METAL-CATALYZED BORYLATIVE CYCLIZATION REACTIONS OF POLYUNSATURATED SUBSTRATES FOR THE SYNTHESIS OF HETEROCYCLES

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Abstract. *Metal-catalyzed borylative cyclization reactions are important tools for organic synthesis, since they permit the preparation of heterocyclic scaffolds that can be further functionalized thanks to the incorporation of a boron moiety in their structure. The use of metal catalysis with polyunsaturated precursors allows for the control of the regioselectivity of the process. Different products varying the type of cyclic structure formed or the position where the boron group incorporates can be obtained in most cases selectively, depending on the metal and the reaction conditions of choice.*

Contents

1. Introduction

The development of new methodologies of cyclization has a great impact in organic chemistry, above all for the synthesis of heterocyclic structures, due to their myriad of applications. Of particular interest are those methodologies of cyclization/functionalization that allow the incorporation of additional functionalities in the cyclic scaffolds. In this regard, transition metal-catalyzed borylative cyclizations constitute an efficient

strategy to synthesise carbo- and heterocycles incorporating a new C–B bond in their structure.[1-3] Boron derivatives are very versatile since they are easily transformed into a variety of functional groups[4] and new C–C bonds,[5-12] as well as used as eco-friendly precursors of alkyl radicals in photocatalytic transformations.[13,14] These reasons have promoted the use of boron compounds as versatile intermediates in organic synthesis.[15-17] Besides, the substitution of carbon functional groups for boronic acids has allowed the development of new drugs with antiviral, antibacterial, and antitumor activity.[18-20]

Without considering difunctionalization processes, the first reported example of a borylative cyclization was a synthesis of functionalized cyclopentanes and cyclohexanes developed by Molander in 2001,[21] although the obtained organoboranes were oxidized *in situ* due to their instability. Since then, a wide variety of methodologies have appeared in the literature, being the development of this type of reactions an active topic, from which new reports continue to appear to date.

The boron reagents utilized for borylative cyclization processes are usually of the types H-B$(OR)_2$ (boranes) or $B_2(OR)_4$ (diboronic esters). The former type is used for hydroborylative cyclization processes and is more atom-economical, since both, the hydrogen and the boron units, incorporate to the structure of the final product. Regarding diboronic esters, they have also been used for hydroborylative cyclization methodologies amongst other types of reactions, but in those cases, one of the boron moieties is not incorporated in the product, and the H comes from another reagent. Recent studies about diborylative cyclizations using diboron reagents have demonstrated that the use of both boron groups from $B_2(OR)_4$ is possible. Among the different OR groups, the most frequently encountered in the literature are the derivatives of pinacol, catechol and diaminonaphthalene.

Although the synthesis of boron containing heterocycles has been described by different means,[22] this overview will focus on the synthesis of this type of heterocycles *via* metal-catalyzed borylative cyclization reactions in polyunsaturated substrates. In most of the cases, only the synthesis of heterocyclic structures is indicated. However, some examples of the formation of carbocycles have been included when it helps to understand a particular methodology. The chapter has been divided into sections, starting with borylative cyclization reactions, in which each section has been named according to the substrate described. In each section, a subdivision has been made for each metal catalyst. There is a last section covering diborylative cyclizations in which two boron moieties are incorporated to the final structure of the product. However, reactions in which a difunctionalization is produced, introducing a boron and another functionality in the same step, such as silylborylative cyclizations or borylstannilative cyclizations, have not been included. These last methodologies are covered by previous reviews.[1-3]

It should be noted that in this review a particular emphasis is made on the mechanisms governing each transformation, since the authors believe it is important to highlight the different type of reactivities provided by different metal catalysts, and sometimes, even by the same metal.

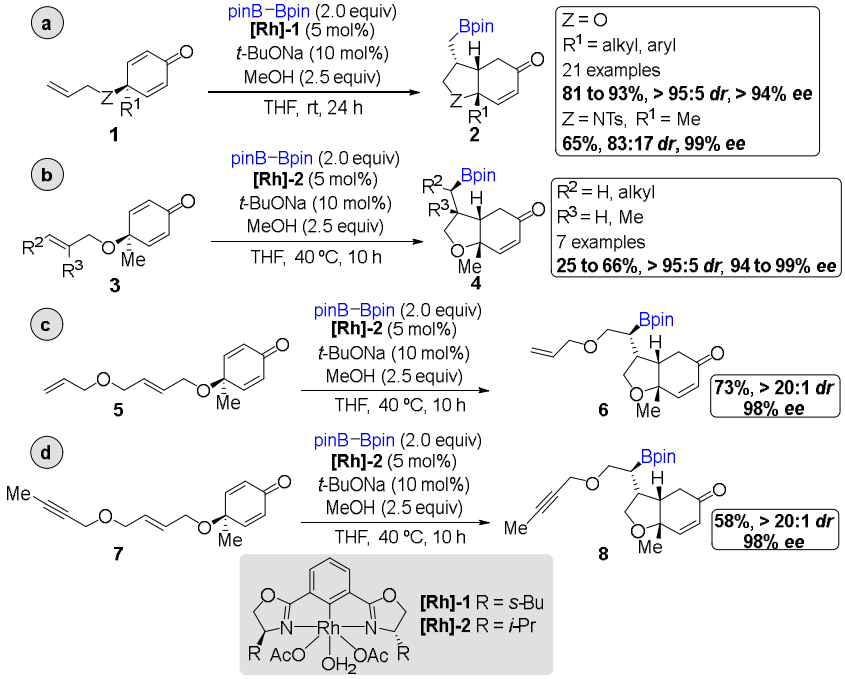
2. Borylative cyclization reactions of dienes

Borylative cyclization reactions of dienes have not been extensively studied, mainly due to the difficulty found in the differentiation of both olefin moieties. The main strategy followed to control the selectivity has been the use of cyclohexadienone-containing 1,6-dienes, in which the steric and electronic properties of both alkenes are different enough to permit a differentiation. Some examples of these methodologies can be found in the literature and are described below divided by the metal catalyst.

2.1. Rhodium-catalyzed borylative cyclizations

In 2019, the first enantioselective borylative cyclization of dienes was published (Scheme 1).[23] In this example described by the groups of Tian, Hong and Li, the use of cyclohexadienone-containing 1,6-dienes **1** afforded *cis*-bicyclic structures **2** with high diastereo- and enantioselectivities. Products **2** are fused bicycles of 5 and 6 membered rings containing an enone moiety that could be further functionalised. Interestingly, no hydroboration of the enone moiety in bicycles **2** was observed during the process. The reaction was catalyzed by Rh in the presence of a Phebox (bisoxazolinyl-phenyl) ligand and using as the borylating agent bis(pinacolato)diboron (B_2pin_2). It took place not only with terminal alkenes **1** (Scheme 1a) but also with 1,1-disubstituted alkenes and (*E*)-1,2-disubstituted alkenes **3**, although with lower yields for products **4** (Scheme 1b). Notably, (*Z*)-1,2-disubstituted-alkenes did not undergo the reaction and tosylamide derivatives gave worse results than ether derivatives. When the reaction was carried out with the cyclohexadienone with

two formal 1,6-diene moieties **5** (Scheme 1c), the results showed to be selective towards the alkene on the cyclohexadienone, giving **6**. Crucially, the first boryl-metallation of the olefin took place at the internal olefin of the tethered chain, instead of the most kinetically accessible terminal olefin unit. Similar results were also obtained when a substrate containing formal 1,6-diene and 1,6-enyne was used (substrate **7** to give product **8**) (Scheme 1d). These results suggested that an interaction between alkene and cyclohexadienone was enhancing the reactivity of the non-activated olefins.



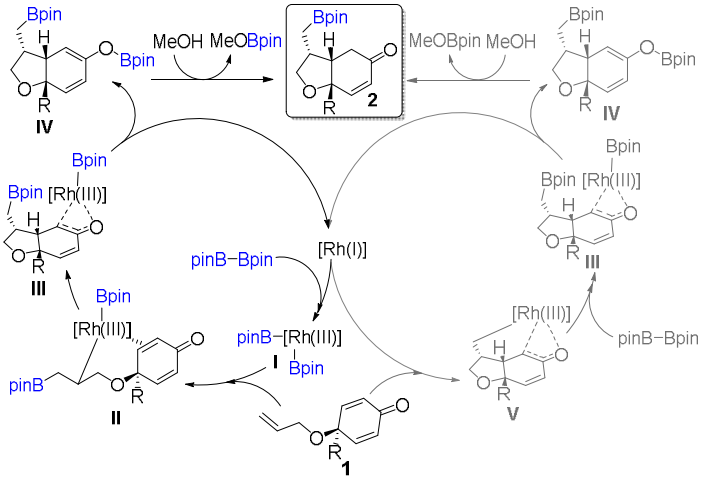
Scheme 1. First enantioselective hydroborylative cyclization of dienes described by Tian, Hong and Li.

There were two possible mechanisms for this transformation (Scheme 2), but DFT calculations showed that a mechanism *via* an insertion step was the most favourable one (Scheme 2, left side). This catalytic cycle would consist of the formation of bisboryl-Rh(III) intermediate **I** by oxidative addition of B_2pin_2, followed by a borylmetallation of the electron-richer alkene, leading to **II**. Then, insertion of the alkene of the enone system to form the intermediate alkyl-Rh(III) **III** and reductive elimination would produce the diborylated intermediate **IV**, which, in the presence of MeOH would afford product **2**. The other plausible mechanism (Scheme 2, right side) would start with an oxidative cyclometallation to form intermediate **V**, followed by a σ-bond metathesis with B_2pin_2 and a final reductive elimination.

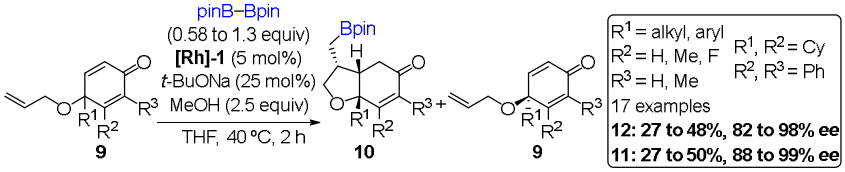
One year later, the authors extended this methodology to the kinetic resolution of racemic cyclohexadienones **9** that afforded products **10** (Scheme 3).[24]

2.2. Copper-catalyzed borylative cyclizations

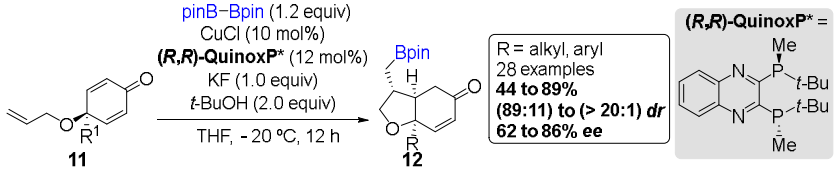
In 2020, the group of Tian and Li reported a enantioselective Cu-catalyzed hydroborylative cyclization of cyclohexadienone containing 1,6-dienes **11** (Scheme 4).[25] With a Cu-catalyst, B_2pin_2 and a QuinoxP* (bis(*tert*-butylmethylphosphino)quinoxaline) ligand, the authors observed the formation of the *cis-cis* products **12**, which were complementary to the *trans-cis* products observed with Rh-catalysis.[23] This methodology provided high diastereoselectivities and good enantiocontrol, but substituted alkenes or 1,7-dienes were not suitable substrates for the reaction. A mechanistic proposal was not described for this transformation.



Scheme 2. Possible mechanisms for the enantioselective Rh-catalyzed reaction.



Scheme 3. Kinetic resolution of cyclohexadienones *via* Rh-catalyzed borylative cyclization.

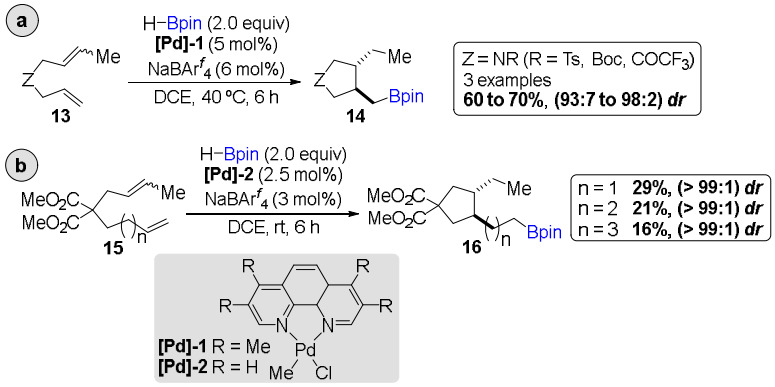


Scheme 4. Cu-catalyzed enantioselective hydroborylative cyclization of dienes described by Tian and Li.

