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Cyclization reactions of bis(allenes) for the synthesis of polycarbo(hetero)cycles

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The chemistry of allenes is an appealing topic which fascinates chemists nowadays. Their reactivity and versatility makes this skeleton a useful moiety to create a great variety of structures depending on the functional groups attached and the reaction conditions used. Recently, there is a growing interest in the study of the reactivity of bis(allenes) inspired in the chemistry developed in simple allenes. In this review a collection of examples of cyclization reactions of bis(allenes) is presented as well as the future perspectives.

1 Introduction

During the last 25 years, chemists worldwide have focused their attention on the study of allenes.[1] In fact, its beauty has been recognized in a diversity of allenic natural products, many of them showing interesting or promising therapeutic activities. Nowadays, around 150 natural products containing an allenic or cumulenic structure have been identified.[2] In the meantime, the reactivity of allenes has been studied. Thus, a lot of novel interesting reactivity patterns have been reported where chemo-, regio- and diastereoselectivity issues have been addressed. Cycloaddition, cross-coupling and cycloisomerization reactions among others, have been carried out affording a huge collection of structures. As long as allenes are showing us their interesting reactivity, many strategies deal with the synthesis of allenic derivatives.[1a,3] Recently, the synthesis of conjugated bis(allenes), and their rich chemistry have been revised and it will not be covered in the present overview.[4] Thus, the intention

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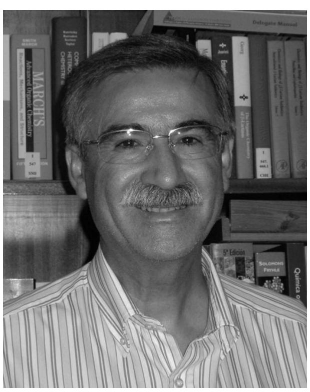

Benito Alcaide

Benito Alcaide was born in Aldea del Rey, Ciudad Real, Spain, in 1950. He received his BS degree (1972) and PhD degree (1978) from the Universidad Complutense de Madrid (UCM) under the supervision of Prof. Franco Fernández. After a 4-year period working on the chemistry of α-iminoketones and related compounds, he began working on β-lactam chemistry. In 1984 he assumed a position of Associate Professor of Organic Chemistry and in 1990 was promoted to Full Professor at the UCM. His current reserach interests include β-lactam chemistry, asymmetric synthesis of compounds of biological interest, allene chemistry, metal-promoted cyclizations, and organocatalysis.

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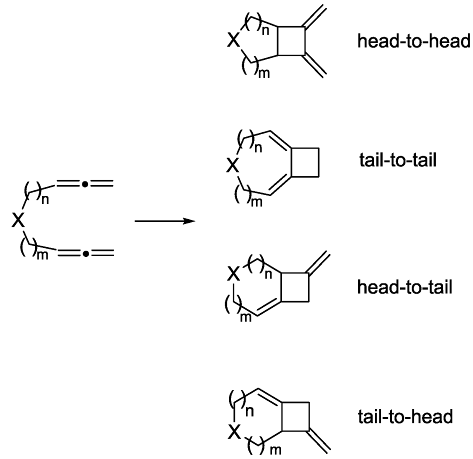
of this review is to present the state of the art of the cyclization chemistry of non-conjugated bis(allenes), in order to give the reader the future perspectives of this skeleton in Organic Synthesis.[5] Our aim is to show how discoveries concerning the reactivity of simple allenes have served to inspire chemists to apply, extend and develop the chemistry of this family of bis(allenes). This review has been divided into two sections, namely, cycloaddition[6] and cyclization reactions. For each section, both the allene–allene reactivity and the interaction of the bis(allene) moiety with another functionality present in the same molecule are discussed.



Scheme 1 Possible regioisomers formed in the intramolecular [2+2] cycloaddition of bis(allenes).

2 Cycloaddition reactions

2.1 [2+2] Cycloaddition reactions

2.1.1 Reactivity allene–allene. The cyclobutane skeleton can be found in natural products.[7] Besides, the inherent ring strain makes this alicyclic scaffold an excellent molecular building block in Organic Synthesis for the construction of different molecules.[8] One of the most popular and ancient reaction of allenes is the [2+2] cycloaddition. The interest on this cycloaddition is due to its applicability to obtain the cyclobutane or cyclobutene rings in a single step.

The inter- and intramolecular [2+2] cycloaddition of allenes with alkenes and alkynes has been studied under photochemical, thermal and metal-catalyzed conditions, affording the corresponding cyclobutanes/cyclobutenes regioselectively in most cases.[9] As the thermal process is not allowed by the Woodward–Hoffmann rules[10] and the Fukui's frontier orbital theory,[11] most of the examples have been explained *via* a stepwise diradical mechanism. However, when the reaction is catalyzed by a transition metal catalyst the reaction mechanism has been explained in terms of reductive elimination of metallacyclopentanes or metallacyclopentenes intermediates. On the other hand, the regioselectivity has been controlled by the nature of the substituents attached to the allene moiety; however, in some cases it has been modulated by the reaction conditions. By resemblance with both enallenes and ynallenes, when we raise the study of the intramolecular [2+2] cycloaddition of bis(allenes), it is essential to consider the number of possible regioisomers, their formation dependent on the π-component involved in the process. Then, if we use a symmetric bis(allene), four possible regioisomers can be formed, head-to-head, tail-to-tail, head-to-tail and tail-to-head adducts (Scheme 1).

Recently, the [2+2] cycloaddition of 1,5-bis(allenes) **1** and **2** under both thermal and Pd(0)-catalytic conditions has been studied. This work has shown how the reaction conditions can control the regioselectivity of the final compounds independently of the structure of the starting materials. Thus, treatment of bis(allenes) **1** and **2** in toluene at reflux temperature afforded tail-to-tail regioisomers **3** in moderate to good yields.[12] It has been observed that the reaction is very sensitive to dilution, and that the optimal conditions were the use of a 0.04 M solution of compounds **1** in refluxed xylene. On the

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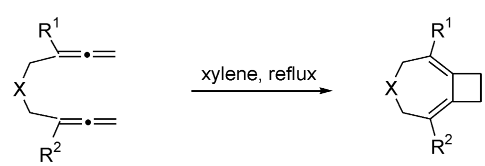


1a, $R^1 = R^2 = H$, X = NTs	**3a**, 43%
1b, $R^1 = R^2 = H$, X = $C(SO_2Ph)_2$	**3b**, 61%
1c, $R^1 = R^2 = H$, X = $C(CO_2Et)_2$	**3c**, 38%
1d, $R^1 = R^2 = H$, X = $C(CO_2Me)(SO_2Ph)$	**3d**, 61%
2a, $R^1 = R^2 = Et$, X = $C(SO_2Ph)_2$	**3e**, 74%
2b, $R^1 = R^2 = Et$, X = $C(CO_2Me)_2$	**3f**, 70%
2c, $R^1 = Me$, $R^2 = H$, X = $C(SO_2Ph)_2$	**3g**, 69%

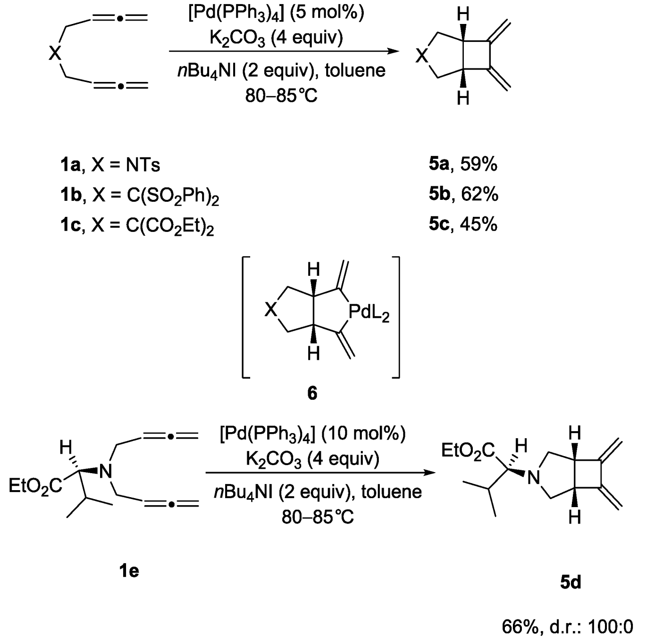
Scheme 2 Thermal intramolecular [2+2] cycloaddition of bis(allenes) **1a–d** and **2a–c**.

other hand, substituted allenes gave better yields due to stabilization of the presumable radical intermediates involved in the reaction. In addition, a very bulky X group, such as $C(CO_2Me)_2$ and $C(SO_2Ph)_2$ instead of N-Ts, makes both allene functionalities closer favouring the [2+2] cycloaddition according to the Thorpe–Ingold effect, increasing the yields of compounds **3** from 43 to 74% (Scheme 2).

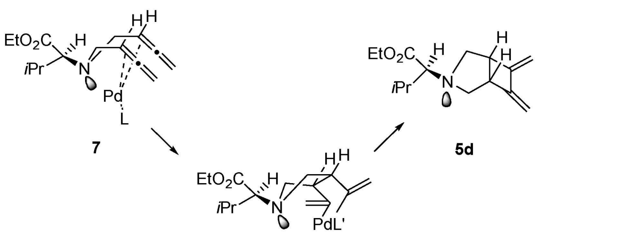
Formation of fused strained bicycles **3** could be rationalized by a mechanism that includes an exocyclic diradical intermediate **4a**, through initial carbon–carbon bond formation involving the central carbon of both allenes moieties (Scheme 3). An alternative pathway for this thermal cycloaddition would involve an endocyclic diradical intermediate **4b**, arising from the initial attack of the distal carbons of both allenes. For both cases, the final step must involve a rapid ring closure of the diradical intermediates before bond rotation can occur. Although there is no evidence of which proposed alternatives is the true mechanism, it seems possible that the substituents R^1 and R^2 must stabilize the exocyclic diradical, promoting the bis(allylic) radical **4a** over the alternate endocyclic vinylic radical **4b**.

Interestingly, when the same substrates, bis(allenes) **1a–c**, where treated under palladium catalysis, head-to-head bicyclic cyclobutanes **5** were obtained instead (Scheme 4). Furthermore, reaction of compound **1e**, containing the chiral L-valine ester moiety, under the same metal-catalytic conditions, gave compound **5d** without racemization of the α-amino ester. By contrast with the thermal [2+2] cycloaddition, which takes place *via* diradical intermediates, when the [2+2] cycloaddition is performed with transition metal catalysts, the process is explained in terms of the reductive elimination of metallacyclopentanes **6** as the key step in the formation of the four-membered rings (Scheme 4). Interestingly, the use of K_2CO_3 and nBu_4NI are both essential to obtain cyclobutanes **5**. Presumably, nBu_4NI must facilitate the reductive elimination step.

A plausible model for the highly diastereoselective Pd(0)-catalyzed [2+2] cycloaddition of 1,5-bis(allenyl) compound **1e** is shown in Scheme 5. Coordination between the Pd atom and the



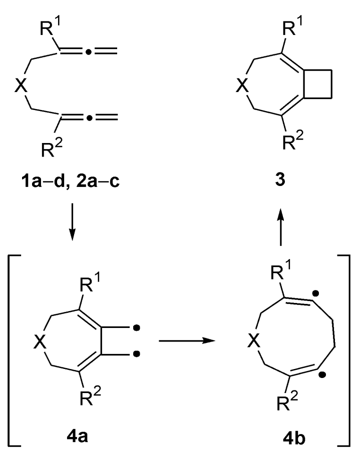
Scheme 4 Pd(0)-catalyzed intramolecular [2+2] cycloaddition of bis(allenes) **1**.



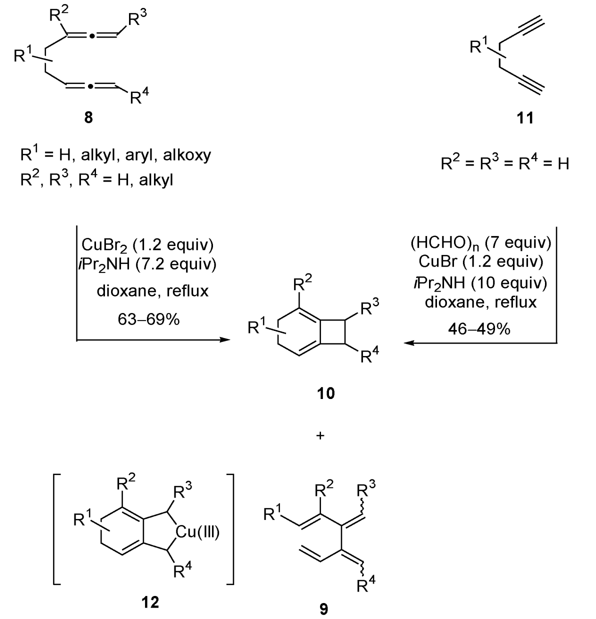
Scheme 5 Explanation of the highly diastereoselective Pd(0) catalyzed [2+2] cycloaddition of bis(allene) **1e**.

lone pair of electrons of the N atom in intermediate **7**, along with the requirement of the Pd atom to be distant from the bulkier CO_2Et group, would lead to the exclusive formation of **5d**. The inversion of the nitrogen center may be very difficult in this case because of the presence of the bicyclic skeleton. In addition, this model would explain why the formation of the head-to-head regioisomer **5** is favored over the tail-to-tail regioisomer observed under thermal conditions. If the coordination between Pd atom would involve the external double bond of both allene moieties, coordination with the lone pair of the nitrogen atom would not be possible.

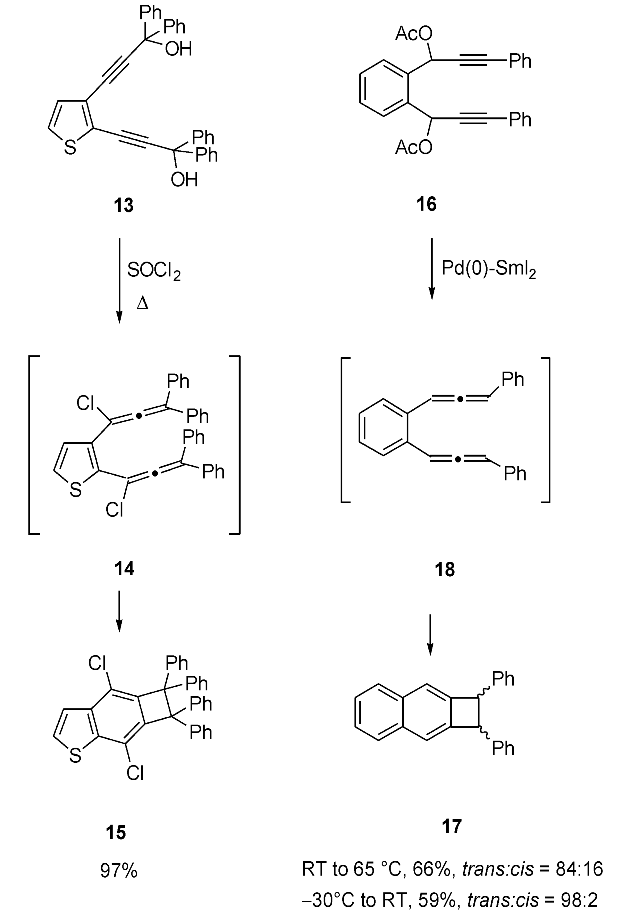
In some cases it is possible to predict the regiochemistry of the [2+2] cycloaddition, in particular when the formation of a more stable ring is favored over another one. For example, recently, [2+2] cycloaddition of 1,4-bis(allenes) **8** has been studied. Interestingly, treatment of compound **8** under thermal conditions gave [3,3]-sigmatropic rearrangement product **9** as major product and the desired [2+2] cycloadduct **10** in low yield.[13] After testing different reaction conditions using $Mo(CO)_6$, $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ as transition metal



Scheme 3 Mechanistic proposal for the thermal intramolecular [2+2] cycloaddition of bis(allenes) **1** and **2**.



Scheme 6 Cu-promoted intramolecular [2+2] cycloaddition of bis(allenes) **8**.



Scheme 7 Intramolecular [2+2] cycloaddition of *in situ* generated bis(allenes) **14** and **18**.

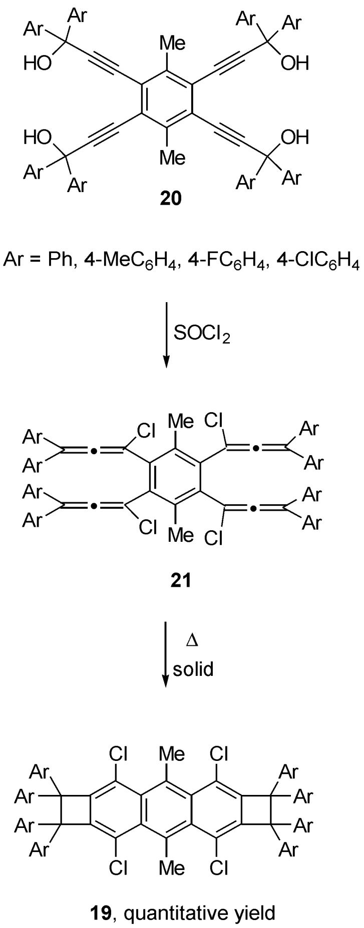
catalysts, the authors found that the combination of $CuBr_2$ and iPr_2NH afforded the corresponding [2+2] product **10** in good yields, minimizing the formation of compound **9** (Scheme 6). Different substitution in the ether as well as on the allene moiety was well tolerated. The process was investigated through a one-pot protocol from the corresponding 1,4-bis(alkynes) **11**, using Crabbé homologation conditions. Interestingly, compounds **10** were obtained in moderate yields. Although the authors did not present mechanistic details, it is presumed that the [2+2] cycloaddition takes place *via* formation of a cupracyclopentane **12**. Clearly, formation of the tail-to-tail regioisomer is favoured over the corresponding head-to-head isomer due to the formation of a six-membered ring fused to a cyclobutane.

On the other hand, sigmatropic rearrangements are the second most important synthetic methodology to obtain allenes, after prototropic isomerizations. This methodology has taken advantage to prepare bis(allenes) *via* double [2,3] sigmatropic rearrangements of propargyl sulfenates and propargyl sulfinates to afford allenic sulfoxides and sulfones, respectively. In fact, in an early example, it was found that the [2+2] cycloaddition of bis(allenes), generated *in situ* from enediynediols, to afford cyclobutane-fused arenes under thermal conditions. Thus, compound **13** by treatment with $SOCl_2$ rearranges to form bis(allene) intermediate **14**, which after thermal cyclization leads to **15** (Scheme 7).[14] Reaction of compound **16** with Pd(0)-SmI_2 followed by ring closure, afforded adduct **17** (mixture of *trans*- and *cis*; 84 : 16) *via* a [2+2] cycloaddition in 66% yield, involving intermediate bis(allene) **18**.[15] When the reaction was performed at −30 °C and the mixture was stirred at room temperature for several hours, the diastereoselectivity was improved (*trans* : *cis* = 98 : 2) while the yield just slightly decreased (59%). Formation of both cycloadducts **15** and **17** is preferred over the corresponding head-to-head isomers due to the size of the ring formed and the aromaticity observed in the final cycloadducts.

Thus, when the aromaticity of the final compound is the driving force of the process, it is easy to predict which regioisomer would be observed.

This behaviour has been observed in a more recent work. The synthesis of anthracyclobutene derivatives **19** *via* crystal-to-crystal thermal [2+2] cycloaddition of compounds **20**, involving bis(allene) intermediates **21** has been reported (Scheme 8).[16] Probably, rotation of the bulky diarylallene groups is necessary for the cyclization reaction.

