4-*exo*-dig Cyclocarbopalladation, discovery and application in the synthesis of complex polycyclic molecules

Gaëlle Blond and Jean Suffert

Université de Strasbourg, CNRS, LIT UMR 7200, F-67000 Strasbourg, France

Corresponding authors e-mail: jean.suffert@unistra.fr, gaelle.blond@unistra.fr

Preface

The 4-*exo*-dig cyclocarbopalladations has been efficiently used to produce molecular complexity in a straightforward manner. Strained 1,2-cyclobutanediols are rapidly obtained, usually under microwave irradiation, in high yields. In many cases, the cyclocarbopalladation cascade reaction is associated with a 6 or 8 π electrocyclic reactions. Polycyclic skeletons of **unnatural** or natural products can be prepared in few steps from simple starting material. Very strained aromatic polycycles, taxanes framework, **cyclooctatrienes**, cyclooctatetraenes, fenestranes and fenestrenes have been obtained following in all cases as a first step a 4-*exo*-dig cyclocarbopalladation reaction.

1 Introduction

The potential of palladium-catalyzed process in organic synthesis has not yet been fully explored. For more than 25 years the investigation of new methodologies for the preparation of complex molecules has been extensively pursued for the development of short, highly efficient, atom- and step-economic pathways. For this purpose, catalytic systems using noble metals are tools of choice and many examples are now available in this context using palladium, rhodium, ruthenium, platinum and others from the transition element class. The usefulness of strategies based on palladium cyclization cascades has been demonstrated in the past leading to polycyclic frameworks in regio- and stereoselective manner.¹ The formation of new polycyclic systems is an important challenge in organic synthesis and cyclocarbopalladation is often the key step for the preparation of rings of different size.

One of the most efficient cyclization processes that have been used in the literature concerns the intramolecular attack of an organopalladium activated species on a tethered triple bond. Most of the time, an initial 5-*exo*-dig, 6-*exo*-dig, or 7-*exo*-dig cyclocarbopalladation is involved followed by a terminating cross-coupling reaction with various organometallic reagents.² Significant studies for almost 20 years in our laboratory were and are directed at the development of cyclocarbopalladation to design and elaborate complex polycyclic molecules from simple starting material. In this context, we report herein our investigations in the study of cascade reactions involving 4-*exo*-dig cyclocarbopalladations, its discovery and its power in the synthesis of targets that are difficult to obtain by more classical ways.

2 Discovery of the 4-*exo*-dig cyclocarbopalladation in the first synthesis of cyclobutenediol and application to the synthesis of strained polycyclic compounds.

2.1 The 4-*exo*-dig / 6π electrocyclization

The power of the intramolecular cyclization in order to prepare cyclic and polycyclic scaffolds is well documented in the literature for decades and is often used in the total synthesis of natural or unnatural compounds.³ The formation of five, six or larger rings has been reported using classical methods, cyclization of charged atoms, radical cyclization and more recently using noble metal catalyzed reactions. In this context palladium is a metal of choice for the synthesis of polycyclic derivatives. Usually the processes using this metal are extremely efficient and deliver easily five or six membered ring structures through a 5-*exo*, 6-*exo* trig or dig cyclization following the Baldwin rules. The reaction involved in this type of cyclization is a *syn*-Heck type addition on a double or triple bond.

The cyclocarbopalladation process was described for the first time in 1988 by Grigg⁴ shortly followed by Negishi.⁵ This reaction afforded stereodefined exocyclic alkenes. 5-, 6-, or 7-*exo*-dig cyclocarbopalladations have been performed with success. The reaction can be ended by a terminating cross coupling reaction either with a hydride source, an alkene, CO, or various organometallic reagents (aluminum, zirconium, boron, zinc, or tin derivatives) (Scheme 1).

SCHEME 1 The cyclocarbopalladation approach to cyclic derivatives

In the beginning of the 2000 we were particularly interested in the study of a new type of carbopalladation reactions following an unlikely 4-*exo*-dig reaction that is not supported by the classical Baldwin rules (Scheme 2). But in this case the use of palladium in this approach could potentially force the process to occur.

SCHEME 2 The 4-*exo*-dig cyclocarbopalladation

The approach of the molecule **3** or **3'** was based on the simple idea that the vinylbromide **1** bearing a properly positioned triple bond, should smoothly cyclized under palladium catalysis through a 4-*exo*-dig cyclocarbopalladation to give the palladium derivative **2**. The former should react with an organometallic specie or a terminal alkyne to eventually give a substituted cyclobutane **3** or **3'** bearing two exocyclic double bonds. A very important fact can be point out, the two double **bonds** are conjugated that must be crucial for further reactivities.

This process has never been studied in the past and should give useful **compounds** that can be transformed or decorated in further reactions. Our goal was first to design a convenient molecule that can efficiently undergo the 4-*exo*-dig cyclocarbopalladation avoiding the possibility of a direct cross coupling reaction. Our initial idea was to force the side chain bearing the reactive triple bond to be located in face of the palladium atom inserted into the C-Br bond. In this manner the palladium was very close to the triple bond and thus is perfectly settled to form a new carbon-carbon bond leading to a four unsaturated membered ring structure. In this direction, we decided to start with the unsaturated bromoketone **5** that is easily prepared in large scale from enone **4a/4b**. Addition of a properly doubly protected propargylic lithium derivative gave a mixture of *anti* and *syn*-diol **6a/6b** and **7a/7b** in a ratio average around 70/30. These two diastereomers can be easily separated by chromatography after treatment of the crude by *p*-TsOH in MeOH to remove the protecting group on the propargylic alcohol (Scheme 3).

SCHEME 3 The synthesis of *anti*- and *syn*-diols

With **6a** in hand, we thought that the possible formation of a hydrogen bond between the proximal OH should favor a favorable conformation of the molecule during the insertion of the palladium on the C-Br bond and it subsequent insertion on the proximal triple bond through a 4-*exo*-dig cyclocarbopalladation. In this direction, **6a** was treated with Pd(PPh₃)₄ and tributylvinyl stannane **8** in benzene at 90°C for 6h. Despite the consumption of all starting material, to our surprise, no trace of the expected bicyclic product **9** was observed under these conditions but a different compound was the only product isolated. After extensive NMR experiments, the structure of the final product **10** was elucidated (Scheme 4). During this process, a tricyclic compound was formed. After the cross coupling reaction between the palladium intermediate and the vinylstannane a spontaneous 6π-electrocyclization of the formed triene occurred at 90 °C giving rise to a very strained product **10** including a cyclobutene ring shared by two other cycles. The low stability of **10** probably explains the low yield observed (32 %). When the starting material **6b** including a seven membered ring was subjected

to the same reaction conditions an identical product **11** was isolated in a better yield (62%). No traces of the direct Stille coupling product **12** between the starting vinyl bromide **6a** and the vinylstannane **8** was observed in both cases.⁶

SCHEME 4 The 4-*exo*-dig followed by a 6 π -electrocyclization

If the *trans*-bis(tributylstannyl)ethylene **13** was used instead the vinylstannane **8** under the same conditions, new products **18a** and **18b** were formed that doesn't include the cyclobutane moiety. The proposed mechanism for the formation of **18a** or **18b** is shown in Scheme 5. A 6 π -electron disrotatory electrocyclization results in the strained tricyclic diol **15**. The *anti*-stereochemistry between the proton 6 and the tributylstannyl group is fixed by the electrocyclization process. Intermediate **15** undergoes a concerted elimination of SnBu_3 and ring opening of the cyclobutenediol leading to the enol **16**. The formation of the conjugated diene **17** is then followed after prototropy by an intramolecular attack of the alcoholate on the ketone from the concave face to form the last stereocenter, resulting in the hemiketal **18** in respectively 62 % for $n = 1$ and 24 % for $n = 2$.

