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ARTICLE

[4 + 2] and [4 + 3] Catalytic Cycloadditions of Allenes

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Fernando López*[a,b] and José L. Mascareñas*[a]

This feature review describes the developments of catalytic [4 + 2] and [4 + 3] cycloadditions of allenes, as efficient and practical methodologies for assembling six and seven-membered cyclic systems. The different methodologies have been classified depending on the type of key reactive intermediate that was proposed in the catalytic cycle.

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1. Introduction

Allenes are cumulated systems with two contiguous carbon-carbon double bonds. Compared to alkenes, allenes are intrinsically more reactive owing to their higher strain, and can exhibit axial chirality, something of interest in the area of asymmetric synthesis. For a long period of time allenes were considered not very stable and difficult to make; therefore, they were underestimated for the development of new synthetic methodologies. However, over the last two decades there have been many advances on the development of new synthetic approaches to prepare different types of allenes, which have fueled an intense activity to further uncover their synthetic potential.[1,2] One of the consequences is that the number of reports on the synthesis of natural products that involve as key step the reaction of an allene moiety has experienced an extraordinary growth.[3,4]

From the different transformation possibilities of allenes, those consisting of cycloaddition reactions are particularly appealing. Cycloadditions, by allowing the generation of at least two bonds and one cycle in a single operation, are unique tools to convert simple precursors into target relevant cyclic products in a rapid and efficient manner. Also importantly, cycloadditions generally involve the simple addition of two or more molecules, thereby being atom economical; and in many cases they take place with high regio- and stereo-control.[5]

Classical examples of cycloadditions of allenes include thermally- or photochemically-induced pericyclic processes such as Diels-Alder and 1,3-dipolar cycloadditions, or transformations proceeding through diradical intermediates, like many [2 + 2] processes. However, the scope of classical cycloaddition reactions is relatively small and restricted to precursors presenting a suitable electronic complementarity. Therefore, the development of catalysts that can afford new cycloaddition patterns is of enormous interest.

Transition metal complexes, owing to their multiple coordination and activation properties, offer excellent opportunities for this purpose. Accordingly, a number of transition metal catalyzed transformations involving allenes, including [2+2], [2+2+1], [3+2], [2+2+2], [4+2], [3+2+2], [5+2] or even [6+2] annulations, have been reported. Most common transition metal catalysts used to induce these reactions include Rh, Pd, Ni, Mo or Au complexes.[3,6] Generally, the allene acts as a 2C component, reacting by one of the two double bonds, although some examples describing the participation of the allene as a 3C component have also been recently reported.

One the other hand, it has also been extensively shown that allenes activated with electron withdrawing groups (e.g CO_2R or PO_3R_2) can participate in cycloaddition reactions by using Lewis base catalysts, such as phosphines. The ability of these nucleophilic catalysts to add to the central position of these electron deficient allenes allows the generation of a dipole capable of reacting with different cycloaddition partners.[7]

This feature review will focus on catalytic [4 + 2] and [4 + 3] cycloadditions of allenes, as efficient ways of assembling six- and seven-membered cyclic systems. We have classified the different approaches according to the mechanism that was originally proposed for the cycloadditions. Thus, we first include several catalytic cycloadditions of allenes that are proposed to proceed through putative **metallacyclic intermediates**. These are usually promoted by transition metal catalysts of Rh, Pd or Ni, metals which easily engage in redox processes involving oxidative addition and reductive elimination steps. Secondly, we will discuss those cycloadditions that proceed through **acyclic zwitterionic intermediates**. These species might be generated with carbophilic metal complexes (e.g. Pt or Au complexes) or by Lewis-base catalysts. The allene moiety can eventually act in these annulations as a two-, three- or even as a four-atom carbon component. For the latter case (4C), the participation of at least one additional carbon adjacent to the allene is required (Figure 1).

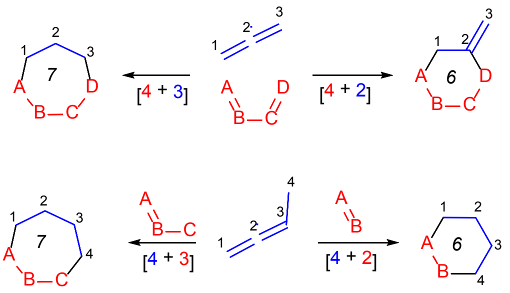


Figure 1. Model annulations of allenes working as two or three carbon partners, and α-substituted allenes as four carbon components (A-D: carbon or heteroatoms).

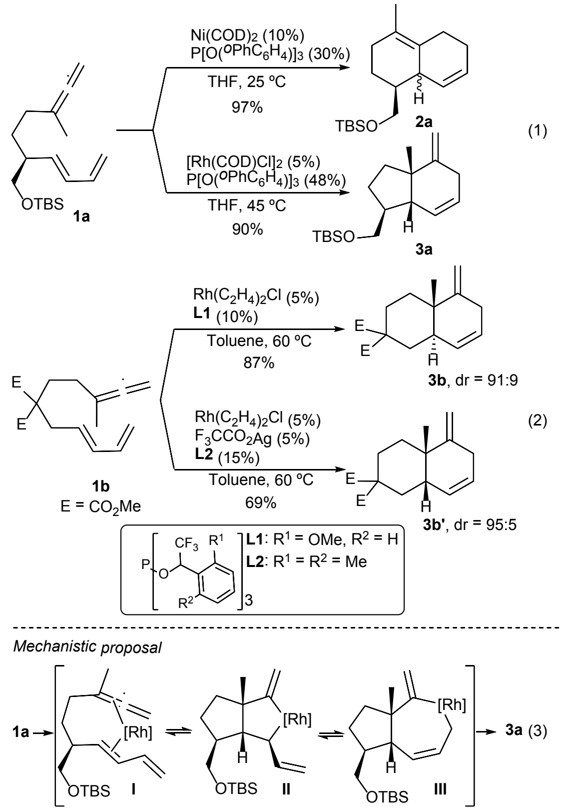
2. Catalytic cycloadditions through metallacyclic intermediates

During the last decades, a variety of transition metal catalyzed [4 + 3] cycloadditions for the synthesis of seven-membered heterocyclic and carbocyclic systems have been reported.[8] Some of them relied on the use of Pd or Ni catalysts, and have been proposed to proceed through metallacyclic intermediates. However, to the best of our knowledge, none of these catalytic cycloaddition reactions involve allenes as reaction components.

On the other hand, although there are many examples of metal catalyzed [4 + 2] cycloadditions involving 1,3-dienes as 4C components and alkynes as 2C partners, most of them using Rh, Ni or Pd catalysts,[5,6] only a handful of related [4 + 2] cycloadditions involving allenes have been described. The most relevant and interesting examples are described herein.

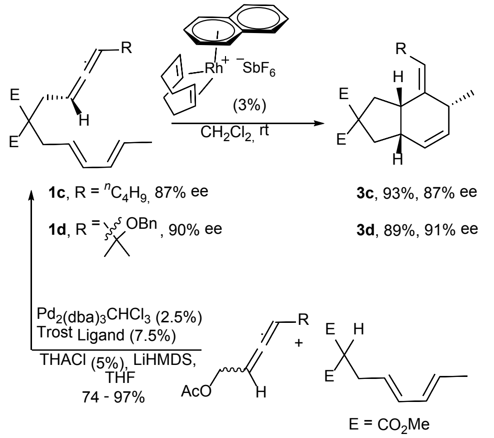
The first examples of a transition metal-catalyzed [4 + 2] cycloadditions with allenes were published by Wender and coworkers in 1995.[9] In particular, these authors demonstrated that allenedienes of type **1a** and **1b**, which incorporate a terminally unsubstituted allene, can undergo intramolecular [4 + 2] cycloadditions when treated with an appropriate Rh or Ni catalyst. The chemoselectivity and stereoselectivity of the process could be controlled by the selection of a precise transition metal catalyst. Thus, while treatment of **1a** with the Ni catalyst Ni(COD)$_2$/P[O(*o*Ph-C$_6$H$_4$)]$_3$ provided the 6,6-fused ring product **2a**, the use of a Rh catalyst such as [Rh(COD)Cl]$_2$/P[O(*o*Ph-C$_6$H$_4$)]$_3$ provided the *exo*-methylene cycloadduct **3a** in excellent yield (Scheme 1, eq 1). Moreover, [4 + 2] cycloadditions of allenedienes **1b** can provide bicyclic products with either a *trans* or a *cis* fusion by modifying the ligand and additives [for trans: **L1** (10 mol%); for *cis*: **L2** (15 mol%) and AgO$_2$CCF$_3$ (5 mol%)] (Scheme 1, eq 2).

