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New Palladium-Catalyzed Cascades: 4-*exo*-dig Cyclocarbopalladation Reaction Followed by Suzuki–Miyaura or Sonogashira Cross-Coupling

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Abstract: Herein we describe new accesses to dienynes and trienynes using new cascade reactions: 4-*exo*-dig cyclocarbopalladation followed by a Suzuki–Miyaura or Sonogashira cross-coupling.

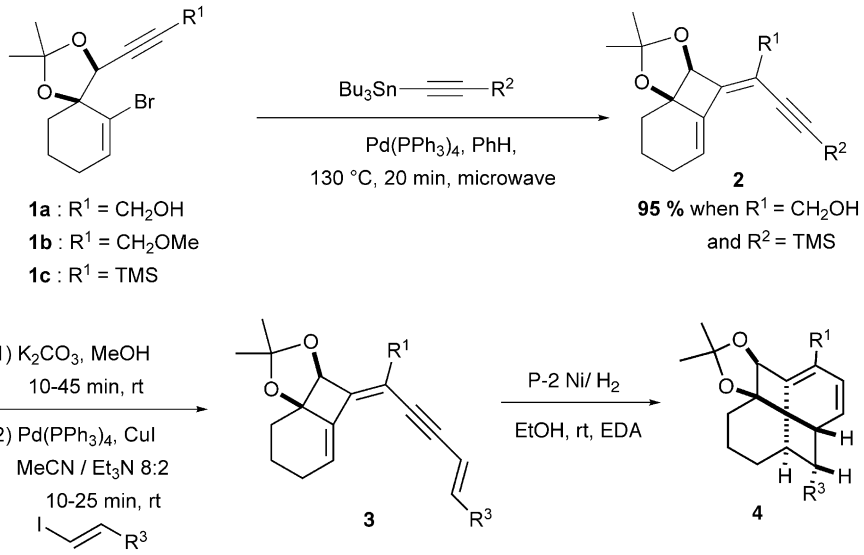
Keywords: cascade reactions; cyclocarbopalladation; Sonogashira reaction; step economy; Suzuki–Miyaura reaction

The preparation of complex molecules starting from simple compounds in a minimum number of steps is a challenging goal in organic synthesis.[1] Many efforts have been focused on the design and discovery of reactions that provide fundamentally new ways of accessing ring systems, commonly encountered in natural and designed polycyclic targets. The synthesis of highly functionalized polycyclic compounds has been greatly advanced by the development of cascade reactions catalyzed by transition metals.[2] By triggering such cascade events with well-defined functionalities in the structure of the starting material, they have become a major tool for organic chemists to form multiple carbon-carbon bonds in a one-pot operation. Working in this direction, one of the major research goals in our group is the design and development of new palladium-catalyzed cascades. We previously described the 4-*exo*-dig cascade cyclocarbopalladation followed by a Stille cross-coupling giving dienyne derivatives of type **2** starting from the 6-membered ring **1** (Scheme 1).[3] These kind of compounds are, for example, useful intermediates in the synthesis of fenestradienes **4** and cyclooctatrienes, new compounds that were recently described in previous articles.[4] Fenestradienes are of great interest due to their structural features and their potential bioactivity.[5,6]

In spite of the high yield reached for the synthesis of dienynes **2**, the toxicity of the stannane compounds used in this approach remains a major problem. Another issue brought up by this type of cascade is the difficulty to completely eliminate the stannane residues from the isolated product.

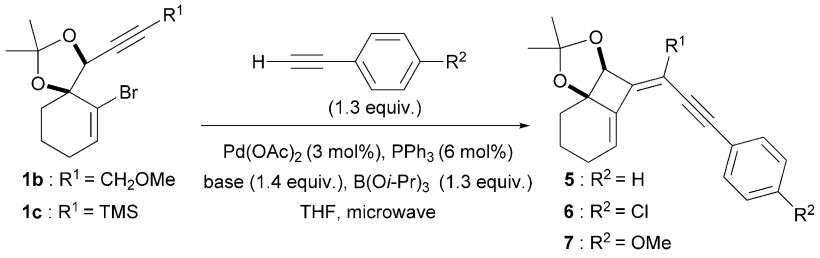
We were looking for a greener and faster route to form **2** with different functionalities, by means of a cascade 4-*exo*-dig cyclocarbopalladation followed by another type of cross-coupling reaction. Moreover, by using enynes in this cascade, it could also be possible to directly access trienynes **3** from **1**, which would be even better in terms of step economy. In this communication we report our results using either a Suzuki–Miyaura or a Sonogashira cross-coupling. These new approaches present major advantages: (i) the boronic derivatives and alkynes used are not 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 **3**.

