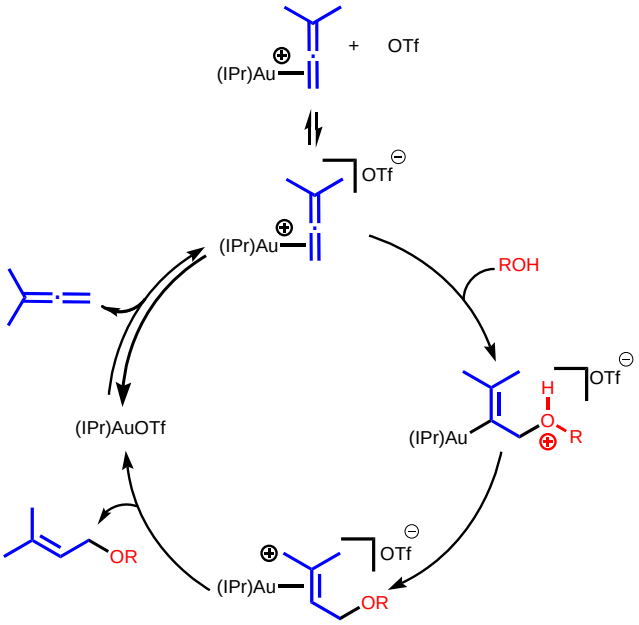
Scheme 119: Au-catalyzed interconversion of allylic ether.

The group of Lee succeeded in switching the regioselectivity described above,[258] delaying the isomerization process by performing the reaction in DMF with a large excess of alcohols.[259] While employing enantiopure 1,3-disubstituted allenes, the reaction was initially reported with poor chirality transfer, this limitation was overcame in these new conditions catalyzed by gold complex (Scheme 120).[260] Various alkyl *tert*-allylic ethers were then obtained with an excellent chirality transfer from a large scope of 1,3-disubstituted allenes and alcohols.



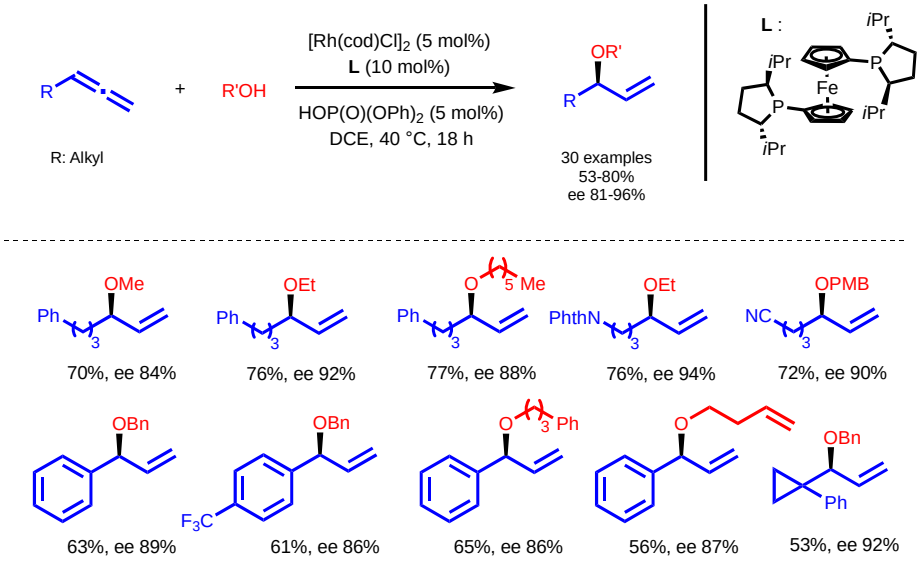
Scheme 120: Hydroalkoxylation of enantioenriched 1,3-disubstituted allenes with excess of alcohols co-catalyzed by Au/Ag.

In 2018, Widenhoefer and co-workers re-evaluated the interconversion hypothesis, as no interconversion was experimentally observed when the tertiary allylic ether was used as substrate.[261] They studied the hydroalkyxolation of 1,1-dimethylallene with 1-phenylpropan-1-ol and suggested an alternative mechanism. This mechanism begins by the reversible formation of a cationic gold cationic gold π-allene complex, favored as a tight-ion pair with OTf^-. This addition is then followed by a direct outer-sphere addition of the alcohol to the complex, then by protodemetallation giving formation of the primary allylic ether, also leading to the regeneration of the cationic Au(I) active specie (Scheme 121). They also pointed the potential effect of reaction medium on the mechanism of the reaction, as non-polar solvent favored the tight ion-pair intermediate.