SCHEME 5 Mechanism of the formation of **18a** or **18b**

The presence of the diol functionality in **6a** was crucial for the exclusive 4-*exo*-dig reaction to proceed. When one replaced the homopropargylic OH by a hydrogen in **19**, we observed the formation of two products under identical experimental conditions. A mixture of the 4-*exo*-dig and the direct cross-coupling products was obtained in low yield (23%) with a ratio of 65:35 respectively for **20:21** (Scheme 6).

SCHEME 6 Reactivity of the propargylic alcohol **19**

In this particular case, no rearranged product was observed by a possible elimination of the tributylstannyl moiety. The structure of **11** as well as **18a** was confirmed by X-Ray diffraction analysis as shown on figure 1.

FIGURE 1 X-Ray diffraction analysis of strained tricyclic products **11** and **18a**

With these primary results in hand, we decided to study the scope and limitation of this unique cyclization that has been described for the first time. First, *syn*-diols **7a** and **7b** were also tested under the classical reaction conditions.

SCHEME 7 The 4-*exo*-cyclocarbopalladation on the *syn*-diols

In the majority of the cases studied, we obtained a mixture of the 4-*exo*-dig and the direct Stille cross-coupling products again showing the importance of the relative stereochemistry of the diol function. This fact supported our hypothesis that a possible hydrogen bond was formed forcing the two reactive sites to be close to each other and giving the 4-*exo*-dig cyclization

exclusively. Therefore the **anti-diol** favors the cyclocarbopalladation process, whereas the **syn-diol** conducts to a mixture of both products.

TABLE 1 Scope and limitations of the 4-*exo*-dig cyclocarbopalladation

starting diol				
entries	1	2	3	4
stannane R^3-SnBu_3	products			
a				
b				
c				
d				
e				
f				

A systematic study was envisaged starting with **four different** vinylbromides (entries 1-4, Table 1) and **six** different stannanes (Entries a-f, Table 1). During these investigations, **four** different products can be obtained (Products A-D). Without going in details on Table 1, one can observe that, in general, the 4-*exo*-dig cyclization was observed in most of the cases with yields ranging

from 12 to 84%. The use of the simple vinylstannane **8** as a coupling partner (Entry d), gave, after formation of the cyclobutane ring and a 6 π -electrocyclization, the unusual strained tricyclic systems **10**, **46**, **47** and **11**. In some cases (with **6a**, **28** and **30**), the cyclobutene ring formed after a 6 π -electrocyclization, rearranged to finally furnish the hemiacetal derivatives (Entry e, products **18a**, **48**, **18b**). The protection of the diol moiety didn't affect deeply the yields of the products (Entries 3a to 3e).⁷

The use of the *syn*-diol as starting material gave in general a mixture of the 4-*exo*-dig and Stille direct cross coupling products in the few cases studied. It is only on the 7 membered vinylbromide starting compound that we obtained only the 4-*exo-exo*-dig product. The cyclocarbopalladation can be easily scale up by increasing the reaction by 10 fold without relevant yield loss.

The importance of the ring size and the presence or absence of the diol function as well as the nature of the substituent on the triple bond have been studied. The starting compound shows the best yield and exclusive formation of the 4-*exo*-dig product when it contains a 6 membered ring, an *anti*-1,2- diol and a SiMe₃ substituent on the alkyne.⁸

We have extended this methodology to the synthesis of cyclobutane diols bearing a dienynes functionality, obtained in very good yields. The introduction of the triple bond was performed using the alkyne stannylated reagent under microwave irradiation at 130 °C. The yields of **53a-n** were between 71 to 86%. Identically when a stannylated furan or thiophene were used, the cyclobutanediols **54** and **55** were obtained in acceptable yields respectively 63 % and 46 %.

When the reaction was done in presence of the *trans*-bis(tributylstannyl)ethylene, a further 6 π -electrocyclization occurred giving rise to the bicyclic cyclohexadienes **57a-d**. Yields are better if the diol are protected as a dioxolane.⁹

SCHEME 8 Synthesis of cyclobutanediols température sur le schéma

This study was followed by an extensive use of the 4-*exo*-dig cyclocarbopalladation for the synthesis of much more complex molecules always through efficient cascade reactions. Our next objective was the use of an 8 π -electrocyclization for the synthesis of polycyclic scaffolds including a cyclooctatriene moiety.¹⁰

2.2 Cascade 4-*exo*-dig / 8 π -electrocyclization

The 6 π -electrocyclization has been used for a powerful synthesis of some very strained tricyclic scaffolds as it has been demonstrated above. The conditions used, 90 °C, Pd(PPh₃)₄ in benzene

gave exclusively the 4-*exo*-dig cyclocarbopalladation followed by an electrocyclic closure of the triene formed when the starting compound was properly decorated.

Next, we turned our attention to the synthesis of molecules containing a 8-membered ring structure following the same kind of approach than before. If one is able to build a derivative containing **four** contiguous conjugated double bonds with the required configuration, we have the possibility to produce a cyclooctatriene through a 8π -electrocyclization process. This substructure is commonly represented in the natural products family. Over 100 compounds shared a cyclooctane moiety. But due to the high degree of ring strain, unfavorable entropic and enthalpic factors and *trans*-annular interactions, their preparation is often difficult. Therefore the metalcatalyzed route using transition metal like the palladium remains a good solution to this end. The basic tri and tetracyclic structures of ophiobolin A (**58**)¹⁰ and aleurodisal (**59**)¹¹ contain respectively a 5,8,5-tricyclic and 5,6,8,5-tetracyclic core and were chosen to illustrate this methodology.