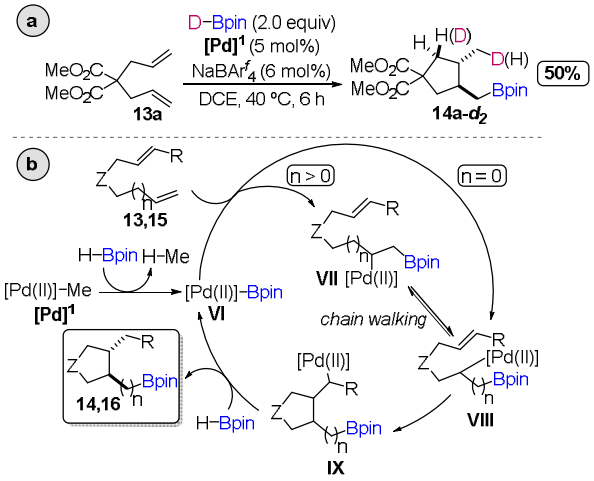
2.3. Palladium-catalyzed borylative cyclizations

In 2023, the group of Kochi reported a Pd-catalyzed *remote* hydroborylative cyclization of dienes (Scheme 5), using HBpin as the boron source and phenanthroline-derived ligands.[26] Catalytic amounts of $NaBAr^f$ (Ar^f=3,5-$(CF_3)_2C_6H_3$) were required for the methodology to work. The reaction was first optimized for 1,6-dienes **13**, obtaining the 5-membered rings **14** as the product (Scheme 5a). Later on, the authors hypothesized that the initial borylpalladation could be followed by a chain walking process furnishing the *remote* borylation when using 1,7-dienes or even longer ones **15** (Scheme 5b). However, the yields for this last transformation were poor and it was only applied for the synthesis of carbocycles **16**.

To understand the mechanism, they performed a deuteration experiment in **13a** using DBpin under their optimized reaction conditions. Deuterium incorporation in methyl and methylene carbons of product **14a** was observed in a 5:1 ratio (Scheme 6a). With that result in mind, the authors proposed that the Pd-catalyst would react with HBpin to form boryl-Pd species **VI** by a σ-bond metathesis (Scheme 6b). A regioselective borylpalladation of the olefin (the distal one with n>0 and the less substituted with n=0) would take place to afford **VII**, followed by a chain walking mechanism when n>0 (consecutive β-hydrogen eliminations and 1,2-insertions, which produce the displacement of the metal in the carbon chain) that would lead to **VIII**. The 1,2-insertion to the other olefin would form the 5-membered ring in **IX**. Finally, a σ-bond metathesis with HBpin would release the product and regenerate the boryl-Pd complex **VI**.



Scheme 5. Pd-catalyzed remote hydroborylative cyclization described by Kochi.



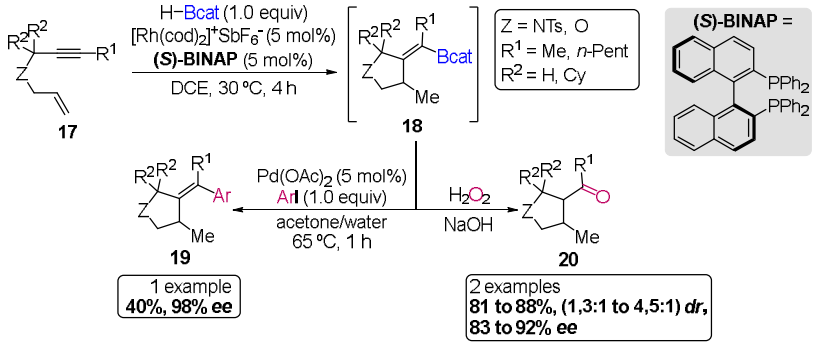
Scheme 6. Proposed mechanism for the Pd-catalyzed remote hydroborylative cyclization.

3. Borylative cyclization reactions of enynes

Enynes are probably the most explored substrates in borylative cyclization processes.[1-3] Not only have they been studied under noble metal catalysis, such as Rh and Pd, but also with more eco-friendly first row transition metals such as Fe, Co, Ni, and Cu. The use of different transition metals has allowed the discovery of new reactivities, and it has permitted the preparation of different regioisomers starting from similar substrates. Therefore, a great variety of products can be synthesized using these methodologies.

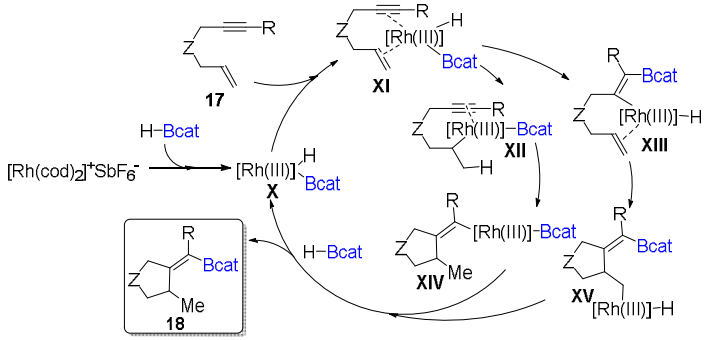
3.1. Rhodium-catalyzed borylative cyclizations

The first hydroborylative cyclization of enynes **17** was described by Widenhoefer in 2006. It is the only described example of a Rh-catalyzed borylative cyclization reaction of enynes and it was developed in its asymmetric version.[27] A (*S*)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) ligand was used in the presence of $[Rh(cod)_2]SbF_6$ as the metal source and catecholborane (HBcat) as the borylating agent. The use of HBcat afforded better yields compared to any other borylating reagent, but because of the instability of the borylated products **18**, an *in situ* oxidation to **20** or a Suzuki-Miyaura reaction to **19** were performed (Scheme 7). In this methodology, terminal alkynes or substituted alkenes did not furnish the desired products. In addition, the synthetic utility of this approach was highlighted by the *in situ* Suzuki-coupling of intermediate **18**, affording the desired all-carbon-substituted olefin **19**.



Scheme 7. Rh-catalyzed hydroborylative cyclization described by Widenhoefer.

The authors did not carry out any mechanistic experiments, but they considered two possible mechanisms (Scheme 8). Both proposals would start with the oxidative addition of the HBcat to the Rh catalyst to form species **X**. This Rh complex would coordinate to both unsaturations (**XI**) and it could react with either of them. If the Rh complex reacts with the alkene first, a hydrometallation would occur to form **XII**. On the contrary, if the first functionality in reacting is the alkyne, it would be through a borylmetallation to give **XIII**. The next step in both cases would be an insertion of the remaining unsaturation into the C–Rh bond to give **XIV** or **XV**, respectively. Finally, a reductive elimination followed by a new oxidative addition of HBcat would release **18** and restart the catalytic cycle.

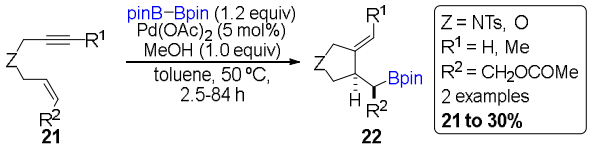


Scheme 8. Proposed mechanisms for the Rh-catalyzed hydroborylative cyclization of enynes.

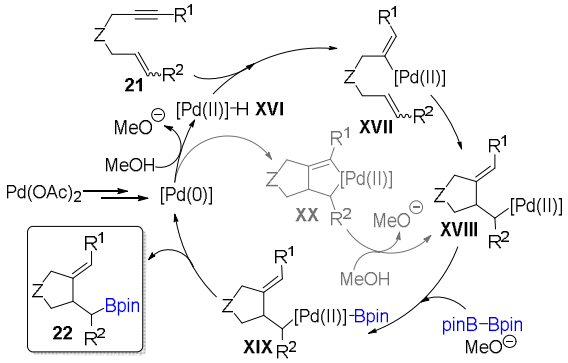
3.2. Palladium-catalyzed borylative cyclizations

The first Pd-catalyzed hydroborylative cyclization of enynes was described by the group of Cárdenas in 2007 (Scheme 9).[28] Palladium acetate in the absence of ligand was used as the catalyst for the transformation of enynes **21** in cyclic boronates **22**. The borylating reagent was B_2pin_2, from which only one of the boron moieties was incorporated in the structure of the final product. Additionally, the reaction required the addition of MeOH.

Two possible mechanisms were proposed for this transformation (Scheme 10). DFT calculations showed that an oxidative cyclometallation pathway (**XX**) had a high activation energy,[29] and therefore, the formation of a Pd-hydride intermediate was proposed as the more plausible mechanism (Scheme 10). The Pd-hydride complex **XVI** would generate from a Pd(0) species in the presence of MeOH and, once formed, it would give the hydropalladation of the alkyne moiety to give intermediate **XVII**. Then, the insertion of the alkene would occur to afford the 5-membered ring **XVIII**, which would be followed by the borylation of the Pd-centre by a methoxy-promoted transmetallation to furnish **XIX**. Finally, a reductive elimination would afford the borylated product **22**, regenerating the Pd(0) species.

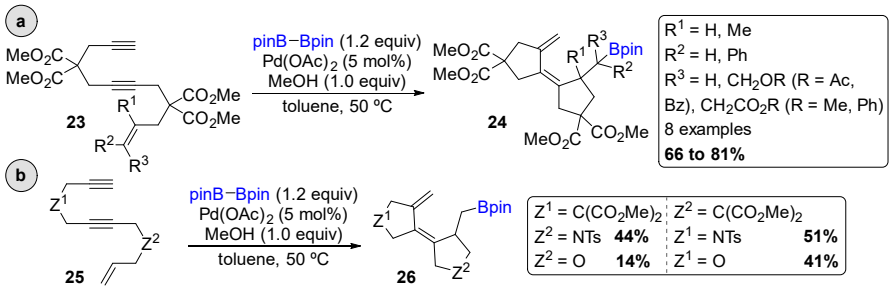


Scheme 9. First hydroborylative cyclization reaction of enynes described by Cárdenas.



Scheme 10. Proposed mechanism for the hydroborylative cyclization reaction of enynes.

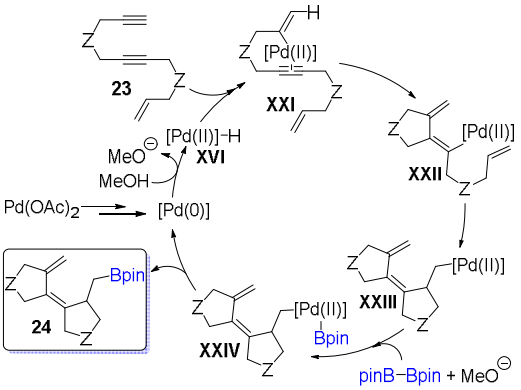
In 2008, the authors extended the Pd-catalyzed hydroborylative cyclization to the use of enediynes alternating the alkyne and alkene moieties,[30] although this methodology was not applied to the synthesis of heterocycles. Nevertheless, starting from a different type of enediynes **23** and **25**, furanes and pyrrolidines, along with carbocycles, **24** and **26**, were prepared (Scheme 11).[31] The combination of two different tethers illustrated that malonate favoured the reaction when it was present in any of the positions (Scheme 11b).



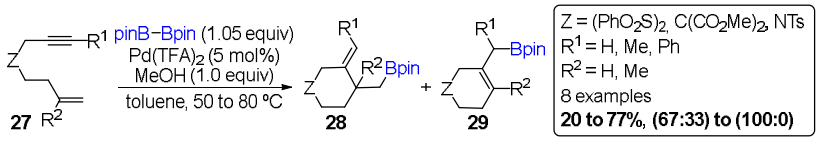
Scheme 11. Hydroborylative cyclization of enediynes described by Cárdenas.

A plausible catalytic cycle (Scheme 12) would start again with the formation of a Pd-hydride **XVI**, followed by the hydropalladation of the terminal alkyne in **23** to give **XXI**. Then, a carbopalladation would take place to afford the first five-membered cycle **XXII**. The insertion of the mono-substituted alkene on the alkenyl-Pd bond would provide the second five-membered ring **XXIII**. Finally, a methoxide-promoted transmetallation (**XXIV**) followed by a reductive elimination would release the desired product **24**, forming a Pd(0) species that would restart the catalytic cycle.

One year later, the same group applied this procedure to 1,7-enynes using $Pd(TFA)_2$ as a precatalyst,[32] Homoallylic derivatives **27** led to a mixture of two different six membered cycles, **28** and **29**, being major or the only product **28**, the one with the exocyclic double bond (Scheme 13). This *exo*-product **28** would be generated by the mechanism already explained for 1,6-enynes (Scheme 10).[28]

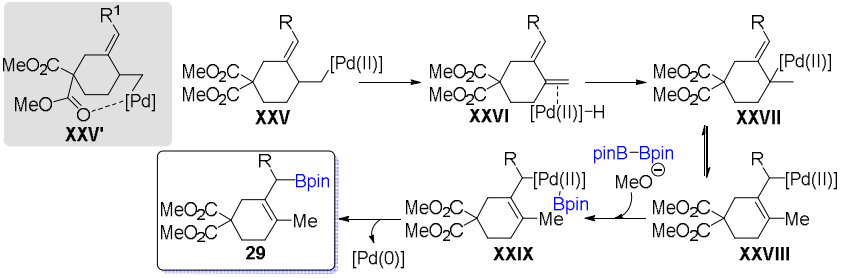


Scheme 12. Proposed mechanism for the hydroborylative cyclization of enediynes.