From a mechanistic point of view, the authors suggested that, in the case of the Rh-catalyzed cycloadditions, there is an initial coordination to the Rh catalyst to both, the allene and the diene, to give an intermediate of type **I**, which undergoes an oxidative cyclometallation to generate the rhodacyclopentane **II** that can isomerize to the rhodacycloheptene **III**. Reductive elimination provides the six-membered carbocycle and regenerates the Rh complex (Scheme 1, eq 3). This path differs from the nickel-catalyzed process, probably because of the preferred coordination of this latter metal to the less sterically encumbered π-bond of the allene, as pointed out by the authors.



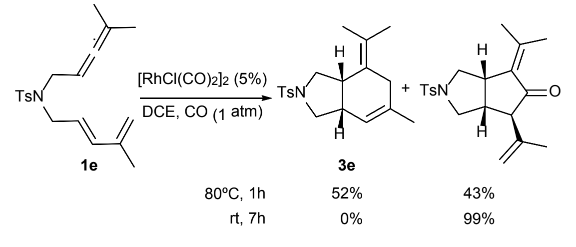
Scheme 1. Pioneering [4 + 2] cycloadditions by Wender.[9]

Despite this powerful demonstration of the potential of allene-dienes to generate different types of fused bicyclic systems, further studies on these cycloadditions have been scarce. In 2005, Trost and coworkers, reported related [4 + 2] cycloadditions using enantiomerically enriched, terminally substituted allene-dienes like **1c** or **1d** (Scheme 2).[10] Curiously, the catalyst [Rh(COD)Cl]$_2$/P[O(*o*Ph-C$_6$H$_4$)]$_3$ was ineffective; however, the employment of the cationic Rh catalyst [(C$_{10}$H$_8$)Rh(COD)]SbF$_6$, which was shown to be very active in related cycloadditions, allowed the desired cycloadducts to be obtained with good yields, complete diastereoselectivity and full chirality transfer. Interestingly, the allenic precursors could be generated in an optically enriched fashion by a dynamic kinetic asymmetric allylic alkylation; thus, the method provides an interesting entry to enantioenriched 5,6-bicyclic structures in a two-step sequence from simple racemic allenes (Scheme 2). It is worth noting that despite the progress in the development of enantioselective transition metal-catalyzed cycloadditions of dienes and alkynes proceeding through metallacyclic intermediates,[11] related asymmetric processes using allenes have not been reported.



Scheme 2. Enantiospecific Rh-catalyzed [4 + 2] allene-diene cycloadditions [THACl = tetrahexyl ammonium chloride].

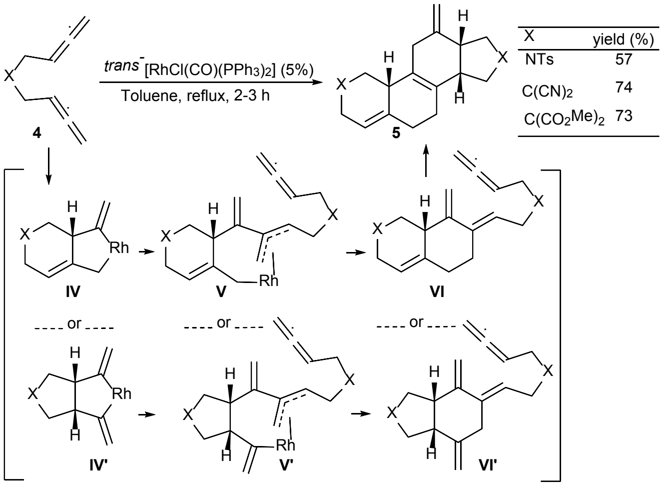
One year later, in 2006, in the context of the development of Rh-catalyzed [2 + 2 + 1] cycloadditions between allene-dienes and carbon monoxide, Wender discovered that treatment of allene-dienes featuring a terminally disubstituted allene (**1e**) with $[RhCl(CO)_2]_2$, at 80ºC and under 1 atmosphere of CO provides, not only the expected cyclopentanone adducts, but also products arising from a formal [4 + 2] cycloaddition (**3e**). Curiously, when this reaction is performed at rt, the [4 + 2] pathway is completely suppressed, so that the [2 + 2 + 1] adducts are exclusively obtained in 99% yield (Scheme 3).[12]



	3e	
80ºC, 1h	52%	43%
rt, 7h	0%	99%

Scheme 3. [4 + 2] *vs* [2 + 2 + 1] allene-diene cycloadditions.

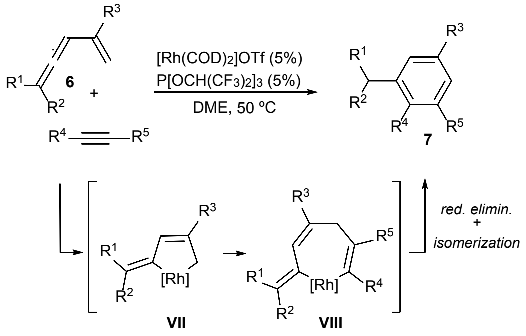
In 2005, Ma and coworkers reported a very efficient cycloaddition cascade to 18,19-norsteroid derivatives from bisallenes like **4**, by using a catalytic amount of *trans*-$[RhCl(CO)(PPh_3)_2]$ (Scheme 4).[13] From a mechanistic point of view, the authors suggested an initial cyclometalation to afford **IV** (or **IV'**), which may then undergo a carbometalation with one of the two allene moieties of a second unit of **4** to yield, after a reductive elimination, the allenediene intermediate **VI** (or **VI'**). Species **VI** could then undergo an intramolecular [4+2] reaction to form the 18,19-norsteroid skeleton **5**. The participation of the metal as catalyst in this latter step has not been unambiguously established since these intermediates (**VI** / **VI'**) could not be isolated.



X	yield (%)
NTs	57
C(CN)2	74
C(CO2Me)2	73

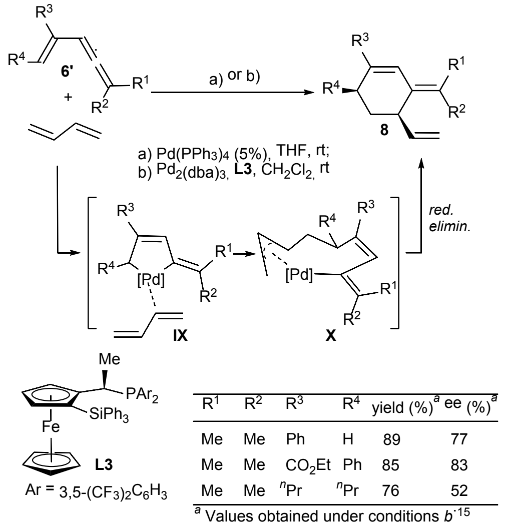
Scheme 4. Rh-catalyzed cascade cycloadditions of bisallenes **4**

To the best of our knowledge, intermolecular variants of the above allene-diene cycloaddition processes are unknown. However, intermolecular [4 + 2] cycloadditions using vinyl allenes as 4C components have been explored with different metal catalysts. In particular, Ito and Murakami have shown that vinyl allenes like **6** can engage into a Rh-catalyzed [4 + 2] cycloaddition with an external alkyne. The resulting benzene derivatives (**7**) were obtained with excellent regioselectivities and very good yields.[14] The catalyst of choice consisted of an equimolar mixture of $[Rh(COD)Cl]_2$ and a phosphite ligand, $P[OCH(CF_3)_2]_3$, in DME at 50 ºC (Scheme 5). A plausible mechanism proposed by the authors involves the initial formation of a five-membered rhodacycle intermediate (**VII**). Coordination of the alkyne, followed by a carbometallation step would provide a seven-membered rhodacycle of type **VIII**. This process occurs with complete regioselectivity, leading to the less sterically congested intermediate. A reductive elimination followed by isomerization to gain aromaticity yields the final arene (Scheme 5).



Scheme 5. [4 + 2] cycloaddition of vinyl allenes and alkynes.