Scheme 121: Proposed mechanism for the Au/Ag-co-catalyzed hydroalkoxylation of 1,1-dimethylallene

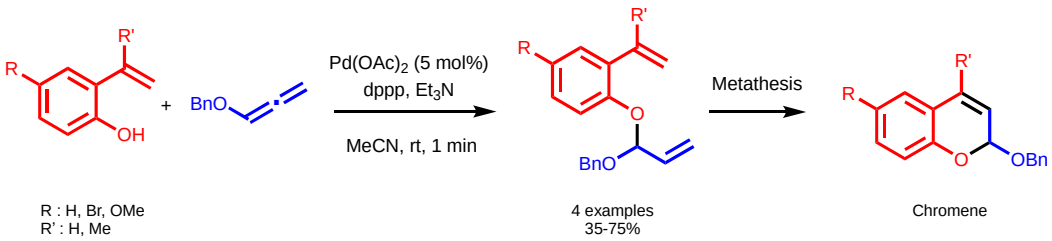
Finally, the rhodium-catalyzed hydroalkoxylation of allenes was also reported by the group of Breit in 2016. Using a ferrocene-based chiral ligand called (*S*,*S*)-*i*Pr-ferrocelane associated with a rhodium dimer, the enantioselective obtention of *tert*-allylic ethers was performed with mono-substituted allenes and alkyne analogues with a large scope of aliphatic and benzylic alcohols (Scheme 122).[262]



Scheme 122: Rh-catalyzed enantioselective hydroalkoxylation of terminal allenes with aliphatic and benzylic alcohols.

- Aromatic alcohols

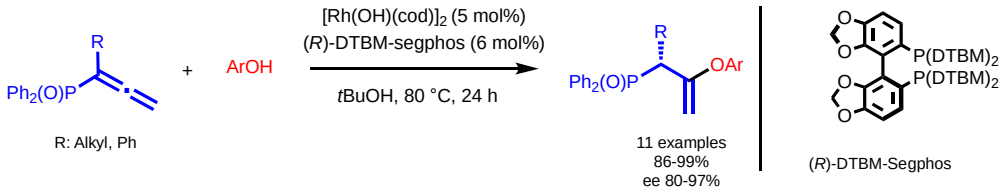
The hydroalkoxylation of allenes with aromatic alcohols was originally observed as a side reaction by Alper and co-workers during a study about palladium-catalyzed carbonylation of mono- and di-substituted allenes.[243] In 2000 Rutjes described the palladium-catalyzed hydroalkoxylation of allenes with phenols bearing a free-alkene in ortho, as a key step for the synthesis of chromenes via ring-closing metathesis (Scheme 123).[263] Noteworthy, the reaction proceeded at room temperature and allowed the formation of the diene in only one minute.



Scheme 123: Hydroalkoxylation of terminal allenes with phenols catalyzed by Pd.