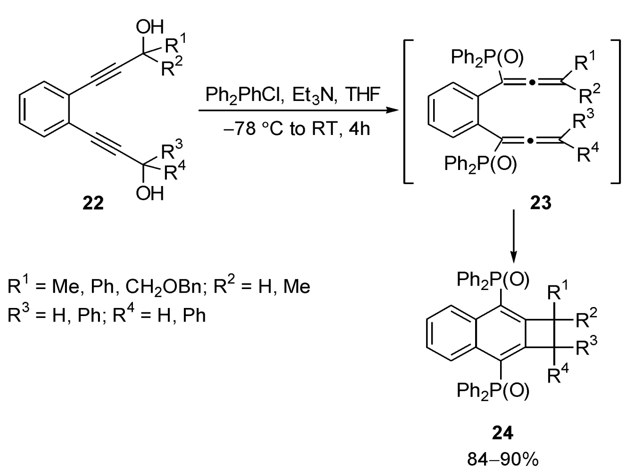
Analogously, propargyl phosphites and propargyl phosphinates are also feasible substrates to obtain allenes *via* [2,3] sigmatropic rearrangement. Thus, benzene-bis(phosphinylallenes), derived from benzene-bis(propargyl alcohols) and chlorodialkylphosphines, underwent intramolecular [2+2] cycloaddition leading to naptho[*b*]cyclobutenes.[17] It has been postulated that dual [2,3]-sigmatropic rearrangement of the bis(alkynols) **22** takes place, giving 1,2-bis(α-phosphinylallenyl)benzenes **23**, which



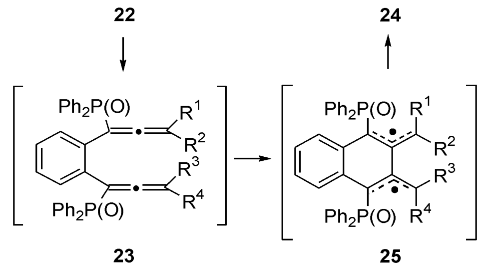
Scheme 8 Crystal-to-crystal thermal [2+2] cycloaddition of compounds **21**.

spontaneously undergo intramolecular [2+2] cycloaddition to afford compounds **24** in excellent yields (Scheme 9).

Formation of compounds **24** has been rationalized *via* the intermediacy of diradical intermediates **25** as shown in



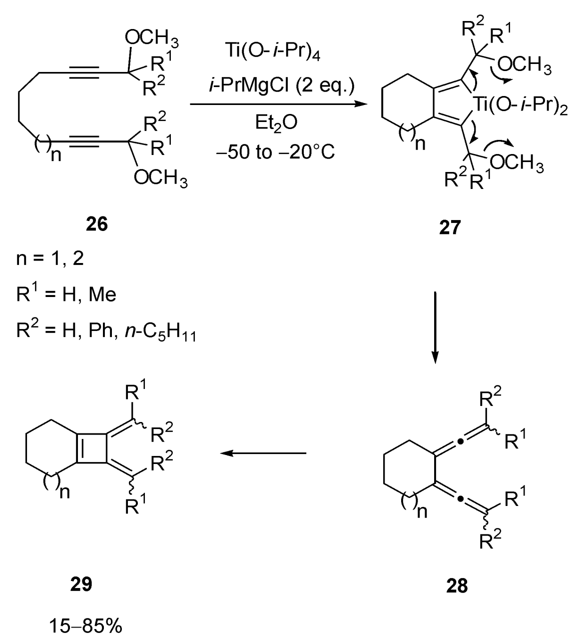
Scheme 9 Intramolecular [2+2] cycloaddition of bis(phosphinylallenes) **23**.



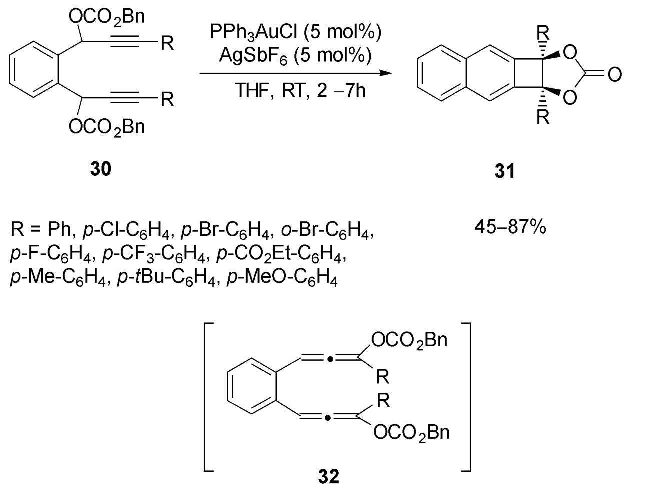
Scheme 10 Mechanistic explanation for the synthesis of compounds **24** *via* the intermediacy of bis(allenes) intermediates **23**.

Scheme 10. The bis(phosphinylallenes) **23**, derived from the corresponding bis(propargylicphosphinites) by [2,3]-sigmatropic rearrangement, would be converted into the diradical species **25**, which subsequently undergo ring closure to produce tricycles **24**. The aromaticity of the final products is also a remarkable feature in the regiochemistry observed of the [2+2] cycloaddition, and is probably the driving force to obtain compounds **24** as sole regioisomers.

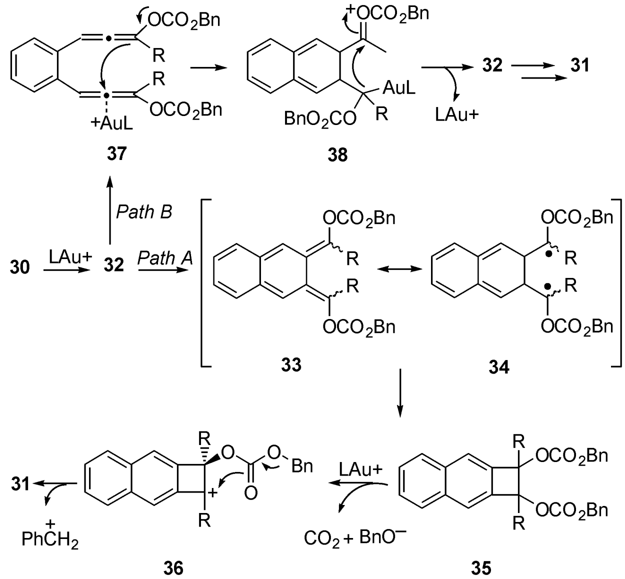
In the same context, it has been reported that titanium-mediated intramolecular cyclization of bis(allenes), prepared from bis(propargylic alcohol) derivatives, affording bicyclic cyclobutenes bearing six-and seven-membered rings.[18] Treatment of tethered bis(propargyl alcohol) derivatives **26** with titanium complex (η^2-propene) Ti(O-i-Pr)$_2$, generated *in situ* by treatment of Ti(O-i-Pr)$_4$ with two equivalents of i-PrMgCl, allowed the formation of titanacycles **27** *via* cyclometalation. Elimination of the methoxy group with concomitant demetallation generated bis(allenes) intermediates **28**, which after formal [2+2] cycloaddition gave bicyclic cyclobutenes **29** in low to good yields (Scheme 11).



Scheme 11 Intramolecular cyclization of bis(allenes) **28**.



Scheme 12 Synthesis of functionalized naphtha[*b*]-cyclobutanes **31** from 1,7-dyin-3,6-bis(propargyl carbonates) **30** involving bis(allene) intermediates **32**.



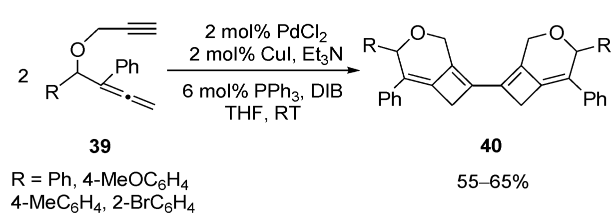
Scheme 13 Mechanistic explanation for the synthesis of compounds **31** involving bis(allenes) intermediates **32**.

1,7-Diyn-3,6-bis(propargyl carbonates) **30** may undergo cycloisomerization under gold-catalyzed conditions affording naphtha[*b*]cyclobutenes **31** (Scheme 12).[19] The process involves the generation of bis(allenyl carbonate) **32** as key intermediates, which are ideal substrates to react *via* [2+2] cycloaddition of both allene moieties. After testing different gold complexes, the authors found that the use of PPh_3AuCl (5 mol%) in combination with $AgSBF_6$ (5 mol%) in THF at room temperature were the optimum reaction conditions. The scope of this cycloisomerization reaction has been investigated using a variety of aromatic substituents in the terminal alkyne position. The electronic nature of the aromatic rings did not have a strong influence on this reaction. In fact, both electron-deficient and electron-rich substituents were tolerated during the reaction.

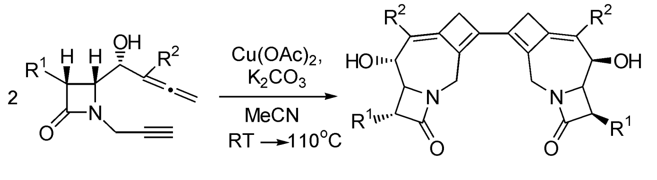
Formation of compounds **31** is explained in Scheme 13 and involves a double 3,3-rearrangement reaction through the nucleophilic attack of the benzyloxycarbonyl group on the gold(I)-activated alkyne moiety leading to the formation of the bis(allenyl carbonate) **32**. Next, 6π-electrocyclic reaction would deliver species **33**, which can be represented by the resonance structure **34**, a highly stabilized biradical. Then, intermediates **33** and **34** would undergo cyclization to provide dicarbonates **35**. Gold-assisted C–O bond cleavage would take place to give a benzylic cation intermediate **36**. Subsequent ring-closure proceeded by attack of the benzyloxycarbonyl group from the top side, which furnishes exclusively *cis*-**31** (Path A). An alternative pathway could be proposed, involving intramolecular nucleophilic attack of the allene moiety on the gold-activated allene **37** to form an oxocarbenium ion intermediate **38**. Subsequent nucleophilic attack of the Au–C(sp^3) bond on the carbonyl moiety of the oxocarbenium ion would give the same dicarbonate **32** (Path B).

2.1.2 Reactivity allene–alkyne. Most of the [2+2] cycloaddition reactions of bis(allenes) reported so far involve the cycloaddition of two π-bonds of both allene moieties. However, in some cases, when the approximation of both allene moieties is not possible due the conformational disposition of the molecule, one allene fragment is susceptible to react with a more proximal functionality. For example, recently it has been shown that the double [2+2] cycloaddition between alkyne and allene moieties from bis(allene)–bis(alkyne) compounds, afford fused bicyclic adducts bearing a cyclobutene ring. This process takes place *via* palladium-catalyzed or copper-promoted domino alkyne homocoupling/double [2+2] allenyne cycloaddition.[20] Interestingly, treatment of ynallenes **39** in the presence of $PdCl_2$ (2 mol%) and CuI (2 mol%) afforded bis(dihydropyran-fused cyclobutenes) **40** in moderate yields (Scheme 14). In order to study the scope of the reaction, 2-azetidinone-tethered ynallenes **41** were tested under the same reaction conditions. However, the Pd–Cu bimetallic catalytic system failed to give the desired product even when the reaction temperature rose to 80 °C. Fortunately, when a stoichiometric amount of copper salt was used the homodimerization/[2+2] bis(cycloaddition) sequence proceeded smoothly to afford enantiopure attached-ring bis(tricyclic) β-lactams **42** in good yields (Scheme 15).

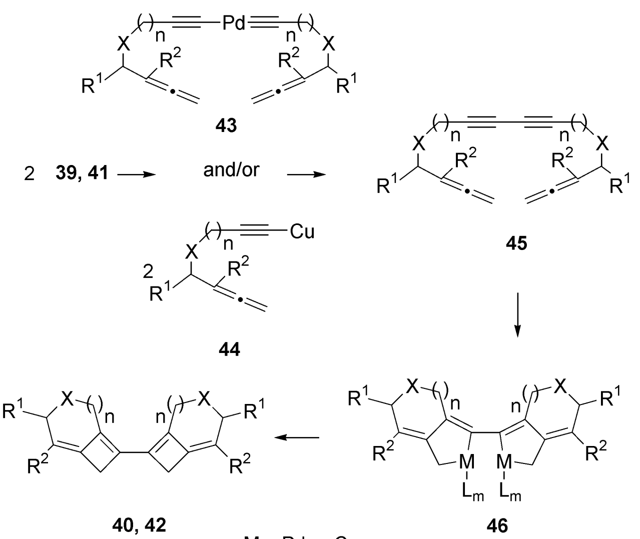
A tentative mechanistic proposal for the metal-promoted alkyne homocoupling/[2+2] allenyne bis(cycloaddition) of allenynes is depicted in Scheme 16. It may involve the formation of dialkynylpalladium complexes of type **43** or copper(I) acetylides



Scheme 14 Palladium-catalyzed or copper-promoted domino alkyne homocoupling/double [2+2] allenyne cycloaddition of ynallenes **39**.



Scheme 15 Copper-promoted domino alkyne homocoupling/double [2+2] allenyne cycloaddition of azetidinone-tethered ynallenes **41**.



Scheme 16 Mechanistic proposal of the palladium-catalyzed or copper-promoted domino alkyne homocoupling/double [2+2] allenyne cycloaddition of ynallenes **39** and **41**.

of type **44**, which are then transformed into the corresponding diynes **45**. For the double [2+2] allenyne cycloaddition, it is believed that initially the metal salt regioselectively forms a π complex with both the triple bond and the double bond of substrates **45**. Such π complexes may undergo migratory C–C coupling to give pallada- or cupracyclopentenes of type **46**. Following this step, intermediates **46** would undergo rapid reductive elimination to give bis(cyclobutenes) **40** and **42** as the final products. The observed high regioselectivity of the reaction could be explained in terms of the regioselective formation of metallacycles of type **46**, which would be controlled by the stereoelectronic effects of the aryl substituents (R^2) in allenynes **39** and **41**. Cyclization towards the internal allenic double bonds is probably restricted by the steric hindrance between the metal ligand moiety and the aryl substituent at the quaternary stereocenter.

Later on, a related synthesis of bis(tricycles) from bis(β-lactam-allenynes) *via* double intramolecular [2+2] cycloaddition under thermal conditions has been reported.[21] The starting materials, C_2-symmetric bis(β-lactam-allenynes) **47** and unsymmetrical allenynes **48** have been prepared *via* homodimerization reaction using modified classical copper-promoted conditions and copper-catalyzed Cadiot–Chodkiewicz cross-coupling reaction, respectively. Treatment of compounds **47** and **48** under thermal conditions afforded C_2-symmetric attached-ring bis(tricyclic) β-lactams **42** and unsymmetrical bis(tricycles) **49** by a double [2+2] allenyne cyclization (Scheme 17). It is interesting to observe that the reaction was completely regioselective and only depicted distal cycloadducts were the isolated isomers.

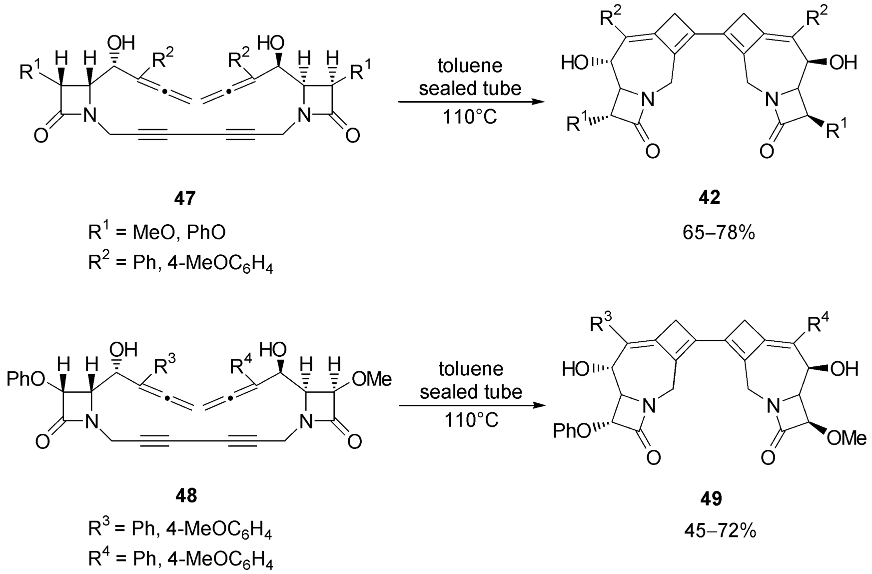
It was proposed that bis(tricycles) **42** and **49** were formed from bis(β-lactam-allenynes) precursors, *via* formation of tetraradical intermediates. This proposal would include the intermediacy of an exocyclic tetraradical intermediate **50** through initial double carbon–carbon bond formation, involving the central allene and the proximal alkyne carbon atoms (Scheme 18). Then, the final step must involve a rapid double ring closure of the tetraradical intermediates, before bond rotation can occur. Alternatively, another reaction pathway could be involved, in which one β-lactam-allenyne cyclizes first with subsequent cyclization of the second allenyne moiety.

2.2 [2+2+1] Cycloaddition: The Pauson–Khand reaction

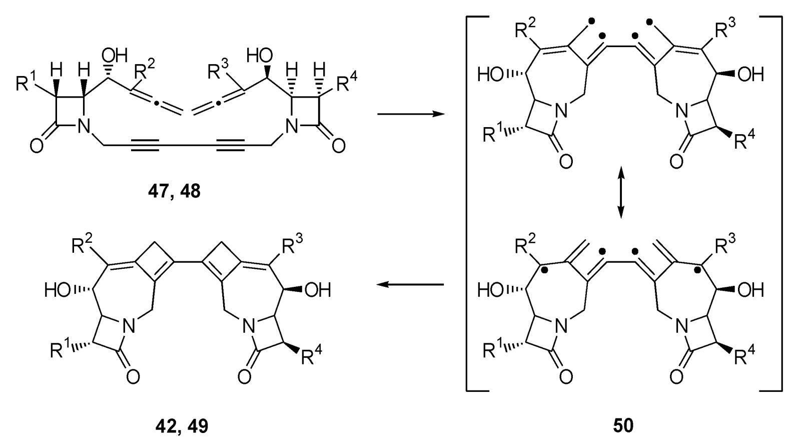
2.2.1. Reactivity allene–allene. The Pauson–Khand reaction involves an alkyne π bond, an alkene π bond and carbon monoxide, affording cyclopentenones *via* [2+2+1] cycloaddition promoted by different transition metal catalysts, such as Co, Rh, Ir, Mo, Zr and Ti.[22] In addition, this reaction has been studied intramolecularly in allenynes instead of enynes for the construction of cyclopentenone-fused bicyclic frameworks.[23] However, the [2+2+1] cycloaddition of bis(allenes), which requires the participation of the two double bonds, has been studied scarcely and so far there are only two examples in the bibliography. In fact, due to the participation of a metallacycle intermediate in both [2+2] and [2+2+1] cycloaddition mechanisms, usually it has been observed the formation of a mixture of both cycloaddition products. It is important to remark that, for both cycloaddition processes, the external double bond of each allene moiety is involved in the cyclization reaction, avoiding the possible steric effect of the substituents in the starting material.

A few years ago, the Rh(I)-catalyzed carbonylative [2+2+1] cycloaddition of bis(allenes) **51** and **52** was evaluated.[24] Treatment of bis(allenes) **51a–c**, **52a**, and **52b** with $[RhCl(CO)dppp]_2$ in toluene at 80 °C under atmosphere of CO afforded the expected Pauson–Khand products **53a–c**, **54a**, and **54b** (Scheme 19). By contrast, reaction of malonate derivative bis(allene) **51d** in the presence of $[RhCl(CO)dppp]_2$ furnished a mixture of [2+2] cycloadduct product **55** as the major product (70%) along with the Pauson–Khand product **53d** (20%). A satisfactory yield of Pauson–Khand products were observed when bis(allene) **51d** was reacted with $[RhCl(CO)_2]_2$ instead of $[RhCl(CO)dppp]_2$, yielding Pauson–Khand product **53d** in 83% and [2+2] cycloaddition product **55** in 16% (Scheme 20).