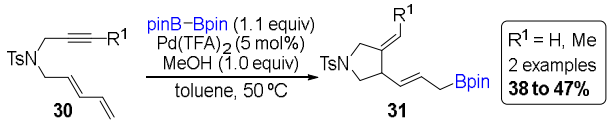
Scheme 13. Pd-catalyzed hydroborylative cyclization of 1,7-enynes described by Cárdenas.

To explain the formation of the endocyclic olefins **29**, the authors carried out DFT calculations, observing that malonate-tethered substrates could easily evolve through β-hydrogen elimination in intermediate **XXV** to give **XXVI**, followed by a hydropalladation, to generate allyl-Pd complex **XXVII-XXVIII** (Scheme 14). Then, methoxide-promoted transmetallation (**XXIX**) and reductive elimination would take place to form the *endo*-product **29**. The ability of the Pd-centre to coordinate with the carbonyl moiety of the malonate in **XXV'** would be responsible for the favoured β-hydrogen elimination. A similar stabilisation could occur for tosylamide-tethered substrates.



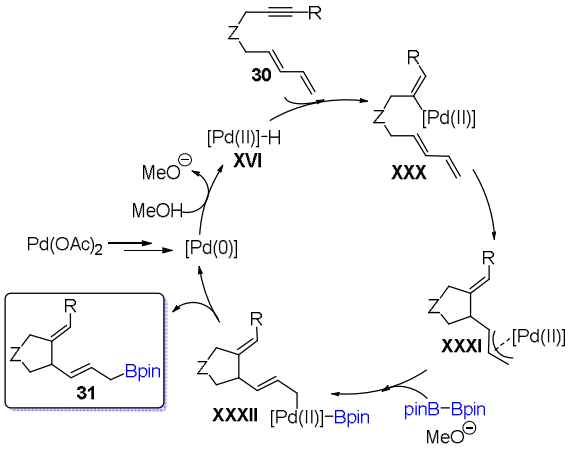
Scheme 14. Proposed mechanism for the formation of *endo*-product.

In 2013, the Pd-catalyzed hydroborylative cyclization of 1,3-dien-8-ynes **30** was published (Scheme 15).[33] The reaction was performed with $Pd(TFA)_2$, B_2pin_2 and MeOH and furnished pyrrolidines substituted with an allylboronate moiety **31**.



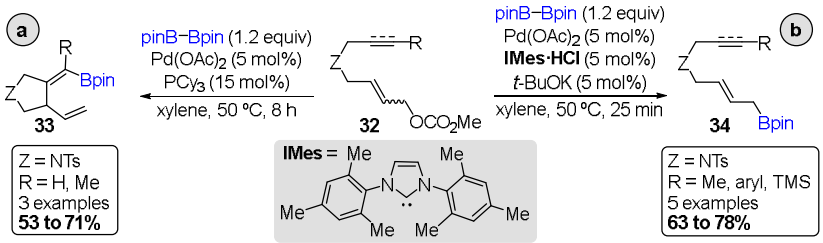
Scheme 15. Pd-catalyzed hydroborylative cyclization of dienynes described by Cárdenas.

The reaction would proceed through the same mechanism described for 1,6-enynes (Scheme 10), but once the cyclic scaffold is created from **XXX**, allyl-Pd intermediate **XXXI** would be formed. This allyl-Pd complex would react with the B_2pin_2, leading to the boron group incorporation in the less hindered position of the allyl-Pd species and forming **XXXII** (Scheme 16).



Scheme 16. Proposed mechanism for Pd-catalyzed hydroborylative cyclization of dienynes.

One year later, the reaction was described for 1,6-enynes with an allyl carbonate moiety **32**. The addition of different ligands led to different regioselectivities.[34] Cyclic alkenylboronates **33** were obtained with tricyclohexylphosphine (Scheme 17a), whereas the use of an NHC (*N*-heterocyclic carbene) ligand gave rise to allylboronates **34**, deriving from a simple cross-coupling reaction without cyclization (Scheme 17b).

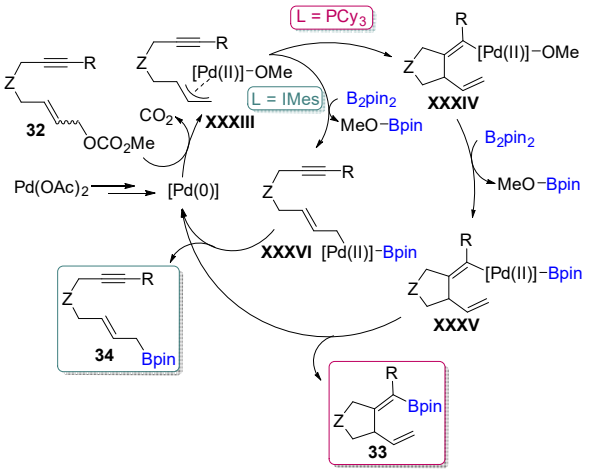


Scheme 17. Ligand-controlled divergent formation of allyl- or alkenyl-boronates.

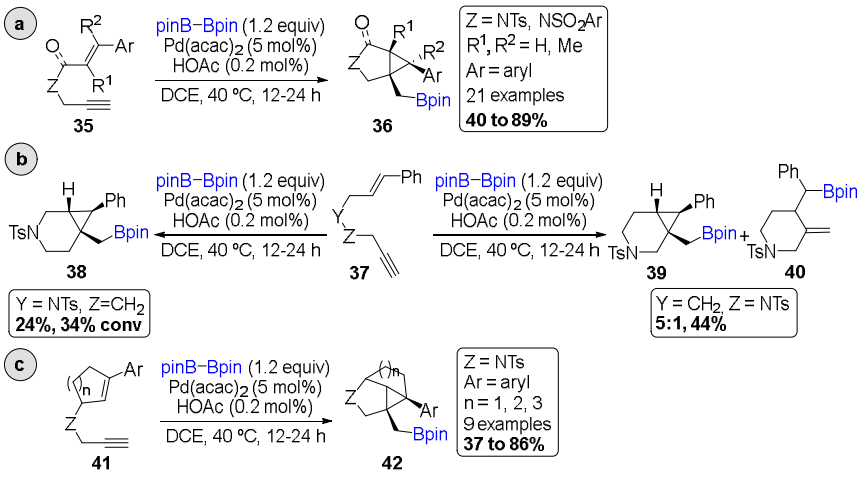
To explain the results, the authors proposed that the reaction would start with an oxidative addition of the carbonate **32** and subsequent decarboxylation generating allyl-Pd complex **XXXIII** (Scheme 18). This intermediate would evolve by either transmetallation (**XXXVI**) and reductive elimination to give the allylboronate **34** (when IMes is used) or by insertion of the alkyne (when PCy_3 is used) to form a five-membered cycle with an alkenyl-Pd moiety **XXXIV**. Finally, transmetallation (**XXXV**) and reductive elimination would afford the cyclic borylated product **33**. The explanation for the formation of both products would be that insertion of the alkyne needs a coordination vacant, which is more easily attained with PCy_3 as the ligand than with IMes.

Recently, the group of Zhou investigated a Pd-catalyzed borylative cyclization and cyclopropanation of terminal alkyne-derived enynes **35**, affording borylated bicycles **36** (Scheme 19a).[35] A cascade cyclization/cyclopropanation was developed using $Pd(acac)_2$ as the catalyst in the presence of B_2pin_2 and acetic acid as proton donor. The reaction was limited to terminal alkynes, and 1,7-enynes **37** gave the corresponding bicyclic products **38** or **39**, albeit in low yield and, in one case, as a mixture of products **39** and

40 (Scheme 19b). To increase the complexity of the heterocyclic products, 1,6-enynes in which the alkene was included in a cyclic moiety **41** were assayed as substrates, affording the bridged products **42** (Scheme 19c).

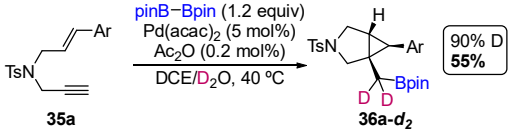


Scheme 18. Proposed mechanism for the borylative cyclization of allyl carbonates.



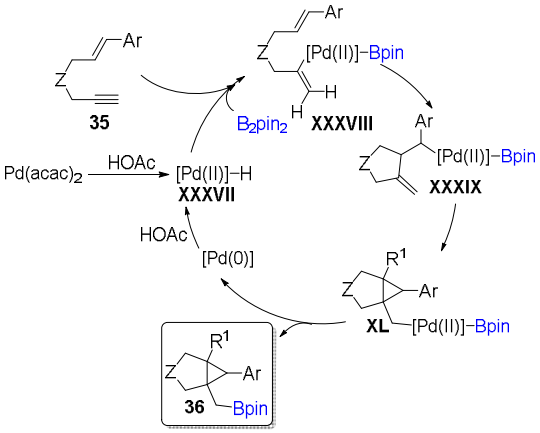
Scheme 19. Pd-catalyzed borylative cyclization/cyclopropanation of enynes described by Zhou.

To gain some insight into the mechanism, a deuteration experiment was performed on **35a** by substituting the acetic acid by a mixture of Ac_2O and D_2O (Scheme 20). Under these conditions, the bicyclic product **36a-*d*$_2$**, in which deuterium incorporation had occurred in the methylene next to the boron group, was obtained.



Scheme 20. Deuteration experiment for the borylative cyclization/cyclopropanation.

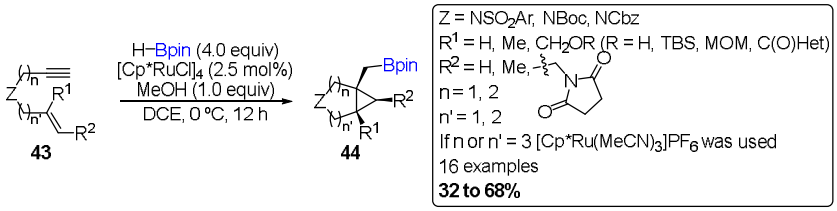
The proposed mechanistic route for this transformation would occur through the formation of Pd-hydride **XXXVII** (Scheme 21). This Pd–H species would evolve through a hydrometallation of the alkyne and formation of boryl-Pd complex **XXXVIII**. A first double bond insertion would form intermediate **XXXIX**, from which a second insertion could take place forming the cyclopropane ring in **XL**. From **XL**, a reductive elimination would afford the bicyclic product **36**, and reaction with the acetic acid would regenerate the Pd-hydride **XXXVII**.



Scheme 21. Mechanism proposed for the borylative cyclization/cyclopropanation.

3.3. Ruthenium-catalyzed borylative cyclizations

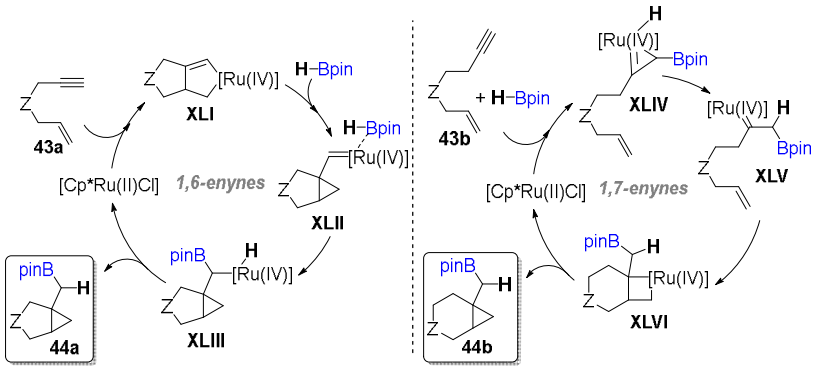
The group of Sun described in 2022 an efficient reaction for the synthesis of fused bicycles **44** using Ru-catalysis (Scheme 22). The borylating agent was pinacolborane and the reaction required the addition of methanol.[36] The procedure consisted of a geminal hydroborylative cyclization in which the H and the Bpin units were incorporated in the same unsaturation of the enyne **43**. This methodology worked well with (*E*)-1,2-disubstituted alkenes but not with (*Z*)-olefins or alkenes disubstituted in the terminal position, which failed to form the bicyclic products. However, a variety of functional groups were well tolerated, and even free alcohol gave good results. In addition, 1,7- and 1,8-enynes afforded the corresponding bicyclic products, although in moderate yields.



Scheme 22. Ru-catalyzed geminal hydroborylative cyclization described by Sun.

DFT calculations allowed the authors to propose a mechanism for 1,6-enynes **43a** (Scheme 23, left side). Initially, an oxidative cyclometallation would take place (**XLI**) followed by a rearrangement to form Ru carbene **XLII**. Then, oxidative addition of the borane and migratory insertion would form the C–B bond in **XLIII**. Finally, a reductive elimination would generate the observed product **44a**. A different mechanism was proposed for 1,7-enynes **43b** (Scheme 23, right side), since DFT calculations showed lower energy barriers for the activation of the alkyne than for the oxidative cyclometallation. The cycle would start with the formation of a ruthenacyclopropene complex **XLIV** by oxidative borylmetallation. Then, a hydrogen

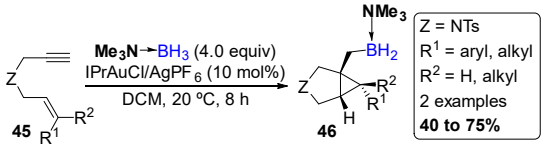
migration (**XLV**) and 1,2-insertion to the olefin would furnish the bicyclic-Ru intermediate **XLVI**, which would finally release the product **44b** by reductive elimination.