FIGURE 2 The structure of ophioboline A and aleurodisal

Thus, we decided to use the stannylated diene **61-65** ($X = \text{CCO}_2\text{Et}$, $\text{C}(\text{CH}_2\text{OH})_2$, $\text{C}(\text{CH}_2\text{OC}(\text{CH}_3)_2\text{OCH}_2)$, **NTs**, **O**) that can be easily prepared in large scale by a straightforward method developed by Lautens *et al.*¹²

SCHEME 9 Synthesis of cyclooctatrienes through a 4-*exo*-dig cyclocarbopalladation

It is important to note that in this particular case the use of the 5-membered vinyl bromide **60a** or **60b** allows the 4-*exo*-dig cyclocarbopalladation because it is followed by an 8π -electrocyclization reaction. In the case of a possible 6π -electrocyclization the formation of a 5,4,6 tricyclic product was not permitted due to the large strain contained in this system. The reaction of **60a,b**, **6a** and **28** with the stannylated dienes **61-65** gave in **one-pot** operation the corresponding 5,8,5 **66-73** and 6,4,8,5 or 6,5,8,5 **74-85** polycycles with low to moderate yields (11 to 63 %). All these compounds were formed as a single diastereomer. The modest yields observed are compensated by the structural complexity of the final products obtained and the limited number of steps in the reaction sequence.

On Scheme 10, we presents the proposed mechanism for the preparation of the substructure of the polycyclic scaffold present in the ophioboline natural product family. The starting compound **60a** was reacted with the stannylated diene **61** in the presence of $\text{Pd}(\text{PPh}_3)_4$, at 85 °C in benzene. After the initial insertion of palladium (0) into the C-Br bond and *syn*-4-*exo*-dig addition on the proximal triple bond the tetraene **86** was formed but cannot be isolated. Under the reaction conditions it immediately underwent a conrotatory 8π -electrocyclization that furnish the tetracyclic system **87**. This unstable compound is very strained and gave after a 4π -electrocyclic opening the bis(enol) **88**. This molecule was able to give 2 different products **89/90** in a ratio 3:1 following two routes. Compound **90** was simply formed through the bis(enol)/ketoaldehyde equilibrium and the keto allylic alcohol **89** by the 1,5-hydrogen shift of the bis(enol) as shown on scheme 10.¹³

SCHEME 10 Mechanism of the 4-*exo*-dig/ 8π -electrocyclization/ring opening cascade

The strategy developed and described above was based on a cascade reaction consisting of a 4-*exo*-dig cyclocarbopalladation, Stille cross-coupling reaction, and conrotatory 8π electrocyclization. To date, only rare examples of this pericyclic reaction for the direct formation of eight-membered rings have been described. Thus, we have shown that its potential as an efficient route to stable cyclooctatrienes should be considered.

2.3 The 4-*exo*-dig cyclocarbopalladation in the synthesis of strained aromatic derivatives

During the search and investigations to propose a new way to produce cyclooctatrienes derivatives we were pleased to discover a new route and family of new strained tricyclic scaffolds through a very efficient cascade reaction involving a 4-*exo*-dig carbopalladation as a starting trigger. The proposed strategy for the synthesis of cyclooctatrienes was based on a three different ways that are described in scheme 11. The starting vinylbromide bearing two triple bond or eventually another third triple or double bond on the tether should have reacted

The most probable mechanism is described in Scheme 12. Due to kinetic reasons the

SCHEME 12 Synthesis of strained aromatic derivatives

We were able to synthesized a number of compounds of this type including different heteroatoms, substituents, size cycle, in good to very good yields (50 to 92 %, see Figure 3). Even when the terminal triple bond on **91a** or **b** was substituted by a tether containing an extra triple or double bond in place of the SiMe_3 group, we obtained the same type of aromatic derivatives but in relatively low yields (traces to 47 %).

FIGURE 3 Synthesis of strained aromatic polycycles through a 4-*exo*-dig cyclocarbopalladation

All these compounds are quite stable and can be purified without any difficulties. We never succeeded in the preparation of single crystal of any type of these strained compounds since it was very interesting to study the X-Ray crystallographic structure of one product and particularly the nature of the tight bond between the aromatic and the dioxolane function.

2.4 4-*exo*-dig followed by ring expansion in the synthesis of taxane skeleton

The discovery of the taxol **95**, an anticancer drug, highlighted the synthetic and biological interest of such complex polycycles. Still today, the access of the polycyclic systems of the taxane family is of great interest and several important contributions have been proposed these last decades in order to efficiently synthesize new taxanes particularly those that would overcome resistance of the taxol itself. In our laboratory, we were particularly interested in the synthesis of the ABC core scaffold (Scheme 13) present in the natural product, which could be decorated to achieve activity comparable or superior to taxol. The idea to access to the 6,8,6 sub-structure of the taxane came from our discovery on the synthesis of strained aromatic polycycles that has been performed through a cascade reaction involving the 4-*exo*-dig cyclocarbopalladation. In that work, we were able to prepare these compounds following the route described in Scheme 12. The starting compound included a chain ending by a terminal substituted triple bond. In place of the triple bond, if we use a terminal double bond substituted or not, we could envisage to produce **96** from **98** by a cascade reaction including a 4-*exo*-dig cyclization, a 6-*exo*-trig cyclization, a β -HPd elimination and eventually a 6π electrocyclicization. This reaction sequence should produce the tetracyclic derivative **97** bearing a central cyclohexadiene. If one could selectively cleave selectively the 4 membered ring double bond it is possible to obtain the tricyclic compound **96** nicely decorated by three different ketones.

SCHEME 13 Retrosynthetic approach of the taxane core structure of taxol

The starting compounds **98a-i** were prepared in 60 to 90 % yields in 5 steps sequence from 2-bromo-cyclohex-2-one **5a**. The configuration of the double bond can be *E* or *Z* and sometime was a mixture of the *E* and *Z* configuration depending of the nature of the R group. Several compounds of type **98a-i** were treated under palladium catalysis and microwave irradiation. In all cases, the cascade occurred following the mechanism depicted in Scheme 14. When the R group was an aromatic, in some cases we observed the formation of a mixture of the *cis* and *trans* tetracyclic derivatives. For example, starting with a 100:0 phenyl substituted *Z*-double bond, we obtained at the end of the cascade a 83:17 mixture of the *cis:trans* products in 62 % yield. This observation was explained as a result of a possible *anti*-hydride elimination in **100a-i** to give **103a-i** before the 6 π -electrocyclization in order to avoid the strong stereoelectronic interactions between the aromatic moiety and the cyclohexene.

SCHEME 14 Proposed mechanism for the synthesis of tetracyclic derivatives

When the R group was different from an aromatic moiety, the reaction was completely diastereoselective. A *Z* configuration of the double bond giving only the *cis* product, an *E* one giving only the *trans* one. The structure of one of the product **102g** was confirmed by X-Ray structure analysis (Figure 4).

With **102a-i** in hand, the next step was to increase the reactivity of the cyclobutenic double bond *versus* the allylic double bond towards an oxidative cleavage. To this end the allylic alcohol **102a-i** was oxidized using Dess-Martin periodinane in CH₂Cl₂ at room temperature for 2h producing **105a-i** in good yields (68-90 %). After checking several oxidizing systems we decided to use the RuCl₃ in presence of NaIO₄ in a mixture CCl₄/CH₃CN/H₂O. The cleavage of the more reactive cyclobutenic double bond was very fast at 0°C within 30 min. Yields were acceptable, ranging from 40 to 62 %.