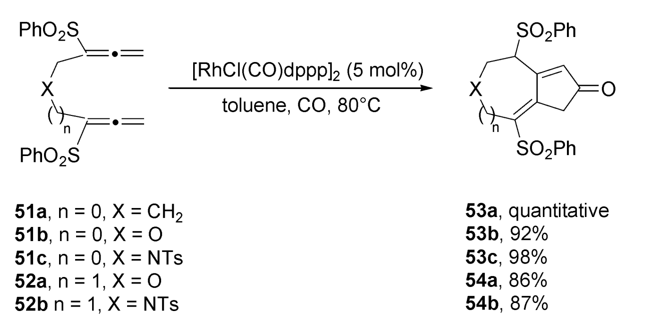
Formation of both Pauson–Khand and [2+2] cycloaddition products has been explained *via* cyclometalation between the



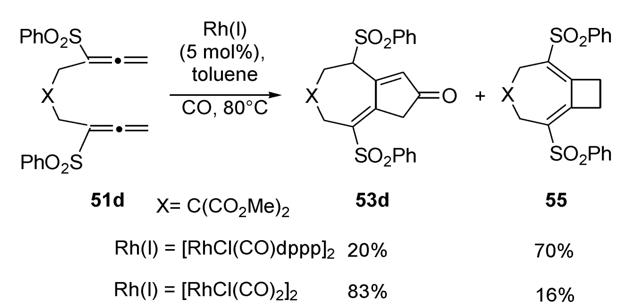
Scheme 17 Intramolecular [2+2] cycloaddition of C_2-symmetric bis(β-lactam-allenynes) **47** and unsymmetrical allenynes **48** under thermal conditions.



Scheme 18 Mechanistic explanation of the intramolecular [2+2] cycloaddition of bis(β-lactam-allenynes) **47** and **48** *via* formation of tetraradical intermediates **50**.

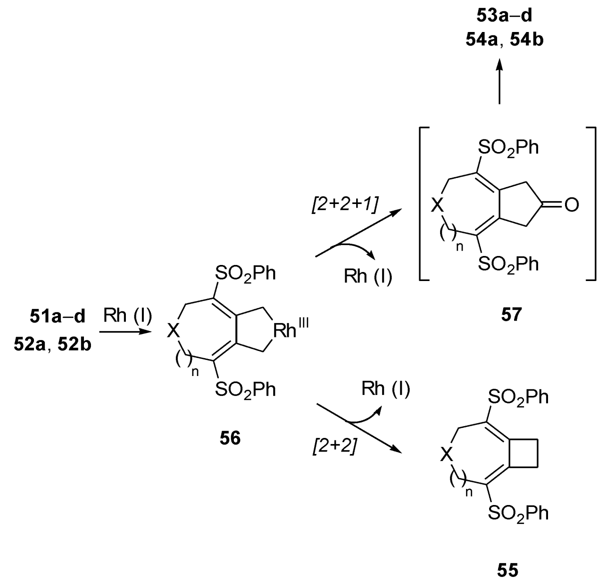


Scheme 19 Synthesis of compounds **53** and **54** *via* Pauson–Khand reaction of bis(allenes) **51** and **52**.



Scheme 20 Synthesis of compounds **53d** and **55** *via* competition of Pauson–Khand and [2+2] cycloaddition reactions, respectively.

two external double bonds of the allenyl moieties of bis(allenes) **51** and **52**, involving formation of rhodacycle **56** and subsequent isomerization of the initially formed 1,3-diene derivative **57** to form the α,β-unsaturated ketones **53a–d**, **54a**

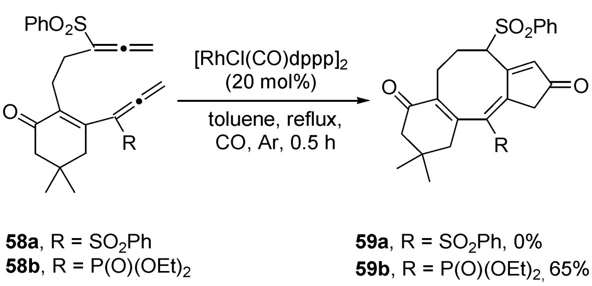


Scheme 21 Possible reaction pathways to explain the formation of [2+2+1] and [2+2] adducts.

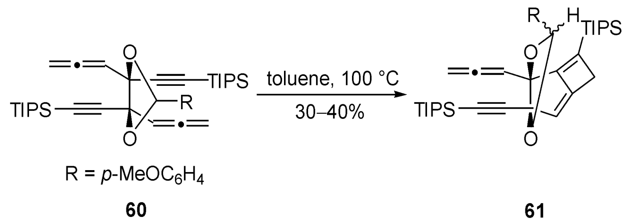
and **54b** (Scheme 21). It is presumed that the presence of two bulky phenylsulfonyl groups on both functionalities, should suppress the cyclometalation between two internal double bonds or between a terminal and an internal double bond of two allenyl groups, orienting two terminal double bonds of the allenyl moieties. Compound **55** would form by reductive elimination of intermediate **56** (Scheme 21).

In a more recent work, the same authors have successfully applied this methodology for the construction of a 6-8-5 tricyclic ring system from a bis(allene) derivative.[25] Treatment of allene **58a** in the conditions reported previously gave a complex mixture. Fortunately, when the reaction was carried out with the bis(allene) derivative **58b** possessing phosphonate and sulfonyl groups on the bis(allene) moiety, compound **59b** was obtained as a single product in 65% yield (Scheme 22).

2.2.2. Reactivity allene–alkyne. In this context, competition of the [2+2+1] and [2+2] cycloaddition has been observed in bis(allene)–bis(alkyne) compound **60**.[26] Thus, reaction of compound **60** under thermal conditions has afforded compound **61** in low yield, *via* [2+2] monocycloaddition of one allene with one alkyne (Scheme 23). However, when



Scheme 22 Synthesis of 6-8-5 tricyclic system **59** *via* Pauson–Khand reaction of **58**.



Scheme 23 Reactivity of bis(allenes) **60** under thermal conditions.

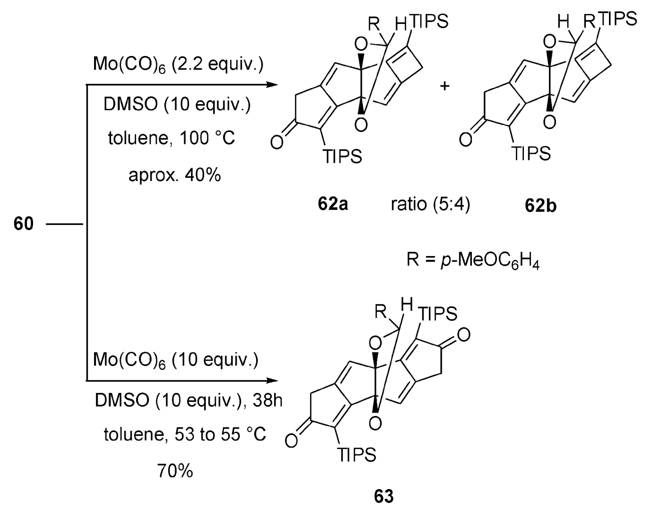
bis(allene)–bis(alkyne) **60** was heated in toluene at 100 °C in the presence of a slight excess of $Mo(CO)_6$ (2.2 equiv.) and DMSO (10 equiv.), [2+2]/[2+2+1] cycloadduct hybrid **62** was obtained as a mixture of diastereoisomers. Interestingly, reaction of bis(allene)–bis(alkyne) **60** in presence of 10 equiv. of $Mo(CO)_6$ at 53 to 55 °C afforded compound **63** *via* double [2+2+1] cycloaddition allene–alkyne (Scheme 24).

2.3 [4+2] Cycloadditions. Reactivity allene–allene

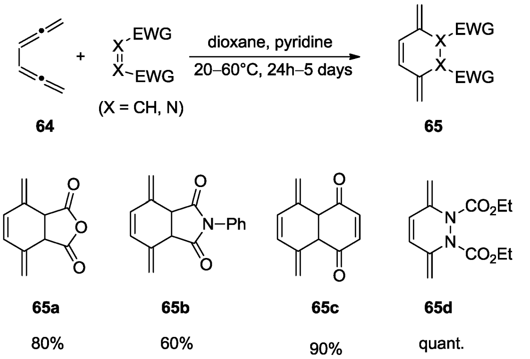
Bis(allenes) can also participate in Diels–Alder cycloadditions as diene component, affording complex ring structures. First examples reported in the literature were carried out through the reaction of 1,2,4,5-hexatetraene **64** with different dienophiles, affording the corresponding [4+2] cycloadducts **65** in excellent yields (Scheme 25).[27]

Interestingly, NMR studies of the [4+2] cycloaddition carried out with a mixture of *syn*- and *anti*-bis(allenes) **66** in presence of *N*-phenylmaleimide have shown that the reaction is stereospecific. Thus, [4+2] cycloadduct **67a** was detected after 22 h, leaving *anti*-**66** unaltered (Scheme 26).[28] However, bis(allene) *anti*-**66** reacted with *N*-phenylmaleimide after 5 days, affording cycloadduct **67b**. This behaviour can be explained taking into account that the dienophile approaches by the less sterically hindered face of the bis(allene).

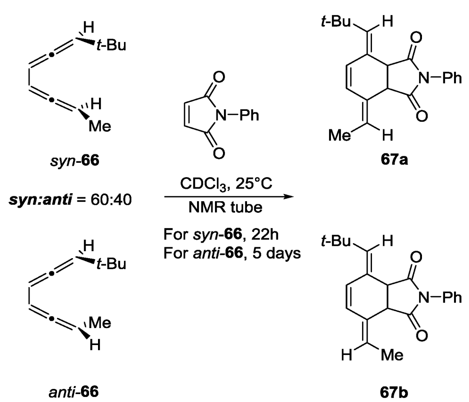
On the other hand, once again, taking advantage of the [2,3]-sigmatropic rearrangement of bis(propargylic alcohol)



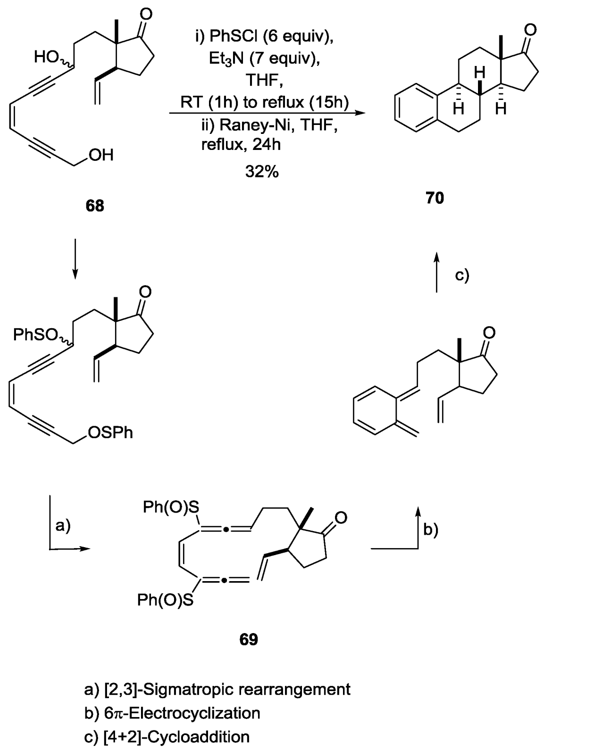
Scheme 24 $Mo(CO)_6$-promoted competitive [2+2] and [2+2+1] processes of bis(allene)–bis(alkyne) **60**.



Scheme 25 [4+2] Cycloaddition of bis(allene) **64** with different dienophiles.



Scheme 26 Stereospecific [4+2] cycloaddition of bis(allenes) **66** with *N*-phenylmaleimide.



Scheme 27 Synthesis of the steroid framework **70** *via* intramolecular allenic [4+2] cycloaddition.

derivatives to form the corresponding bis(allenes), it has been described the synthesis of the steroid skeleton *via* a sigmatropic rearrangement/6π-electrocyclic reaction/intramolecular [4+2] cycloaddition sequence.[29] Thus, treatment of ene-bis(progargylic alcohol) **68** with benzenesulfenyl chloride effected the consecutive four-step conversion in one operation. It involves the intermediacy of bis(allene) **69**, which is converted in the diene component of the cycloaddition process through 6π-electrocyclization. Finally, providing the steroid framework, namely compound **70**, in 32% overall yield (Scheme 27).

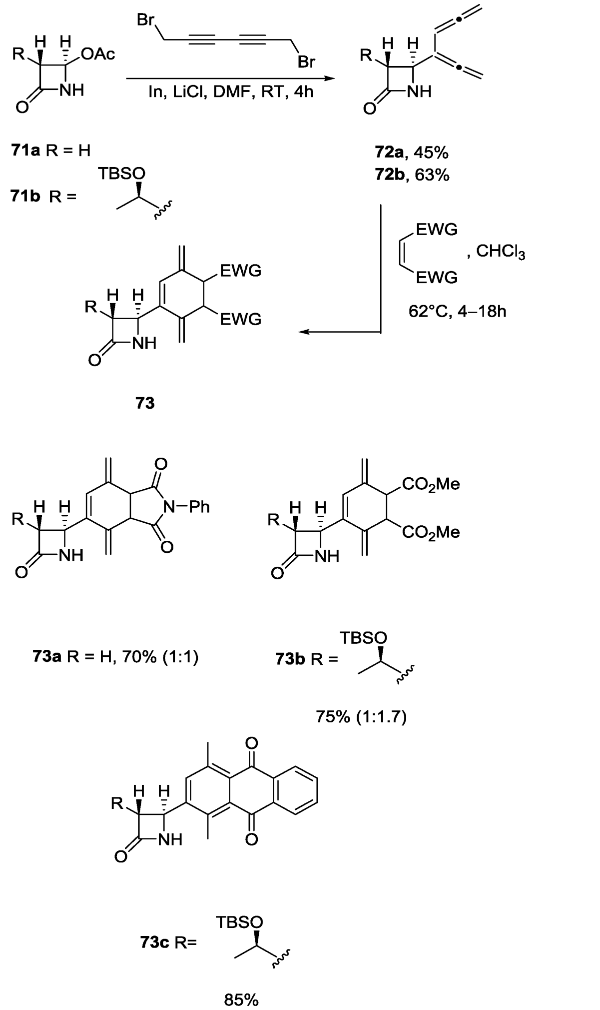
Recently, it has been described the synthesis of bis(allene β-lactams) by reaction of 4-acetoxy-2-azetidinones with organoindium reagents followed by intermolecular Diels–Alder reaction with a variety of dienophiles.[30] Synthesis of β-lactam bis(allenes) has been achieved by reaction of 4-acetoxy-2-azetidinone **71** with organoindium reagent generated *in situ* from indium and 1,6-dibromo-2,4-hexadiyne in the presence of LiCl as additive, producing compound **72** in good yield (Scheme 28). Next, the authors studied the Diels–Alder reaction of bis(allenes) **72** with various dienophiles affording highly functionalized β-lactams **73** in good yields.

3 Cyclization reactions of bis(allenes)

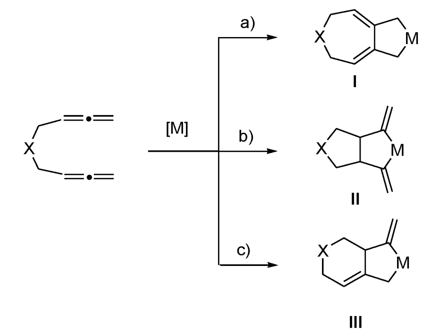
Transition-metal-catalyzed reactions of polyunsaturated compounds have captivated chemists of all areas. This is mainly due to the huge synthetic potential for the preparation of a variety of carbo- and heterocyclic structures under mild conditions with high yields and stereoselectivity.[31] In particular, metal-catalyzed cyclization of allenes has led to many synthetically useful transformations.[1] In the following section we discuss the examples reported in the bibliography concerning the reactivity of bis(allenes) in the presence of different metal catalytic systems. This section has been divided into two subsections: (a) formation of new C–C bonds (carbocyclizations), and (b) formation of new C–O bonds (heterocyclizations).

3.1 Formation of new C–C bonds: carbocyclizations

3.1.1 Reactivity allene–allene. The presence of four π components in the molecule of a bis(allene) can produce three different types of cyclometalations in the presence of a transition metal catalyst (Scheme 29): (a) metal coordinative cyclization between both terminal double bonds to form intermediate I, (b) metal coordinative cyclization between both internal double bonds to form intermediate II, and (c) metal coordinative cyclization between an internal double bond and a terminal double bond to form intermediate III. Formation of each intermediate can be controlled by the



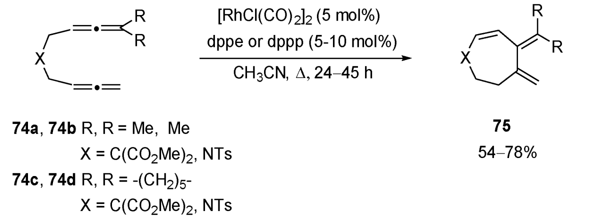
Scheme 28 Synthesis of cyclohexenyl β-lactams **73** *via* [4+2] cycloaddition of bis(allenes) **72** with different dienophiles.



Scheme 29 Possible types of cyclometalations of a bis(allene) in the presence of a transition metal catalyst.

metal catalyst, the reaction conditions and the structure of both starting material and the final compound.

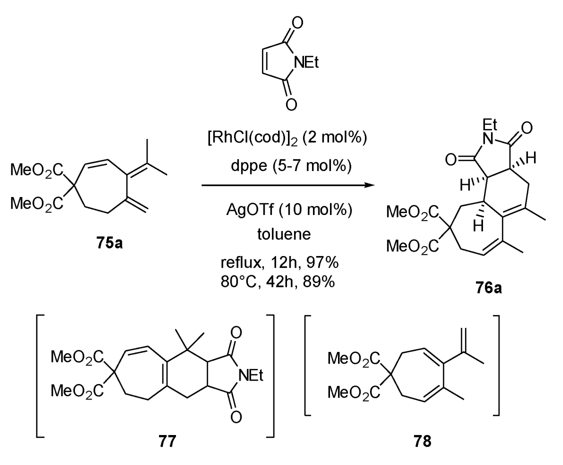
The reactivity of 1,5-bis(allenes) in presence of catalytic amounts of $[RhCl(CO)_2]_2$ has been studied.[32] Reaction of bis(allenes) **74** in presence of 2 mol% of $[RhCl(CO)_2]_2$ in acetonitrile as solvent afforded seven-membered cross-conjugated trienes **75** (Scheme 30). Apparently, the use of acetonitrile as solvent is crucial. Probably, the nitrile group may coordinate the catalytically active rhodium species to suppress the formation of oligomeric byproducts. The scope of the reaction has been studied using different alkyl substituents and tethers. In addition, to make the most of this methodology, the diene unit of the cross-conjugated triene has been reacted with different dienophiles to afford complex polycyclic compounds (Scheme 31).[33] For example, when compound **75a** was treated with *N*-ethylmaleimide under catalysis of $[RhCl(cod)]_2$/dppe/AgOTf, tricyclic compound **76a** was obtained instead the expected [4+2] adduct **77**. Formation of compound **76a** could be formed *via in situ* generated triene **78**.