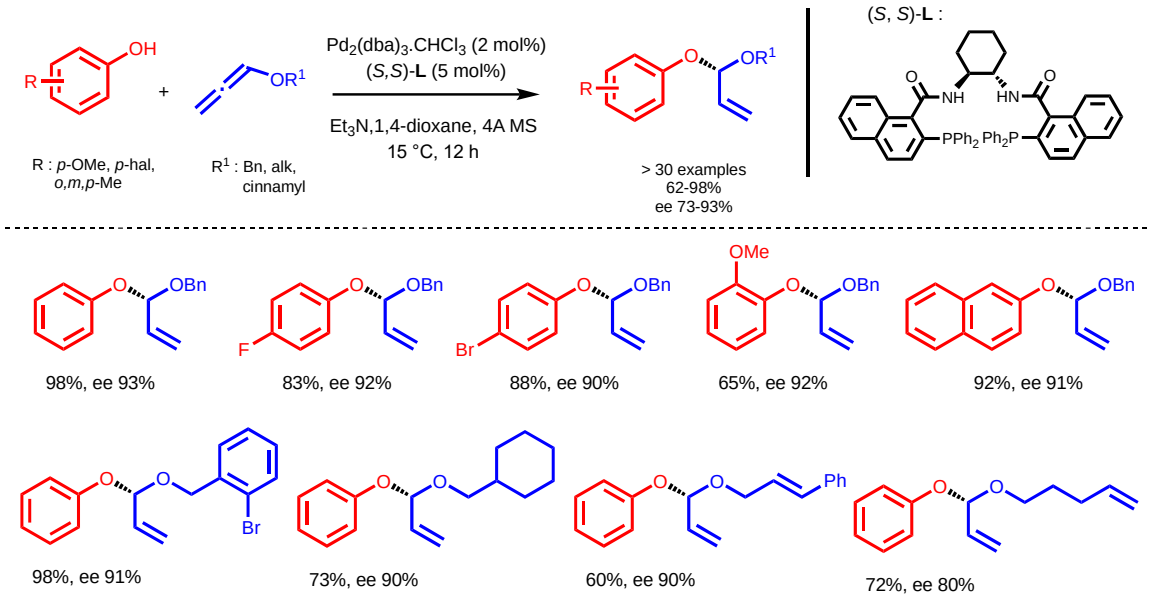
Similar conditions were also used for the obtention of allylic O,O- and N,O-acetals with aliphatic and aromatic alcohols.[244–248] A gold catalytic system described by Zhang and co-workers,[257] using $(PPh)_3AuNO_3$ with alkoxyallenes was exploited indifferently with aliphatic and aromatic alcohols.

Hayashi performed the hydroalkoxylation of diphenylphosphinyallenes with a rhodium catalyst and a chiral ligand (Scheme 124). The reaction which was the first reported intermolecular asymmetric addition of phenols to allenes, afforded access to an original family of phosphorous ligand.[264]



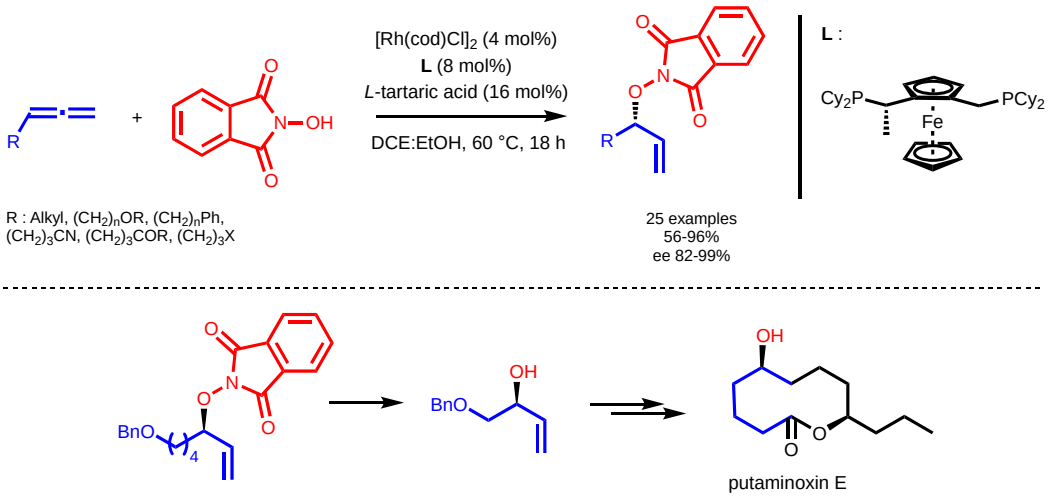
Scheme 124: Enantioselective Rh-catalyzed hydroalkoxylation of diphenylphosphinyallenes with phenols.

In 2015, the group of Cao published the palladium/PNNP ligand-catalyzed asymmetric intermolecular hydroalkoxylation of benzyloxyallenes and derivatives with phenols (Scheme 125).[265] This method was tolerant to a large scope of phenols and alkoxyallenes, and gave excellent regio- and enantioselectivities, probably due to the steric hindrance.



Scheme 125: Enantio- and regioselective hydroalkoxylation of alkoxyallenes with phenols catalyzed by Pd/chiral ligand system.