The same authors also demonstrated that related [4 + 2] cycloadditions between vinylallenes **6'** and unactivated 1,3-dienes could also be efficiently promoted by $Pd(PPh_3)_4$ (5%) in THF at rt (Scheme 6).[15] In this case, it has been postulated the formation of an initial palladacylopentene intermediate of type **IX**. A subsequent carbometallation of the 1,3-diene leads to a π-allyl complex of type **X**, which has the R^4 group in a pseudoequatorial orientation. Finally, a reductive elimination affords the [4 + 2] cycloadduct (**8**) as a single diastereoisomer. The regio- and stereochemical outcome of the reaction has been rationalized assuming a pseudoequatorial orientation of the π-allyl moiety in the intermediate **X**, which helps to minimize repulsive steric interactions between this group and others substituents of the metallacycle. In the year 2000, the same group developed an enantioselective variant of this cycloaddition using a chiral palladium catalyst. The best enantioselectivities, of up to 83% ee, could be achieved using a catalyst made from $Pd_2(dba)_3$ (2.5%) and the ferrocenyl phosphine ligand **L3** (6%), in CH_2Cl_2 at rt (Scheme 6).[16] In the above examples the use of allenic precursors is probably key for success owing to the formation of bonds between the metal and their activated unsaturated carbon atoms.



R^1	R^2	R^3	R^4	yield (%)[a]	ee (%)[a]
Me	Me	Ph	H	89	77
Me	Me	CO_2Et	Ph	85	83
Me	Me	^{n}Pr	^{n}Pr	76	52

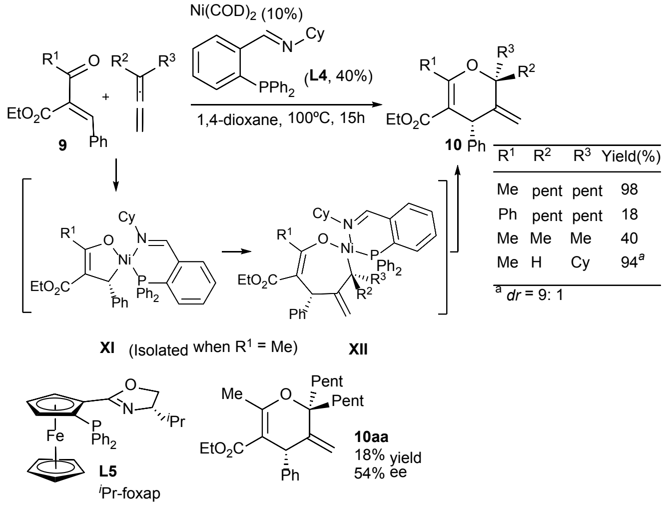
[a] Values obtained under conditions *b*.[15]

Scheme 6. Pd-catalyzed [4 + 2] cycloadditions of vinylallenes.

In 2011, Matsubara and Kurahashi reported the first examples of the participation of allenes in any type of transition metal-catalyzed hetero-[4 + 2] cycloaddition that proceeds via metallacyclic intermediates. In particular, these authors described the cycloaddition between enones of type **9** and 1,1-disubstituted allenes to afford synthetically relevant highly substituted dihydropyrans of type **10** in good yields.[17] The reaction is promoted by a nickel catalyst preformed from $Ni(COD)_2$ and a iminophosphine ligand (**L4**). Moderate stereoselectivities were obtained when monosubstituted allenes were used (Scheme 7).

From a mechanistic point of view, the authors proposed the initial oxidative cyclization of Ni(0) to the enone to form the oxanickelacycle intermediate **XI**. Subsequent coordination of the allene and migratory insertion into the C−Ni bond would lead to the seven-membered oxa-nickelocycle **XII** which, upon reductive elimination, delivers the final adduct and regenerates the catalyst. Supporting this mechanistic pathway, the authors reported the quantitative generation of the oxa-nickelacycle **XI** (R^1 = Me), from the stoichiometric reaction between the benzylideneacetoacetate **9a** (R^1 = Me) and $Ni(COD)_2$ / **L4** at rt. Treatment of this adduct with the allene partner (R^2 = H, R^3 = Cy) in toluene at 100 ºC (15 h) led to the corresponding [4 + 2] cycloadduct in 85% yield, supporting the formation of this nickelacycle as reaction intermediate.

A preliminary exploration of an enantioselective variant of this method allowed to discover that the use of ^{i}Pr-foxap (**L5**), a chiral ferrocenyl iminophosphine ligand, in combination with $Ni(COD)_2$, provides the cycloadduct **10aa** in a promising 54% ee, although in a poor 18% yield.[17] Therefore, the development of an efficient enantioselective variant remains to be achieved.



R^1	R^2	R^3	Yield(%)
Me	pent	pent	98
Ph	pent	pent	18
Me	Me	Me	40
Me	H	Cy	94[a]

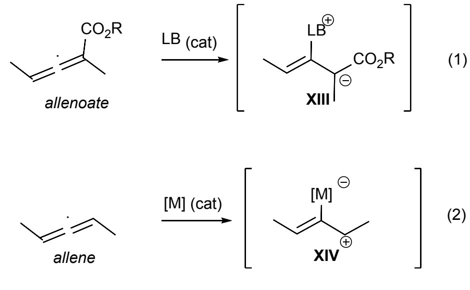
[a] *dr* = 9: 1

Scheme 7. Hetero-[4 + 2] cycloaddition between allenes and enones.

To sum up, a variety of examples of transition metal-catalyzed [4 + 2] cycloadditions involving allenes which proceed through metallacycles have already been reported; however the scope lags far behind that of related cycloadditions with alkynes, for which several types, including enantioselective and hetero-variants have been successfully developed. On the other hand and to the best of our knowledge, [4 + 3] versions of this type of catalytic chemistry are unknown. Undoubtedly, the recent progress on the development of efficient methods for the synthesis of allenes,[2] should help to further develop this field in the near future.

3. Catalytic cycloadditions through zwitterionic intermediates

In this section we describe a series of [4 + 2] and [4 + 3] catalytic cycloadditions involving allenes which have been proposed to proceed through zwitterionic intermediates. Depending on the type of catalyst that is used, two major types of processes can be considered, either those promoted by Lewis bases, (e.g. phosphines) and others promoted by carbophilic transition metal-catalysts (e.g. Pt(II) and Au(I) complexes). The former makes use of allenoates which, upon reaction with the Lewis base, are transformed into nucleophilic dipoles like **XIII** (Figure 2), which undergo a subsequent cycloaddition reaction. On the contrary, those based on carbophilic catalysts tend to generate electrophilic dipoles like **XIV**, which participate as 2C or 3C synthons in formal [4 + 2] or [4 + 3] cycloadditions with dienes. In some cases, enantioselective versions have also been developed, by using either chiral phosphines or chiral transition metal complexes.



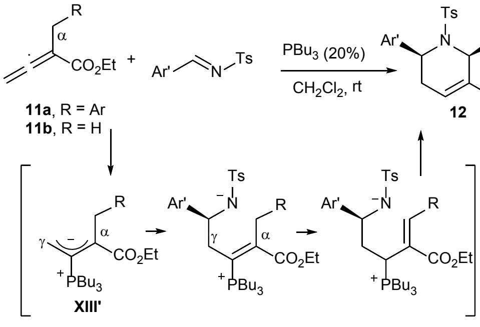
LB: Lewis Base; [M]: Carbophilic metal complex

Figure 2. Types of zwitterionic intermediates proposed in catalytic [4 + 2] and [4 + 3] cycloadditions of allenes.

Reactions promoted by Lewis-base catalysts

In 1995 Lu and coworkers reported that 1,3 dipoles of type **XIII** could be generated from the addition of PPh_3 to allenoates. This type of dipoles undergo very interesting [3 + 2] cycloadditions with electron-deficient alkenes, imines and other unsaturated 2-atom partners.[3,7]

In 2003, Kwon and co-workers demonstrated that, if the α-position of the allenoate is substituted by an alkyl group such as in **11a** or **11b**, the addition of the resulting zwiterionic intermediate of type **XIII'** to a tosyl aldimine exclusively takes place through the less hindered γ position. Two consecutive proton transfers followed by a ring closure with expulsion of the phosphine leads to tetrahydropyridines of type **12**, which are isolated in good to excellent yields (Scheme 8).[18] Therefore, the overall process can be considered as a formal [4 + 2] cycloaddition in which all the three carbon atoms of the allene, together with its adjacent sp^3 carbon, are incorporated into the newly formed cycloadduct.