Our first objective was to determine the optimum conditions to carry out the sequence 4-*exo*-dig cyclocarbopalladation/Suzuki–Miyaura cross-coupling.[7] Soderquist et al., Fürstner et al. and Colobert et al. described the addition of a borane to alkynyllithium reagents which gives access to stable borate complexes to undergo effective Suzuki cross-coupling.[8] This pathway was thus considered. Palladium acetate with triphenylphosphine in THF appeared to be the best conditions. We focused on the most effective base to deprotonate the alkyne under microwave conditions (Table 1). The starting material was also reviewed: substrate **1a** appeared to be unreactive in this cascade reaction, whereas **1b** and **1c** led to the desired



Scheme 1. Synthesis of fenestradiene **4**.

Table 1. 4-*exo*-dig/Suzuki cascade with aromatic alkynes.

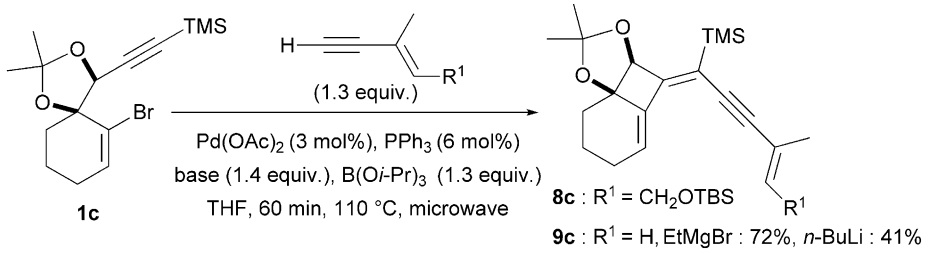


Entry	**1**	R^2	Base/microwave conditions	**5**, **6** or **7**	Yield [%] **5**, **6** or **7** (**1**)
1	**1b**	H	EtMgBr/15 min/110 °C	**5b**	90
2	**1b**	H	*n*-BuLi/15 min/110 °C	**5b**	4 (13)
3	**1c**	H	EtMgBr/15 min/110 °C	**5c**	77
4	**1b**	Cl	EtMgBr/15 min/110 °C	**6b**	44 (29)
5	**1b**	Cl	*n*-BuLi/15 min/110 °C	**6b**	25
6	**1c**	Cl	EtMgBr/15 min/130 °C	**6c**	52 (39)
7	**1c**	Cl	EtMgBr/60 min/130 °C	**6c**	42 (40)
8	**1b**	MeO	EtMgBr/60 min/110 °C	**7b**	28 (54)
9	**1b**	MeO	*n*-BuLi/15 min/110 °C	**7b**	26
10	**1c**	MeO	EtMgBr/60 min/130 °C	**7c**	69 (28)
11	**1c**	MeO	*n*-BuLi/60 min/130 °C	**7c**	29

products. Usually, the Grignard reagent (ethylmagnesium bromide) appears to be a more efficient base than *n*-butyllithium (entries 1 *vs.* 2, 4 *vs.* 5, and 10 *vs.* 11). Moreover, with the Grignard reagent, the reaction proceeds cleanly, whereas several by-products are formed using *n*-butyllithium. With phenylacetylene, the silylated starting material **1c** was a bit less effective than the methoxy-protected substrate **1b** (entries 1 and 3). Indeed, 90% yields of the desired product were obtained with the Grignard reagent as a base, after 15 min under microwave irradiation at 110 °C (entry 1). With *p*-chlorophenylacetylene and *p*-methoxyphenylacetylene, some starting material **1b** or **1c** still remains in the reaction mixture and longer reaction times or higher temperatures result only in degradation (entries 4–11).

Therefore, the best experimental conditions were as follows: palladium acetate with triphenylphosphine in THF, in the presence of ethylmagnesium bromide and triisopropoxyborane.

Then, these reaction conditions were tested with enynes in order to obtain trienynes in one step instead of three (Scheme 2).



Scheme 2. Synthesis of trienyne **9**.

It appears from this study that up to 72% of the trienyne **9c** is formed from **1c**. As previously noted, the use of *n*-butyllithium is not as efficient as the Grignard reagent. It seems difficult to extend this method to other enynes, **8c** was never observed with the usual conditions (EtMgBr or *n*-BuLi). With **1b**, the desired product **8b** or **9b** was not obtained, whatever the conditions.