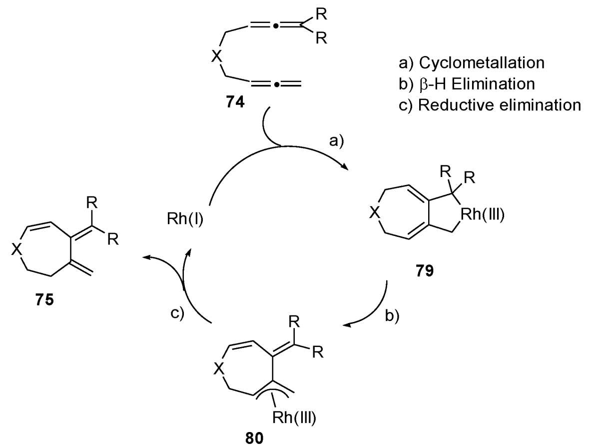
Scheme 30 Rh(I)-catalyzed cyclization of bis(allenes) **74**.

A possible mechanism for the formation of compounds **75** has been proposed (Scheme 32). First, bis(allene) **74** undergoes cycloisomerization to afford seven-membered bisallylic rhodium intermediate **79**, which would undergo highly regioselective β-H elimination affording intermediate **80.** Subsequent reductive elimination would afford compounds **75** with regeneration of the rhodium catalyst.

Fascinated by these results, the same research group continued studying the reactivity of 1,5-bis(allenes). Interestingly, changing the substitution of the bis(allene), the metal catalyst and the reaction conditions, a different reactivity has been studied. In the event, researchers observed that the rhodium-catalyzed reaction of bis(allene) **1a** lacking substitution at the terminal position of both allene moieties, afforded



Scheme 31 Synthesis of tricyclic compound **76a** *via* [4+2] cycloaddition of compound **75a** with *N*-ethylmaleimide.

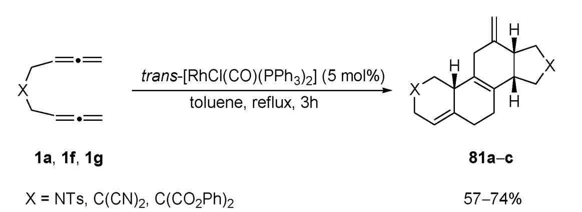


Scheme 32 Mechanistic proposal to explain the formation of compounds **75** from bis(allenes) **74**.

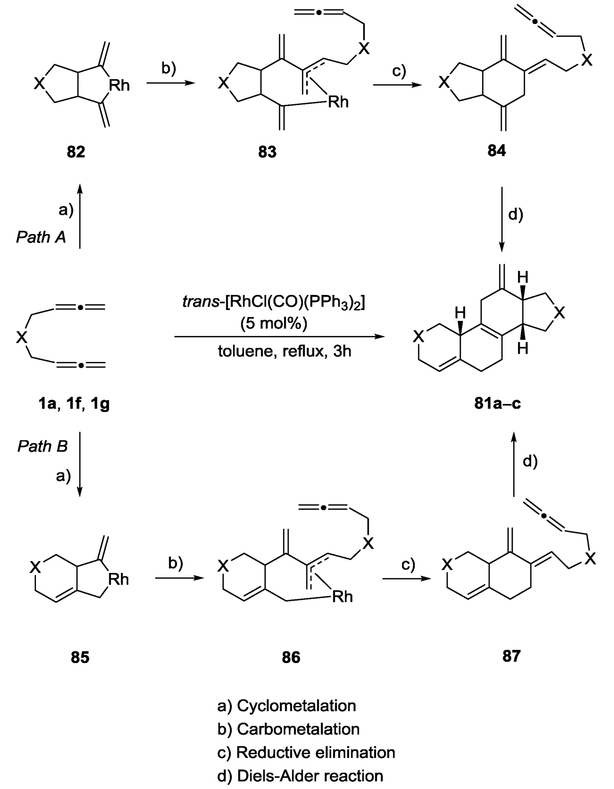
heterosteroid compound **81** in moderate to good yields (Scheme 33).[34] The scope of the reaction was studied using other bis(allenes), **1f** and **1g**, affording compounds **81a–c** in moderate to good yields.

Compounds **81** have been obtained by reaction of two molecules of the starting bis(allene). The reaction mechanism would involve cyclometalation between both internal double bonds of the bis(allene) **1** to give intermediate **82**, which would undergo carbometalation with one of the two allene moieties in **1** to afford **83** (Path A, Scheme 34). Subsequent reductive elimination of intermediate **83** would afford **84**, which could then undergo a Diels–Alder reaction to form the 18,19-norsteroid **81**. An alternative pathway would involve the formation of intermediate **85**, formed by cyclometalation between one internal double bond of one allene and the external double bond of the other allene moiety of bis(allene). An analogous route would be proposed for the formation of **81** *via* intermediates **85–87** (Path B, Scheme 34).

In order to explore the dimerization of bis(allenes) **1**, it has been studied the Rh(I)-catalyzed cyclization between two different 1,5-bis(allenes).[35] In the event, four possible isomers could be obtained. The cross-cyclization of two different tethered bis(allenes) **1** was tested using the conditions described previously. Thus, reaction of both bis(allenes) in presence of *trans*-[RhCl(CO)(PPh$_3$)$_2$] in toluene at reflux temperature afforded a mixture of steroid-scaffold products **81** and **88–90** (Scheme 35). Notably, only two products were obtained when the heteroatom was oxygen. Probably, the large angle of the C–O–C bond in



Scheme 33 Synthesis of heterosteroid **81** *via* rhodium-catalyzed reaction of bis(allenes) **1**.

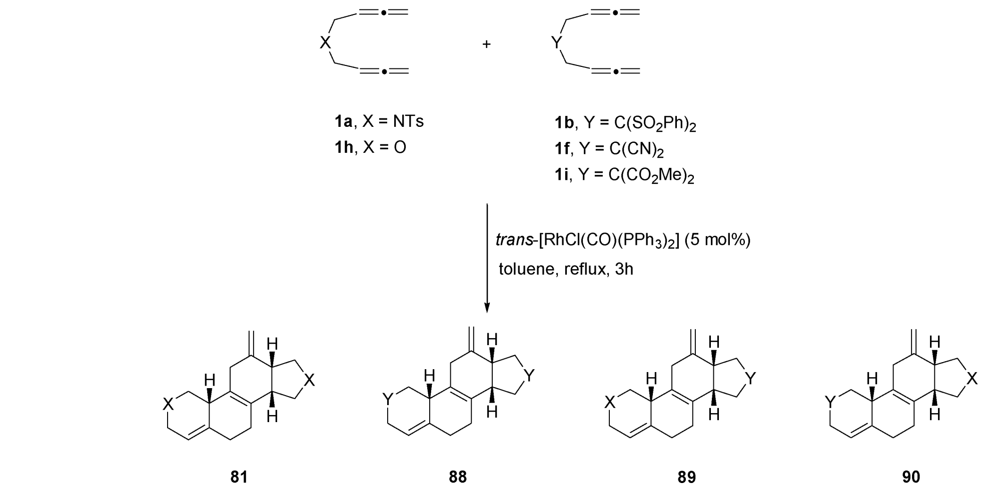


Scheme 34 Mechanistic proposal for the rhodium-catalyzed synthesis of steroid skeletons from 1,5-bis(allenes) **1**.

bis(allene) **1h**, makes cyclometalation of its two allene moieties more difficult. This hypothesis was confirmed when the treatment of bis(allene) **1h** (X = O) with Rh(I) did not afford the dimerization compound **81**. The reaction showed good stereoselectivity in all cases, thus, although three new stereogenic centers are form in the reaction, only one diastereomer with *cis* conjunction of the rings was formed.

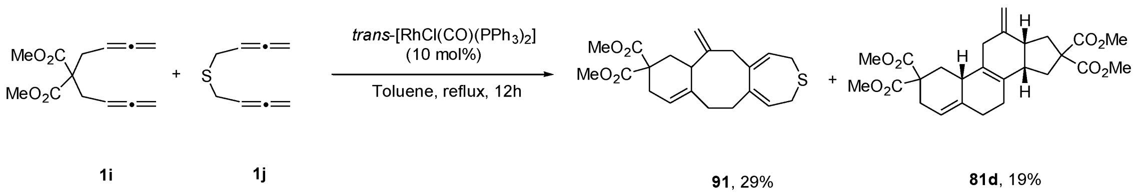
Interestingly, tricyclic product **91** was formed along with tetracycle **81d** when bis(allene) **1i**, X = C(CO$_2$Me)$_2$, and bis(2,3-butadienyl)sulfide **1j** were used in the reaction (Scheme 36). The mechanistic explanation for the formation of compound **91** is proposed in Scheme 37. First, cyclometalation of the bis(allene) **1i** with Rh(I) catalyst affords the intermediate **92**. The rhodium atom in this intermediate coordinates with the sulfur atom in bis(allene) **1j**, which leads to the formation of vinylic rhodium intermediate **93** through regioselective carbometalation. The subsequent intramolecular carbometalation of **93** with the terminal C=C double bond of the allene moiety forms intermediates **94** or **95**. Reductive elimination of **94** or **95** affords the tricyclic product **91** and regenerates the Rh(I) catalyst. Notably, the formation of product **96**, which would involve cyclometalation between both internal double bonds of the bis(allenes) was not observed in the reaction of **1i** and **1j**.

Later on, the synthesis of bicyclo[4.4.0] decene skeletons *via* rhodium catalyzed cyclization of 1,5-bis(allenes) in the presence of monoallenes has been described.[36] If the reaction conditions, such as dilution and slow addition of one of the

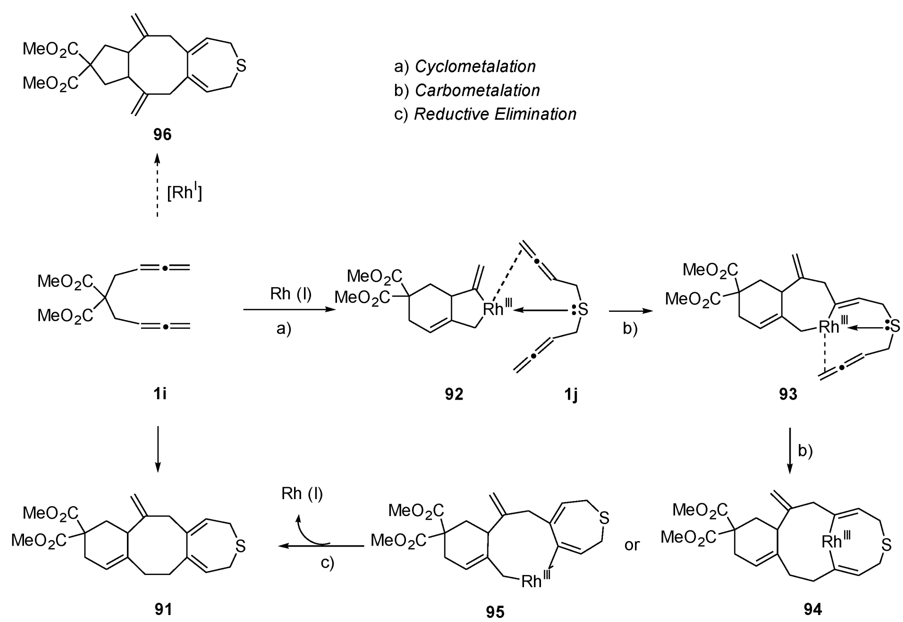


	81	88	89	90
X = NTs, Y = $C(CO_2Me)_2$	20%	30%	12%	9%
X = NTs, Y = $C(CN)_2$	18%	33%	13%	9%
X = O, Y = $C(SO_2Ph)_2$	-	38%	-	7%

Scheme 35 Synthesis of heterosteroids **81**, **88–90** *via* rhodium-catalyzed reactions of bis(allenes) **1**.



Scheme 36 Synthesis of compounds **81d** and **91** *via* rhodium-catalyzed reaction of bis(allenes) **1i** and **1j**.



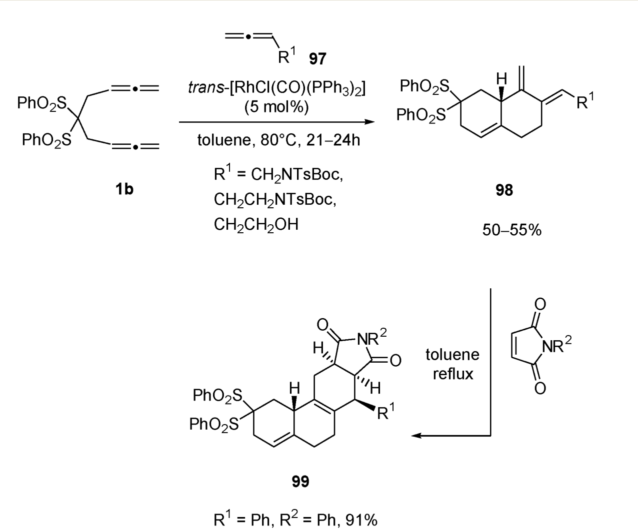
Scheme 37 Synthesis of compound **91** *via* intermolecular rhodium-catalyzed reaction of bis(allenes) **1i** and **1j**.

reagents can be controlled, bis(allene) **1b** can react with allenes **97**, without formation of the dimerization product previously described. Thus, reaction of bis(allene) **1b**, X = $C(SO_2Ph)_2$, and allenes **97** using *trans*-$RhCl(CO)(PPh_3)_2$ as catalyst afforded bicyclo[4.4.0]decene product **98** in moderate yields. Subsequent Diels–Alder reaction of the conjugated exocyclic diene of **98** in the presence of maleimides provided tetracyclic skeleton **99** with high diastereoselectivity and yield (Scheme 38).

More recently, during the studies on carbonylative [2+2+1] cycloaddition of bis(sulfonylallenes), its rhodium(I)-catalyzed cycloisomerization has been reported.[24b] Thus, reaction of bis(sulfonylallene) **100** using $[RhCl(CO)dppp]_2$ (10 mol%) as catalyst under CO atmosphere in toluene at reflux, afforded a mixture of cycloisomerization product **101a** (69%) and [2+2+1] cycloaddition product **102** (5%) (Scheme 39). Obviously, CO was not involved in the cycloisomerization. For this reason, when the reaction was performed with bis(allene) **101a** in absence of CO, nine-membered cycle **101a** was obtained as sole product in 96% yield. Other carbon- and nitrogen-analogs were obtained in reasonable yields, although in one case, for bis(allene) **100d**, a small amount of [2+2] cycloaddition product **103** was isolated. The reaction of bis(allenes) **52c** and **52d** under the same reaction conditions afforded cyclooctene derivatives **104** in high yields along with a small yield of [2+2+1] cycloaddition by-products **105** (Scheme 39).

Formation of compounds **101** and **104** from bis(allenes) **52c**, **52d** and **100a–e**, could be explained through formation of rhodacycle intermediate **106**, formed *via* metal coordinative cyclization between both terminal double bonds followed by thermal [1,5]-H shift (Scheme 40). The resulting intermediate **95** would afford compounds **101** and **104** *via* a reductive elimination step.

On the other hand, the cyclization reaction of 2,3-allenoic acids in the presence of simple alkyl- or aryl-substituted allenes has been studied.[37] In fact, reaction of allenoic acids **108a** with allenes **109** in the presence of $Pd(OAc)_2$ (2 mol%), $LiBr{\cdot}H_2O$ and benzoquinone in acetic acid at 60 °C afforded compounds **110**



Scheme 38 Synthesis of compounds **98** *via* intermolecular rhodium-catalyzed reaction between bis(allene) **1b** with allenes **97** and subsequent Diels Alder to form compounds **99**.

in moderate to good yields. A plausible mechanism involves the cyclic oxypalladation of 2,3-allenoic acid **108a** with Pd(II) to the furanoyl palladium intermediate **111**, which could be trapped by the simple allene to form a π-allylic intermediate **112** (Scheme 41). This intermediate could be attacked by a bromide anion to yield compounds **110**. The *in situ* formed Pd(0) was efficiently converted to the catalytically active Pd(II) species by benzoquinone in acetic acid.

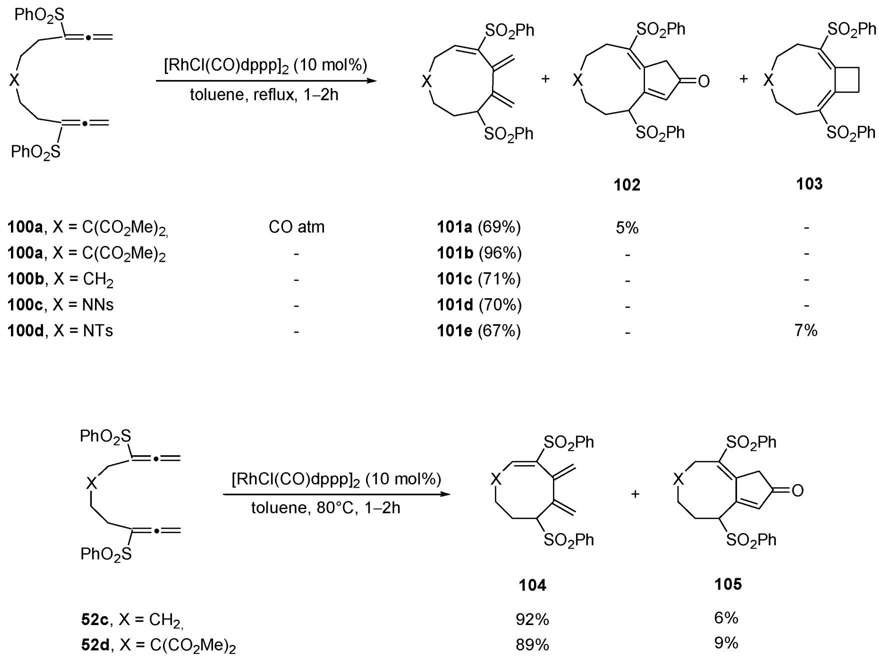
Based on the above precedent, the authors reasoned that the cyclization of 2,3-allenoic acids in the presence of 1,5-bis(allenes) may involve further cyclization to form compounds **113** (Scheme 42).[38] However, when bis(allene) **1a** was treated with 2,3-allenoic acid **108b** using the above reaction conditions, an unidentified mixture was obtained instead of the expected compound **113**. Interestingly, when the reaction between substrates **1a** and **108b** was catalyzed by $[PdCl_2(PhCN)_2]$ in DMSO, two tricyclic products *cis*-**114a** and **115a** were obtained without incorporation of the bromide anion (Scheme 43). In order to improve the selectivity of *cis*-**114**/**115** different conditions were tested. Taking into account, that $LiBr{\cdot}H_2O$ is not involved in the formation of both compounds, it was suppressed. Then, the optimum reaction conditions were the use of $[PdCl_2(PhCN)_2]$ (5 mol%) and 1,4-bis(diphenylphosphino)butane (5 mol%) as ligand. Thus, sandwich-type compounds **114** were obtained with excellent stereoselectivity and yields (Scheme 43).

Interestingly, when the enantioenriched (*S*)-2,3-allenoic acid **108d** was treated with bis(allene) **1l** under the optimal conditions, the optically active product (*S*,*R*,*S*,*S*)-**114b** was isolated. This example showed the excellent chirality transfer from the axial chirality of the optically active allenoic acid to the product (Scheme 44).

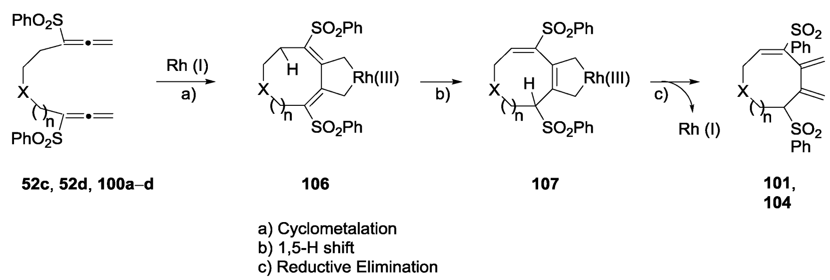
A possible mechanism for this transformation would start with the stereoselective cyclic *anti*-oxypalladation of (*S*)-**108d** to form intermediate **111** with a center of chirality (Scheme 45). Subsequent carbopalladation of one allene moiety in bis(allene) **1** with **111** would form the π-allylic intermediate **116a** or **116b**. Taking into account the steric interaction between the pseudoaxial proton and the 2(5*H*)-furanonyl vinyl group in **116b**, the reaction proceeds *via* the intermediate **116a** to generate *cis*-**117**. A second molecule of 2,3-allenoic acid (*S*)-**108d** would undergo sequential coordination and *anti*-oxypalladation with the vinyl palladium *cis*-**117** to generate *cis*-**118**, which upon reductive elimination would release the final tricyclic product (*S*,*R*,*S*,*S*)-**114b** and Pd(0). The Pd(II) catalyst would be finally regenerated by the reaction of Pd(0) with BQ and H^+.