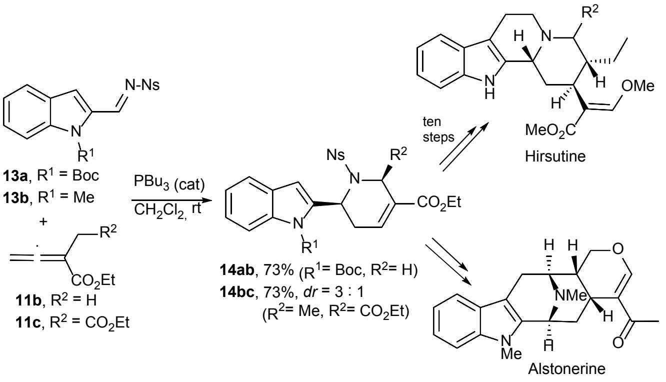


R	Ar'	**12**, Yield
H	Ph	98%
H	*p*-MePh	95%
H	*p*-FPh	95%
Ph	Ph	99%[a]
Ph	*p*-OMePh	99%[a]
Ph	*p*-NO$_2$Ph	90%[a]

[a] *dr* > 95 : 5

Scheme 8 [4 + 2] Cycloadditions between α-substituted allenoates and imines.

The synthetic utility of this method has also been demonstrated by Kwon and coworkers by applying the phosphine-catalyzed [4 + 2] cycloaddition to the total synthesis of Hirsutine.[19] The annulation between the indol imine **13a** and the allenoate **11b** provided **14ab**, an advanced precursor of the target alkaloid Hirsutine, which was eventually obtained after a sequence of ten steps. A related strategy using the imine **13b** and allenoate **11c** also enabled the formal synthesis of related alkaloids such as Alstonerine (Scheme 9).[20]



Scheme 9. Applications to natural product synthesis of the Kwon's [4 + 2] annulations.

In 2005, Fu reported the development of the first enantioselective version of these formal [4 + 2] cycloadditions between allenoates such as **11c** and several tosyl imines, using 5 mol% of phosphepine **15** as catalyst. The cycloadditions proceed at room temperature with excellent diastereoselectivities and with enantioselectivities of up to 98%.[21] More recently, Zhao and coworkers developed a second enantioselective catalyst, namely a bifunctional *N*-acyl aminophosphine (**16**), which also provided excellent enantiomeric excesses and very good yields in the same [4 + 2] cycloadditions (Figure 3).[22]

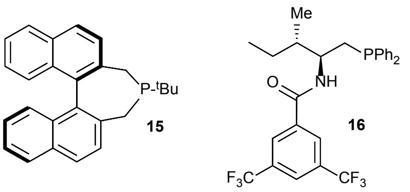
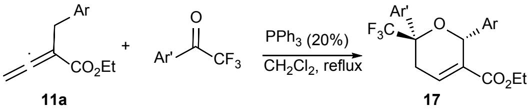


Figure 3. Chiral catalysts for enantioselective [4 + 2] cycloadditions between allenoates and imines.

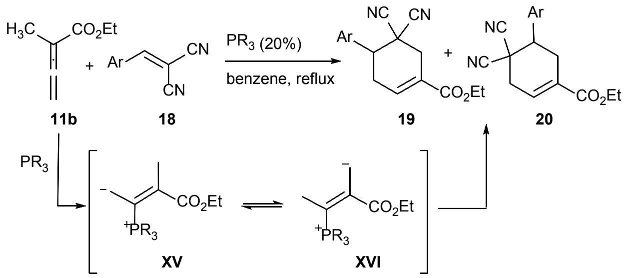
In 2010, Ye and coworkers demonstrated, for the first time, that carbonyl components can also participate in these [4 + 2] cycloadditions. In particular, these authors reported a Ph_3P-catalyzed cycloaddition reaction between α-benzyl allenoates (**11a**) and trifluoromethyl ketones. The corresponding dihydropyranic cycloadducts (**17**) are obtained with excellent diastereoselectivities and good yields (Scheme 10).[23]



Ar	Ar'	*dr*	**17**, yield
Ph	Ph	14:1	76%
p-MePh	Ph	15:1	75%
o-BrPh	Ph	14:1	85%
Ph	*p*-MePh	11 : 1	66%
Ph	*p*-ClPh	25 : 1	85%
Ph	*p*-MeOPh	10 : 1	53%

Scheme 10. [4 + 2] Cycloadditions of allenoates and ketones.

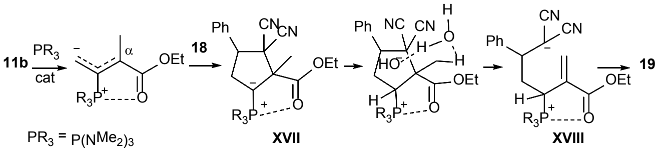
The development of all-carbon variants of this [4 + 2] cycloaddition, employing alkenes instead of imines, has also been pioneered by Kwon, who reported the first examples using highly activated arylidenemalononitriles like **18** as 2C partners (Scheme 11).[24] Importantly, the regioselectivity of the cycloaddition could be controlled by choosing appropriate phosphorous-based catalysts. Thus, while hexamethyl phosphorous triamide $P(NMe_2)_3$ promoted the formation of regioisomers **19**, the use of triarylphosphines such as $P(p\text{-}F\text{-}C_6H_4)_3$ favored the reaction through the regioisomeric dipole **XVI**, eventually providing cycloadducts of type **20**.



PR$_3$: P(NMe$_2$)$_3$: product **19**, Ar = Ph, 98% yield
P(4-F-C$_6$H$_4$)$_3$: product **20**, Ar = Ph, 93% yield

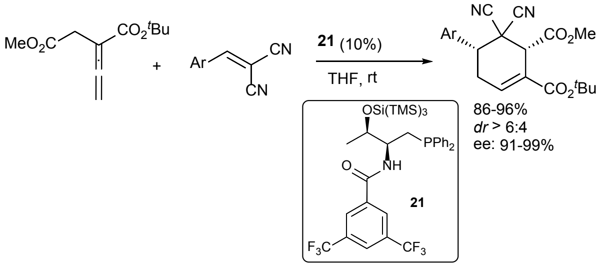
Scheme 11. [4 + 2] cycloadditions between α-methyl allenoate and benzylidenemalononitriles **18**.

Recent theoretical calculations by Wang and coworkers suggest that these formal [4 + 2] cycloadditions catalyzed by $P(NMe_2)_3$ could also be the result of a sequential process involving an initial [3 + 2] cycloaddition to give a zwitterionic species (**XVII**) that undergoes a water aided 1,3-H transfer to give acyclic intermediate (**XVIII**) This species undergoes a ring closure with concomitant release of the catalyst to yield the experimentally observed [4 + 2] adduct **19** (Scheme 12).[25] In the strict absence of water, a mechanism like that originally proposed by Kwon based on a stepwise [4 + 2] cycloaddition is also computationally viable, since the malononitrile moiety can also act as hydrogen transfer mediator.



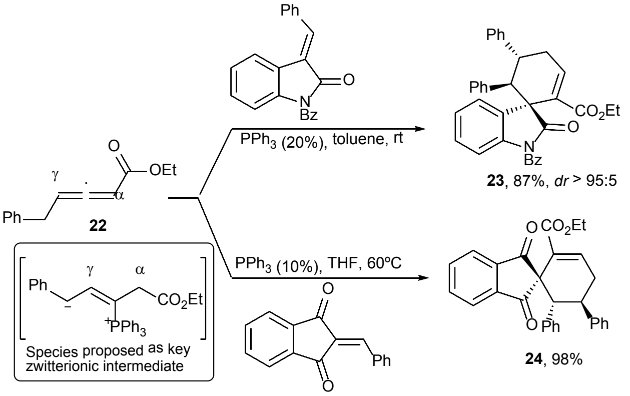
Scheme 12. Mechanistic proposal, based on DFT calculations.

The enantioselective version of this all-carbon [4 + 2] cycloaddition was not achieved until very recently, when Lu and coworkers reported that the chiral amino acid-based phosphine **21**, derived from L-threonine, is able to promote the cycloadditions between α-substituted allenoates and arylidenemalononitriles with excellent yields and enantioselectivities up to 99% (Scheme 13).[26]



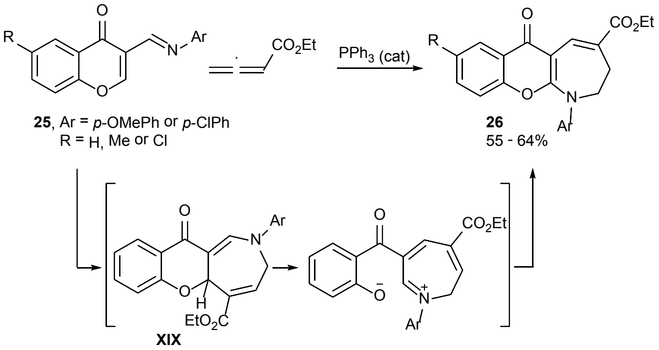
Scheme 13. Enantioselective [4 + 2] cycloadditions of allenoates.