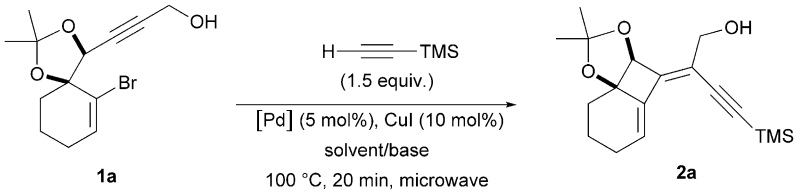
In order to assure a greater variety, the scope of a 4-*exo*-dig cascade cyclocarbopalladation/Sonogashira cross-coupling was explored.[9] The alkyne used in the optimization study was trimethylsilylacetylene, and the variation parameters were the palladium catalyst, the base and solvent (Table 2).

The use of **1b**, which requires one more step, was not necessary since **1a** was effective enough to be used as model. The highest yield obtained with $Pd(PPh_3)_4$ as catalyst and Et_3N as solvent was 66% (entry 3). With such a system, the conversion could not be improved even when the temperature was increased to 130 °C. Other catalysts were screened: $Pd(PPh_3)_2Cl_2$ never allowed a complete conversion (entries 5 to 11) whereas $Pd(OAc)_2$ did. With the combination of triphenylphosphine, palladium acetate in diisopropylamine as a solvent and starting material **1a**, 91% of the desired product were isolated (entry 13). These optimized conditions were used to extend the method through different examples (Table 3). The cascade reaction with aromatic and aliphatic alkynes afforded the corresponding dienynes **10**–**22** in high yields.

One hour is required for the total reaction to give **10** (entry 1), since 20% of the starting material **1a** were isolated after only 20 min. For the synthesis of **15**, **16** and **20**, we observed the same reactivity (entries 6, 7 and 11). However, the reaction seems to be faster when the alcohol is protected and the purifications are easier (entries 2 to 5). It is also possible to use propargylamine with good yields (entries 6 and 7).

After demonstrating the scope offered by the starting material with a free propargylic alcohol **1a**, the re-

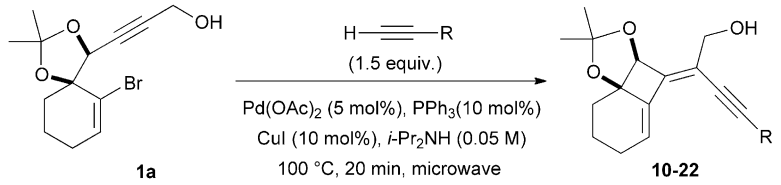
Table 2. 4-*exo*-dig/Sonogashira cascade with trimethylsilylacetylene.



Entry	[Pd]	Base/Solvent	Yield [%] **2a** (**1a**)
1	$Pd(PPh_3)_4$	$(i\text{-Pr})_2NH$/PhH: 1/2	34 (56)
2	$Pd(PPh_3)_4$	Et_3N/PhH: 1/2	49 (27)
3	$Pd(PPh_3)_4$	Et_3N[a]	66 (13)
4	$Pd(PPh_3)_4$	$(i\text{-Pr})_2NEt$[a]	13 (49)
5	$Pd(PPh_3)_2Cl_2$	$(i\text{-Pr})_2NH$/PhH: 1/2	45 (36)
6	$Pd(PPh_3)_2Cl_2$	Et_3N/PhH: 1/2	42 (35)
7	$Pd(PPh_3)_2Cl_2$	$(i\text{-Pr})_2NH$/THF: 1/2	32 (28)
8	$Pd(PPh_3)_2Cl_2$	$(i\text{-Pr})_2NH$/PhH: 1/2	13 (68)
9	$Pd(PPh_3)_2Cl_2$	$(i\text{-Pr})_2NH$[a]	71 (14)
10	$Pd(PPh_3)_2Cl_2$	Et_3N[a]	20 (56)
11	$Pd(PPh_3)_2Cl_2$	pyrrolidine[a]	degradation
12	$Pd(OAc)_2/PPh_3$: 1/2	Et_3N[a]	32 (58)
13	$Pd(OAc)_2/PPh_3$: 1/2	$(i\text{-Pr})_2NH$[a]	91

[a] The base was used as solvent.