Scheme 23. Proposed mechanism for the Ru-catalyzed geminal hydroborylative cyclization.

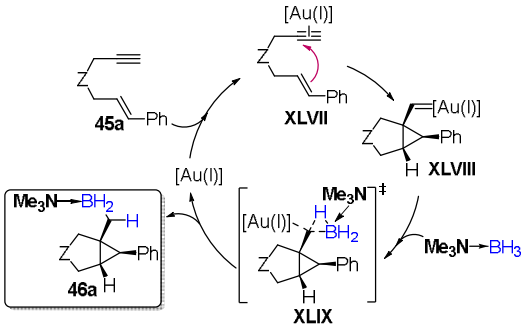
3.4. Gold-catalyzed borylative cyclizations

The group of Wang and Zhao reported the synthesis of the same type of bicycles described with Pd and Ru catalysis starting from enynes **45** and using Au (Scheme 24).[37] As it was the case with the previous methodologies, the protocol was also limited to terminal alkynes. Besides, the substitution in the internal position of the olefin failed to give the desired product **46**.



Scheme 24. Au-catalyzed hydroborylative cyclization described by Wang and Zhao.

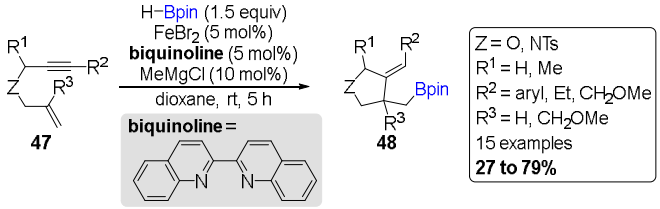
By deuterium labelling, the authors observed that boron and deuterium were introduced on the same carbon, which allowed them to propose the mechanism represented in Scheme 25. After the coordination of the Au to the alkyne **XLVII**, a 5-*exo-dig* cyclization would take place to form the *exo*-cyclopropyl Au carbene **XLVIII**. Then, the insertion into the B–H bond of the boron adduct through **XLIX** would generate the desired product **46a** and regenerate the catalysts.



Scheme 25. Proposed mechanism for the Au-catalyzed hydroborylative cyclization.

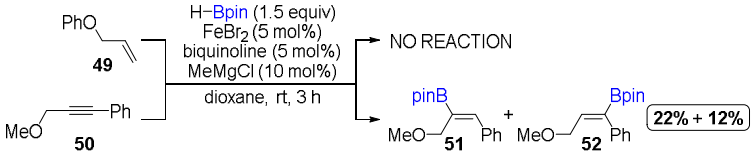
3.5. Iron-catalyzed borylative cyclizations

There is only one example of Fe-catalyzed hydroborylative cyclization, which was reported by the group of Cárdenas in 2018.[38] This methodology used $FeBr_2$ as precatalyst, biquinoline as the ligand, pinacolborane as the borylating agent and methyl magnesium bromide to activate the catalyst, and provided the 5-membered rings with an alkylboronate moiety **48** from 1,6-enynes **47** (Scheme 26). The formation of *N*- and *O*-containing heterocycles proceeded with good yields, but carbocycles were obtained with moderate yields. The substitution of the internal carbon of the alkene resulted in a high decrease in the yield and the substitution of the propargylic position provided the product as a mixture of diastereoisomers.



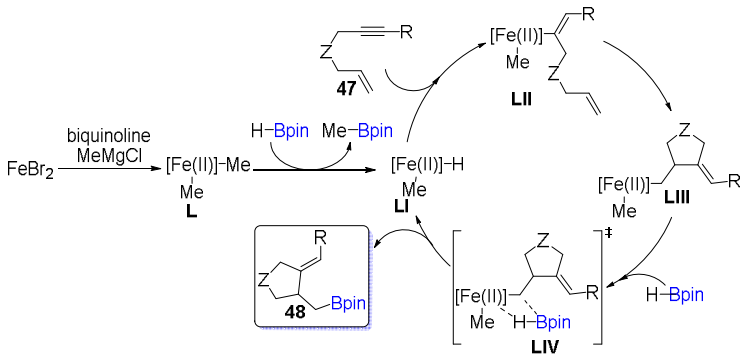
Scheme 26. Fe-catalyzed hydroborylative cyclization of enynes described by Cárdenas.

No reaction was observed when an alkene model fragment of the enyne **49** was subjected to the optimal conditions (Scheme 27). However, the alkyne fragment **50** afforded the hydroborylated products **51** and **52**.



Scheme 27. Mechanistic experiments for the Fe-catalyzed hydroborylative cyclization of enynes.

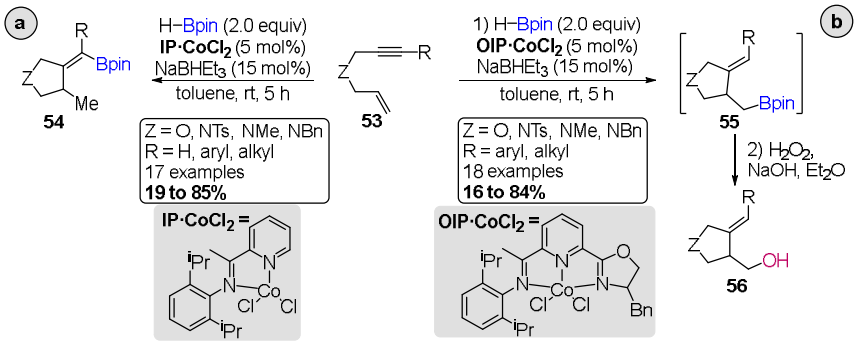
These results, together with DFT calculations, suggested a non-redox catalytic cycle involving the initial reaction of the alkyne with the Fe catalyst (Scheme 28). The proposed mechanism would start with the formation of the catalytically active Fe-hydride species **LI** by double transmetallation with the Grignard reagent affording dialkyl-Fe species **L**, followed by σ-bond metathesis with the HBpin. Then, the enyne would evolve through hydrometallation of the alkyne **LII** and insertion of the alkene into the alkenyl-Fe bond to form the 5-membered ring derivative **LIII**. Finally, σ-bond metathesis with HBpin through **LIV** would lead to the desired product and regenerate Fe-hydride **LI**.



Scheme 28. Proposed catalytic cycle for the Fe-catalyzed hydroborylative cyclization of enynes.

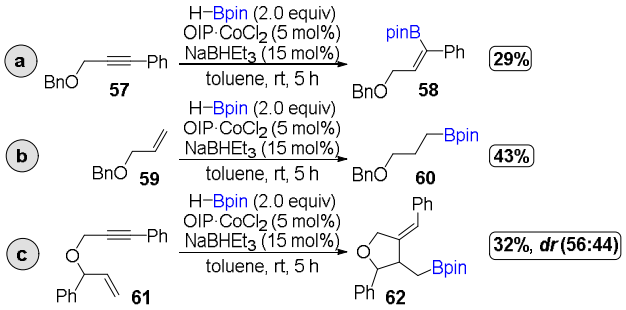
3.6. Cobalt-catalyzed borylative cyclizations

In 2017, the group of Lu developed the first Co-catalyzed hydroborylative cyclization of 1,6-enynes **53**.[39] In this procedure, the ligand controlled the regioselectivity of the process, obtaining alkenylboronates **54** with IP·$CoCl_2$ (IP=iminopyridine) (Scheme 29a) and alkylboronates **55** using OIP·$CoCl_2$ (OIP=oxazoline iminopyridine) (Scheme 29b). Boronates **55** were *in situ* oxidized to the corresponding alcohol **56** to facilitate their isolation. The methodology used HBpin and an additional reducing agent, $NaBHEt_3$, in a substoichiometric amount. In the first case, complex mixtures were obtained with electron-deficient enynes and, in both procedures, the TMS-protected alkyne was not a suitable substrate.



Scheme 29. Regioselective Co-catalyzed hydroborylative cyclization of enynes described by Lu.

To elucidate the mechanism, the authors carried out some experiments. Both alkyne **57** and alkene **59**, model fragments of the enyne, reacted under their optimized conditions to form the hydroborylated products **58** and **60** (Scheme 30a and b). Besides, the substitution in the allylic position of substrate **61** resulted in **62**, isolated as a mixture of diastereomers (Scheme 30c), which suggested that the oxidative cyclometallation pathway was not involved in the mechanism.

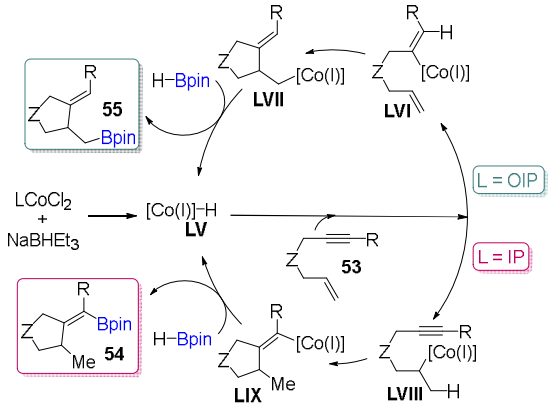


Scheme 30. Mechanistic experiments for the Co-catalyzed hydroborylative cyclization of enynes.

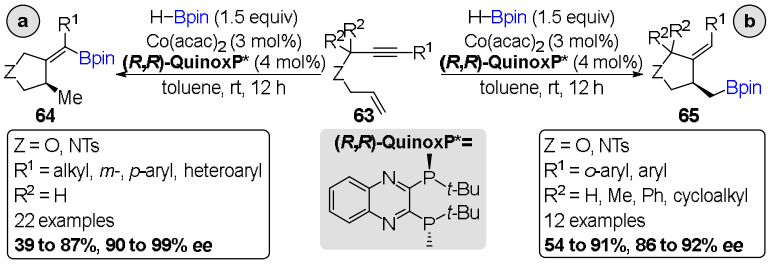
Two different mechanisms could be followed depending on the product formed. The proposed mechanisms (Scheme 31) would be initiated by the formation of Co-hydride **LV** in the presence of $NaBHEt_3$. This hydride would react by a hydrometallation of the alkyne giving **LVI** when alkylboronates **55** are formed, or hydrometallation of the alkene giving **LVIII** when alkenylboronates **54** are obtained as products. Then, the insertion of the other unsaturation in the Co–C bond to give **LVII** or **LIX**, respectively, followed by a σ-bond metathesis with HBpin, would lead to either product with the regeneration of the Co-hydride **LV**.

In the same year, the group of Ge reported an enantioselective version of the above-mentioned reaction. The Co-catalyzed hydroborylative cyclization of enynes **63** was carried out with (*R,R*)-QuinoxP* as the ligand and HBpin as the boron source (Scheme 32).[40] In this procedure, the presence of *ortho*-substituted aryl substituents in the terminal position of the alkyne, as well as the substitution in the propargylic position, led

to the alkylboronates **65** instead of the alkenylboronates **64**. The reaction was compatible with functional groups such as halides, ketones, esters, and aldehydes. However, the substitution in the alkene did not provide the desired products.

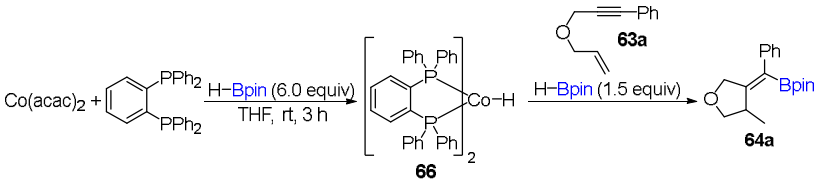


Scheme 31. Proposed mechanism for the Co-catalyzed hydroborylative cyclization of enynes.



Scheme 32. Enantioselective Co-catalyzed hydroborylative cyclization of enynes described by Ge.

The authors observed that the stoichiometric reaction of $Co(acac)_2$ with dppbz (1,2-bis(diphenylphosphino)benzene) and HBpin provided a Co-hydride **66**, which generated the product **64a** in the presence of 1,6-enyne **63a** and HBpin (Scheme 33). This result suggested that a Co-hydride would be the catalytically active species.

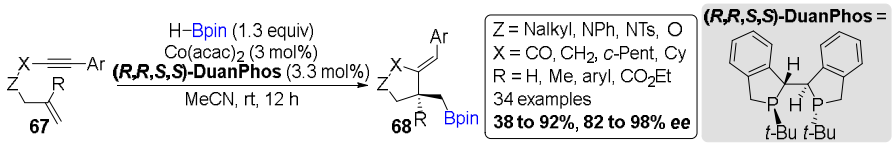


Scheme 33. Stoichiometric experiments.