Working with rhodium/chiral diphosphine system, Breit and Liu showed that hydroxyphthalimides could be added on terminal allenes with excellent regio- and enatioseselectivity (Scheme 126).[266] With this new method, authors obtained allylic alcohols which are intermediates for the synthesis of putaminoxin E (cytotoxic agent).

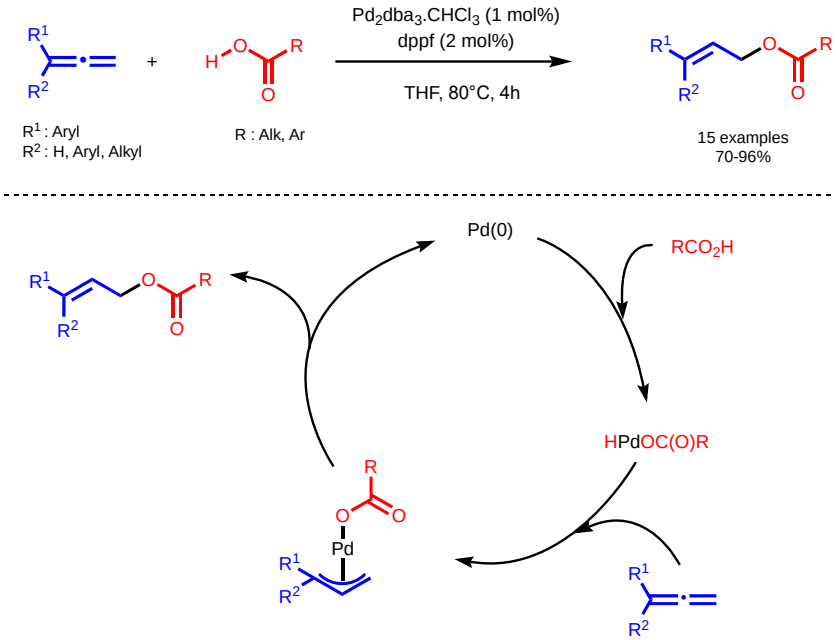


Scheme 126: Enantio- and regioselective Rh-catalyzed addition of hydroxyphthalimides to terminal allenes.

4.2. Hydrocarboxylation

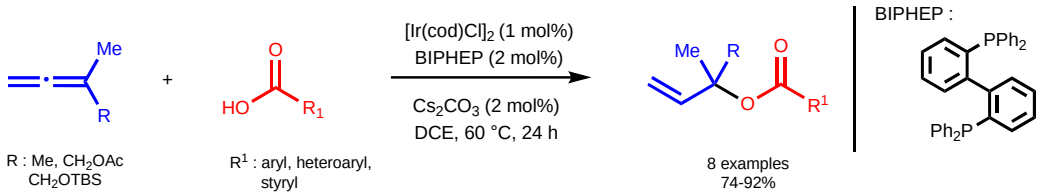
Compared to the addition of alcohols, the addition of carboxylic acids to allenes has been rarely reported. The first hydrocarboxylation of allenes was described in 1967 by Shier.[267] During their studies about dimerization and polymerization of allenes in presence of a palladium catalyst and sodium acetate, traces of hydrocarboxylated products were observed.

The first dedicated study of this reaction was published by the group of Yamamoto in 1998.[268] Using 1 mol% of palladium and a diphosphine ligand (dppf), the addition of aliphatic and aromatic carboxylic acids on terminal carbon of mono-substituted allenes was performed with total regio- and stereoselectivities while starting from 1,1-disubstituted allenes a mixture of *E* and *Z* products was obtained (Scheme 127). Authors suggested that this reaction occurs *via* the generation of a palladium hydride able to activate an allene to give an allyl palladium intermediate. The latter affords the allyl carboxylates expected with regeneration of a Pd(0) by reductive elimination.