SCHEME 15 Ring expansion by oxidative cleavage of the cyclobutenic double bond

One of the compounds (**106d**) bearing a phenyl group as R group gave nice crystals, which were suitable for X-Ray structure analysis (Figure 4). The highly substituted tetracyclic scaffold related to the taxane family was obtained in only 7 steps from 2-bromocyclohexen-2-one. When compound **106d** was treated with methylorthoformate in methanol in the presence of PPTS at room temperature it furnished derivative **107d**. The three ketones were completely and selectively differentiated as an enoether, a hemiacetal and a remaining ketone function on the 8 membered ring.

FIGURE 4 X-Ray crystal structures of compounds **102** (R = CF₃) and **106** (R = Ph)

An unusual reactivity was observed when the oxidative conditions that have been used for the synthesis of the taxane derivatives were applied to compound **108** ($R = \text{Ph}$). In this molecule, the less bulky methylene unit was used for the diol protection instead of the *gem*-dimethyl (Scheme 16). Surprisingly, in this case, the double bond of the α,β -unsaturated ketone was cleaved and not the tight cyclobutenic double bond. It resulted in the formation of a substituted 10 membered ring **109** that can be find in the structure of brianthein A (Scheme 16), a natural product isolated from *gorgonian braireum excavatum*. No traces of product **110** were found. It is clear that steric effect also influence the selectivity that was achieved in the cleavage process.

SCHEME 16 Synthesis of the tricyclic core structure of Brianthein A

2.5 4-*exo*-dig in the synthesis of Original Polycyclic Structures Containing 3-, 4-, 5- and 6-Membered Rings

In the course of the synthesis of complex polycyclic compounds, we were interested in the synthesis of derivatives containing two small strained rings in their structures, a cyclobutene (via the 4-*exo*-dig cyclocarbopalladation) and a cyclopropane (via a 3-*exo*-trig cyclocarbopalladation). To achieve this goal, we designed a starting compound **111** containing a substituent R^1 on the double bond to avoid the β -hydride elimination that would generate a new double bond prone to trigger a 6π -electrocyclization. Consequently, this reaction should give access to unique scaffolds bearing 3-, 4-, 5- and 6-membered rings in their structures. As a first model, we choose to synthesized compound **111a** ($R^1 = \text{Me}$) that was available from 2-bromocyclohexen-2-one in 7 steps.

SCHEME 17 Catalytic cycle in the synthesis of compounds **117**

After careful optimization of the reaction conditions, **111a** was reacted under microwave irradiation with $\text{Pd}(\text{PPh}_3)_4$ (10 % mol) in a mixture of benzene/methanol/triethylamine in a ratio 6/2/1 for 30 min at 100°C to give the corresponding desired compound **117a** in 82 % yield. The effect of methanol on the full process is still unclear but without MeOH as a co-solvent, the yield of the reaction dropped to only 45 %. The mechanism of the reaction is depicted in Scheme 17. After an oxidative insertion of the palladium on the vinylic bromide on **111** to produce **112**, the 4-*exo*-dig cyclocarbopalladation gives the compound **113** bearing a four membered ring that immediately collapse to compound **114** through a 5-*exo*-trig reaction. This palladium intermediate now continues to evaluate through a 3-*exo*-trig carbocyclization that produces the organopalladium derivative **115**. Follow a π -allyl palladium shift from the 4 membered ring to the 6 membered ring of **116** that eventually gives the final product **117** by a reductive β -hydride palladium elimination.

The cascade reaction was totally diastereoselective. This observation can be explained by the following proposition. The 5-*exo*-trig cyclocarbopalladation that occurred just after the 4-*exo*-dig cyclization, pre-organized the side chain ended by the double bond and controlled the four-centered C-Pd/alkene transition states **113A** and **113B**. In **113A** there is only few interactions between the pseudo-axial methyl group and the proton in the α -position of the oxygen of the dioxolane, therefore the formation **114A** is favored. In the transition states **113B** this interaction between the methyl group and the dioxolane is important and strongly disfavored the formation

of **114B**. The stereochemistry of the 3-*exo*-trig carbocyclization is now imposed by the structure of **114A** to give **115A** and eventually **117** (Scheme 18).

SCHEME 18 Diastereoselectivity of the cascade

Several polycyclic compounds of this type have been obtained. The reaction is general and usually the yields are good. Only when the tether contained sulfur or when a 7 membered ring was present in the starting product instead of a 6 membered ring the yield dropped considerably. On Figure 5 are represented the compounds **117a-j** synthesized by this approach.

FIGURE 5 New polycyclic scaffolds synthesized through a cascade cyclocarbopalladation

3 The 4-*exo*-dig cyclocarbopalladation to the synthesis of fenestradienes and cyclooctatrienes

3.1 First generation of fenestradienes and cyclooctatrienes

We have previously reported the straightforward preparation of 5-8-5 or 6-8-5 condensed polycycles that employs a 8π electrocyclization reaction starting from simple alkenyl bromides and common palladium catalysts (cf part **2.2**).¹³ Even if yields are modest, we were encouraged by these promising results and we investigated new methodologies further in hope of developing a new versatile and efficient route to this type of cyclooctatriene derivatives in higher yields.

In 2008, in order to synthesize stable 1,3,5-cyclooctatrienes **120**, we have designed trienynes of type **118** able to undergo 8π -electrocyclization after Ni-catalyzed semi-hydrogenation of the triple bond (Scheme 19).¹⁴ During our initial investigations, we were pleased to discover that a subsequent 6π electrocyclization reaction took place at room temperature after the 8π process providing in excellent yields a new class of fenestranes: the [4.6.4.6]fenestradienes **119**. We also shown that it was possible to access cyclooctatrienes **120**, with the same reaction conditions, only by slightly increasing the reaction temperature (70 °C) or from **119** simply by microwaves heating at 110 °C.