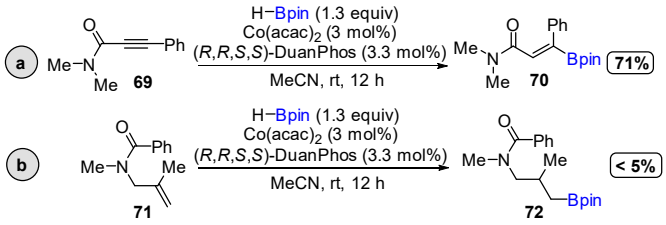
One year later, the authors could solve the problem of the inactivity of the substituted alkenes **67** using *(R;R;S;S)*-DuanPhos as the ligand in acetonitrile, and they described the formation of the borylated products **68** containing a quaternary centre (Scheme 34).[41]

To elucidate the mechanism, model fragments of the enyne containing either alkyne **69** or alkene **71** moieties were tested under their optimized reaction conditions, which gave rise to the hydroboration of the alkyne **70** (but with the opposite selectivity than the one observed in the enyne) (Scheme 35a), and <5% yield of the hydroboration of the alkene leading to product **72** (Scheme 35b). These results suggested that the

mechanism would begin *via* hydroboration of alkyne, although coordination of the two unsaturations to the metal would be necessary to obtain the correct selectivity.

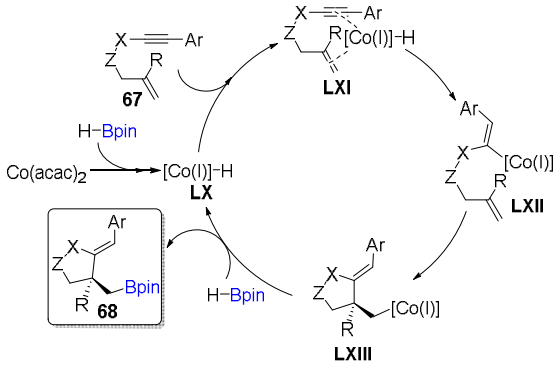


Scheme 34. Extension of enantioselective Co-catalyzed hydroborylative cyclization described by Ge.



Scheme 35. Mechanistic experiments of Co-catalyzed hydroborylative cyclization.

The authors proposed the initial formation of a Co-hydride **LX** from the activation of $Co(acac)_2$ with HBpin (Scheme 36). This hydride, after double coordination to afford **LXI**, would give the hydrometallation of the alkyne forming intermediate **LXII**. Then, insertion of the alkene would take place generating **LXIII**, followed by a σ-bond metathesis with HBpin, leading to the desired product and regenerating the Co–H.

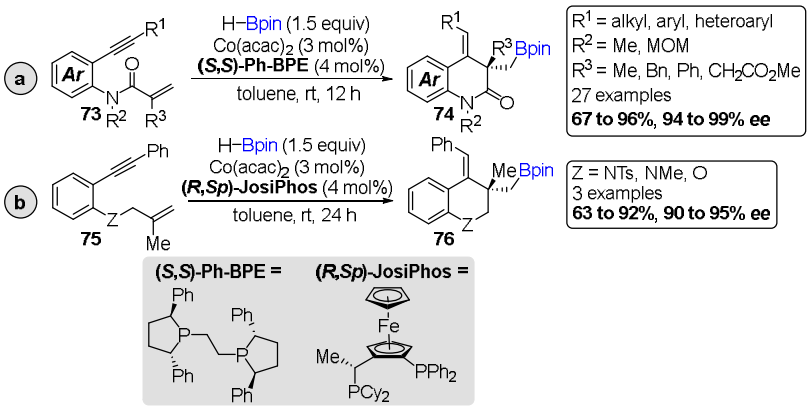


Scheme 36. Proposed mechanism for the Co-catalyzed hydroborylative cyclization of enynes.

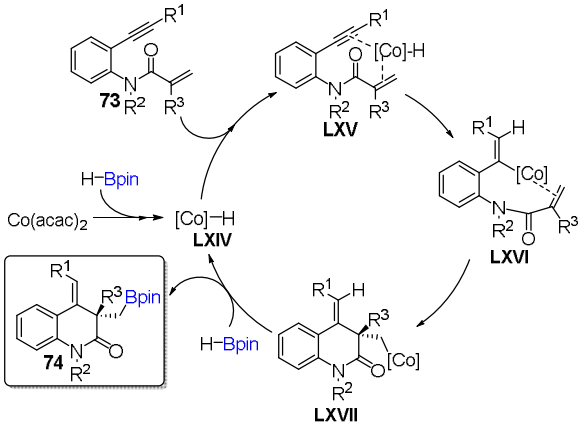
In 2019, the group of Ge also described the asymmetric synthesis of quinolinones **74** using 1,7-enynes **73** and with a phosphine-type ligand (Scheme 37).[42] The reaction showed excellent functional group tolerance to ester, amide and cyano functionalities. However, *ortho*-substituted aryls in the terminal position of the alkyne, terminal alkyne and primary anilide did not undergo this reaction. Besides, in the absence of the carbonyl moiety (substrate **75**), it was necessary to change the ligand to achieve good results in the formation of **76** (Scheme 37b).

Some control experiments were carried out to obtain mechanistic evidence. The use of alkyne and alkene model fragments of the enyne did not provide any product.[42] These results suggested that chelation of 1,7-enyne to the Co catalyst was necessary to obtain the desired product. The authors proposed a mechanism in which the initial step would be the chelation of alkene and alkyne to a Co-hydride **LXV**, formed from the precatalyst and HBpin. This coordination would be followed by a hydrometallation of, first the alkyne **LXVI**,

and then the alkene to give the new cycle in **LXVII**. A final σ-bond metathesis with H-Bpin would furnish the product, **74**, and regenerate the Co-hydride **LXIV** (Scheme 38).



Scheme 37. Asymmetric synthesis of quinolinones described by Ge.



Scheme 38. Proposed mechanism for the asymmetric synthesis of quinolinones.

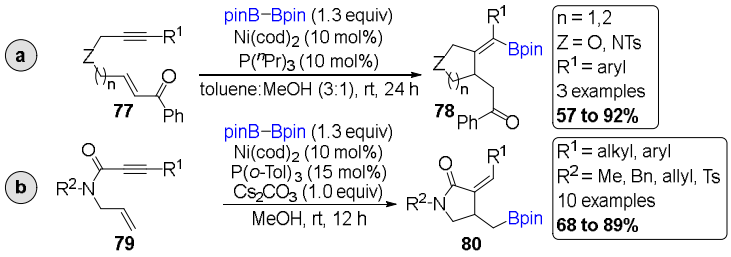
3.7. Nickel-catalyzed borylative cyclizations

The group of Cheng reported in 2016 the first example of the Ni-catalyzed hydroborylative cyclization of 1,6-enynes **77** (Scheme 39a).[43] The procedure used B_2pin_2 as the boron source and phosphine ligands, and it afforded the corresponding alkenyl-boronates **78**. Strong electron-donating groups substituted on the alkyne gave lower yields than electron-withdrawing ones, and a six-membered ring could also be obtained starting from a 1,7-enyne. However, with the use of both terminal alkenes and propiolamides **79**, the alkylboronate regioisomers **80** were obtained (Scheme 39b).

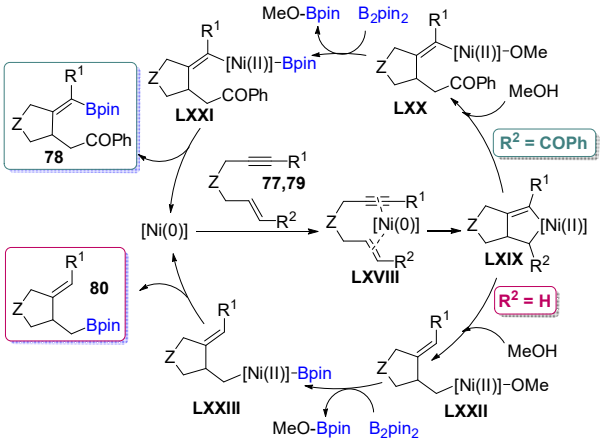
The authors proposed a mechanism for the formation of both products based on the initial coordination of the Ni(0) catalyst to alkene and alkyne moieties that would afford **LXVIII** (Scheme 40). An oxidative cyclometallation would then form nickelacycle **LXIX**. Selective protonation would lead to the formation of **LXX** or **LXXII** depending on the substituent present on the alkene. After a transmetallation, **LXX** and **LXXII** would form the boryl-Ni intermediates **LXXI** or **LXXIII**, respectively. The last step would be a reductive elimination to give the corresponding products, **78** or **80**, and regenerate the active Ni(0) species.

One year later, the group of Cárdenas published the Ni-catalyzed hydroborylative cyclization of enynes **81** using HBpin as the borylating agent and Xantphos (4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene) as

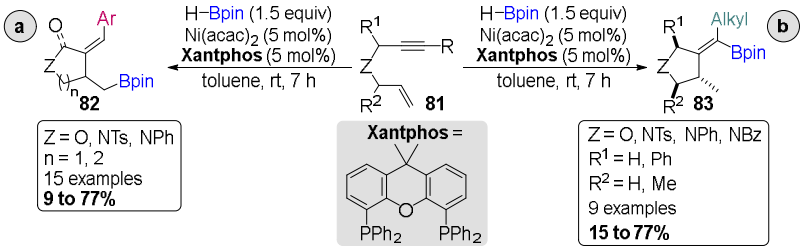
the ligand (Scheme 41).[44] The regioselectivity of this reaction depended on the substitution of the alkyne. Substrates containing an aryl group generated alkylboronates **82** (Scheme 41a), while alkyl derivatives afforded alkenylboronates **83** (Scheme 41b). The reaction showed to be more efficient with *N*-tethered enynes and the 6-membered ring was obtained starting from the *O*-tethered 1,7-enyne, but with poor yield.



Scheme 39. First Ni-catalyzed hydroborylative cyclization of enynes described by Cheng.



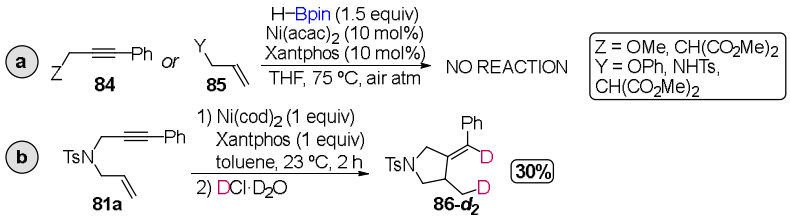
Scheme 40. Proposed mechanism for the Ni-catalyzed hydroborylative cyclization of enynes.



Scheme 41. Ni-catalyzed hydroborylative cyclization of enynes described by Cárdenas.

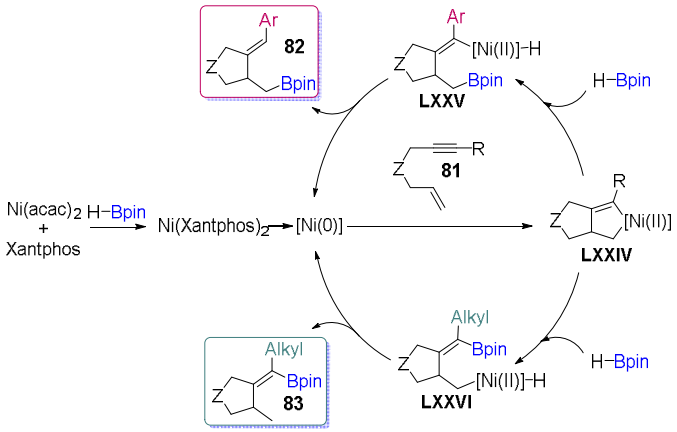
To obtain some evidence on the mechanism, the reaction using alkyne **84** and alkene **85** fragments was explored and no borylation product was observed with any of them (Scheme 42a). The stoichiometric reaction of $Ni(acac)_2$, Xantphos and enyne **81a**, followed by quenching with $DCl{\cdot}D_2O$, provided the dideuterated cyclised product **86** (Scheme 42b), suggesting an oxidative cyclometallation pathway. Besides, in the stoichiometric reaction, 3 equivalents of HBpin were necessary to obtain complete conversion, which implied that HBpin was acting as a reducing agent of Ni(II), as well as a boron source. To corroborate this hypothesis, $Ni(acac)_2$ and Xantphos were subjected to the reaction conditions but using two equivalents of HBpin,

resulting in the formation of a red solid, which was characterized as Ni(0)(Xantphos)$_2$. This Ni(0) species was a suitable catalyst for the reaction, generating the borylated products from the enyne.



Scheme 42. Mechanistic experiments.

With these results and information collected by DFT calculations in hand, the reaction was proposed to start with the reduction of Ni(acac)$_2$ to Ni(0)(Xantphos)$_2$ by two σ-bond metathesis with HBpin and reductive elimination of H_2 (Scheme 43). Then, coordination of the enyne to Ni(0) followed by oxidative cyclometallation (**LXXIV**) and σ-bond metathesis with HBpin would afford two possible Ni(II)-hydride species, **LXXV** and **LXXVI**, depending on the substitution of the alkyne. These intermediates would suffer a C–H reductive elimination, affording the cyclic hydroborylated products **82** and **83**. The selectivity of the process would be determined in the σ-bond metathesis step. When an aryl-substituted substrate is used, the most favourable pathway would correspond to the formation of alkenyl Ni-hydride **LXXV**, which would lead to the formation of the alkylboronate **82**. However, when the reaction takes place with an alkyl-substituted enyne, the intermediate obtained would be alkyl Ni-hydride **LXXVI**, formed by the same process but in which the HBpin interacts with the C(sp^2)-Ni bond, affording the alkenylboronates **83**.