Multicomponent reactions are very powerful synthetic processes, which allow achieving both complexity and diversity in a single and simple experimental step with high efficiency and atom economy.[39] The applicability of the multicomponent reactions has been widely demonstrated in the synthesis of natural products,[40] and medicinal chemistry.[41]

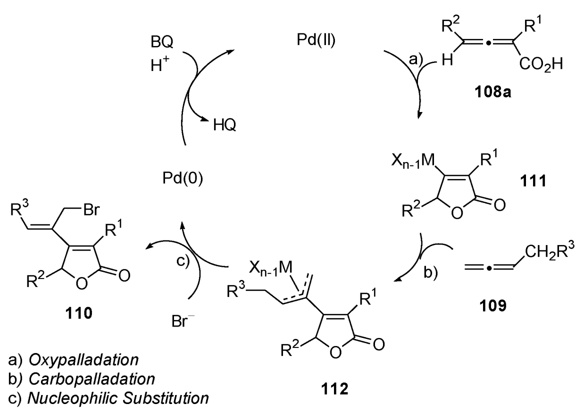
It has been reported that palladium-catalyzed coupling reaction of propargylic carbonates with boronic acids or organozinc reagents afford alkynes or allenes depending on the steric hindrance of the starting materials.[42] Taking into account this methodology, recently, Ma and col. have reported



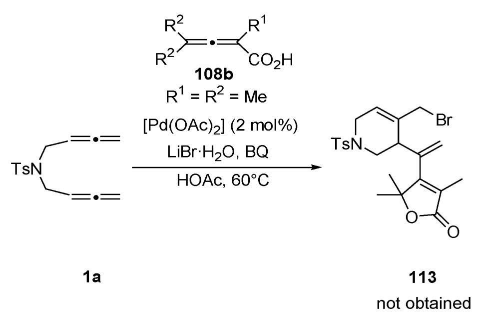
Scheme 39 Rhodium-catalyzed cycloisomerization of compounds **52c** and **52d**.



Scheme 40 Mechanistic explanation for the synthesis of compounds **100** and **104** from bis(allenes) **52c**, **52d** and **100**.

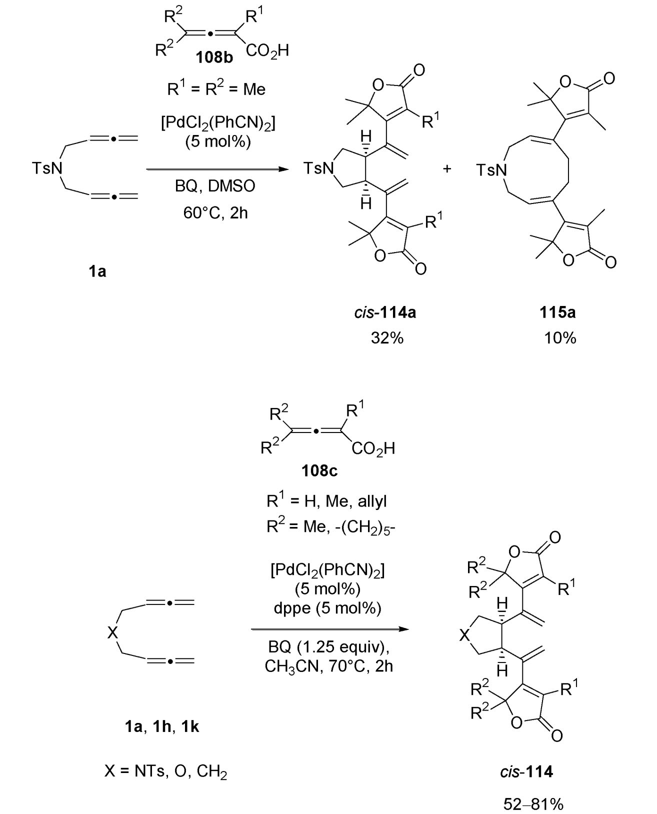


Scheme 41 Synthesis of furans **110** *via* cyclization reaction of 2,3-allenoic acids with substituted allenes.

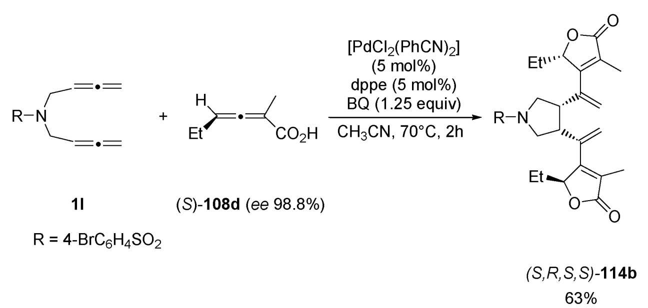


Scheme 42 Failed reaction of bis(allene) **1a** and 2,3-allenoic acid **108b**.

the palladium(0)-catalyzed three component coupling reaction of 1,5-bis(allenes), propargylic carbonates and organoboronic acids.[43] It is important to note that progargyl carbonates act as 1,2-allenyl intermediates in the process, involving three allene functionalities in the reaction, showing the great complexity of the process. Interestingly, multicomponent reactions between bis(allenes) **1a**, **1b** and **1m**, propargyl carbonates **119** and phenyl boronic acids **120** catalyzed by [Pd(dba)$_2$] (5 mol%),



Scheme 43 Synthesis of compounds **114** and **115** by reaction of bis(allenes) **1** and 2,3-allenoic acids **108**.



Scheme 44 Enantioenriched synthesis of compound **114b** from bis(allene) **1l** and 2,3-allenoic acid (*S*)-**108d**.

afforded bicyclic products **121** as single *cis*-diastereomers (Scheme 46). Interestingly, compounds **121** were not obtained in the absence of Na_2CO_3, while the optimum catalyst was the use of $[Pd(dba)_2]$ in the presence of a phosphine. The reaction was very general for bis(allenes) **1** and propargylic carbonates **119**. Phenyl boronic acids **120** with electron-withdrawing and electron-donating substituents were all suitable substrates.

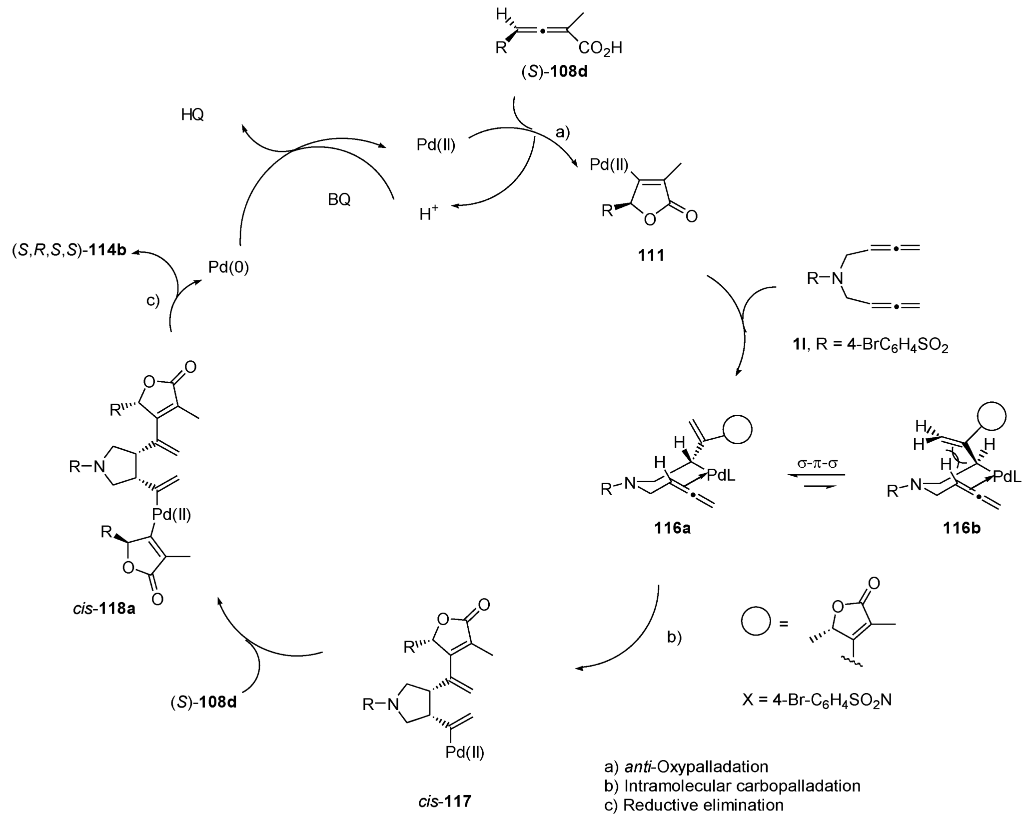
A plausible mechanism for the formation of compounds **121** is shown in Scheme 47. The catalytic cyclization starts by the oxidative addition of palladium(0) with the propargyl carbonate **119**, generating the 1,2-allenyl palladium species **122**. Subsequent carbopalladation of 1,5-bisallene **1** with **122** would form the π-allylic species *syn*-**123**, which intramolecularly undergoes carbometalation to afford the vinyl palladium species *cis*-**124** highly stereoselectively. The *cis*-stereoselectivity has been explained by the fact that π-allylic intermediate **125** would easily isomerizes to the more stable **126** to avoid the steric repulsion between the Pd center and the R^1 group ($R^1 \gg R^2$) by a π–σ–π process. Intermediate **125** would further isomerizes to **126** because of the presence of the upper exo C=C bond. The final product **121** is subsequently formed by the Suzuki-type coupling of **127** with the organoboronic acid **120**. It is presume that K_2CO_3 and the phosphine must promote this last step.

As we discussed previously, propargyl carbonates are ideal starting substrates for the *in situ* generation of the allene functionality. Taking into consideration this transformation, a recent investigation describes the reaction of allene carbonates **128** in the presence of carbon nucleophiles, involving a bis(allene) intermediate.[44] After screening a range of nucleophiles and reaction conditions, the authors found that the reaction of allene propargylic carbonates **128** with malonates using 5 mol% $Pd(PPh_3)_4$, 1.5 equivalents of K_3PO_4 in DMSO at 70 °C (or DMF at 90 °C) gave bicyclic compounds **129** in moderate to good yields (Scheme 48).

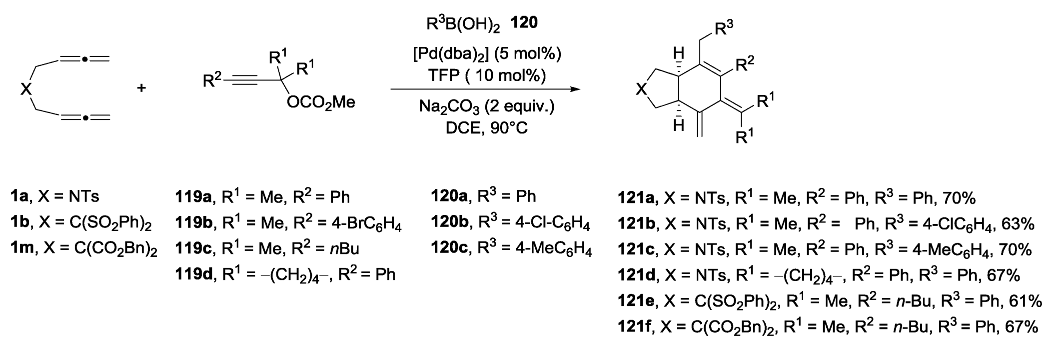
Compounds **129** could be formed by the mechanism shown in Scheme 49. First, oxidative addition of allene carbonate **128** with Pd(0) would afford the allenylpalladium intermediate **130**, which may undergo subsequent transformations by two possible pathways. Path A would involve intramolecular carbopalladation of the allene moiety which generate the allyl palladium species **131**, which is attacked by the geminal bis(nucleophile) regioselectively due to a steric effect, to give monocyclization product **132** with concomitant regeneration of the catalyst Pd(0). Further cyclization of the vinylallene **132** under basic conditions would then give compound **129**. On the other hand, Path B would involve the attack of the allenylpalladium intermediate **130** by the geminal bis(nucleophile) to form the intermediate **133**, which then would undergo intramolecular carbopalladation of the allene moiety to furnish the π-allyl palladium species **134**, which is then attacked by the nucleophilic moiety under basic conditions to yield the bicyclic product **129** and regeneration of the Pd(0) catalyst.

The synthesis of tetracenes **135** from bis(propargylic carbonates) **136** and organoborons catalyzed by Pd(0) involving the formation of a bis(allene) intermediate has been developed (Scheme 50).[45] Reaction of compounds **136** with electron-neutral or electron-poor arylboronic acids in the presence of catalytic amounts of $Pd(PPh_3)_4$ afforded the corresponding tetracenes **135** in excellent yields. Although, two regioisomers may be formed because both aryl groups in carbonate **136** and arylboronic acid might undergo ring-closure reaction, a single regioisomer was isolated. As discussed previously, the aromaticity of the final compounds explains why compounds **135** are isolated as single isomers. However, when electron-rich arylboronic acids were employed, two regioisomers **135a** and **135b** were obtained.

A tentative mechanism has been proposed for this transformation (Scheme 51). First, double S_N2' attack of Pd(0) on the



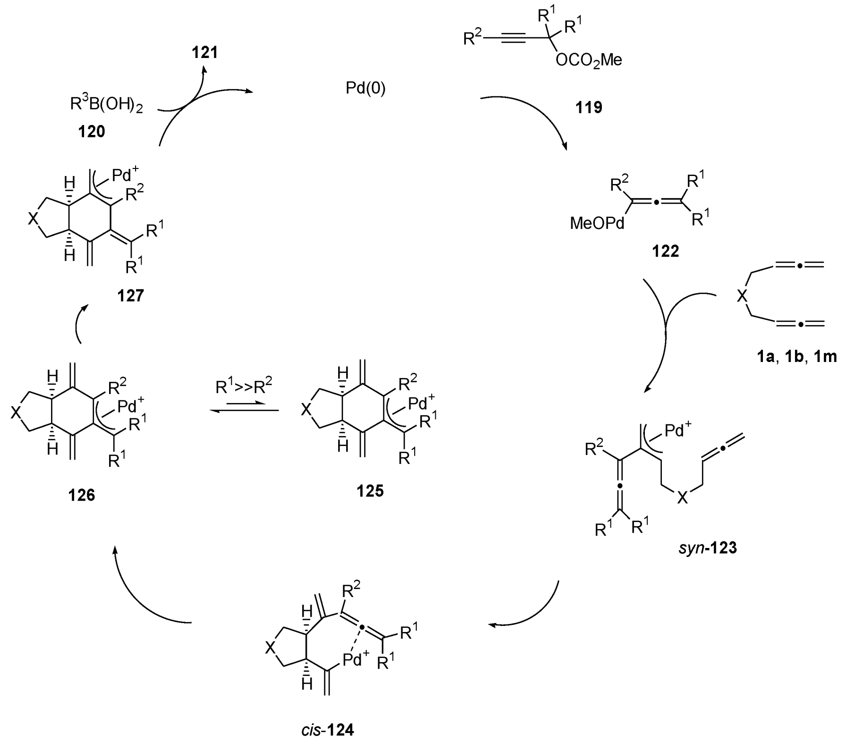
Scheme 45 Mechanistic explanation for the excellent chirality transfer observed in compound (*S*,*R*,*S*,*S*)-**114b**.



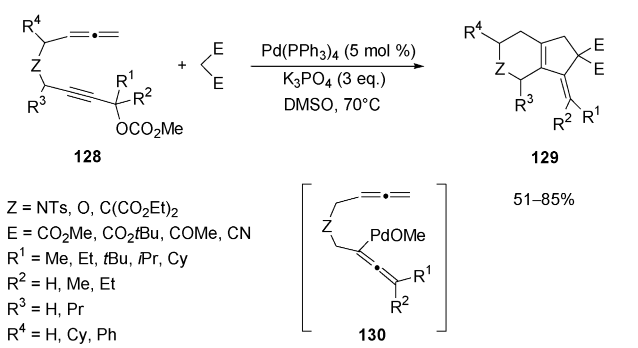
Scheme 46 Synthesis of compounds **121** *via* three component coupling of 1,5-bis(allenes) **1**, propargyl carbonates **119** and phenyl boronic acids **120**.

propargyl carbonate **136** would form bis[(σ-allenyl)palladium(II)] intermediate **137**. 6-π-Electrocyclic ring closure of bisallene **137** would lead 2,3-naphthaquinodimethane **138** as the reactive alkene isomer, which can also be represented as the resonance structure **139**, a highly stabilized biradical. Then, disrotatory 6π-electrocyclization of naphthaquinodimethane **138** would occur to afford intermediate **140**, in which the palladium and the hydrogen are in *cis* configuration. β-Hydride elimination would furnish arylpalladium intermediate **141**. Suzuki-type coupling of intermediate **141** with an organoboronic acid would give the tetracene **135** and release of Pd(0). The formation of tetracene regioisomers **135a** and **135b** could be explained due to competitive coupling reactions of intermediates **137** or **138**/**139** with the arylboronic acid.

Bis(allenes) **1** reacted with (trimethylsilyl)tributylstannane in the presence of a catalytic amount of $Pd(PPh_3)_4$ (5 mol%) in refluxing THF, affording *trans*-fused cyclized compounds **142** in good yields.[46] By contrast, when the same allenes **1** were treated with $Bu_3SnSnBu_3$, the Pd(0)-catalyzed cyclization process took place smoothly to afford *cis*-fused distannanes **143** (Scheme 52). Analogously, similar Pd-catalyzed cyclizations of 1,5-bis(allenes) with germylstannanes have been accomplished under the conditions described above.[47] Thus, when Y group



Scheme 47 Plausible mechanism for the formation of compounds **121**.



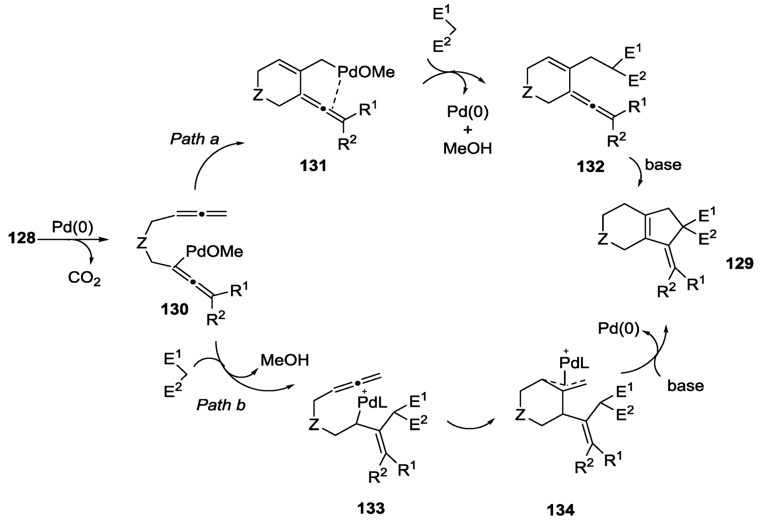
Scheme 48 Synthesis of bicyclic compounds **129** from allene propargyl carbonates **128**.

was Bu_3Ge, *cis* products **142** were obtained in 41–51% yields, while with Y being Ph_3Ge group, *trans* products **143** were formed in 61–77% yields. In addition, in some cases, when the reaction time was prolonged to 12 hours, *cis*-fused bicyclic dienes **144** were isolated in low yield, formed *via* [2+2] cycloaddition of both terminal double bonds of the bis(allene) (Scheme 52).