SCHEME 19 Ni-catalyzed semi-hydrogenation of the trienynes triple bond

The fenestranes are strained organic molecules containing a quaternary carbon shared by four rings. Due to their fascinating structure, several groups have examined these compounds extensively for more than 35 years, particularly from a theoretical standpoint. These studies focused mainly on exploring the deformation space between the tetrahedral and planar $C(C)_4$ structures, as well as their stability, strain and reactivity. In 2013, we have published an update on fenestranes in synthesis.¹⁵ The first part recalls the definition and nomenclature of fenestranes followed by an account on the natural products with [m.n.p.q]fenestrane scaffolds, as well as their achieved syntheses. The [m.n.p]fenestranes are also considered, as they are common both in nature and in synthesis. A particular focus is on the experimentally determined bond angles around the central carbon and the comparison to theoretically predicted values. Several new syntheses of fenestranes have recently been advanced.¹⁶

In order to explain the formation of **119** and **120**, we have proposed the following mechanism (Scheme 20). Partial reduction of the alkyne functionality in **118** generates tetraene **121**, which can undergo a 8π -conrotatory electrocyclization to form cyclooctatrienes **120** or **122** depending on the direction of the rotation. Unlike **120** obtained at 70 °C, intermediate **122** undergoes a 6π -disrotatory electrocyclization to provide **119** as the sole product isolated at room temperature. No traces of intermediates **121** or **122** were isolated during the process. The reaction was stereoselective and only one diastereomer of the [4.6.4.6]fenestradiene was obtained with the relative stereochemistry shown on Scheme 20 as determined by NOESY

experiments. It is interesting to note that the stereochemistry of compound **120** is the opposite on compound **119** and that we never observed the formation of fenestrane **123**.

SCHEME 20 Proposed mechanism

DFT calculations have been done in order to explain these results (Scheme 21). The energy differences of the first transition structures control the diastereoselectivities in the cascade reactions. The six-membered ring TS toward the stereoisomer **122** is 0.9 kcal mol^{-1} lower in energy than toward **120**. As a result, fenestrane **119** is the kinetic product and cyclooctatriene **120** the thermodynamically favored product, as cyclooctatriene **120** is the lowest-lying minima.

SCHEME 21 DFT calculation

The scope and limitations of this reaction were next investigated and some fenestranes **119a-e** were isolated with yields up to 93 % (Scheme 22).

SCHEME 22 Scope of the reaction

When compounds of type **119** were stored at -20°C under air for several hours, it rearranged slowly to give a new product that possesses all characteristic data corresponding to the [4.6.4.6]fenestrene **124** (Scheme 23). The transformation of **119** into **124** can be explained by a spontaneous oxidation of the highly strained [4.6.4.6]fenestradiene **119** with molecular oxygen. To confirm the oxidation sequence, **119** was submitted to one equivalent of *m*-CPBA in CH_2Cl_2 at 0°C , compounds **124** were isolated in yields up to 68 %. These experiments suggest that epoxide **123** is generated as a non-isolable intermediate, which leads to **124** by an S_N' attack of the alcohol on the double bond opening the epoxide **123** as shown on Scheme 23. The stereochemistry observed for this rearrangement is completely controlled by the shape of the rings and occurred from the less hindered face of the molecule.

SCHEME 23 [4.6.4.6]fenestrenes formation

Structural confirmation was obtained through X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative **125** (Scheme 24). This X-ray structure showed interesting features in the distortion of the central carbon atom that is dependent on the size and configuration of the fused rings. The [4.6.4.6]fenestrene **125** possess a central quaternary carbon that has a strong distortion. The two important orthogonal bond angles α and β are respectively widened to 118° and 124° .

SCHEME 24 X-ray crystal structure of the 3,5-dinitrobenzoate derivative **125**. The majority of H are omitted for clarity

SCHEME 25 Scope of the semi-hydrogenation of trienynes **126**

Unlike trienynes **118** bearing a six-membered ring, which gave fenestradienes **119** at room temperature, stable **cyclooctatrienes 127** were obtained when the seven-membered ring trienynes **126** were hydrogenated at room temperature (Scheme 25). The only products isolated in 63 to 88% yields were the stable 7-4-8 fused systems **127** and we never observed any

fenestradienes. Reactions were again completely stereoselective as only one diastereomer is observed with opposite torquoselectivity compared to the formation of fenestradienes **119**. DFT calculations have been done in order to explain the results (Scheme 26). The cyclooctatriene **127a** is the kinetically as well as the thermodynamically favored product, in line with experiment.

Cyclooctatrienes and fenestranes previously reported were tested for their pro-apoptotic activities on two human cancer cell lines (THP-1, and SW620) (Figure 6).¹⁷ Among the 20 new compounds tested, two compounds (**127b** and **127e**) presented specific activities on the colon carcinomas TRAIL-resistant metastatic cell SW 620 but a minor action on the monocytic leukemia THP1 cell line. Such differential pro-apoptotic activities, point out these two molecules as potent pharmacological tools to study TRAIL associated cellular mechanisms.

FIGURE 6 Pro-apoptotic activities considerations

3.2 4-*exo*-dig cyclocarbopalladation followed by a Sonogashira coupling

The previously described cascade to obtain cyclooctatrienes and fenestradienes uses trienynes derivatives (Scheme 27). This kind of compounds has been synthesized in three steps from alkenyl bromide **128**. The first step is the cascade 4-*exo*-dig cyclocarbopalladation/Stille cross-coupling reaching **129** which undergoes a silyl deprotection and a Sonogashira cross-coupling. In spite of the high yield reached for the synthesis of trienynes **118**, the toxicity of the stannane compounds used in this approach remains a major problem. Another issue brought by this type of cascade is the difficulty to completely eliminate the stannane residues from the isolated product. We were looking for a greener and faster route to form **118** with different functionalities, by means of a cascade 4-*exo*-dig cyclocarbopalladation/Sonogashira

cross-coupling in order to access directly to trienynes **118** from **128**, which would be even better in terms of step economy. These new approaches present major advantages: (i) the alkynes used are non-toxic; (ii) they are commercially available, that means an easier access to a large variety of alkynyl derivatives; (iii) it represents a rapid access to trienynes **118** and by the way fenestradienes **119** or cyclooctatrienes **120**.

SCHEME 27 New strategies to access fenestradienes **119** and cyclooctatrienes **120**

In order to assure a greater variety, the scope of a cascade 4-*exo*-dig cyclocarbopalladation/Sonogashira cross-coupling was explored. The alkyne used in the optimization study was trimethylsilyl acetylene, and the variation parameters were the palladium catalyst, the base and solvent (Table 2). The highest yield obtained with $\text{Pd}(\text{PPh}_3)_4$ as catalyst and Et_3N as solvent was 66 % (entry 3). With such system, the conversion could not be improved even when the temperature was increased to 130°C . Other catalysts were screened: $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ never allowed a complete conversion (entries 5 to 11) whereas $\text{Pd}(\text{OAc})_2$ did. Combined with triphenylphosphine, palladium acetate in diisopropylamine as a solvent and starting material **128**, 91 % of the desired product **129** was isolated (entry 13). These optimized conditions were used to extend the method through different examples.