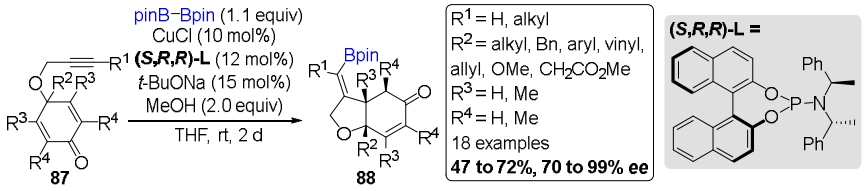
Scheme 43. Proposed mechanism for the Ni-catalyzed hydroborylative cyclization of enynes.

3.8. Copper-catalyzed borylative cyclizations

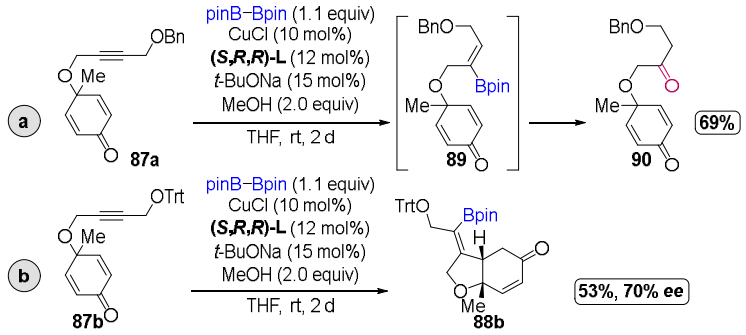
In 2013, the group of Tian and Lin reported the first Cu-catalyzed borylative cyclization of enynes (Scheme 44).[45] This methodology used prochiral cyclohexadienones **87** as starting materials, resulting in an asymmetric synthesis of hydrobenzofuranes **88**. B_2pin_2 was used as the boron source and the presence of sodium *tert*-butoxide (*t*-BuONa) and MeOH was required for the reaction to work. In this protocol, substrates with high steric hindrance in the alkyne provided lower enantioselectivities.

N-Tethered substrates did not give the desired product, and some experiments were carried out to understand the influence of the *O*-tether in the mechanism (Scheme 45). The use of a substituent in the alkyne bearing a more coordinating oxygen than that of the tether **87a** afforded a very unstable vinylboronate **89**, which was oxidized under air to the corresponding ketone-containing product **90** (Scheme 45a). However, the

use of a more hindered *O*-substituent **87b** gave the desired product **88b** (Scheme 45b). To explain these results, the authors postulated that the coordination of the Cu-centre to the *O*-tether could control the regioselectivity of the process, although they did not make a proposal for the mechanism of this transformation.

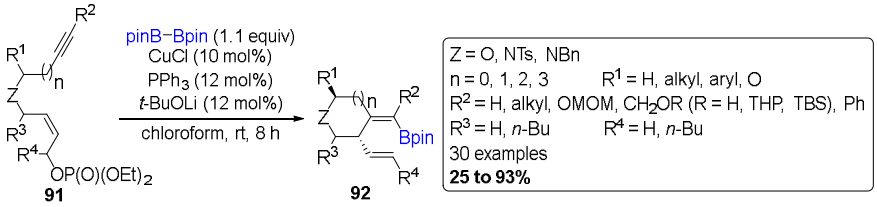


Scheme 44. Asymmetric Cu-catalyzed borylative cyclization described by Tian and Lin.



Scheme 45. Influence of *O*-tether coordination in the regioselectivity.

The group of Bai and Zhu described in 2017 the Cu-catalyzed borylative cyclization of enynyl phosphates **91** to obtain 5-membered rings **92** (Scheme 46).[46] The reaction was carried out with B_2pin_2 and using *t*-BuOLi and a PPh_3 ligand. This procedure tolerated the presence of a hydroxyl group and provided only one diastereomer when the propargylic position was substituted. However, the reaction did not occur with a *t*-Bu group in the terminal position of the alkyne. The methodology was successfully extended to the formation of 6- and 7-membered rings with good yields, but the 8-membered ring was obtained with only a 25% yield.

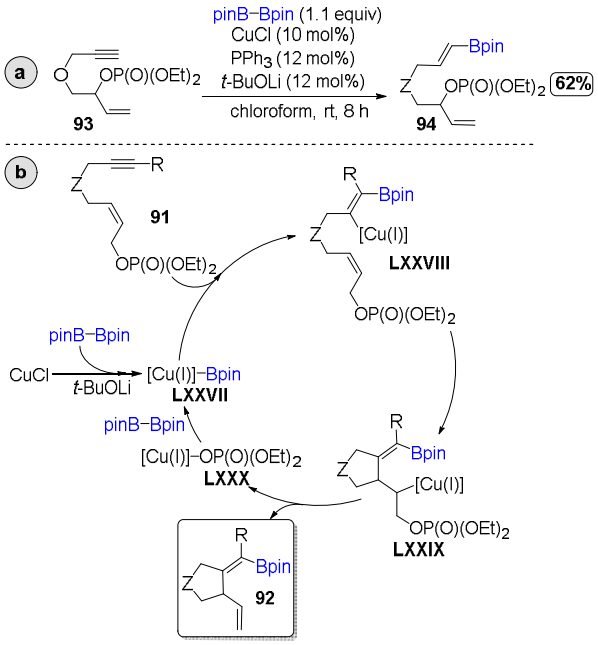


Scheme 46. Cu-catalyzed borylative cyclization of enynyl phosphates described by Bai and Zhu.

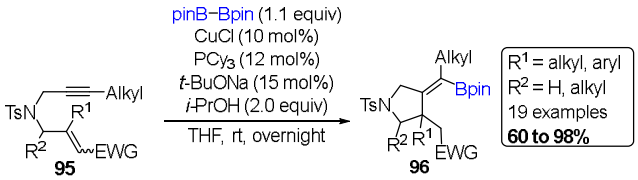
The authors explored the outcome of the reaction when the substrate with the opposite regioisomer of the allyl-phosphate **93** was used (Scheme 47a), obtaining **94** as the product, which would come from the hydroboration of the alkyne. Therefore, the formation of an allyl-Cu intermediate was discarded and the authors proposed that the reaction would occur through a boryl-metallation of the alkyne **LXXVIII**, followed by the insertion of the alkene **LXXIX** and β-phosphate elimination to furnish **LXXX** (Scheme 47b). Finally, the boryl-Cu species **LXXVII** would be regenerated by a σ-bond metathesis with B_2pin_2.

In 2018, the group of Carretero described the Cu-catalyzed synthesis of hydroborylative cyclization products **96** with a quaternary centre starting from enynes **95** with high yields in most cases. They studied in

depth the mechanism of this carboboration of alkynes, especially the role of the sodium *tert*-butoxide salt, needed for the process to work (Scheme 48).[47]



Scheme 47. Mechanistic evidence for the Cu-catalyzed borylative cyclization of enynyl phosphates.



Scheme 48. Cu-catalyzed hydroborylative cyclization of enynes described by Carretero.

The catalytic cycle proposed by the authors is shown in Scheme 49. Initially, the alkoxide would generate the catalytically active species of Cu, a Cu alkoxide **LXXXI**, that would then be transformed into boryl-Cu intermediate **LXXXII** by reaction with B_2pin_2. The borylmetallation of the alkyne **LXXXIII**, followed by the insertion of the alkene, would furnish intermediate **LXXXIV**. In this scenario, the Cu-OR catalyst would be regenerated by protonolysis of Cu–C bond with the corresponding alcohol, forming at the same time products **96**.

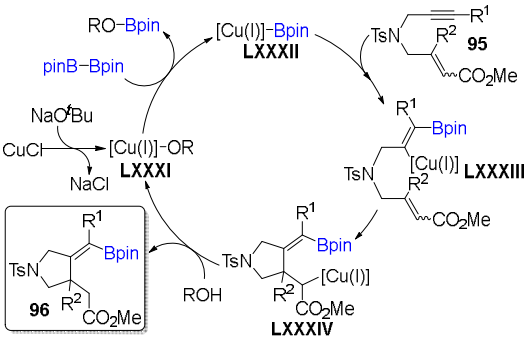
4. Borylative cyclization reactions of diynes

Transition-metal-catalyzed borylative cyclization of diynes is still under development, and only two examples of this type of reaction have been reported to date.

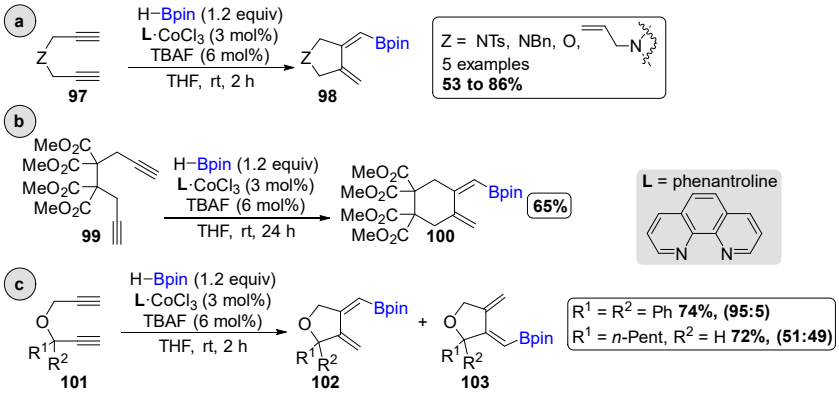
4.1. Cobalt-catalyzed borylative cyclization

The first example was described in 2019 by the group of Zhu and consisted of a Co-catalyzed hydroborylative cyclization of 1,6-diynes **97** with HBpin and in the presence of catalytic amounts of TBAF (Scheme 50).[48] The methodology gave the borylated 1,3-dienyl compounds **98** with moderate to good yields and could be extended to 1,7-diynes to give the six-membered cycle **100**, but only with tetra-ester derivatives

99 (Scheme 50b). With substitution in one of the propargylic positions (**101**), the boryl group added preferentially to the less sterically hindered alkyne, but a mixture of products **102** and **103** was obtained (Scheme 50c).



Scheme 49. Proposed mechanism for the Cu-catalyzed hydroborylative cyclization of enynes.



Scheme 50. Co-catalyzed hydroborylative cyclization of diynes described by Zhu.

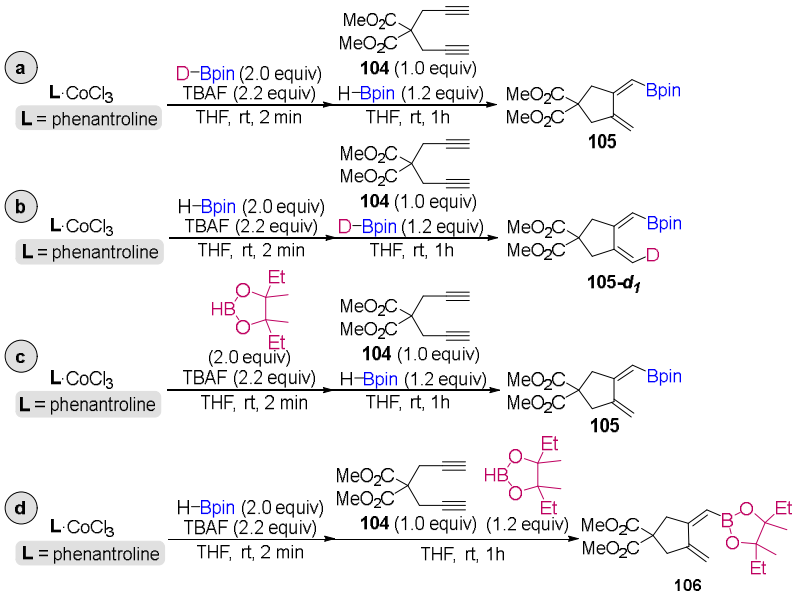
To understand the mechanism of the reaction, the authors carried out some experiments. Thus, when DBpin was used only as activating agent of the precatalyst, but then HBpin was added to the reaction with diyne **104**, the product obtained, **105**, did not contain deuterium. However, when the opposite experiment was made, and DBpin was used as a hydride and boron source, the formation of the deuterated product **105-*d*$_1$** was observed (Scheme 51a and b). This experiment allowed the authors to discard the formation of a Co-hydride complex as the catalytically active species in the mechanism. Similar experiments were performed with a partially ethyl-substituted borane, obtaining similar results. The formation of **105** when the ethyl-substituted borane was added first, and the formation of **106** when it was added together with the enyne (Scheme 51c and d), indicated that a boryl-Co complex was not involved in the process.

To account for the experimental results, the authors proposed the catalytic cycle depicted in Scheme 52. First, the Co-precatalyst would react with HBpin and TBAF to afford the Co(0) active species **LXXXV**, which would be coordinated by the diyne to furnish **LXXXVI** and would then undergo an oxidative cyclometallation leading to the 5-membered cobaltacycle **LXXXVII**. Subsequently, a σ-bond metathesis with HBpin would take place (**LXXXVIII**), followed by a reductive elimination that would produce the desired product **98**.