Formation of compounds **142** and **143** can be explained by the mechanism shown in Scheme 53. First, Bu_3SnPdY species are generated *via* oxidative addition and then added to the allene moiety. Next, the Y group is attached irreversibly to the central carbon of the allene, while palladatributyltin species added to the allene moiety to form complexes **145a** and **145b**, which undergo further cyclization with another allenyl group. Thus, the selectivity of *cis* and *trans* products must be controlled by the steric effect between Y group and allene moiety in intermediates **146** or **147**, respectively. When Y is a bulky group such as TMS or $GePh_3$, *trans* products **142** are formed. However, when Y group is $SnBu_3$ or $GeBu_3$, formation of *cis* products **143** is favoured. It is important to remark that the steric hindrance of the TMS group compared to Bu_3Sn is the shorter Si–C bond length and a larger effective size. However, formation of cyclobutanes **144** must be explained *via* palladacyclopentane intermediate **148**, followed by reductive elimination.

Although for long time gold has been considered to be catalytically inactive, this metal has recently shown a rich coordination and organometallic chemistry, leading a high number of interesting contributions in both heterocyclic and carbocyclic synthesis.[48]

In 2007, the cycloisomerization of enynes catalyzed by an NHC gold(I) catalyst to obtain tetracyclo[3.3.0.0.^{2,8}0^{4,6}] was reported.[49] Based on this work, latter on, this group has reported the cycloisomerization reaction of bis(allenes) using the same catalyst (Scheme 54).[50] Cycloisomerization has been studied using *N*-substituted bis(allenes) **149** using 10 mol% of [Au(IMes)Cl]/$AgBF_4$ as catalytic system affording compounds **150** in excellent yields. The presence of substituents on the internal double bonds of both allenyl groups did not inhibit the desired reaction; however, the cycloisomerization did not tolerate substitution at the terminal allenyl carbon atom. Interestingly, although four possible compounds could be expected, namely head-to-head, tail-to-tail, head to tail and twisted head-to-head [2+2] cycloadducts, only the last ones were obtained. To



Scheme 49 Mechanistic proposal for the formation of compounds **129** from allene propargyl carbonates **128** involving the formation of bis(allene) intermediates **130**.

elucidate the formation of compounds **150**, the authors carried out DFT calculations. From these calculations, the Au-catalyzed cycloisomerization reaction of bis(allenes) occurs *via* a stepwise process. Coordination of the gold salt to the allene moiety to give **151** is followed by the nucleophilic attack of the other allenyl group to the gold-bound allene, with concominant formation of a C1–Au–C2′ bridge forming intermediate **152**. The positive charge must be stabilized by the gold atom, facilitating the formation of C–C bond between C1 and C2′ in intermediate **152**, which would afford 6,7-dimethyleneazabicyclo[3.1.1]heptane skeleton **150** from intermediate **153** (Scheme 55).

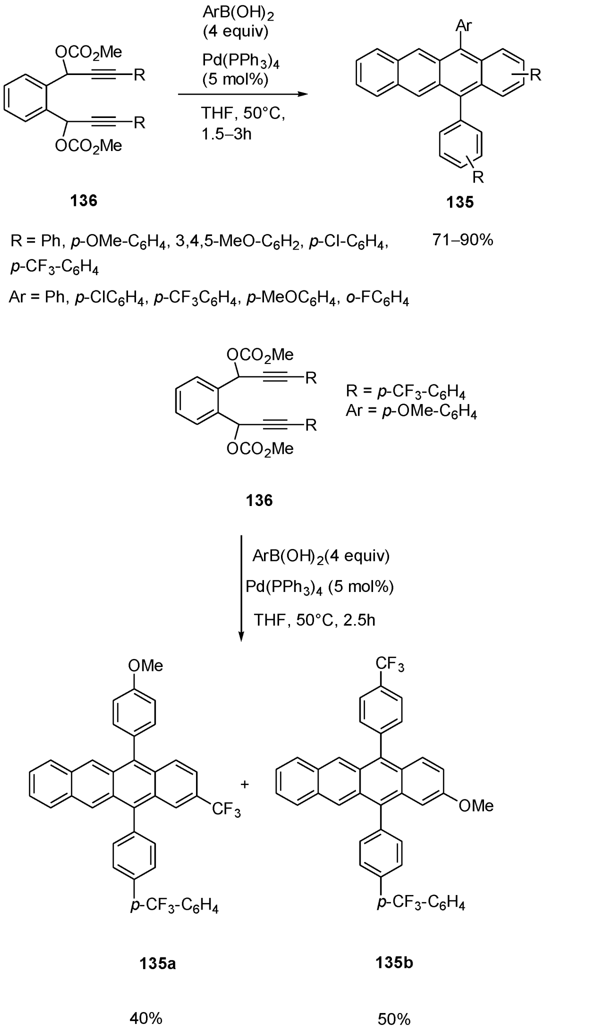
While the olefin metathesis reaction has experienced spectacular achievements in organic synthesis with interesting applications in natural product synthesis,[51] the olefin metathesis in allenes has been scarcely investigated and in the examples described so far, the final compounds have been isolated in very low yields.[52] It is presumed that both, formation of very large size rings and conformational disposition of the starting material, are the main factors involved in the poor results obtained. Thus, during the studies of ring closing metathesis (RCM) between alkenes and allenes in order to obtain cyclophanes, the synthesis of allenic macrocycles by treatment of α,γ-bis(allenes) **154** and **155** with Grubbs' first generation catalyst under high dilution conditions was reported (Scheme 56).[53] Thus, the desired 15- and 17-membered allenes **156** were isolated in reasonable yields. However, the analogous bis(allene) bearing an aromatic spacer afforded allenic cyclophane **157** with only 9% yield.

During the studies on the transannular intramolecular [4+3] cycloaddition reaction, en route to the ABCD ring structure of cortistatins,[54] it has been studied the RCM of bis(allenes). RCM of bis(allene) **158** using Grubbs' first generation catalyst under high dilution conditions gave allenic macrocycle **159** in 47% yield (Scheme 57). Transannular [4+3] cycloaddition was achieved by treatment of allene **159** with 10 mol% $Pd(OAc)_2$ in the presence of LiBr to give compound **160** in 37% yield.

The potential and utility of radical reactions in the construction of carbocyclic and heterocyclic compounds has been widely demonstrated.[55] Concerning the reactivity of allene derivatives, for a long time, this peculiar functionality has been discriminated against radical processes due to the lack of chemo-, regio-, and stereoselectivity. However, in recent years, interest in radical-based transformations of allenes has been revitalized due to the accomplishment of the synthesis of target molecules and the results obtained from theoretical investigations. Radicals derived from allenes undergo cyclizations related to those of their olefinic counterparts.[56] The efficiency of this transformation depends on the chain length separating both reactive entities and is the major factor for regiocontrol. Thus, radical cyclization can take place on the central carbon atom *via* the *dig* mode of ring closure or to the internal carbon atom *via* the *trig* mode of ring closure.

Reaction of bis(allenes) **1** with *p*-tosyl bromide or *p*-tosylseleniumbromide in the presence of a catalytic amount of AIBN afforded *trans*-fused cyclopentane compounds **161**, incorporating vinyl sulfones, vinyl bromides or selenophenyl functionalities in their structure (Scheme 58).[57] The addition of tosyl radical to the central carbon atom of one allene moiety gives an allylic radical intermediate **162**. This propagation step is followed by cyclization with the other tethered allene moiety in a stereoselective *trans* fashion in radical **162** to give intermediate **163**. Finally, intermediate **163** is trapped by the corresponding bromide or selenophenyl radicals to afford the energetically more favorable and more stable *trans* product **161**.

The Garratt–Braverman cyclization is a multistep process which involves a diradical intermediate, which collapse to the final product *via* self-quenching, forming two new C–C bonds. In a recent work, it has been reported the synthesis of 1-indol-3-yl-carbazoles **164** *via* Garratt–Braverman cyclization, involving

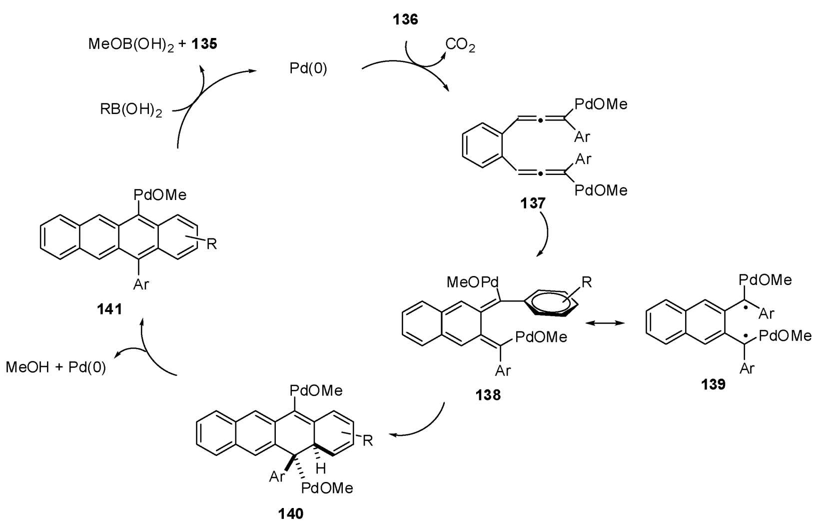


Scheme 50 Synthesis of tetracenes **135** from dicarbonates **136** involving a bis(allene) intermediate.

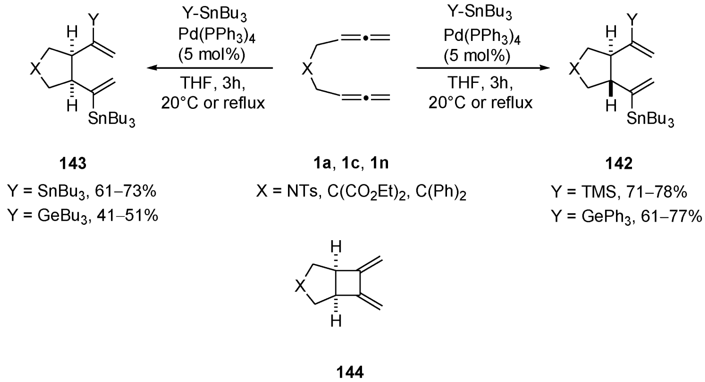
bis(allene) intermediate **165** and diradical intermediate **166** (Scheme 59).[58] The corresponding bis(indoles) were prepared from indole or indole derivatives. The Garratt–Braverman cyclization was studied in compounds **167** using Et_3N in $CDCl_3$. The reaction with bis(indole) sulfone was more successfully accomplished using DBU, thus compound **164** was obtained in 80% yield. In addition, cyclization of bis(indole) ether and bis(indole) amine were successfully achieved using KO^{t}Bu in refluxing toluene, affording both indolyl derivatives **164** in 75% yield. It is important to note that during the cyclization step of the radical intermediate **166** to compounds **164**, isomerization of the six membered-ring takes place.

Latter on, a related research work has studied the competition between 6π-electro- and Garratt–Braverman cyclizations in bis(allene) sulfones.[59] Thus, reaction of bis(alkyne) sulfones **168** in the presence of 10 mol% of Et_3N afforded a mixture of Garratt–Braverman products **169** as major products along with 6π-electrocyclization products **170** (Scheme 60). It has been observed that increasing the steric bulk of the R^2 group has a minimal effect on the selectivity of the reaction. However, lowering the temperature of the reaction favoured the formation of compound **169** (kinetic product), while higher temperature favoured the 6π-electrocyclization compound **170** (thermodynamic product). Formation of compounds **169** has been explained *via* bis(allene) intermediate **171** and diradical **172**.

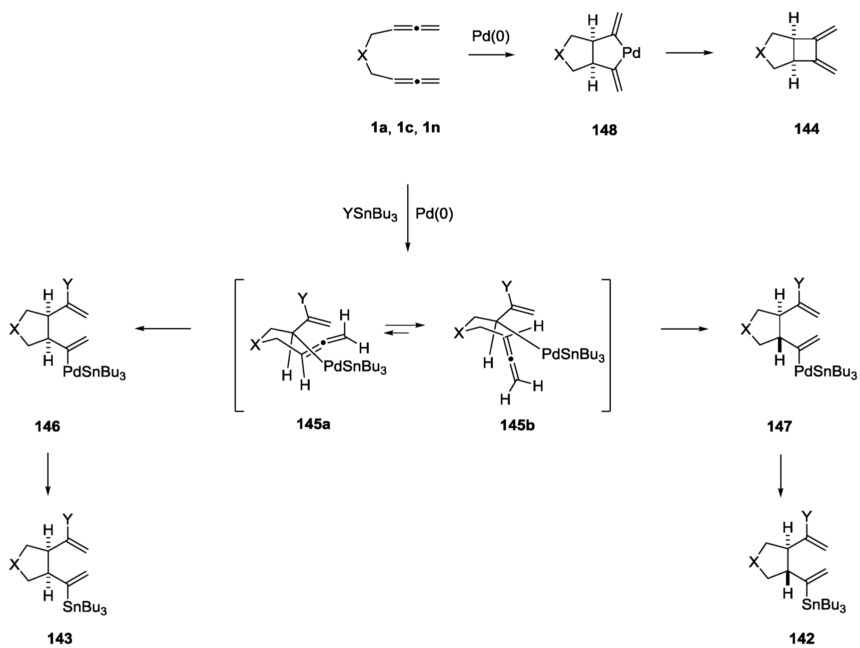
3.1.2 Reactivity allene–non allene. Recently, the synthesis of carbazoles and bis(carbazoles) from indole-C2-tethered allenols under mild conditions has been reported.[60] Although NH-indole-tethered allenols have diverse reactive sites, at which different transformations (C-cyclization *versus* O-cyclization *versus* N-cyclization) can take place, carbocyclization products have been exclusively obtained. Besides, reaction of bis(allenes) **173** with allyl bromides under palladium catalysis afforded bis(carbazoles) **174** in reasonable yields (Scheme 61).



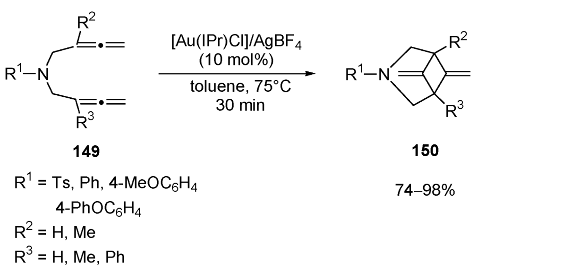
Scheme 51 Mechanistic explanation of compounds **135** involving a bis(allene) intermediate **137**.



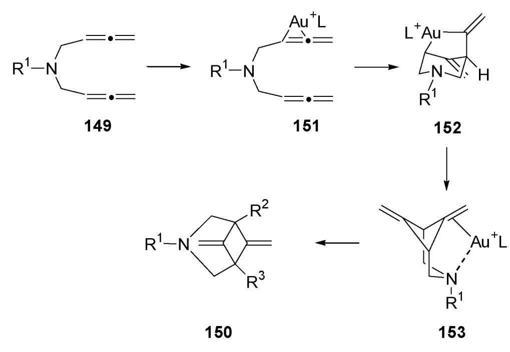
Scheme 52 Reaction of bis(allenes) **1** with (trimethylsilyl)tributylstannanes and with germylstannanes.



Scheme 53 Pd-catalyzed reaction of 1,5-bis(allenes) with $YSnBu_3$.

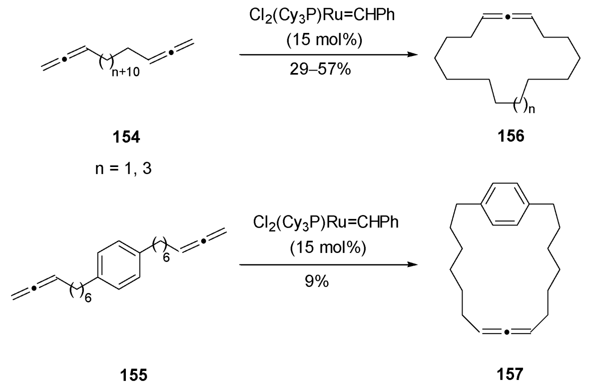


Scheme 54 Transformation of *N*-tethered 1,5-bis(allenes) to compounds **150**.

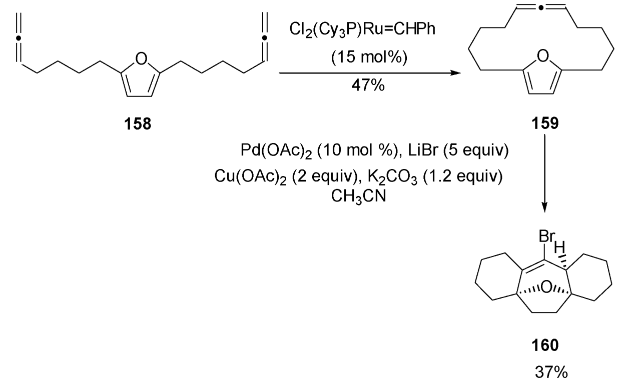


Scheme 55 Proposed catalytic mechanism for the synthesis of compounds **150**.

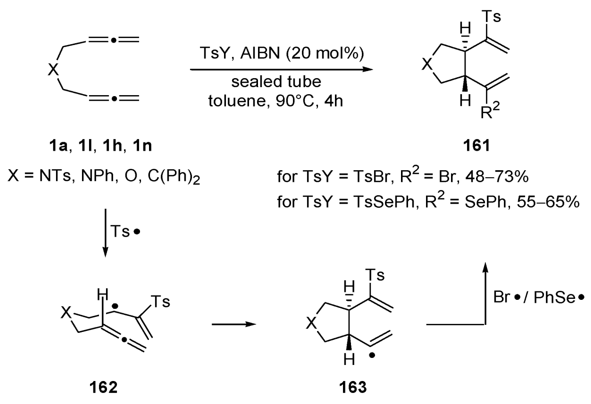
A likely mechanism for the palladium-catalyzed generation of functionalized carbazoles **174** is outlined in Scheme 62. First, Pd(II) coordination to both allene moieties would give a bis(allenepalladium) complex **175**. Species **175** would suffer a



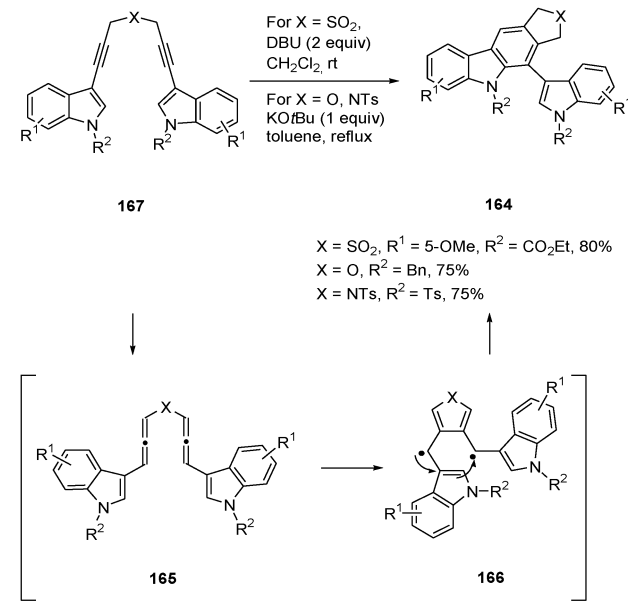
Scheme 56 Ring closing metathesis of compounds **154** and **155**.



Scheme 57 Synthesis of the ABCD ring core of cortistatins *via* RCM of compounds **158** followed by [4+3] cycloaddition.