Entry	[Pd]	Base/Solvent	Yield (%) 129 (128)
1	Pd(PPh ₃) ₄	<i>i</i> -Pr ₂ NH / PhH : 1/2	34 (56)
2	Pd(PPh ₃) ₄	Et ₃ N / PhH : 1/2	49 (27)
3	Pd(PPh ₃) ₄	Et ₃ N ^{a)}	66 (13)
4	Pd(PPh ₃) ₄	<i>i</i> -Pr ₂ NEt ^{a)}	13 (49)
5	Pd(PPh ₃) ₂ Cl ₂	<i>i</i> -Pr ₂ NH / PhH : 1/2	45 (36)
6	Pd(PPh ₃) ₂ Cl ₂	Et ₃ N / PhH : 1/2	42 (35)
7	Pd(PPh ₃) ₂ Cl ₂	<i>i</i> -Pr ₂ NH / THF : 1/2	32 (28)
8	Pd(PPh ₃) ₂ Cl ₂	<i>i</i> -Pr ₂ NEt / PhH : 1/2	13 (68)
9	Pd(PPh ₃) ₂ Cl ₂	<i>i</i> -Pr ₂ NH ^{a)}	71 (14)
10	Pd(PPh ₃) ₂ Cl ₂	Et ₃ N ^{a)}	20 (56)
11	Pd(PPh ₃) ₂ Cl ₂	Pyrrolidine ^{a)}	degradation
12	Pd(OAc) ₂ /PPh ₃ : 1/2	Et ₃ N ^{a)}	32 (58)
13	Pd(OAc) ₂ /PPh ₃ : 1/2	<i>i</i> -Pr ₂ NH ^{a)}	91

a) Solvent as base

The cascade reaction with aromatic and aliphatic alkynes afforded the corresponding dienynes **129a-m** in high yields (Scheme 28).

SCHEME 28 Scope of the cascade 4-*exo*-dig cyclocarbopalladation/Sonogashira cross-coupling

After demonstrating the scope offered by the starting material **128** with various alkyne derivatives, the 4-*exo*-dig/Sonogashira cascade was next examined on enynes, alkynyl imine and oxime (Scheme 29). Trienynes of type **130** were available with this process in good yields (64-83 %). This represents a faster access to fenestradienes. Only a one-pot operation is

required instead of three steps and the use of stannanes is no more necessary. Some new azatrienynes were also obtained from an alkynyl imine and oxime with good yields (64 - 70 %).

3.3 The second generation of fenestradienes and cyclooctatrienes

Thereafter, in 2013, following this work, we have reported a palladium-catalyzed one-step procedure that provides facile access to substituted fenestradienes **131** directly from alkenylbromides **128** (Scheme 30).¹⁸ This process was developed in order to overcome the problems of the use of sensitive nickel(0) catalyst, hydrogen and stannane, and the polymerization problems with some trienynes **118** if not subjected to appropriate care.

Our approach was inspired by Trost et coll. works concerning the selective synthesis of head-to-tail enynes in the presence of $\text{Pd}(\text{OAc})_2$ and tris(2,6-dimethoxyphenyl)phosphine (TDMPP).¹⁹ Gevorgyan et coll. have developed as well the head-to-head palladium-catalyzed dimerization of aryl acetylenes, which is catalyzed under analogous conditions.²⁰ The high regio- and stereoselectivities of these reactions have been explained by the strong steric influences of the ester group R^2 and specific agostic interactions between the ortho proton of the aromatic ring and the palladium, respectively (Scheme 31).

According to Trost and Gevorgyan works, we thought that the initial Sonogashira type reaction of the alkenylbromides **128** should easily generate **132** following our recent results. This trienyne **132** could be subjected to a regioselective alkynylation of a disubstituted triple bond producing the tetraene **133** which undergoes a 8π and a 6π electrocyclizations giving **131** (Scheme 32).

SCHEME 32 New strategies to access the second generation of fenestradienes **131**

Drawing on this analysis, we have described the preparation of new types of fenestradienes **131** based on a straightforward, fully controlled introduction of an enyne moiety on a non-activated disubstituted triple bond in a one-pot operation from the alkenylbromides **128** (Scheme 33).

SCHEME 33 Scope of cascade

All the highly substituted fenestradienes of this new family are reasonably stable at room temperature and do not oxidize and cyclize, as is the case for the first generation products obtained from the P-2 Ni reduction giving **fenestrenes 124**. They represent the first examples of fenestradienes possessing a conjugated trienyne and incorporate differentiated functionality for further elaboration.

The reaction is stereoselective and only one diastereomer of the [4.6.4.6]fenestradiene was obtained in each case as determined by NOESY experiments. The structures of the [4.6.4.6]fenestradienes **131d** were confirmed through NMR and MS studies. Structural confirmation was obtained through X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative **134** (Scheme 34). This X-ray structure shows interesting features in the significant distortion of the central quaternary carbon atom that is attributable to the size and configuration of the fused rings. The two important orthogonal bonds angles α and β are widened to 126° and 122° , respectively.

SCHEME 34 X-ray crystal analysis of the 3,5-dinitrobenzoate derivative **134**

It is interesting to note that when the reaction of compound **128** was conducted at 130°C in the presence of 3 equivalents of the enyne, palladium acetate, PPh_3 and copper iodide, the cyclooctatriene **135a** was cleanly obtained in very good yield (**98%**) without any trace of the corresponding fenestradiene (Scheme 35). As anticipated by our previous observations, the torquoselectivity of this reaction was opposite to the one observed in the formation of the fenestradiene. Undoubtedly, the cyclooctatriene **135** represents the thermodynamically more stable product in this reaction. In order to confirm this hypothesis, the fenestradiene **131a** was heated under microwave irradiation at 130°C for 30 min affording **135a** in 26 % yield. This low yield can be explained by the unstability of the fenestradiene **135a** at 130°C . This behavior is general for all other fenestradienes submitted to similar reaction conditions.

SCHEME 35 Thermodynamic/kinetic control of the reaction.

The reaction was applied on **128** with different enyne substrates (Scheme 36). The yields of this cascade reaction are generally very high if one consider the complexity of the process. For example with enyne $R^1 = \text{CH}_3$ and $R^2 = \text{H}$ a quantitative yield was obtained for **compound 135a**. In only one case ($R^1 = \text{CH}_3$, $R^2 = \text{CH}_2\text{OTBS}$), a disappointing yield of 16% (**135h**) was obtained while this one raised to 80 % (**135g**) when the free allylic alcohol was used.

SCHEME 36 Synthesis of 6,4,8 polycycles

The reactivity of the seven membered ring **136** were also satisfying and the corresponding tricyclic products 7-4-8 **137a-h** were synthesized with good yields between 32 and 89 % again considering the complexity of the process (scheme 37). The formation of the trienynes issued from a single addition of the enyne moieties were also observed in non-negligible amount rising as a sole product in 95 % yield when $R^1 = \text{Me}$ and $R^2 = \text{CH}_2\text{OTBS}$.

SCHEME 37 Synthesis of cyclooctatrienes **137**

3.4. Conclusion

During this work on fenestradienes and cyclooctatrienes, we have greatly improved the way of the preparation of these compounds. In the first generation, a four steps process was necessary to obtain fenestradienes **119** and cyclooctatrienes **120** with the use of hydrogen, tin under very delicate experimental conditions, particularly the fragility of the P2-Ni(0). Due to the high sensitivity of the trienynes intermediates, it was important to find a new way that exclude the formation of this trienyne. Therefore the second approach, for the synthesis of the second generation of fenestradiene **131** and cyclooctatrienes **135**, elegantly solved this problem. Only one step in a one-pot procedure was used to produce these unusual molecules that had no

precedent in the literature. More interesting was the better stability toward manipulation of the second generation versus the first one.