Also very recently, Marinetti[27] and Huang[28] increased the synthetic scope of these [4 + 2] annulations demonstrating that not only α-substituted allenoates (**11**) could participate in the [4 + 2] cycloaddition, but also related γ-benzyl-substituted allenoates like **22** are suitable 4C-components for the reaction. These allenes undergo the phosphine catalyzed cycloaddition with 3-arylideneoxindoles and 2-arylidene-1H-indene-1,3(2H)diones to give interesting spirocyclic products (**23** and **24**) in good or excellent yields as well as excellent diastereoselectivities. Two representative examples are included in the Scheme 14.



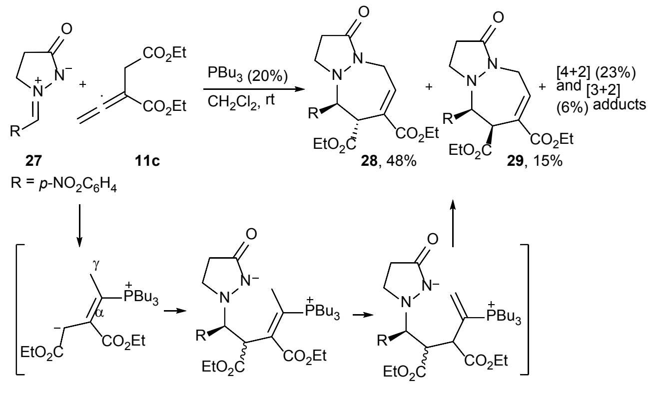
Scheme 14. [4 + 2] cycloadditions between γ-substituted allenoates.

Allenoates have also been shown to participate as three carbon components in phosphine-catalyzed [4 + 3] cycloaddition reactions. In particular, Ishar and coworkers reported in the year 2000 a few examples of a curious Ph_3P-catalyzed [4 + 3] annulation between 3-(*N*-aryliminomethyl)chromones (**25**) and ethyl 2,3-butadienoate. From a mechanistic point of view, it has been proposed that the resulting *N*-aryl-2,3-dihydro-4-ethoxycarbonylchromano[2,3-*b*]azepine-6-ones (**26**) are the result of a tandem rearrangement of the initially formed [4 + 3] adducts (**XIX**) involving a ring opening-ring closure process, followed by a 1,5-hydrogen shift (Scheme 15).[29]



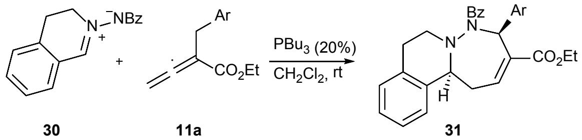
Scheme 15. [4 + 3] cycloadditions between ethyl 2,3-butanoenoate and 3-(*N*-aryliminomethyl)chromones **25**.

On the other hand, in 2011, Kwon and Guo described a series of [3 + *N*] cycloaddition reactions between azomethine imines and allenoates, including a [4 + 3] cycloaddition between the allenoate **11c** and an azomethine imine like **27**.[30] Although the reaction provides a mixture of diastereomeric cycloadducts in 48% and 15% yield, together with minor amounts of [3 + 2] (6% yield) and [3 + 3] (23% yield) adducts, it represents the first example of the use of an allene as a 4C-atom component in any type of [4 + 3] cycloaddition (Scheme 16).



Scheme 16. [4 + 3] cycloadditions of azomethine imines and allenoates.

The same authors demonstrated in 2012 that the selectivity of these [4 + 3] cycloaddition processes could be increased by using C,N-cyclic azomethine imines of type **30** and an α-benzyl substituted allenoate (**11a**). The use of P^nBu_3 as catalyst is also critical to obtain the [4 + 3] adducts and minimize the formation of competitive [3 + 2] products. The tetrahydroisoquinoline derivatives **31** are thus obtained in very good yields (Scheme 17).[31]



Ar	**31**, Yield[a]	Ar	**31**, Yield[a]
Ph	90%	*p*-ClPh	84%
o-MePh	42%	*p*-FPh	92%
m-MePh	55%	*p*-BrPh	93%

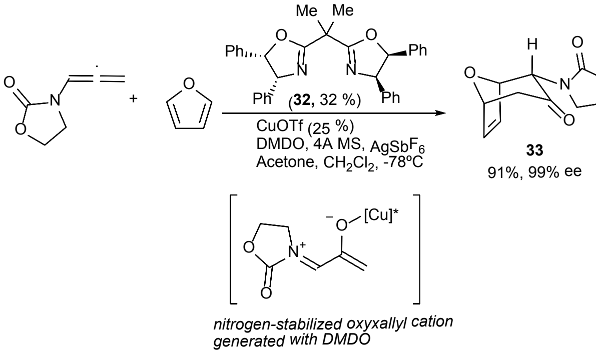
[a] In addition to **31**, [3 + 2] side products were typically isolated in <5% yield

Scheme 17. [4 + 3] cycloadditions of azomethine imines and α-benzyl substituted allenoates.

To sum up, since the original report by Kwon on a phosphine-catalyzed [4 + 2] cycloaddition of α-alkyl allenoates, the use of allenoates as 4C-atom partners in cycloaddition processes, including enantioselective versions, has been considerably extended. Although the first cases of [4 + 3] cycloadditions with azomethine imines as 3-atom synthons have already been described, further examples of these Lewis base-catalyzed reactions to make different type of seven-membered heterocycles are expected in the future. Finally, the use of allenoates as 3C components in [4 + 3] cycloadditions with 4π-components has been limited to the reactions shown in Scheme 15, so further progress in this type of phosphine-catalyzed cycloadditions might also be anticipated.

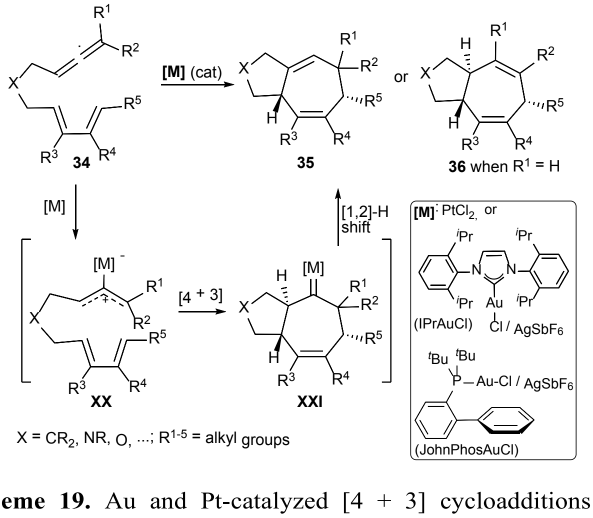
Reactions promoted by transition metal catalysts

[4 + 3] Cycloadditions. In 2001, Hsung and coworkers reported the use of oxazolidinone-substituted allenamides as 3C partners in [4 + 3] cycloadditions to conjugated dienes.[32] Although the initial method was not catalytic, few years later the same authors reported an enantioselective variant that is catalytic on the activating Lewis acid.[33] The authors demonstrated that a chiral copper complex containing a bisoxazoline ligand (**32**) was able to provide excellent enantioselectivities in intermolecular [4 + 3] cycloadditions of oxazolidinone-substituted allenamides and furans, using DMDO as stoichiometric oxidant to generate the reactive nitrogen-stabilized oxyallyl cation. The corresponding oxabicyclic adducts like **33** were obtained in good yields and up to 99% ee. An illustrative example is depicted in Scheme 18.



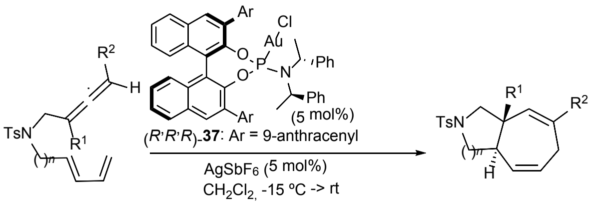
Scheme 18. Asymmetric [4 + 3] cycloaddition of allenamides and furans.