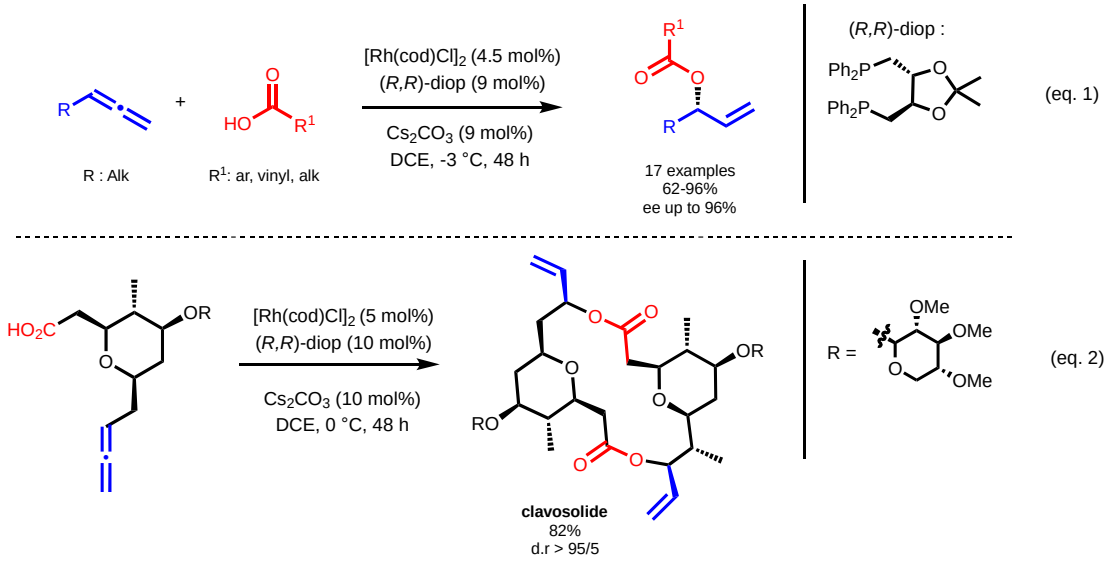
Scheme 127: Hydrocarboxylation of allenes with carboxylic acids catalyzed by Pd and proposed mechanism.

For more than 10 years, no other example for the hydrocarboxylation of allenes have been reported. In 2008 the team of Krische succeeded in completing this reaction using an iridium-based catalyst associated to a diphosphine ligand. The system allowed the hydrocarboxylation of terminal allenes with carboxylic acids on the most hindered carbon with very good yield. Even if the scope was limited to three allenes in this article, the reaction tolerates a large variety of functions on the acid partner (Scheme 128).[269]



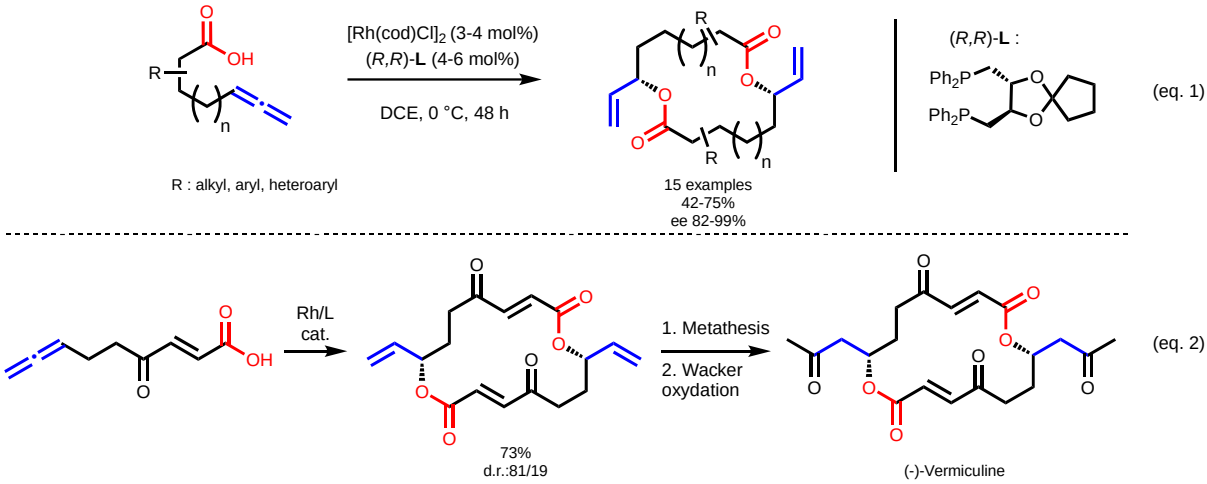
Scheme 128: Hydrocarboxylation of 1,1-disubstituted allenes with carboxylic acids catalyzed by Ir.