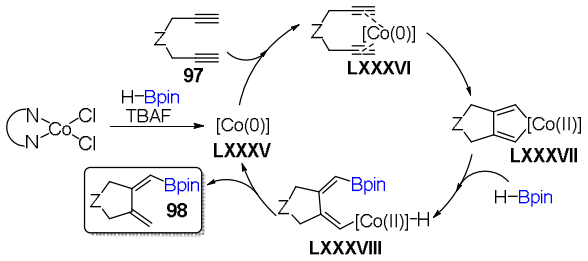
4.2. Copper-catalyzed borylative cyclization

The second reported example of borylative cyclization of diynes was the Cu-catalyzed reaction of 1,5-diynes **107** to give pyrrols **108** described by Shi and Ye in 2021 (Scheme 53), in which a

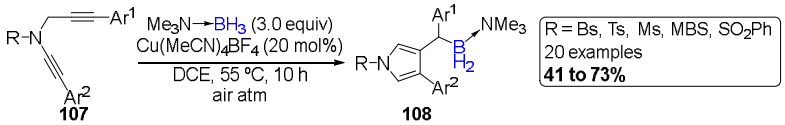
trimethylamineborane adduct was the borylating agent used.[49] The procedure was restricted to the use of aryl moieties in the terminal positions of the alkynes. Besides, only electron-rich arenes in the Ar^1 position could be used.



Scheme 51. Mechanistic experiments for the Co-catalyzed hydroborylative cyclization of diynes.

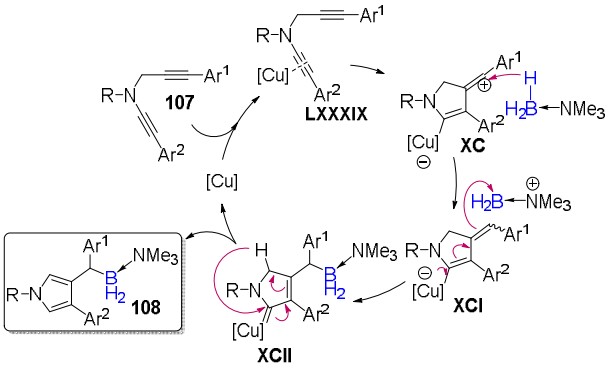


Scheme 52. Catalytic cycle for the Co-catalyzed hydroborylative cyclization of diynes.



Scheme 53. Cu-catalyzed hydroborylative cyclization of diynes described by Shi and Ye.

The authors proposed the mechanism shown in Scheme 54. First, the Cu(I)-catalyst would coordinate to the more reactive amide-tethered triple bond **LXXXIX**, which would undergo a nucleophilic attack by the other alkyne, generating vinyl cation **XC**. Then, the hydride of the borylating agent would trap the vinyl cation affording **XCI** and an amine-borane cation, which would then be trapped to give Cu-carbene **XCII**. Finally, a demetallative 1,4-shift would form the observed product **108**.



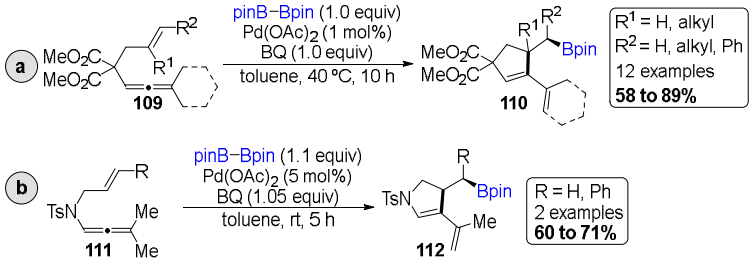
Scheme 54. Proposed mechanism through the formation of a vinyl cation.

5. Borylative cyclization reactions of allenynes and enallenes

So far, the use of allenynes and enallenes in borylative cyclization reactions has mainly been described with Pd as the catalyst, with only one example of a Ni-catalyzed methodology.

5.1. Palladium-catalyzed borylative cyclization

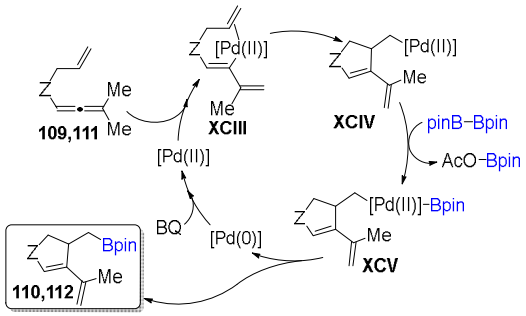
The literature of Pd-catalyzed borylative cyclizations of polyunsaturated substrates containing allenes can be classified into two groups: 1) oxidative-borylative cyclization,[50] and 2) hydroborylative cyclization reactions.[51] The group of Bäckvall has studied in depth the oxidative-borylative carbocyclizations of allenynes and enallenes.[52-57] Although most of these methodologies have been applied to the synthesis of carbocycles, there is one example in which an azacycle is formed. This article was published in 2011, and it described the borylative cyclization of enallenes **109** to form cyclopentenes **110** (Scheme 55a).[58] The reaction was performed with a $Pd(OAc)_2$ pre-catalyst, B_2pin_2 as the boron source, and benzoquinone (BQ) to provide an oxidative media. Enallenes with substituted alkenes reacted smoothly to afford the desired products with a *cis* addition to the alkene (Scheme 55a). Aza-enallenes **111** also worked generating dihydropyrroles **112**, but it was necessary to reoptimize the conditions to avoid the Diels-Alder reaction of the excess of benzoquinone with the borylated product (Scheme 55b).



Scheme 55. First oxidative borylative cyclization of enallenes described by Bäckvall.

The proposed mechanism (Scheme 56) would consist of the initial activation of the allene involving C–H cleavage of a methyl group to give alkenyl-Pd complex **XCIII**, followed by the insertion of the alkene to afford **XCIV**. Then, transmetallation with B_2pin_2 would take place (**XCV**), and reductive elimination would furnish the desired product, regenerating the Pd(II) species with the BQ. However, the authors noted that a Pd(II)/Pd(IV) catalytic cycle could not be discarded under these oxidative conditions.

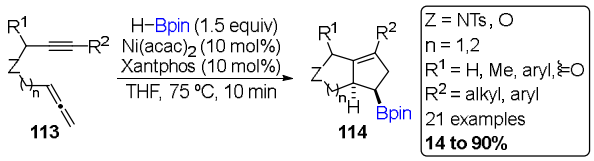
In 2015, the authors reported the enantioselective version of this transformation using a Brønsted acid as a chiral ligand,[59] although they only applied it to the synthesis of carbocycles.



Scheme 56. Proposed mechanism for the Pd-catalyzed oxidative borylative cyclization of enallenes.

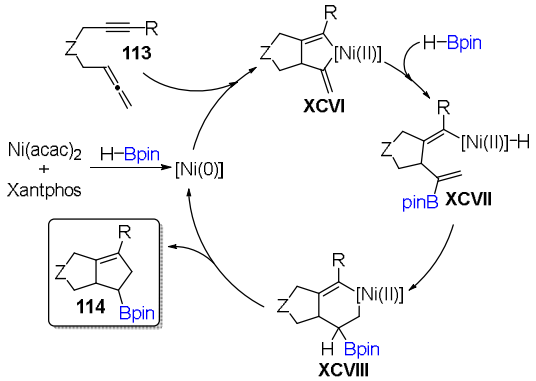
5.2. Nickel-catalyzed borylative cyclization

In 2022, the group of Cárdenas and Quirós developed the first Ni-catalyzed hydroborylative cyclization of 1,6-allenynes **113** for the synthesis of fused 5,5-membered rings **114**, forming two new C–C and one C–B bond in a single synthetic operation (Scheme 57).[60] The reaction was carried out with $Ni(acac)_2$ as the precatalyst, Xantphos as the ligand and pinacolborane as the borylating agent. The methodology had a wide tolerance to functional groups and a six membered ring could be prepared, albeit in low yield. The shortcoming of the process was that it was limited to terminal allenes.



Scheme 57. Ni-catalyzed hydroborylative cyclization of allenynes.

Stoichiometric experiments led to the formation of a Ni complex characterised as $Ni(Xantphos)_2$, observed previously by the group in the borylative cyclization of enynes.[44] This complex, in the presence of HBpin and the allenyne, gave rise to the formation of the bicyclic product. Besides, the reaction worked in the presence of Ni(cod)(DQ) as the catalyst. These results, together with DFT calculations led the authors to propose a catalytic cycle based on a Ni(0) catalytically active species (Scheme 58).



Scheme 58. Mechanism proposed for Ni-catalyzed hydroborylative cyclization of allenynes.

The mechanism would begin with an oxidative cyclometallation to form **XCVI**. Then, a σ-bond metathesis with pinacolborane would take place, giving alkenyl Ni(II)-hydride **XCVII**. Insertion of the alkene

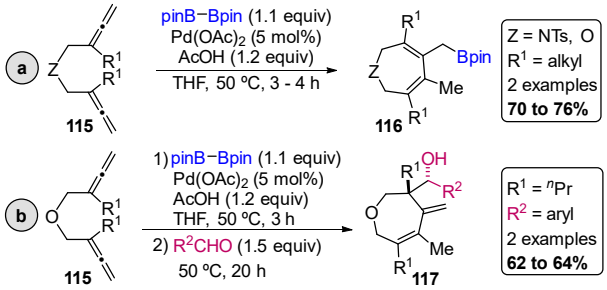
in the Ni–C bond would then occur (**XCVIII**), and reductive elimination to form a C–H bond would afford the observed borylative cyclization product **114** and regenerate the Ni(0) species (Scheme 58).

6. Borylative cyclization reactions of bisallenes

6.1. Palladium-catalyzed borylative cyclization

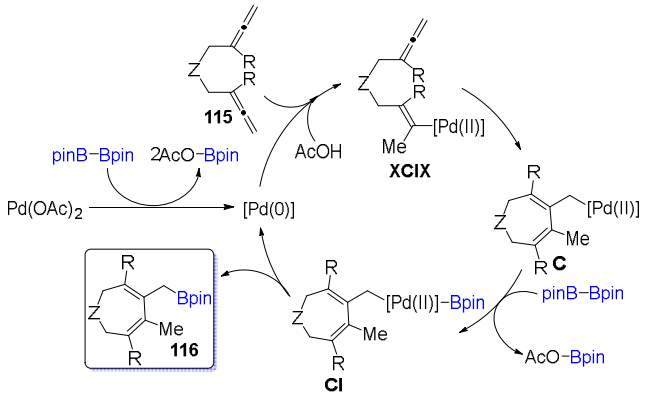
The use of bisallenes in borylative cyclization procedures has hardly been studied. To date, there is only three examples, all of them described by Bäckvall,[61-63] and only in two of them the formation of heterocycles is described. Both examples use a Pd salt as precatalyst and a diboron compound as the boron source.

The first example described the hydroborylative cyclization reaction of 1,7-bisallenes **115**, substituted in the internal position of the allenes, using B_2pin_2 in the presence of AcOH to form dihydrooxepines and dihydroazepines **116** (Scheme 59a).[62] In this reaction, the authors also developed a one-pot reaction for the synthesis of seven membered cycles containing an alcohol group **117** by trapping the boron group with an aldehyde by means of a Brown-type allylation (Scheme 59b). The limitation found in this strategy was that the use of tetra- or monosubstituted allenes provided simple hydroboration or no reaction at all, respectively.



Scheme 59. Hydroborylative cyclization reaction of bisallenes described by Bäckvall.

To understand the mechanism of this reaction, the authors carried out KIE experiments, which showed a K_H/H_D=4,7 when using a 1:1 mixture of AcOH and acetic acid-d^4. This result implied that the proton transfer from acetic acid either to palladium or to the allene would occur during the rate-determining step. DFT calculations led the authors to conclude that Pd(0) was the active catalyst, which was formed by reduction of the $Pd(OAc)_2$ with B_2pin_2, assisted by the coordination of the bisallene. The proposed catalytic cycle (Scheme 60) would start with the hydropalladation of one of the allenes in **115**.

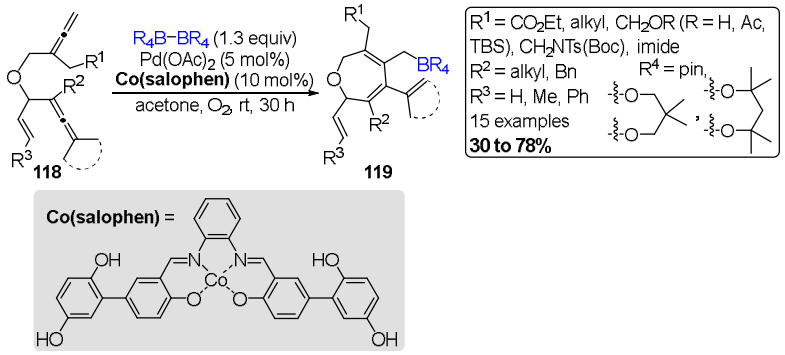


Scheme 60. Proposed mechanism of hydroborylative cyclization of bisallenes.