In 2008, we demonstrated the viability of using allenes as allyl cation surrogates, so that they could participate in [4C(4π)-3C(2π)] cycloadditions with conjugated dienes. We first found that $PtCl_2$ is an excellent catalyst for promoting these intramolecular [4 + 3] cycloadditions of allene-dienes of type **34** (Scheme 19).[34] The activation of the allene by this carbophilic complex generates a key metal zwitterionic intermediate of type **XX**, which undergoes a concerted [4 + 3] cycloaddition reaction with the diene moiety. The resulting metal carbene species (**XXI**) usually evolves through a 1,2-hydrogen shift, leading to seven-membered carbocycles of type **35** and / or **36**. As demonstrated by Toste and by us, the use of a cationic Au^I catalyst containing a σ-donating *N*-heterocyclic carbene ligand (IPrAuCl/$AgSbF_6$) or an electron rich biaryl ditertbutyl phoshine (JohnPhosAuCl/$AgSbF_6$) allows these reactions to be performed under milder conditions, increasing the scope and synthetic utility of the process.[35,36] In general, the reactions tolerate a wide variety of substituents in the allene and the diene, providing the corresponding bicyclo[5.3.0]decane systems in good yields. Moreover, regardless of the metal catalyst employed, the cycloadditions always showed a complete *exo* stereoselectivity resulting from an *exo*-like (or extended) transition state, thus providing a *trans* fusion between the five- and seven-membered carbocycles.



Scheme 19. Au and Pt-catalyzed [4 + 3] cycloadditions of allene-dienes **34**.

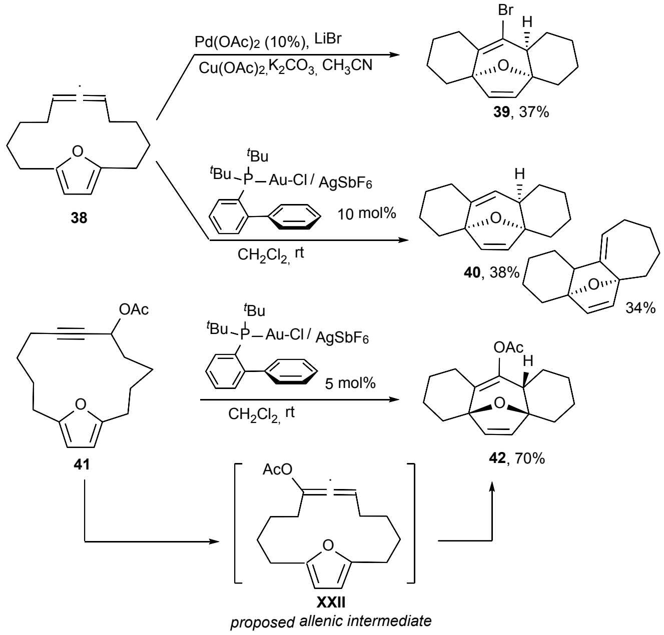
The reaction has been also carried out in an enantioselective manner by using mononuclear phosphoramidite–gold(I) complexes like **37**.[37] The scope of this method, which constituted the first highly enantioselective intramolecular [4C + 3C] cycloaddition promoted by a transition metal complex, encompasses internally monosubstituted allenes (R^1 = H), as well as disubstituted counterparts (R^1 = alkyl). The route offers a direct entry to 5,7- and 6,7-bicyclic systems including those with quaternary stereocenters at the ring fusion. Selected examples are depicted in Scheme 20.



n	R^1	R^2	yield	ee
1	H	Ph	74%	95%
1	Me	Me	78%	95%
1	Me	^{i}Pr	76%	95%
2	Me	Me	95%	98%

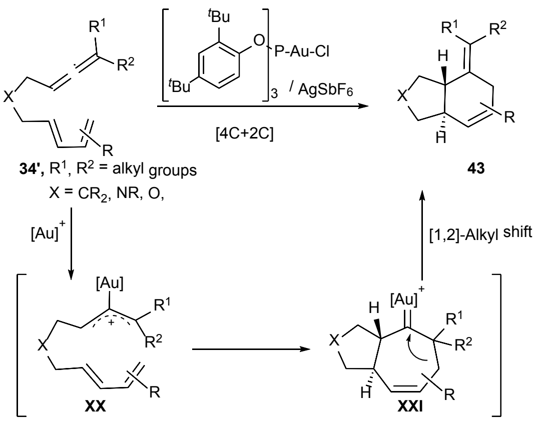
Scheme 20. Enantioselective allene-diene [4 + 3] cycloadditions.

During the last years, Gung and coworkers have demonstrated the viability of performing related [4 + 3] cycloadditions in a transannular manner (Scheme 21). Initially, these authors showed that the [4 + 3] cycloaddition of **38** could be carried out under Pd (II) catalysis, providing the tetracyclic system **39**, which incorporates the core skeleton of Cortistatin A, a potent antiangiogenic natural product.[38] In subsequent papers, they demonstrated that gold catalysts such as JohnPhosAuCl/$AgSbF_6$ were more effective, in particular when the annulation process was carried out using a propargyl ester precursor like **41** (Scheme 21)**,** which in situ rearranges to an allenyl acetate intermediate (**XXII**). Both, the rearrangement and the cycloaddition are catalyzed by the gold complex. Curiously, depending on the ring size of the starting material, different diastereoselectivities were observed.[39]



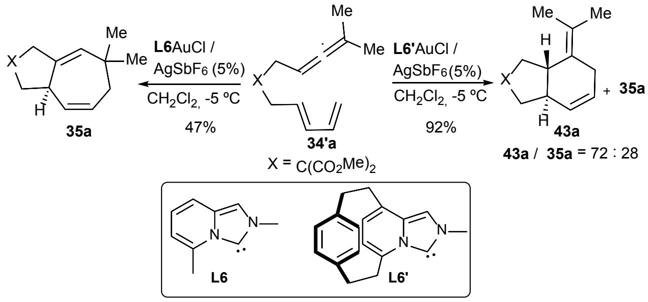
Scheme 21. Allene-diene transannular [4 + 3] cycloadditions.

[4 + 2] Cycloadditions. The groups of Toste and Mascareñas independently demonstrated that the same type of allene-dienes, when disubstituted at the distal position of the allene (**34'**) lead to products formally arising from a [4 + 2] cycloaddition process, provided to the use of a gold(I) catalyst bearing a π-acceptor phosphite ligand (Scheme 22).[36,40] Based on experimental data and on theoretical calculations, it has been proposed that the reaction also begins with a [4 + 3] cycloaddition, as previously shown in Scheme 19, giving the carbene intermediate of type **XXI**. At this stage, the disubstitution at the carbene-α-position as well as the use of a π-acceptor phosphite ligand at gold favors a ring contraction instead of the 1,2-H shift, eventually delivering the six-membered carbocycle. Therefore, the ligand at gold, as well as the type of substituents at the allene terminus, determine the formation of the [4 + 3] (**35** and / or **36**) or [4 + 2] (**43**) cycloadducts.



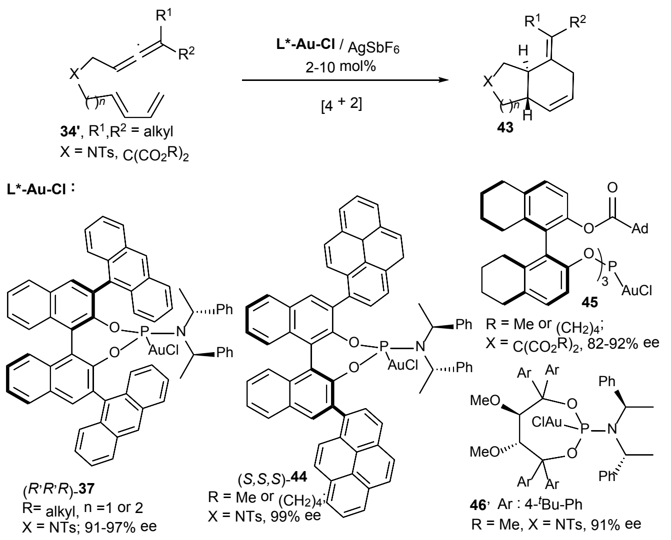
Scheme 22. The allene-diene [4 + 2] cycloaddition.

Fürstner and co-workers described several examples confirming this type of ligand-dependent dichotomy (Scheme 23).[41] In particular, they showed that the π-acceptor properties of NHC ligands such as **L6** could be enhanced by introducing a second aromatic layer spanned over the imidazopyridine-2-ylidene system (**L6'**), whereas the σ-donating abilities of both ligands remain basically equivalent. As a consequence, the gold complexes of ligands **L6** and **L6'** behave in a different manner. While complex **L6**AuCl, containing the less π-acceptor ligand is able to efficiently induce the [4 + 3] cycloaddition of allene-diene **34'a**, the related catalyst with the cyclophanic NHC ligand (**L6'**AuCl), preferentially afforded the [4 + 2] cycloadduct **43a** (Scheme 23).