As part of their work on the hydrofunctionalization of allenes catalyzed by rhodium, the group of Breit reported in 2011 an enantioselective system from terminal aliphatic allenes with a large range of carboxylic acids to obtain branched allylic esters (Scheme 129, eq. 1).[270,271] This method was also used few years later for a flexible protecting-group-free synthesis of Clavosolide (a cytotoxic molecule), via a dimerization of a molecule bearing an allene and a carboxylic acid group (Scheme 129, eq 2).[271] In both case, the use of chiral diphosphine (*R,R*)-diop allowed better activites.



Scheme 129: Rh-catalyzed enantioselective hydrocarboxylation of allenes: application to the synthesis of Clavosolide A

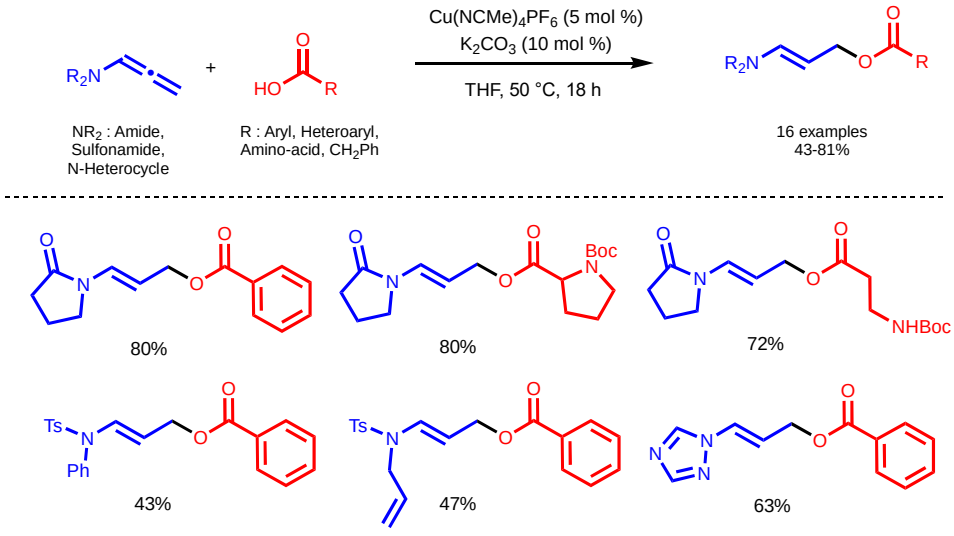
In 2018, the same group reported that this catalytic system, in the absence of base, was able to perform the enantioselective synthesis of *C2*-symmetric bismacrolactones, that constitute a bio-active molecules family. This original way was tolerant to a broad scope of substrates (ω-allenyl carboxylic acids) and the obtained macrocycles, up to 28-membered ring, were formed with excellent enantioselectivity thanks to the use a diop-type ligand (Scheme 130, eq. 1).[272] In 2019, they applied this method to the concise synthesis of (-)-Vermiculine, an antibiotic (Scheme 130, eq. 2).[273]



Scheme 130: Formation of macrocyles by enantioselective Rh-catalyzed hydrocarboxylation of allenes.

In 2014, in addition to the use of palladium, rhodium and iridium, the silver-catalyzed system developed by Guo and co-workers for the C-N bond formation (Scheme 8)[36] was also used to perform the addition of a carboxylic acid on 9-Allenyl-9*H*-purines with total selectivity on the terminal carbon of the allene.