Interestingly, the calculations indicated that **XCIX** would be reached from the Pd(0) active species in a single step, in which the proton of the acetic acid would transfer to the terminal carbon of the allene, instead

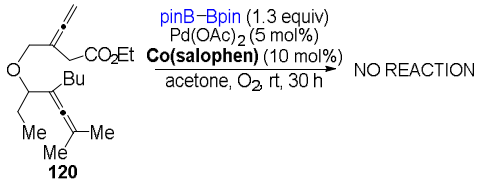
of the expected formation of a Pd–H species. This initial step would be followed by the insertion of the other allene into the Pd–C bond, affording the 7-membered ring with an allyl-Pd moiety **C**. After transmetallation with B_2pin_2 (**CI**), reductive elimination would release the desired product **116**, regenerating the Pd(0) active species (Scheme 60).

In 2020, the group of Bäckvall extended the procedure to the synthesis of *O*-containing 7-membered rings **119** by Pd and Co-catalyzed aerobic oxidative carbocyclization of alkenyl substituted bis-allenes **118** (Scheme 61).[63] The methodology tolerated imide and hydroxyl groups, but the substitution in the terminal position of both allenes did not afford the desired product, probably due to the steric hindrance.



Scheme 61. Synthesis of borylated *O*-containing 7-membered rings described by Bäckvall.

To understand the influence of the olefin, the authors tested a bisallene in which the vinyl group was substituted by an ethyl group **120**, obtaining no reaction at all (Scheme 62). Therefore, the presence of the alkene was proved to be necessary, probably as assisting group.



Scheme 62. Influence of olefin as an assistant group.

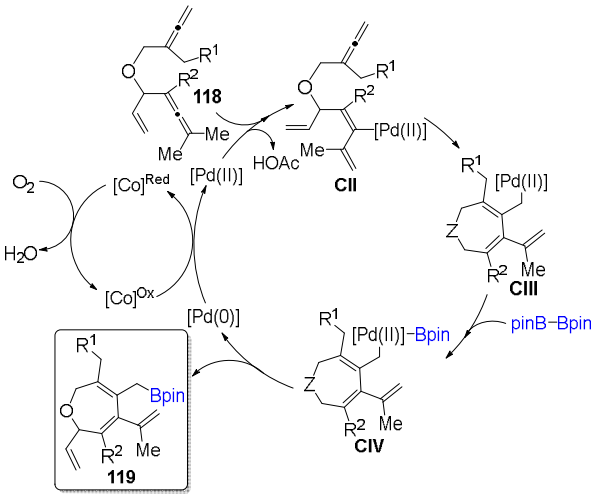
The proposed mechanism (Scheme 63) would consist of the initial reaction of the more substituted allene to give intermediate **CII**, assisted by coordination with the olefin and followed by the insertion of the other allene into the alkenyl-Pd bond. The resulting allyl-Pd complex **CIII** would undergo transmetallation to give **CIV**, which would generate the product after reductive elimination. Finally, Pd(II) would be regenerated by the Co catalyst, which would be reoxidized by oxygen.

7. Diborylative cyclization reactions

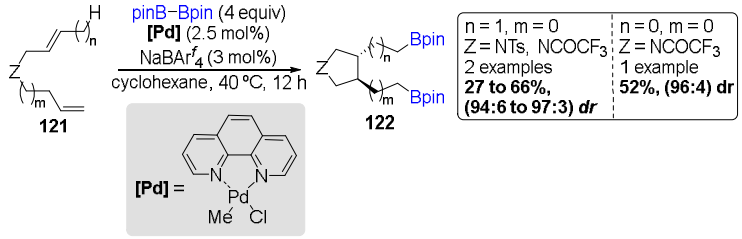
Diborylative cyclization reactions are an emerging area in which not many studies have been made to date. To the best of our knowledge, there are only two examples of this type of methodologies, one with dienes and one with enynes, both of them using B_2pin_2 as the boron source.

7.1. Palladium-catalyzed diborylative cyclization of dienes

In 2021, the group of Kochi described the Pd-catalyzed remote diborylative cyclization of dienes **121** for the formation of bisborylated cyclopentane derivatives **122** (Scheme 64).[64] The reaction took place with 4 equivalents of B_2pin_2, a phenanthroline-Pd complex and in the presence of catalytic amounts of $NaBAr^f_4$ (Ar^f=3,5-$(CF_3)_2C_6H_3$) to remove the chlorine ligand of the catalyst.

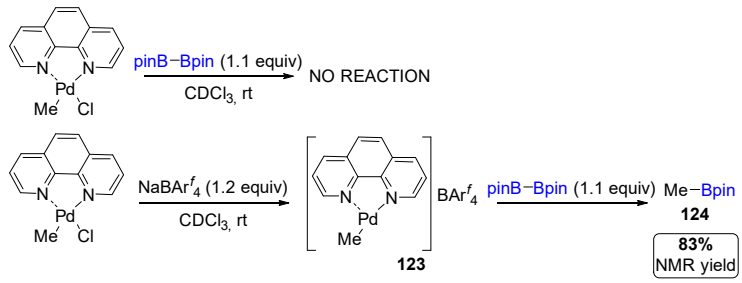


Scheme 63. Proposed mechanism for the synthesis of borylated 7-membered rings.



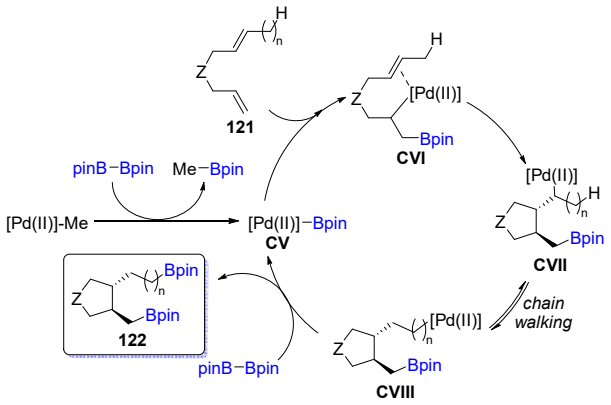
Scheme 64. Pd-catalyzed diborylative cyclization of dienes described by Kochi.

Stoichiometric experiments were performed to shed some light on the mechanism (Scheme 65). The reaction of the Pd complex with B_2pin_2 did not occur in the absence of $NaBAr^f_4$. However, the addition of this reagent led to the formation of a cationic Pd complex **123** that reacted in the presence of B_2pin_2 to form Me-Bpin **124**.



Scheme 65. Mechanistic experiments.

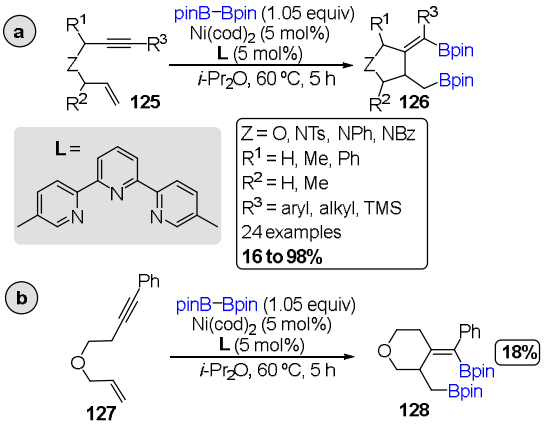
The mechanism proposed for this transformation would start with the formation of a boryl-Pd species **CV** *via* a σ-bond metathesis of the Pd-Me precatalyst with B_2pin_2 (Scheme 66). The terminal alkene would then be inserted into the Pd–B bond forming complex **CVI** that would then evolve through a second insertion forming the cyclic scaffold **CVII**. The chain walking process of the catalyst would occur to form intermediate **CVIII** that after a new σ-bond metathesis would afford the product and regenerate the boryl-Pd complex **CV**.



Scheme 66. Proposed mechanism for the Pd-catalyzed diborylative cyclization of dienes.

7.2. Nickel-catalyzed diborylative cyclization of enynes

In 2019, the group of Cárdenas investigated the Ni-catalyzed diborylative cyclization of 1,6-enynes **125**.[65] The reaction led to the formation of diborylated cyclic products **126**, containing both alkyl- and alkenylboronates, in the presence of B_2pin_2 as the borylating agent, a terpyridine derivative as the ligand and a Ni(0) source as the catalyst (Scheme 67). The methodology could be extended to 1,7-enynes **127**, furnishing pyranes **128**. It is interesting to note that the reaction is atom-economical, since both boron moieties come from the same B_2pin_2 molecule. Besides, the synthetic utility of this methodology lies in the fact that the different nature of both formed C–B bonds allows for an orthogonal functionalization of products **126**.

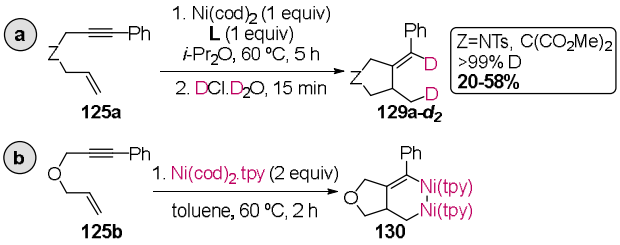


Scheme 67. Ni-catalyzed diborylative cyclization of enynes described by Cárdenas.

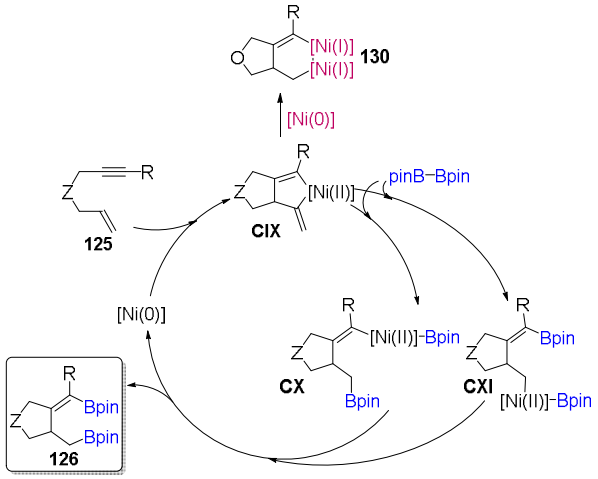
Some experiments were performed to clarify the reaction mechanism. The reaction of simple alkenes and alkynes under the optimized conditions did not lead into the formation of any borylated product. The reaction of enyne **125a** with stoichiometric amounts of catalyst and ligand and in the absence of B_2pin_2, followed by quenching with $DCl{\cdot}D_2O$ afforded the corresponding dideuterared product **129a-*d*$_2$** (Scheme 68a), suggesting an oxidative cyclometallation pathway. Besides, the stoichiometric reaction of **125b** with $Ni(cod)_2$.tpy led to the formation of **130**, a species containing two Ni(I) atoms (Scheme 68b).

Although the formation of the bimetallic species **130** in the reaction media suggested that it might be involved in the mechanism of the reaction, it is difficult to envision a reaction pathway through which this species could evolve. Because of that, it would be more likely to think that the bimetallic complex could be a

resting state. Thus, the mechanism proposed by the authors would involve an initial oxidative cyclometallation to form nickelacycle **CIX**, which would then evolve through a σ-bond metathesis with B_2pin_2 (Scheme 69). This metathesis could occur in any of the C–Ni bonds of the metallacycle. However, DFT results suggest that the formation of the alkyl-Ni complex **CXI** would be more favoured. From any of these intermediates (**CX** or **CXI**), a reductive elimination would form the bisborylated product **126** and regenerate the Ni(0) catalytically active species. The formation of the bimetallic cycle **130** was studied through DFT computational methods.[66] Its formation could be produced from the intermediate nickelacycle **CIX** *via* a comproportionation with Ni(tpy).



Scheme 68. Mechanistic experiments on the diborylative cyclization of enynes.



Scheme 69. Mechanism proposed for Ni-catalyzed diborylative cyclization of enynes.

8. Conclusions

Metal-catalyzed borylative cyclization reactions are a versatile tool for the synthesis of heterocyclic structures. The choice of the metal is fundamental to determine the outcome of the process and different sized cycles and fused bicycles can be obtained depending on the metal of choice. The most developed processes are those giving rise to the formation of five membered cycles. However, the synthesis of 3- to 8-membered cycles or fused bicycles has been described. Furthermore, the heterocycles obtained with these methodologies contain a boron functionality, which allows for further functionalization of the product. The synthesis of boron-containing heterocycles is an interesting outcome since boron compounds are environmentally friendly and they can be easily transformed in a variety of products under mild reaction conditions.

On the other hand, the knowledge of the means of action of different metals under certain reaction conditions is essential to predict the reactivity, since those metals can follow a variety of reaction pathways giving rise to the formation of different scaffolds, by variation of the type of cycle and the position of the boron functional group in the final product. Although the initial mechanistic steps more frequently encountered are

the formation of metal hydrides or boryl-metal species, and the oxidative cyclometallation of M(0) complexes, there is a wide variety of reactivity patterns depending on the metal of choice. This is why borylative cyclizations are still an active area of research in which novel reactivities are still to be uncovered.

Acknowledgements

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