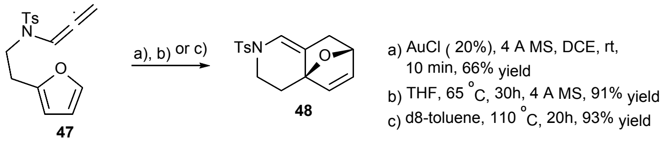
Scheme 23. Influence of the π-acceptor properties of NHC ligands.

Also in consonance with the mechanistic proposal based on the formation of a common carbene intermediate of type **XXI**, we demonstrated that the same phosphoramidite-gold complex that is able to promote enantioselective [4 + 3] cycloadditions ((*R*,*R*,*R*)-**37**, Scheme 20) also induces excellent enantioselectivities in the [4 + 2] cycloadditions of allene-dienes which are disubstituted at the allene terminus (Scheme 24).[40] Independently, Toste and coworkers also reported that the related phosphoramidite-gold complex (**44**) and the chiral phosphite gold catalyst **45** are also able to induce excellent enantioselectivities in these (4 + 2) cycloadditions.[42] Additionally, Fürstner and coworkers showed that Taddol-based phosphoramidite-gold complexes like **46** are also able to induce good enantioselectivities (Scheme 24).[43]



Scheme 24. Chiral gold catalysts for allene-diene enantioselective [4 + 2] cycloadditions.

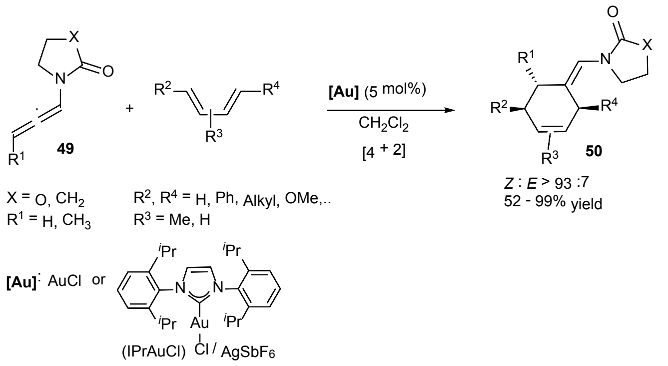
Finally, Hsung and coworkers have developed another intramolecular [4 + 2] cycloaddition between tosylallenamides and furans. Although the reaction can be carried out at room temperature under AuCl catalysis, the authors demonstrated that, for this particular case, the same process can also be achieved under thermal conditions, without any gold catalyst, using temperatures higher than 65ºC (Scheme 25).[44]



Scheme 25. Furan-allenamide intramolecular [4 + 2] cycloadditions.

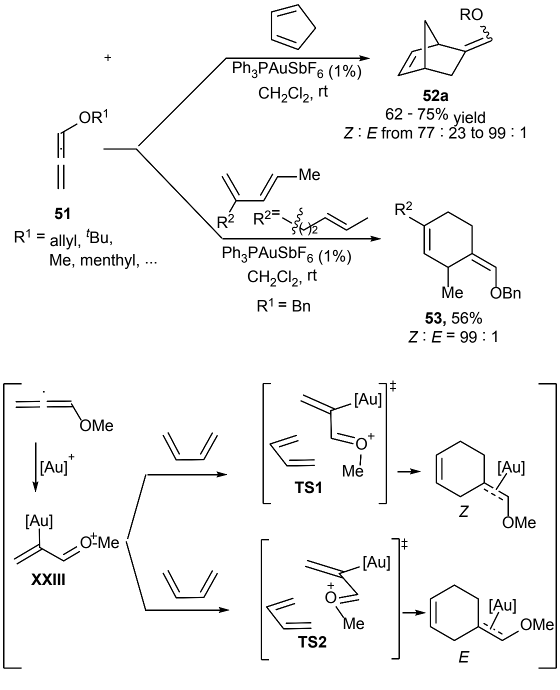
Intermolecular variants of these allene-diene cycloadditions have received less attention. Indeed, the development of an intermolecular [4 + 3] cycloaddition between allenes and dienes remains elusive. However, during the last three years there has been a significant progress in the development of transition metal-catalyzed intermolecular [4 + 2] cycloadditions through metal zwitterionic intermediates.

In 2011, our group reported the first examples of a gold-catalyzed [4 + 2] cycloaddition between allenamides of type **49** and conjugated dienes. The reaction, which is efficiently promoted by AuCl or the *N*-heterocyclic carbene gold catalyst IPrAuCl/AgSbF$_6$, can be performed both, with electron-neutral and electron-rich dienes, providing a straightforward regio- and diastereoselective entry to a variety of differently substituted cyclohexenes (**50**) (Scheme 26).[45]



Scheme 26. Intermolecular Au-catalyzed [4 + 2] cycloaddition of allenamides and dienes.

Almost simultaneously, a [4 + 2] cycloaddition between allenyl ethers (**51**) and dienes was also reported by Goeke using Ph$_3$PAuCl / AgSbF$_6$ as catalyst (Scheme 27).[46] Based on DFT calculations with allenylether **51a** (R^1 = Me) and 1,3-butadiene, and using [Me$_3$PAu]$^+$ as model catalyst, these authors proposed that the cycloaddition occurs through an initial coordination of the gold catalyst to the allenyl ether to generate a zwitterionic metal intermediate of type **XXIII**. This species undergo a [4 + 2] concerted cycloaddition with the diene, directly leading to the observed carbocycles. Depending on the conformation of this species (**XXIII**), two different transition states (**TS1** and **TS2**), respectively leading to the *Z* and *E* isomers, were identified. Transition state **TS1**, leading to the *Z* isomer turned out to be more favorable, by 2.0 Kcal·mol^{-1}, in qualitative agreement with *Z*-selectivity observed with acyclic dienes.



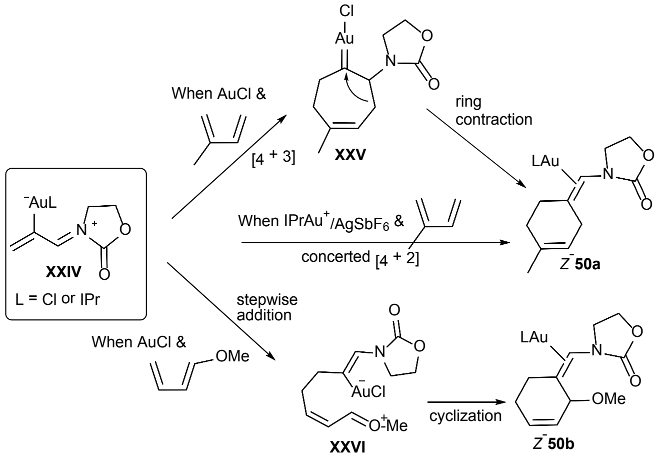
Scheme 27. [4 + 2] Cycloadditions of allenyl ethers and dienes

The mechanism of the [4 + 2] cycloadditions between allenamides and acyclic dienes (Scheme 26) has also been explored by means of a combined experimental and computational approach (Scheme 28).[47] The formation of the major [4 + 2] cycloadducts can be explained by invoking different pathways whose prevalence depend on the nature of the diene (electron-neutral *vs* electron-rich) and the type of gold catalyst (AuCl *vs* $IPrAu^+$).

A common feature for all pathways is the easy activation of the allenamide by the gold catalyst to give a gold zwitterionic species of type **XXIV**. Then, with the cationic gold catalyst [$IPrAuCl/AgSbF_6$] and an electron neutral diene such as isoprene, the formation of the *Z*-[4 + 2] adduct (*Z*-**50a**) can be better explained in terms of a concerted [4 + 2] cycloaddition between the diene, arranged in a *s-cis* conformation, and the gold intermediate **XXIV**. Overall, this pathway resembles that previously proposed by Goeke for the cycloaddition of allenylethers (Scheme 27).