SCHEME 38 First and second generation of fenestradienes and cyclooctatrienes

4 The 4-**exo**-dig cyclocarbopalladation in the synthesis of cyclooctatetraenes

Our next challenge was to introduce four double bonds in eight-membered rings. The obtained structure is a cyclooctatetraene (COT). This motif is hardly represented in Nature, and Caulerpin, a bis-indole alkaloid isolated from algae of the genus *Caulerpa*, is the only representative.²¹ Nevertheless, COTs display important properties, especially as ligands in the field of metal-catalyzed processes²² or in the field of materials.²³ The development of metal mediated syntheses to access highly substituted COTs has been investigated and when we started our investigation in the field, the challenge was the synthesis of fully substituted, unsymmetrical COTs with structural complexity.

Therefore, in 2016, we reported an efficient palladium-catalyzed cascade reaction for the synthesis of the first examples of octasubstituted unsymmetrical COTs and in 2018, an extension of our process (Scheme 39).²⁴

SCHEME 39 Palladium-catalyzed cascade reaction for the synthesis of COTs

4.1 Stille cross coupling

In an initial experiment, classical conditions for palladium catalysis were applied simply using $\text{Pd}(\text{OAc})_2$, PPh_3 as the ligand and vinyltributylstannane as the simplest tin trapping reagent of the final organopalladium species (Scheme 40). The reaction was conducted under microwave irradiation at 100 °C in benzene. After full conversion of the starting compound **138a**, the COT

139aa was isolated in 44% yield. During this process, the side product **140a** was also formed. A 2/1 ratio (as determined by $^1\text{H-NMR}$) between **139aa** and **140a** was observed in the crude reaction mixture indicating a possible competitive pathway during the reaction.

The palladium acetate/triphenylphosphine system provides an excellent conversion but the 2/1 ratio between **139aa** and **140a** was unsatisfactory. Except for triphenylphosphine, the monodentate ligands triphenylphosphite, tricyclohexylphosphine, tri(*ortho*-tolyl)phosphine, and tri(2-furyl)phosphine led to low conversion and low selectivity. The use of a bidentate phosphine (such as dppe, dppe, dppp, XantPhos) increased the selectivity but a poor conversion was observed. Next we turned our attention to the bulkier electron-rich dialkylbiaryl phosphines (such as Buchwald type ligands : SPhos, MePhos, DavePhos). SPhos and DavePhos provided the best balance between conversion (up to 100% with DavePhos) and selectivity ([**139aa**/**140a** = 6/1] and [**139aa**/**140a** = 4/1]). With these systems in hand, the effect of different solvents on the conversion and ratio was tested (DMF, Dioxane, THF, MeCN). Eventually, the use of $\text{Pd}(\text{OAc})_2$ with DavePhos in acetonitrile under microwave irradiation proved to be the conditions of choice to obtain **139aa** (53%) in a 8/1 ratio relative to **140a**.

SCHEME 40 Palladium ligands screening

NMR data and other analytical analyses were consistent with the presence of the COT core in these products, and a structural confirmation was obtained by an X-ray crystallographic analysis (Figure 7). The COT framework adopts a boat-like geometry, which minimizes the steric congestion between the dimethyldioxolane, the dihydrofuran moiety and the trimethylsilyl group, and avoids the antiaromaticity that would result from planarity. The rigidity conferred by cyclobutene ring actually precludes the inversion of the COT. Moreover, this X-ray crystal analysis allowed us to determine the location of the four double bonds. It indicates a complete shift of all unsaturations of the starting material during the reaction. The lengths of the single bonds are around 1.47 Å, whereas the double bonds are around 1.34 Å (Figure 7). By comparison, in a non-substituted COT, the single bonds are longer (1.54 Å) while the double bonds are identical in length.

FIGURE 7 X-ray crystal analysis of the COT and its bonds length.

The scope and limitations of this reaction were next investigated. The starting compounds of type **138** were prepared and tested under the optimized reaction conditions with various vinyl, allyl, alkenyl and heteroaromatic stannanes (R^3SnBu_3 , $Pd(OAc)_2$ (5 mol%), DavePhos (10 mol%), MeCN, MW, 100 °C). The side product **140** were actually found in almost all reaction mixtures, yet they proved separable and their yields did not exceed 15%. Isolated yields for the desired compounds **139** range from 18 to 53% (Scheme 41), which can be considered as good considering the five steps reaction, forming four new C-C bonds.

SCHEME 41 Scope of the reaction

Nevertheless, the toxicity of the stannane compounds and their difficulty in purifying residual tin from the products remain a major concern. We were looking for a greener route to form **139** with alternative functionalities by means of a cascade ending with a different type of cross-coupling reaction.

4.2 Suzuki-Miyaura cross coupling

In addition to the toxicity of stannane reagents, the introduction of aryl group on the structure was not possible with Stille cross-coupling conditions; therefore a new sequence using Suzuki-Miyaura cross-coupling reaction conditions was explored. Different parameters were again tested: the palladium catalyst, the ligand, the base and the solvent mixture (Table 3). The base

first has been varied since it plays an important role in the mechanism of a Suzuki-Miyaura cross-coupling.^[5] In the presence of Na₂CO₃ or K₃PO₄, the reaction was not complete even after 2 h. With Cs₂CO₃, the reaction was complete but the yield was modest, around 30% (entry 1). NaOH leads to the best yield (53 %, entry 2) and we observed that adding more water was not suitable for the reaction (27 %, entry 3). Then the influence of the palladium source was evaluated, and Pd(PPh₃)₄ was used without better result (46 %, entry 4). The use of DavePhos, as ligand dramatically decreased the yield of the reaction (14 %, entry 5). THF was replaced by 1,4-dioxane or MeTHF, and did not show a better result (44 and 34 %, entries 6-7). Eventually, the use of Pd(OAc)₂/PPh₃ with NaOH in a mixture of THF and water under microwave irradiation proved to be the conditions of choice to obtain **139dj** in good yield.