Scheme 58 Synthesis of *trans*-fused cyclopentane compounds **161** from bis(allenes) **1** *via* a radical mechanism.



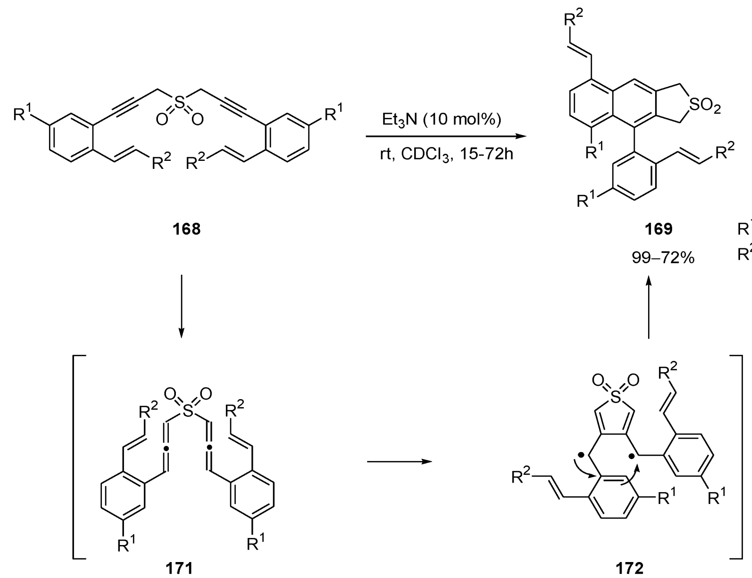
Scheme 59 Synthesis of 1-indol-3-yl-carbazoles **164** *via* the Garratt–Braverman cyclization, involving the formation of a bis(allene) intermediate **165**.

two-fold intramolecular chemo- and regioselective 6-*endo* carbocyclization reaction to give an intermediate bis(palladadihydrocarbazole) **176**, which would react with two equivalents of the allyl bromide *via* **177** to form intermediate **178**. A double *trans*-β-heteroatom elimination with concurrent dehydration under the reaction conditions generates carbazoles of type **174** with concomitant regeneration of the Pd(II) catalyst. Apparently, HX would promote the dehalopalladation, inhibiting the β-H elimination.

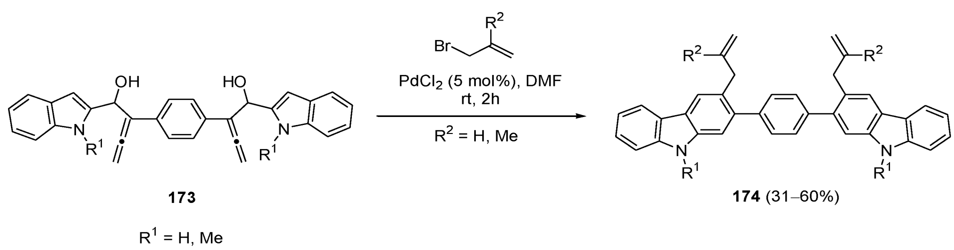
An alternative mechanism to form bis(carbazoles) **174** could also be proposed (Scheme 63). First, oxidative addition reaction of the allyl bromide with palladium would form a π-allyl palladium complex **179**, which would add to the central carbon of the 1,2-diene moiety through carbopalladation, giving rise to a new bis(π-allyl palladium) complex **180**. Intermediate **180** would evolve through double intramolecular 6-*endo* carbocyclization reaction, with concomitant dehydration, to give functionalized bis(carbazoles) with regeneration of the palladium species.

The electrophilic addition of allenes has not been studied in detail due to the difficulty to control the stereoselectivity of the final compounds. There are recent examples concerning the electrophilic interaction of 1-substituted 2,3-allenols with Br_2, NBS and I_2, affording 3-halo-3-alkenals or 2-halo-2-alkenyl ketones in good yields.[61] In this context, it has been reported the ring expansion of bis(β-lactam)–bis(allenes) into bis(tetramic acids) in the presence of *N*-bromosuccinimide (NBS).[62] Thus, reaction of bis(β-lactam)–bis(allene) **181** with one equivalent of NBS afforded compound **182** *via* selective ring expansion of one β-lactam ring (Scheme 64). The use of 3 equivalents of NBS smoothly afforded bis(tetramic acid) **183** formed *via* double ring expansion of both β-lactam rings in compound **181**.

To understand the mechanism of the ring expansion of compounds **181** promoted by NBS, the mechanism of the reaction has been investigated using DFT methods. Thus, the ring expansion of compound **181** to **183** could be explained *via* one-step mechanism involving the addition of Br^+ from NBS to



Scheme 60 Formation of compounds **169** and **170** *via* 6π-electro and Garratt–Braverman cyclizations of compounds **168** involving formation of bis(allenes) intermediates **171**.



Scheme 61 Synthesis of bis(carbazoles) **174** *via* carbocyclization of bis(allenes) **173**.

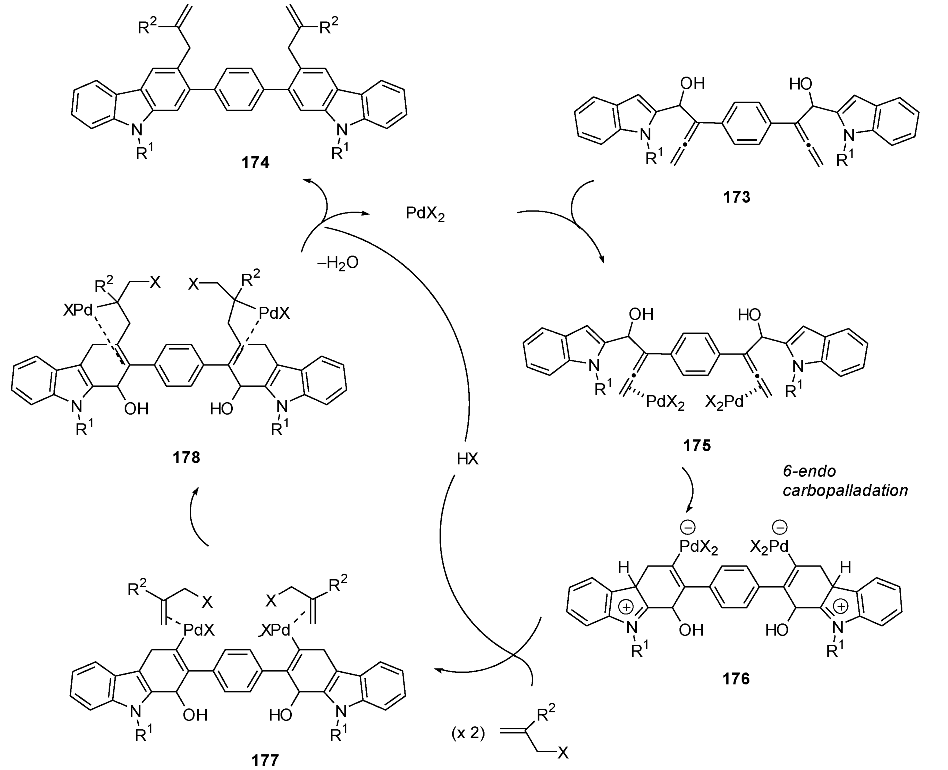
the central sp carbon atom of both allene groups, followed by double ring expansion (Scheme 65). This path would involve a double carbocationic intermediate with hydrogen bonds between one oxygen atom of NBS and the hydroxylic hydrogen atoms. Although two stereoisomers could be formed *via* transition states **184** and **185**, which have similar energies, the presence of a bulky substituent (R^2) is the responsible to control the stereoselectivity of the reaction. In addition, formation of compounds **183** could be explained in two steps, which would involve a single ring expansion of one allene moiety and subsequent ring expansion of the second allene functionality in compound **181**.

3.2 Formation of new C–heteroatom bonds: Heterocyclizations

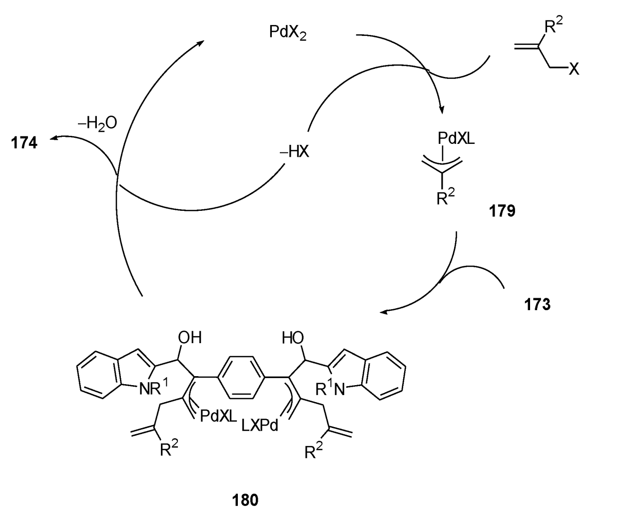
Allenes containing a nucleophilic functional group, such as oxygen or nitrogen, are versatile synthetic building blocks for the construction of different heterocycles depending on the nature of the nucleophilic center.[63,64] In particular, cycloisomerization of α-hydroxyallenes afford 2,5-dihydrofurans, which are present in biologically active compounds,[65] and are excellent building blocks in organic synthesis.[66] This cycloisomerization reaction takes place with axis-to-center chirality transfer when the reaction is promoted by anhydrous acid,[67] silver,[68–70] or gold salts.[71–73] In addition, this transformation has been studied using Pd(II) catalyst to obtain the corresponding 2,5-dihydrofurans smoothly.[74]

A reasonable mechanism would involve metal coordination to one allenic double bond, followed by nucleophilic attack to generate a metalloheterocycle. Subsequent protonolysis of the carbon–metal bond would then yield the product and regenerate the catalyst (Scheme 66).

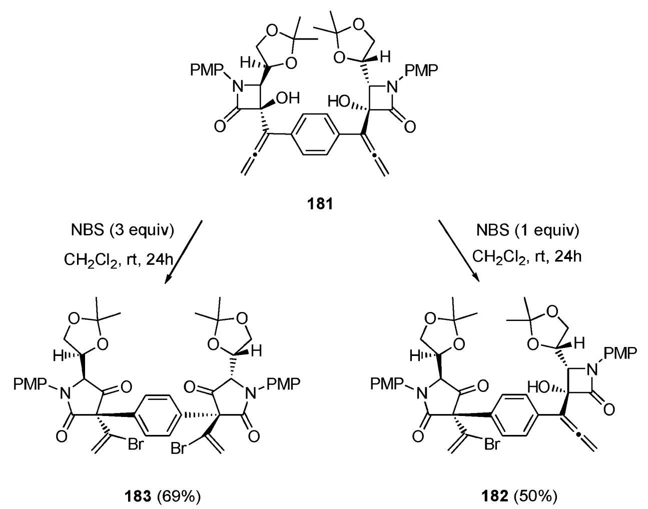
Taking advantage of this cycloisomerization process, this methodology has been applied to the synthesis of bis(2,5-dihydrofurans). Thus, the synthesis of bis(2,5-dihydrofuran) derivatives **186** by silver- or gold-catalyzed cycloisomerization of bis(α-hydroxyallenes) **187** with axis-to-center chirality transfer has been reported.[75] First, conjugated bis(allenes) **187** have been synthesized *via* copper mediated S_N2'-substitution of bis(propargyloxiranes) **188**. Compounds **188** are a mixture of the *meso*- and DL-diastereomers. Interestingly, each propargyloxirane can be subjected to a *syn*- or *anti*- selective S_N2'-substitution. Thus, 8 diastereomeric bis(allenes) could be formed in the reaction. Interestingly, in the event, only a single



Scheme 62 Suggested mechanism for the formation of functionalized carbazoles **174** from bis(allenes) **173**.

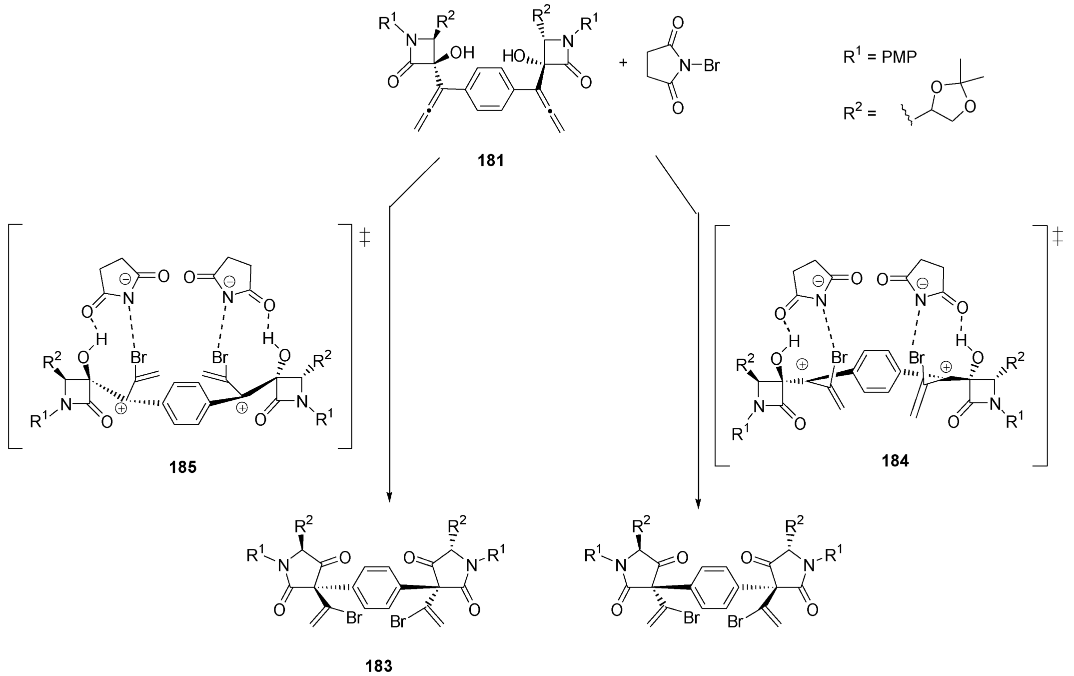


Scheme 63 An alternative mechanism for the formation of functionalized carbazoles **174** from bis(allenes) **173**.

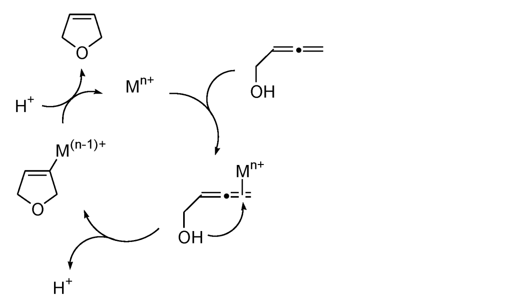


Scheme 64 Synthesis of tetramic and bis(tetramic acids) **182** and **183**, respectively *via* NBS addition to bis(allene) **181**.

diastereomer has been obtained. However, the relative configuration of bis(allenes) **187** has not been assigned because these compounds were not crystalline. The cycloisomerization processes have been studied using gold and silver catalyst. Reaction of bis(allenes) **187** in the presence of silver nitrate gave the corresponding functionalized bis(2,5-dihydrofurans) **186** in moderate yields. However, the reaction of the bis(allene) **187** with an internal substituent more bulky such as iPr, in the presence of silver nitrate, induced a rapid monocyclization to afford the corresponding 2-allenyl-substituted 2,5-dihydrofurans **189** with excellent yield as single diastereomers with axis-to-center chirality transfer (Scheme 67). Fortunately, the second cyclization step was achieved by the combined used of *N*-iodosuccinimide and gold-catalysis. Then, reaction of allenes **189** with 2 mol% of gold(III) bromide in the presence of 1.2 equiv. of NIS in dichloromethane at room temperature



Scheme 65 Mechanistic proposal for the ring expansion of compounds **181**.



Scheme 66 General mechanism for the cycloisomerization of α-hydroxyallenes to afford 2,5-dihydrofurans.

afforded the richly functionalized bis(2,5-dihydrofuran) **190** in 61% yield.

A few years ago, it was reported the cyclization of 2,3-allenoic acids in the presence of 2,3-allenols,[76] as well as the palladium(II)-catalyzed heterocyclization/cross-coupling reaction between an α-allenol and a ester protected α-allenol.[77,78] Besides, the cyclization of one 2,3-allenol in the presence of a different[79] or the same[80] 2,3-allenol, affording 4-(1′,3′-dien-2′-yl)-2,5-dihydrofurans has been described.[81]

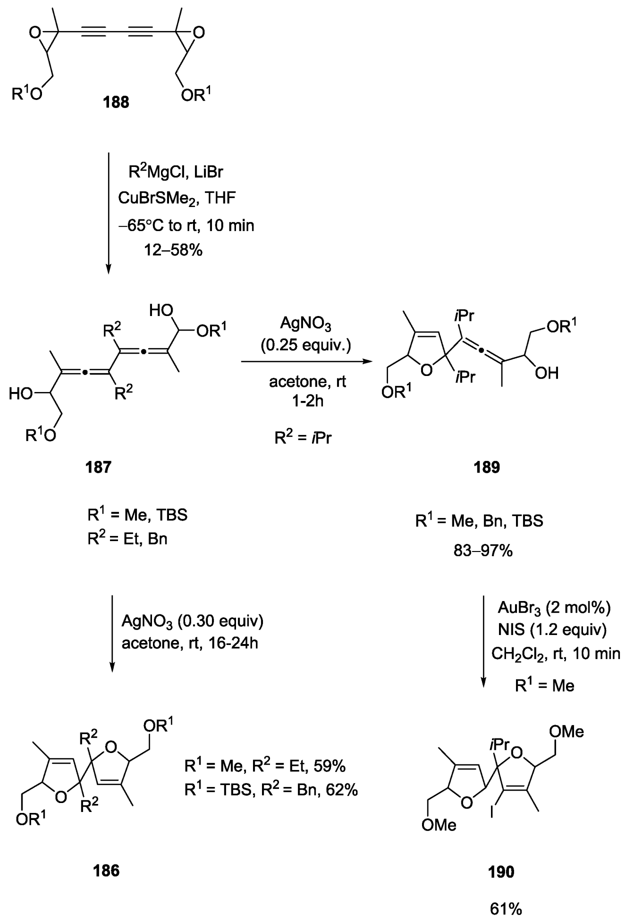
Taking into account this process, it has been reported the synthesis of 2,5-dihydrofuran-fused bicyclic skeletons *via* intramolecular Pd(II)-catalyzed cyclization of 1,ω-bisallenols, where one hydroxyl group can be protected as acetate.[82] Thus, reaction of bis(allenols) **191** in the presence of $PdCl_2$ (5 mol%) has provided the corresponding fused bicycles[5.3.0] **192** in moderate to good yields (Scheme 68). It is important to mention the importance to protect one of the hydroxyl groups as acetate for non symmetric bis(allenols), otherwise a complex reaction mixture is observed.

Formation of 1,5-dihydrofuran-fused bicyclic skeletons **192** has been rationalized by the mechanism shown in Scheme 69. First, oxypalladation of the 1,3-allenol moiety in **191** would form intermediate **193**. Then, regioselective intramolecular carbopalladation of the remaining allene unit in **193** would form the π-allylic palladium intermediate **194**. Subsequent trans-β-hydroxide or acetate elimination would afford products **192** highly stereoselective.

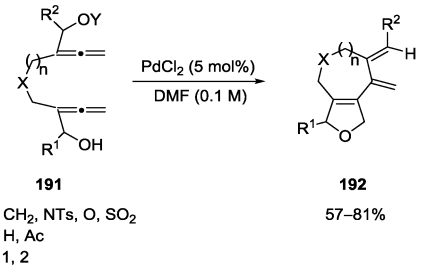
Following observations on allenyl alcohols, it was studied the cycloisomerization of allenyl ketones and allenyl aldehydes **195** to afford substituted furans **196**.[70] Initially, this transformation has been developed using stoichiometric quantities of Ag(I) salts such as $AgNO_3$ and $AgBF_4$. Further studies allowed the reaction using catalytic conditions (0.1–0.2 equiv.) (Scheme 70).