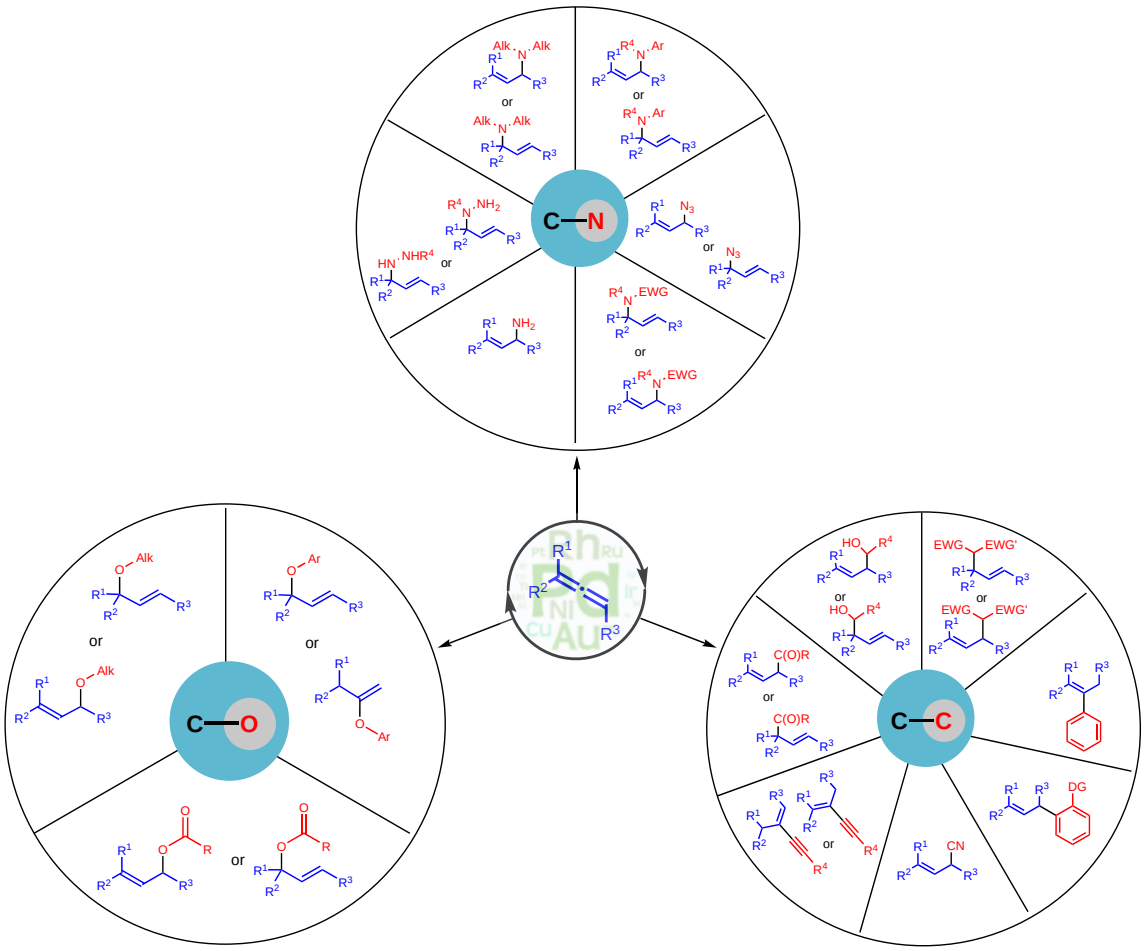
The copper-catalyzed hydrocarboxylation of *N*-allenyl derivatives has also been reported for the first time by our group in 2019.[274] This additional-ligand free catalytic system in the presence of a catalytic amount of base in THF at 50 °C gave selectively the linear allylic compounds with good to excellent yield and was efficient on amino-acid derivatives (Scheme 131).



Scheme 131: Cu-catalyzed hydrocarboxylation of *N*-allenyl derivatives.

5. Conclusion

For a long time, allenes were a forgotten unsaturated molecule family in organic chemistry. However, since the turn of the century, many studies mainly involving catalytic systems based on transition metals, have focused on the reactivity of allenes. In this review, we focused on the discoveries and developments in the intermolecular hydrofunctionalization of allenes for the formation of allylic structures via the creation of C-N, C-C and C-O bonds. A large variety of transition metals complexes was used to catalyze this transformation (Scheme 131). Precious metals as Pd, Rh and Au were predominantly used, but the exploitation of simple catalytic system employing abundant and cheap transition metals is rapidly developing, in order to make this reaction more sustainable. The allylic structures synthesized incorporate alkyl- and aryl ethers, or ester functions obtained via the formation of C-O bond. For the creation of the C-N bond via the allene hydrofunctionalization, a bountiful number of nitrogen nucleophiles such as alkyl- and arylamines, azides, amides, ammonia and hydrazines was used to selectively afford the corresponding allylic structures. Finally, the family of reactions involving the construction of C-C bonds is the most frequently described, with the formation of allylic structures including alkyl, aryl, nitrile, carbon monoxide, carbon dioxide, aldehyde, ketone and alcohol functions. Remarkably, a lot of the methods have been applied to the total synthesis of many natural products or highly potential bio-active molecules. Allene hydrofunctionalizations usually proceed with high regio- and stereoselectivity under smooth conditions with total atom-economy. The recent rationalization of the observed selectivities by mechanistic studies could lead in this field to even more innovative methodologies. In this context we can expect that this type of reaction will progressively become a classic and inevitable strategy for the synthesis of allylic moieties under more sustainable conditions than the historical and classical reactions



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Notes

The authors declare no competing financial interest.