TABLE 3 Suzuki-Miyaura reaction conditions

Entry	[Pd]/Ligand	Base	Solvent	Yield 139dj
1	Pd(OAc) ₂ /PPh ₃	Cs ₂ CO ₃	THF/H ₂ O	35 %
2	Pd(OAc) ₂ /PPh ₃	NaOH	THF/H ₂ O	53 %
3	Pd(OAc) ₂ /PPh ₃	NaOH	THF/H ₂ O ^{a)}	27 %
4	Pd(PPh ₃) ₄	NaOH	THF/H ₂ O	46 %
5	Pd(OAc) ₂ /DavePhos	NaOH	THF/H ₂ O	14 %
6	Pd(OAc) ₂ /PPh ₃	NaOH	dioxane/ H ₂ O	44 %
7	Pd(OAc) ₂ /PPh ₃	NaOH	MeTHF/ H ₂ O	34 %

Reaction conditions: [Pd] (5 mol%), Ligand (10 mol%), base (1.5 equiv.) and 4-methoxyphenylboronic acid (1.3 equiv), solvent (0.1 M)/H₂O, MW 100°C. ^{a)} Solvent/H₂O: 75/25

The scope and limitations of these optimized conditions were next investigated. The starting compound **138d** was used with various aryl boronic acids. The isolated yields for compounds **139dj-dn** range from 15 to 53% (Scheme 42). The presence of a donating group in *meta*-position of the aryl boronic acid hindered the reaction. This was also the case with an electron withdrawing group in the para position. The side product **140d** were actually found in all reaction mixtures, yet they proved separable and their yields ranged between 15% to 43 %.

SCHEME 42 Scope of the reaction

4.3 Sonogashira cross coupling

During our scope explorations, Stille cross-coupling reaction afforded COTs with low yields when alkynyl stannane were used. That why we investigated a new sequence and we decided to end the cascade reaction with a Sonogashira cross-coupling. This study was carried out with alkenyl bromide **138d**. In a preliminary experiment, classical conditions for the palladium catalysis were applied using Pd(OAc)₂, PPh₃, CuI and trimethylsilyl acetylene as the trapping reagent of the final organopalladium species (Table 4). The reaction was conducted under microwave irradiation at 100 °C in diisopropylamine. After full conversion of the starting compound **138d**, COT **139do** was isolated in 58% yield. During this process, two side products were also formed: the same type of aromatic compound **140d** and one another COT **139d**. We then decided to optimize the reaction conditions to increase the selectivity towards **139do**. The reaction parameters examined were the palladium catalyst, the ligand, the copper and the base. Side products **140d** and **139d** were observed in almost all reaction mixtures, yet they proved separable and their yield did not exceed 10-15% for both compounds. Compare to the initial reaction conditions (entry 1), the use of DavePhos, the best ligand used during the previous study, did not give good results, only 32% of COT **139do** was isolated (entry 2). PdCl₂(PPh₃)₂ (entry 3) and Pd(PPh₃)₄ (entry 4) gave almost the same result. The reaction was not complete after 30 min with the use of diisopropylethylamine while it was the case with diisopropylamine (entry 5). With triethylamine, the reaction worked as well as in diisopropylamine (58 %, entry 6). The copper source was also taken into account, and the use of CuCN showed identical result

compared to CuI (entry 7). The presence of a copper source was also essential to enhance the rate of the reaction (entry 1 and 8). Eventually, the use of Pd(OAc)₂/PPh₃ with CuI in diisopropylamine or triethylamine under microwave irradiation proved to be the best conditions to obtain **139do** in good yield.

TABLE 4 Screening of the catalytic systems

Entry	[Pd]/Ligand	[Cu]	Solvent	Yield 139do
1	Pd(OAc) ₂ /PPh ₃	CuI	iPr ₂ NH	58 %
2	Pd(OAc) ₂ /DavePhos	CuI	iPr ₂ NH	32 %
3	Pd(Cl) ₂ (PPh ₃) ₂	CuI	iPr ₂ NH	53 %
4	Pd(PPh ₃) ₄	CuI	iPr ₂ NH	57 %
5	Pd(OAc) ₂ /PPh ₃	CuI	iPr ₂ NEt	nd ^a
6	Pd(OAc) ₂ /PPh ₃	CuI	Et ₃ N	58 %
7	Pd(OAc) ₂ /PPh ₃	CuCN	iPr ₂ NH	53 %
8	Pd(OAc) ₂ /PPh ₃	-	iPr ₂ NH	37 % ^b

a) not determined, mostly starting material **138d**. b) 24 % of **138d** is recovered.

The scope and limitations of this reaction were next investigated. The starting compound **138d** was tested under the optimized reaction conditions with various vinyl, silyl, aryl, alkyl acetylene. COTs was isolated in yields ranging from 50 to 71% and compared to Stille or Suzuki cross-coupling, undoubtedly Sonogashira cross coupling gave our best yields (Scheme 43).

SCHEME 43

Scope of the reaction

4.4 Mechanisms of the COTs and side product formation

Three type of products **139**, **140** and **141** were observed during this process depending on the reaction conditions. We propose the following mechanism to account for the experimental results (Scheme 44).

SCHEME 44

Proposed mechanism

After oxidative addition of the active palladium species into the C-Br bond of **138**, a 4-*exo*-dig and a 5-*exo*-dig cyclocarbopalladations give intermediate **142**. A 8 π -electrocyclization and a 1,3 π -allyl palladium shift takes place to provide **143** followed by a cross coupling reaction leading to the final COT **139**.

Complex **142** is supposed to be a common intermediate towards **139** and the side product **140**. To go to **140**, it undergoes a 6 π -electrocyclization to give intermediate **144**. This complex

finally undergoes a β -carbon elimination giving compound **140** and the alkynyl palladium species **145**.

A transmetalation between the two-organopalladium species **143** and **145** gives intermediate **146**, that after reductive elimination produces the new COT **141**. The presence of the COT **141** also supports the proposed mechanism and confirms the formation of **140** occurring through a unique process of β -carbon elimination.

It is interesting to note that when Stille or Suzuki cross-coupling reaction conditions are used, compound **141** was not observed while it was not the case with the Sonogashira cross-coupling. That means that the transmetalation of a stannane or a boronic acid is faster than a transmetalation of an alkynyl palladium specie.

4.5 Conclusion

In conclusion, we have proposed three routes for the formation of fully substituted cyclooctatetraenes: cyclocarbopalladations followed by an 8π -electrocyclization and ended either by Stille, Sonogashira or Suzuki-Miaura cross-couplings. These approaches present the advantage of extending the structural diversity of fully substituted unsymmetrical COT. The reaction proceeds in a one-pot operation, where three new rings and four bonds are formed.

General Conclusion

We have shown that the 4-*exo*-dig cyclocarbopalladation reaction is a fantastic tools for producing complexity in short and very efficient ways from very simple starting material. The preparations of many unusual polycyclic molecules described above are all the consequences of several impressive cascade reactions trigger by this unique 4-*exo*-dig reaction. Four membered ring, strained aromatic derivatives, taxane scaffolds, cyclooctatrienes, cyclooctatetraenes, fenestradienes and fenestrenes were all obtained, many in very high yields and with always high stereoselectivities by this « magic reaction ». We have been able to understand the mechanistic aspect of all the routes which have been used to afford these products. We probably didn't explore all the power of the 4-*exo*-dig reaction and a lot of efforts are still necessary to discover new application of this tool.

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