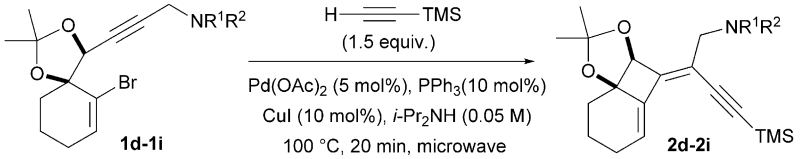
Table 3. 4-*exo*-dig/Sonogashira cascade with different alkynes.

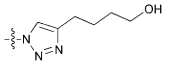
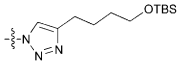


Entry	R	Product: Yield [%]
1	CH_2OH	**10**: 74[a]
2	CH_2OMe	**11**: 70
3	$CH_2OTBDPS$	**12**: 80
4	CH_2CH_2OTBS	**13**: 91
5	$CH_2CH_2CH_2OTBS$	**14**: 94
6	CH_2NHBoc	**15**: 93[a]
7	CH_2NEt_2	**16**: 69[a]
8	CH_2Cy	**17**: 85
9	CH_2CH_2Ph	**18**: 81
10	Ph	**19**: 84
11	Cy	**20**: 68[a]
12	$CH(OEt)_2$	**21**: 84[b]
13	*p*-$MeOC_6H_4$	**22**: 88

[a] 60 min at 100 °C.
[b] The desired product can not be separated from the starting material. The yield is calculated from the ^{1}H NMR spectra, 7% of **1a** were recovered.

Table 4. 4-*exo*-dig/Sonogashira cascade starting from a propargylic amine.



Entry	NR^1R^2	Product: Yield [%]
1	NH_2	**2d**: 55
2	NHBn	**2e**: 92
3	NHPh	**2f**: 83
4	NHBoc	**2g**: 94[a]
5		**2h**: 81
6		**2i**: 62

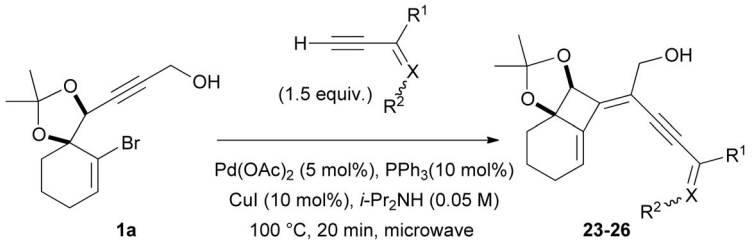
[a] 30 min at 110 °C.

activity of a starting material possessing a propargylic amine **1d–1i** was next examined (Table 4). The protected amines on the substrate afforded higher yields than the primary amine (entries 1 to 4). The reaction is also effective with triazoles in good yields (entries 5 and 6).

Finally the 4-*exo*-dig/Sonogashira cascade was studied on enynes, an alkynylimine and oxime (Table 5). Trienynes **23**–**26** 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 longer necessary. Some new azatrienynes were also obtained from an alkynylimine and oxime with good yields (64 and 70%, entries 3 and 4).

We have demonstrated the scope offered by two new cascades 4-*exo*-dig cyclocarbopalladation followed by a cross-coupling. Concerning the Suzuki–Miyaura reaction, it is necessary to form the alkynylborate complex *in situ* for the conversion to proceed. For several alkynes, this cascade appears to be very effective. For the cases in which this cascade reaction

Table 5. 4-*exo*-dig/Sonogashira cascade with enynes.



Entry	R^1	R^2	X	Yield [%]
1	CH_3	(*Z*)-CH_2OTBS	CH	23: 79
2	H	(*E*)-C(*i*-Bu)$_2$(OH)	CH	24: 83[a]
3	CH_3	(*E*)-OH	N	25: 64[b]
4	*p*-$MeOCOC_6H_4$	(*E*)-*t*-Bu	N	26: 70[c]

[a] 14% of **1a** was recovered.
[b] 40 min at 130 °C. 10% of **1a** were recovered.
[c] The desired product cannot be separated from the starting material. The yield is calculated from the ^{1}H NMR spectra, 28% of **1a** were recovered.

is not satisfactory, a terminal Sonogashira cross-coupling instead of Suzuki–Miyaura cross-coupling has been developped. Optimized conditions appear to be applicable to many other alkynes: propargylic alcohols, ethers, and amines, as well as aliphatic and aromatic alkynes. The same starting material readily undergoes the cascade reaction as well with enynes, alkynylimines and oximes. Studies concerning the transformations of these azatrienynes to azafenestradienes are still in progress. Finally, when the hydroxy group in the starting material is replaced with a nitrogen, the cascade proceeds also in good yields affording the desired products.