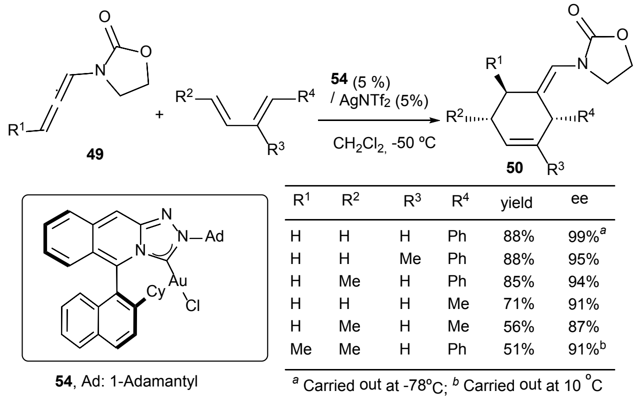
However, with AuCl as catalyst the mechanistic picture is somewhat more complex. The reaction also starts by formation of the intermediate of type **XXIV,** which undergoes a nucleophilic interception by the diene. The calculations suggested that this attack can result in a concerted [4 + 2] cycloaddition, as previously shown for $IPrAuCl/AgSbF_6$, or in a concerted [4 + 3] cycloaddition to give species **XXV**, which eventually leads to the same [4 + 2] adduct (*Z*-**50a**) after a ring contraction event, similarly to that previously proposed in the intramolecular cycloadditions (Scheme 22). Curiously, this latter process, via **XXV**, turned out to be more favorable by 1.7 kcal mol^{-1}. The viability of this route was also demonstrated by a parcial oxidative interception of the gold carbenoid intermediates (**XXV**).[47]

On the other hand, in the case of the AuCl-catalyzed cycloadditions of allenamides and electron rich dienes, such as 1-metoxydiene, the theoretical calculations predict a stepwise cationic pathway through the key intermediate **XXVI**. This acyclic species evolve by nucleophilic attack of the vinyl gold moiety to deliver the [4 + 2] cycloadduct *Z*-**50b**. This mechanistic pathway, also supported by some experimental results, explains the formation of [2 + 2] cycloadducts that are observed in certain cases.[45,48]



Scheme 28. Mechanistic proposal for the allenamide [4 + 2] cycloadditions.

An enantioselective version of these [4 + 2] cycloadditions between allenamides and dienes using the chiral gold complex **54**, which features a triazole unit embedded in a rigid axially chiral cyclic frame, has been recently disclosed (Scheme 29).[49] The catalyst generated from **54** and $AgNTf_2$ was able to promote the [4 + 2] cycloaddition between allenamides (**49**) and conjugated dienes, to give optically active cyclohexene products of type **50,** with complete regio- and diastereoselectivity, and enantioselectivities of up to 99% ee (Scheme 29).

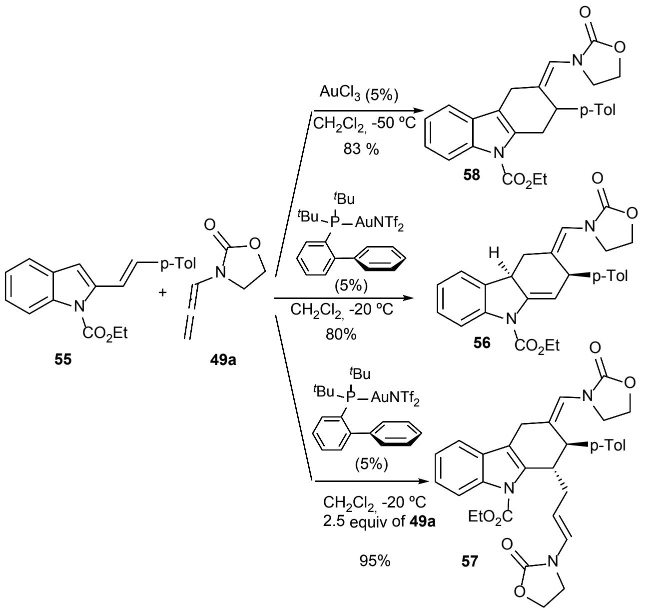


R^1	R^2	R^3	R^4	yield	ee
H	H	H	Ph	88%	99%[a]
H	H	Me	Ph	88%	95%
H	Me	H	Ph	85%	94%
H	H	H	Me	71%	91%
H	Me	H	Me	56%	87%
Me	Me	H	Ph	51%	91%[b]

[a] Carried out at -78°C; [b] Carried out at 10 °C

Scheme 29. Enantioselective Au-catalyzed [4 + 2] cycloaddition of allenamides and dienes.

Finally, very recently Rossi and Vicente reported a variant of these cycloadditions between allenamides and dienes, using 2-vinyl pyrroles (**55**) as 4C components. The corresponding [4 + 2] adducts (**56**) could be isolated in good yields by using $JohnPhosAuNTf_2$ as catalyst (CH_2Cl_2 at -20ºC). When an excess of allenamide (2.5 equiv) is present in the reaction mixture, adducts of type **57**, arising from an aromatization of **56** and a subsequent hydroarylation with a second molecule of allenamide, are obtained in excellent yields. Moreover, carbazole derivatives of type **58**, exclusively resulting from an aromatization of the previously formed [4 + 2] adducts (**56**), could also be selectively obtained if $AuCl_3$ is used as the catalyst (Scheme 30).[50]



Scheme 30. Au-catalyzed [4 + 2] cycloaddition of allenamides and vinyl indoles.

Conclusions

The use of allenes as cycloaddition components in catalytic [4 + 3] and [4 + 2] cycloadditions brings excellent opportunities for the synthesis of a great variety of six and seven membered cyclic and polycyclic structures. Although several methods proceeding through key metallacyclic intermediates have been developed since the earlier reports of 1995, most of the recent examples are based on the use of Lewis bases (i.e. phosphines) and carbophilic catalysts (gold or platinum complexes). Both reagents are able to convert allenes into very reactive zwitterionic intermediates that behave as 2C and 3C cycloaddition partners, or even as 4C components if a vicinal atom participates in the process.

The development of new methods, either with transition metals or Lewis bases seems to be warranted as the number of efficient and versatile methods for the synthesis of allenes keeps growing. On the other hand, further applications of these and related methodologies for the synthesis of natural products and others pharmaceuticals of interests, featuring six and seven-membered cycles, are expected in the near future.

Acknowledgements

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Notes and references

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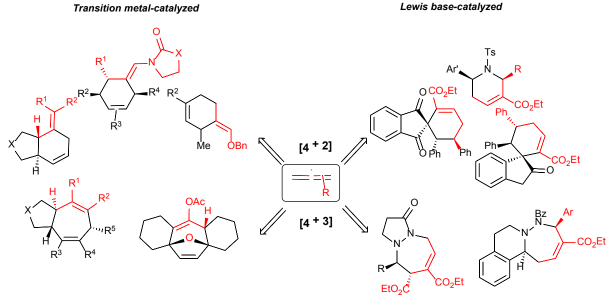
Key Learning Points

1. Allenes, by featuring two consecutive double C-C bonds, present unique reactivity that allows the development of new catalytic cycloadditions.
2. Among the different cycloaddition approaches, [4 + 2] and [4 + 3] cycloadditions are particularly attractive as they constitute a practical way of assembling six and seven-membered cycles.
3. Allenes can participate in these annulations through classical metal-catalyzed mechanisms involving metallacycles or via outsphere processes that can be catalyzed by metals or by Lewis bases
4. The development of enantioselective versions of all these [4 + 2] and [4 + 3] cycloadditions is yet underdeveloped as it is the development of hetero-variants and the application of the methodologies to natural product synthesis.

Graphical Abstract



José Luis Mascareñas completed his PhD at the University of Santiago in 1988. He was a postdoctoral fellow at Stanford University (USA) under the supervision of Prof. Paul Wender (1989-1990); and became permanent professor in 1993, and full professor in 2005, at the University of Santiago. He has been visiting scholar in Harvard University (USA) in the summers of 1992 and 1995, and visiting scientist in the University of Cambridge (UK, 2009) and the MIT (USA, 2013). In 2009 he received the Organic Chemistry award of the Spanish Royal Society of Chemistry, and in 2013 the advanced grant ERC award of the EU. His current research interests are split between a synthesis program focused on the development of metal- catalyzed processes, and a chem-bio program aimed at designing new nucleic acid and protein recognition and sensing tactics.

Fernando López obtained his PhD in 2003 at the University of Santiago de Compostela. From 2004 until 2006, he was a postdoctoral fellow in the group of Professor Ben Feringa at the University of Groningen. In 2006, he joined the University of Santiago de Compostela under the Ramón y Cajal programme and, in 2008, he became Tenured Scientist at the Spanish National Research Council (CSIC-IQOG). In 2009 he received the RSEQ-SIGMA-ALDRICH Young Chemists Award of the Spanish Royal Society of Chemistry. Presently, he has been assigned to the Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CIQUS), at the University of Santiago de Compostela. His research is focused on the development of new transition metal-catalyzed processes with a focus on enantioselective catalysis.

Text: one sentence, of maximum 20 words, highlighting the novelty of the work: This review summarizes the different catalytic [4+2] and [4+3] cycloadditions that have been developed by using allenes as 2C, 3C or even 4C atom partners.