Interestingly, the reaction of allenone **197** in the presence of palladium catalyst involving a combination of C–O and C–C bond formation, afforded compound **198** as the major product with a small amount of furan **199** (Scheme 71).[83,84] Compound **200** was observed as side-product under non-optimized conditions and compound **201** was not isolated.

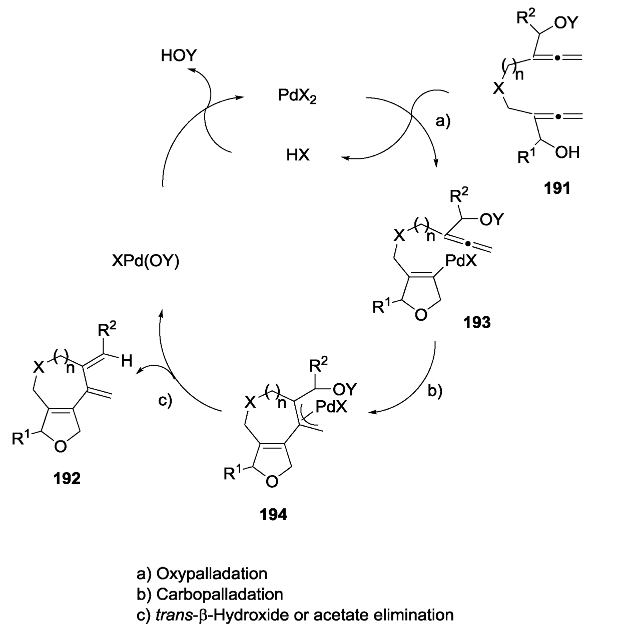
Later on, it was investigated the application of this methodology to the formation of macrocyclic furanophanes from bis(allenylketones) as starting materials. In fact, reaction of bis(allenones) **202** catalyzed by $[PdCl_2(MeCN)_2]$ afforded a mixture of four different products (Scheme 72): (a) 1,*n*-difurylalkanes **203** formed by Marshall reaction (analogous to compounds **196** in Scheme 70); (b) furanophanes **204**, having an (*E*)-configuration of the alkene in the bridge, formed by Pd-



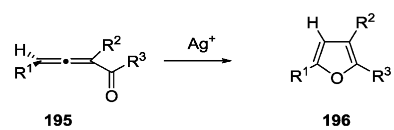
Scheme 67 Silver and gold-catalyzed cycloisomerization of bis(allenes) **187**.



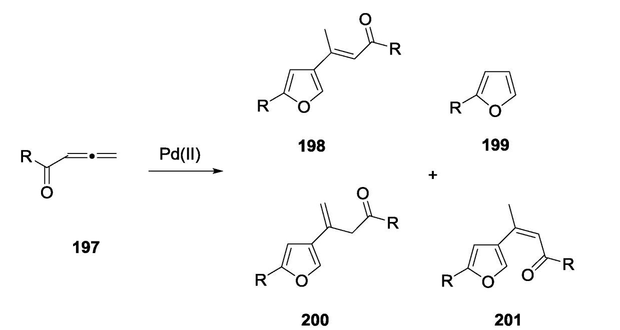
Scheme 68 Synthesis of 2,5-dihydrofuran-fused bicyclic skeletons *via* Pd(II)-catalyzed tandem-cyclization of bis(allenols) **191**.



Scheme 69 Mechanistic proposal for the synthesis of 1,5-dihydrofuran-fused bicyclic skeletons **192**.

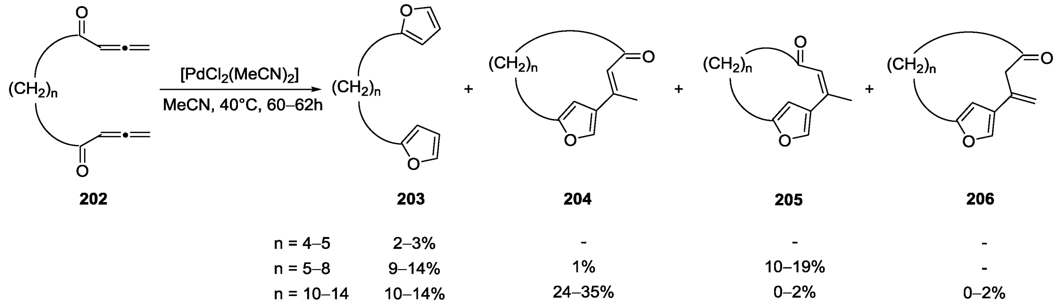


Scheme 70 Cycloisomerization reaction of allenyl ketones and allenyl aldehydes in presence of stoichiometric quantities of Ag(I).



Scheme 71 Pd(II)-catalyzed isomerization of allenones to afford furans.

catalyzed intermolecular coupling of allenyl ketones (analogous to compounds **198** in Scheme 71); (c) furanophanes **205**, with a (*Z*) configuration of the alkene in the bridge, curiously not observed previously in the intermolecular couplings; and (d) furanophanes **206**, having an exocyclic double bond. Interestingly, formation of each compound or a mixture of some of them depends on the length of the tether between both carbonyl groups. Thus, it has been observed that with a short bridge of four or five methylene units, no macrocycles were formed and only difurylalkanes **203** were obtained. A bridge of six to eight methylene units gave compounds **203**, a small amount of compound **204** (1% in all cases), while compounds **205** are the major products and the proportion of **206** increases sequentially. With ten and eleven methylene units, the trend remains for compounds **203** and **204**, which are the major products, while the amounts of **205** and **206** decreased sharply. Finally, with n = 12 and 14, compound **204** was the only macrocycle observed. Thus, formation of compounds depends on the length of the bridge. For long bridges, the meta bridging



Scheme 72 Pd-catalyzed cycloisomerization reaction of bis(allenones) **202**.

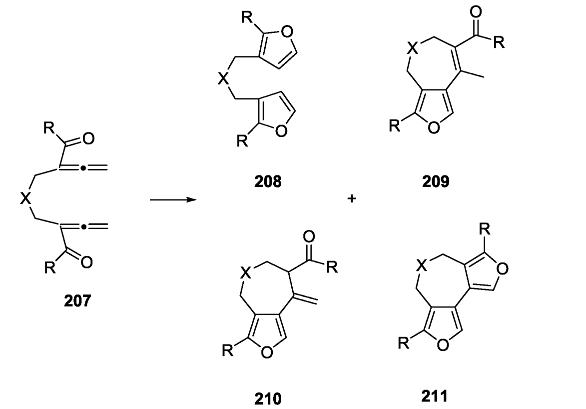
of the furan ring and the (*E*) configuration of the double bond in this bridge are tolerated without difficulties. However, for n = 5–8, the strain seemed to increase; then the double bond geometry in the bridge switches to the (Z) configuration, favoring formation of compounds **205**.

More recently, the transition metal-catalyzed biscyclization of 1,5-bis(1,2-allenylketones) **207** has been investigated.[85] There are four different possibilities: (a) formation of compound **208** by bis(cycloisomerization) of each allenone moiety; (b) formation of bicyclic compounds **209** and **210**, analogous to compounds **204** and **206** (in Scheme 72); and (c) tricyclic products **211** (Scheme 73).

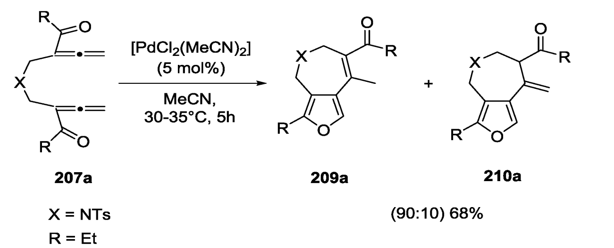
Initially, the reactivity of symmetrical 1,5-bis(1,2-allenylketones) **207a** was tested using 5 mol% of [PdCl$_2$(MeCN)$_2$], affording furo[3,4-*c*]azepine derivative **209a** together with the C=C bond regioisomer **210a** in 90 : 10 ratio in 68% yield (Scheme 74). After variation of several parameters in order to improve the selectivity of the cyclization process, the optimum catalyst was found to be [RhCl(CO)$_2$]$_2$ (Scheme 75). In addition, unsymmetrical diketones **211** selectively afforded the expected cyclization products **212** in moderate to good yields with a small amount of compound **210** in some cases (Scheme 76).

Formation of the 3,4-fused bicyclic furo-skeletons has been rationalized by the mechanism shown in Scheme 77. First, the cyclic oxymetalation of the 1,2-allenyl ketones moieties in **207** and **211** catalyzed by Pd(II) or Rh(I) would form intermediate **214** (M = Pd or Rh). The electron-donating R^1 group increases the nucleophilicity of the carbonyl oxygen atom; explaining the selectivity for unsymmetrical substrates. Then, intramolecular carbometalation of the remaining allene unit in **214** would form π-allylic palladium intermediate **215** due to the low oxophilicity of palladium. Due to the presence of the carbonyl compound, subsequent protonolysis of **215** with H$^+$ may occur. However, such a reaction at the α- or γ-position would afford an isomeric mixture of **209** and **210**, being **209** the major product due to steric effects. Finally the catalytically active Pd(II) species is regenerated. By contrast, oxygen-bound rhodium dienolate intermediates **216** must have formed exclusively using the rhodium catalyst. Therefore, the only observed products are **209** and **212**.

Medium-sized heterocycles are an important class of compounds which are found in a variety of natural products,



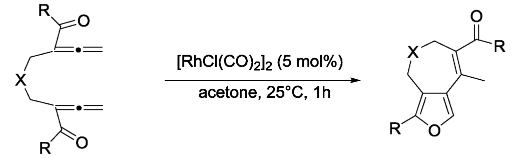
Scheme 73 Metal-catalyzed biscyclization of 1,5-bis(1,2-allenylketones) **207**.



Scheme 74 Palladium(II)-catalyzed cyclization of 1,5-bis(1,2-allenylketone) **207a**.

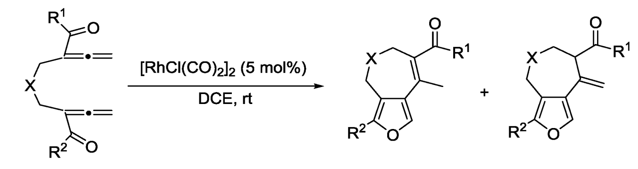
however they are difficult to prepare due to entropic and enthalpic reasons.[86] On the other hand, Pd-catalyzed carbopalladation of allenes may afford the π-allyllic palladium species which can react with a nucleophile to form the allylation product (Scheme 78). Q5

It has been reported both the inter-[87] and intramolecular[88] three-component reactions between allenes, amines and aryl iodides. This transformation could be explained *via* oxidative addition of the organic halide to the Pd(0) species (Scheme 79). The allene would undergo carbopalladation of the species to generate a π-allylpalladium intermediate. Finally, the allylic compound is produced by nucleophilic attack.



207a, X = NTs, R = Et — **209a**, 80%
207b, X = NTs, R = Me — **209b**, 84%
207c, X = SO_2, R = Et — **209c**, 76%
207d, X = $C(CO_2Me)_2$, R = *n*-C_6H_{13} — **209d**, 77%
207e, X = CH_2, R = Et — **209e**, 65%
207f, X = CH_2, R = *i*-C_3H_7 — **209f**, 72%
207g, X = CH_2, R = Ph — **209g**, 44%
207h, X = CH_2, R = Ph — **209h**, 66%

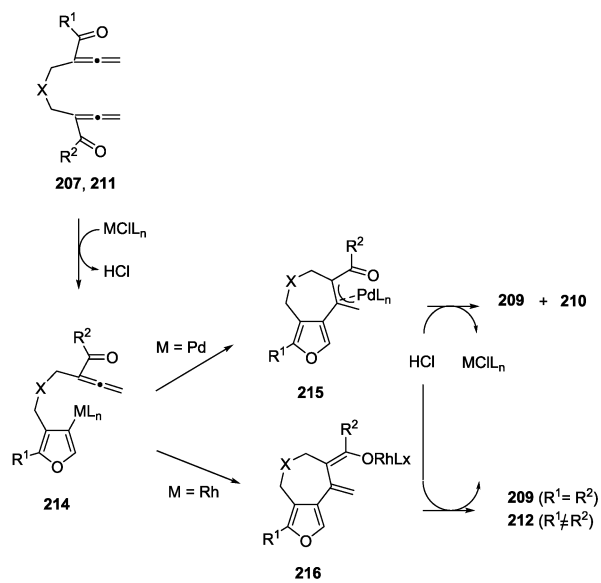
Scheme 75 Rhodium(I)-catalyzed cyclization of symmetrical 1,5-bis(1,2-allenylketones) **207**.



211 **212** 55–77% **213** 0-8%

X = CH_2
R^1 = Ph, 4-NO_2-C_6H_4
R^2 = *i*-Pr, *n*-Bu, Bn

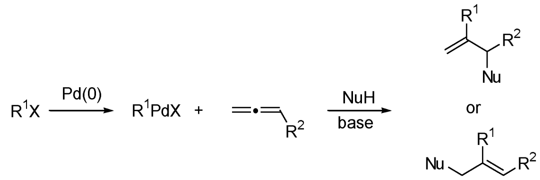
Scheme 76 Rhodium(I)-catalyzed cyclization of non-symmetrical 1,5-bis(1,2-allenylketones) **211**.



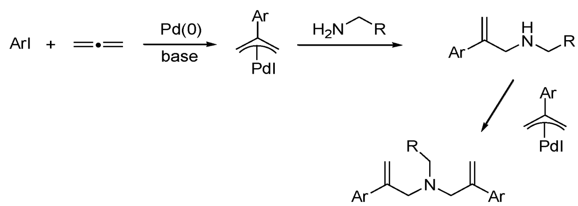
$MClL_n$ = $[PdCl_2(MeCN)_2]$ or $[RhCl(CO)_2]_2$

Scheme 77 Plausible mechanism for the formation of compounds **209**, **210** and **212**.

Based on this reactivity, it has been reported the synthesis of ten-membered heterocycles from 1,5-bis(allenes) *via* formation of two π-allylic Pd intermediates, which may be trapped by a

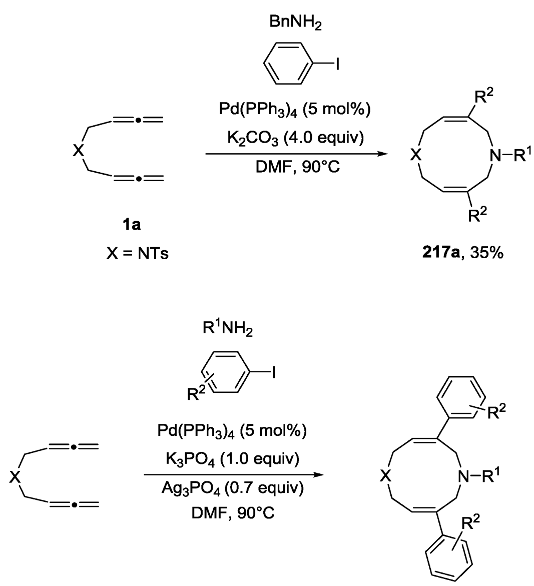


Scheme 78 Formation of allylation products *via* Pd-catalyzed carbopalladation of allenes.



Scheme 79 Three-component reaction between allenes, amines and aryl iodides.

NuH_2-type nucleophile.[89] The first experiment consisted of treatment of bis(2,3-butadienyl)tosylamide **1a** with iodobenzene in the presence of benzylamine, using $Pd(PPh_3)_4$ as catalyst (5 mol%) and K_2CO_3 (4.0 equiv.) as base in DMF as solvent. The expected 10-membered ring **217a** was isolated regio- and stereoselectively in 35% yield as single product (Scheme 82). After, testing the reaction with different catalyst and bases, the optimized reaction conditions were the use of Q6



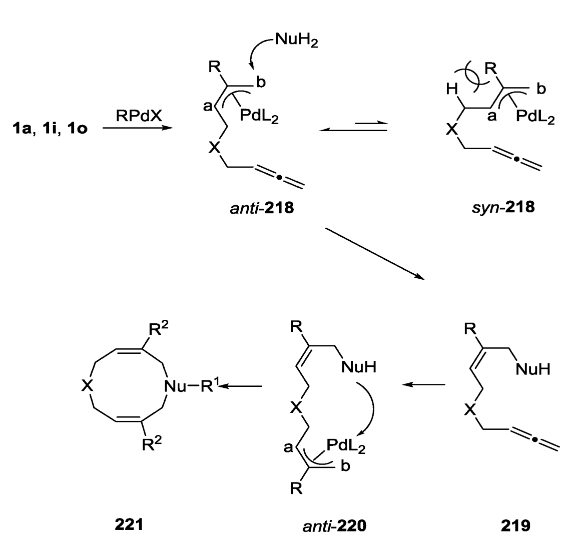
1a, X = NTs
1i, X = $C(CO_2Me)_2$
1o, X = NPh

217a, X = NTs, R^1 = *n*-C_6H_{13}, R^2 = 4-Me, 50%
217b, X = NTs, R^1 = *n*-C_6H_{13}, R^2 = 3-Me, 53%
217c, X = $C(CO_2Me)_2$, R^1 = *n*-C_6H_{13}, R^2 = H, 33%
217d, X = $C(CO_2Me)_2$, R^1 = *n*-C_6H_{13}, R^2 = 4-Br, 40%
217e, X = NPh, R^1 = *n*-C_6H_{13}, R^2 = 4-$EtCO_2$, 38%

Scheme 80 Three-component reaction between 1,5-bis(allenes), amines and aryl iodides.

$Pd(PPh_3)_4$ (5 mol%), Ag_3PO_4 (0.7 equiv.) and K_3PO_4 (1 equiv.) in DMF at 90 °C (Scheme 80). The scope of the reaction was studied using different tethered 1,5-bis(allenes) **1**, aryliodides and amines.

The high regio- and stereoselectivity of this reaction has been explained *via* carbopalladation of one of the two allene groups in the substrate to form π-allylic Pd intermediate *anti*-**218**, more favorable than *syn*-**218** due to the steric interaction of the phenyl group R and the substituent containing the other allene group (Scheme 81). The regioselective intermolecular allylation takes place in *anti*-**218** to form intermediate **219**. Then, carbopalladation of the second allene moiety in the substrate would favor the formation of π-allylic Pd intermediate *anti*-**220**. The regioselective intramolecular allylic substitution of *anti*-**220** would lead to the formation of the ten-membered product **221**.



Scheme 81 Explanation for the selectivity observed in the three-component synthesis of adducts **221**.

Conclusions

In conclusion, the synthesis and reactivity of non-conjugated bis(allenes) studied so far show the synthetic potential to obtain a high amount of different structures. Although, these days the reactivity of allenes is well developed and many applications to the synthesis of interesting molecules has been achieved, bis(allenes) are promising molecules to organic chemists interested in the development of new synthetic methodologies. It is presumable that in the next few years we will observe how this family of bis(allenes) occupies an important role as starting materials or as *in situ* formed intermediates, in the design of target compounds with potential therapeutic activities. Now, it is in our hands to investigate the synthesis of highly different functionalized bis(allenes) as well as to study the reactivity of these molecules.

Abbreviations

Ac	Acetyl
AIBN	2,2′-Azobis(2-methylpropionitrile)
BQ	Benzoquinone
Dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DBU	1,8-Diazabicycloundec-7-ene
DFT	Density functional theory
DIB	Dimethylformamide
DMSO	Dimethylsulfoxide
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
EWG	Electron withdrawing group
HQ	Hydroquinone
NBS	*N*-Bromosuccinimide
NHC	N-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
TBS	*t*-Butyldimethylsilyl
TFP	Tri(2′-furyl)phosphine
Ts	*p*-Toluenesulfonyl

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