Biographies

Rémi Blieck obtained his PhD in 2017 from the National Graduate School of Chemistry of Montpellier (France). During this period, he worked under the supervision of Prof. Florian Monnier and Dr. Marc Taillefer, mainly focusing on the discovery of copper-based catalytic systems able to perform intermolecular hydrofunctionalizations of terminal allenes. Then he joined for one year the COBRA laboratory in Rouen (France) as a postdoctoral fellow, working with Dr. Tatiana Besset on the development of new approaches in transition-metal catalyzed C(sp^3)-H bond activation. In 2019 he moved to ICIQ (Tarragona, Spain) to join the group of Prof. Antonio Echavarren as a postdoctoral fellow, working on the synthesis of poly-aromatic structures. His interests are focused on development of metal-catalyzed reactions and original methodologies.

Florian Monnier is full professor of chemistry at Ecole Nationale Supérieure de Chimie de Montpellier where he has been faculty since 2005 (Assistant professor in 2005, associate professor in 2012, then promoted full professor in 2016). He completed his M.Sc and PhD in Chemistry in 2000 and 2003, respectively, at the University of Rennes under the direction of Professor Pierre H. Dixneuf. He studied and developed several original C-C bond formation methodologies involving alkynes under ruthenium catalysis. In 2003 he moved to a postdoctoral position with Professor E. Peter Kündig at University of Geneva, where his studies centered on the development of ruthenium catalysts. In 2004, he arrived in Montpellier for postdoctoral position with Professor Jean Martinez and Servier Laboratories where he worked on medicinal chemistry. Then he entered the group of Dr. Marc Taillefer in 2005 as assistant professor. His actual research interests cover several areas of catalysis including arylation of nucleophiles, direct amination reactions and hydrofunctionalization of unsaturated compounds such as alkenes, alkynes and allenes. He was awarded in 2013 of the young research award from the region Languedoc-Roussillon. In 2015 he has been the recipient of Institut Universitaire de France (IUF) award as a junior member.

Marc Taillefer studied chemistry and earned his Ph.D. from the University Paul Sabatier, Toulouse, France, under the supervision of Igor Tchatchenko and Jean-Jacques Brunet in 1989. From 1990 to 1991, he was a postdoc at the Technische Universität München, Germany, with Wolfgang A. Herrmann. He became a CNRS researcher at the Ecole Nationale Supérieure de Chimie de Montpellier (ENSCM) in 1992 and CNRS Research Director in 2004. Marc Taillefer is currently the Head of the Architectures Moléculaires et Matériaux Nanostructurés team (AM2N) at the Institut Charles Gerhardt Montpellier (ICGM)/ENSCM. His research focuses on the discovery of breakthrough methodologies in the field of organic synthesis and homogeneous catalysis (C–N, C–O, C–C bond formation via copper- and iron-catalyzed arylation of nucleophiles, transition metal free mediated coupling reaction, and functionalization of unsaturated compounds), as well as phosphorus chemistry (synthesis, reactivity, and applications of phosphonium ylides). Among many other commitments, Marc Taillefer was President of the French Chemical Society's Organic Chemistry Division from 2012 to 2015. He was

awarded the Grand Prix Emile Jungfleisch Académie des Sciences of the *French Academy of Sciences* in 2017, and the European Sustainable Chemistry Award of the *EuChemS* in 2012, among many other honors. Since 2018, Marc Taillefer is the President of the *French Chemical Society* (SCF).

Acknowledgments

Financial support provided by Région Languedoc-Roussillon, École Nationale Supérieure de Chimie de Montpellier, Institut Universitaire de France and Centre National de la Recherche Scientifique (CNRS) are warmly acknowledged with thanks.

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