The tricyclic product including a cyclobutane is obtained in high yields and in a one-pot operation. This method is also quite versatile from the point of view of the introduction of new functionalities, since the triple bond, for example, can then be selectively manipulated. Further studies on this point and related aspects of this chemistry are in progress.

Experimental Section

General Procedure for the Cyclocarbopalladtion 4-*exo*-dig/Sonogashira Cascade

In a 2–5 mL microwave vial were added the compound **1a** or **1d–1i** (1 equiv.), $Pd(OAc)_2$ (0.05 equiv.), copper iodide (0.1 equiv.), and PPh_3 (0.1 equiv.). The vial was sealed with a teflon cap and the reaction mixture was then dissolved in distilled diisopropylamine (3 mL). The reaction mixture was placed under argon, frozen in liquid nitrogen and put under vacuum. The O_2 liberation proceeds when the temperature rises back to ambient temperature. The operation was repeated two times. Then, the terminal alkyne (1.5 equiv.) was added to the reaction mixture. The vial was irradiated in the microwave. The reaction mixture was then filtered through celite to eliminate the metal traces and then concentrated under reduced pressure. The crude product was purified by flash column chromatography.

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References

[1] a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; b) A. de Meijere, F. E. Meyer, *Angew. Chem.* **2004**, *116*, 2886; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2379; c) R. Grigg, J. P. Major, F. M. Martin, M. Whittake, *Tetrahedron Lett.* **1990**, *31*, 7709.

[2] a) L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875; b) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; d) H.-W. Frühauf, *Chem. Rev.* **1997**, *97*, 523; e) M. A. J. Duncton, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1235; f) L. Yet, *Chem. Rev.* **2000**, *100*, 2963; g) K. Sonogashira, in: *Metal-Catalyzed Cross Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, Germany, **1998**, Chapter 5, p. 203; h) T. Vlaar, E. Ruijter, R. V. A. Orru, *Adv. Synth. Catal.* **2011**, *353*, 809.

[3] a) C. Bour, G. Blond, B. Salem, J. Suffert, *Tetrahedron* **2006**, *62*, 10567; b) B. Salem, J. Suffert, *Angew. Chem.* **2004**, *116*, 2886; *Angew. Chem. Int. Ed.* **2004**, *43*, 2826; c) J. Suffert, B. Salem, P. Klotz, *J. Am. Chem. Soc.* **2001**, *123*, 12107; d) B. Salem, P. Klotz, J. Suffert, *Org. Lett.*

2003, ***5***, 845; e) B. Salem, P. Klotz, J. Suffert, *Synthesis* **2004**, 298.

[4] a) C. Hulot, S. Amiri, G. Blond, P. Schreiner, J. Suffert, *J. Am. Chem. Soc.* **2009**, ***131***, 13387; b) C. Hulot, G. Blond, J. Suffert, *J. Am. Chem. Soc.* **2008**, *130*, 5046; c) C. Hulot, G. Blond, J. Suffert, *Chem. Eng. News* **2008**, *86* (13), 26.

[5] C. Hulot, J. Peluso, G. Blond, C. D. Muller, J. Suffert, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6836.

[6] a) R. Keese, *Chem. Rev.* **2006**, *106*, 4787; b) B. R. Venepalli, W. C. Agosta, *Chem. Rev.* **1987**, *87*, 399; c) G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671; d) T. Gaich, J. Mulzer, *Org. Lett.* **2010**, *12*, 272.

[7] A. Suzuki, in: *Metal-Catalyzed Cross Coupling Reactions*, (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, Germany, **1998**; Chapter 2, p. 49 and references cited therein.

[8] a) J. A. Soderquist, K. Mato, A. Rane, J. Ramos, *Tetrahedron Lett.* **1995**, *36*, 2401; b) A. Fürstner, G. Seidel, *Tetrahedron* **1995**, *51*, 11165; c) A.-S. Castanet, F. Colobert, T. Schlama, *Org. Lett.* **2000**, *2*, 3559; d) F. Colobert, A.-S. Castanet, O. Abillard, *Eur. J. Org. Chem.* **2005**, 3334.

[9] a) K. Sonogashira, Y. Tohda, N. Hagira, *Tetrahedron Lett.* **1975**, 4467; b) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874; c) S. Thorand, N. Krause, *J. Org. Chem.* **1998**, *63*, 855.

