C. R. Chimie 20 (2017) 665–681

Contents lists available at ScienceDirect

Comptes Rendus Chimie

www.sciencedirect.com

Preliminary communication/Communication

Synthesis of original polycycles containing five-, six- and seven-membered rings through cyclocarbopalladations/C–H activation cascade reactions

Synthèse de polycycles originaux contenant des cycles à 5, 6 et 7 atomes par réactions en cascade de cyclocarbopalladations/activation CH

Jessie Joussot, Angèle Schoenfelder, Jean Suffert[**], Gaëlle Blond[*]

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

A R T I C L E I N F O

Article history:
Received 28 October 2016
Accepted 23 January 2017
Available online 16 March 2017

Keywords:
Cascade reactions
Cyclocarbopalladations
C–H activation
Palladium
Seven-membered ring
Five-membered ring
Naphthalene derivative

A B S T R A C T

Different types of starting materials have been designed and their ability to undergo cascade reactions has been investigated. New polycycles containing five-, six-, and seven-membered rings are described via original cascade reactions. The process works via a twofold cyclocarbopalladation followed by C(sp^2)-H or C(sp^3)-H activation. During these cascades, the palladium is moving several times along the carbon structure forming three new C–C bonds and three new cycles.

R É S U M É

Mots clés:
Réactions en cascade
Cyclocarbopalladations
Activation CH
Palladium
cycle à 7 atomes
cycle à 5 atomes
dérivé naphthalène

Différents types de substrats de départ ont été conçus et leur capacité à subir des réactions en cascade a été étudiée. De nouveaux polycyles contenant des cycles à 5, 6 ou 7 atomes ont été synthétisés par des réactions en cascade originales. Le processus fonctionne via une double cyclocarbopalladation suivie d'une activation C(sp^2)-H ou C(sp^3)-H. Au cours de cette cascade, le palladium se déplace plusieurs fois sur la structure en formant trois nouvelles liaisons C–C et trois nouveaux cycles.

1. Introduction

The development of new cyclization reactions has been greatly advanced by the use metal-catalyzed processes called cascade or domino reaction [1]. These processes

---

[*] Corresponding author.

[**] Corresponding author.

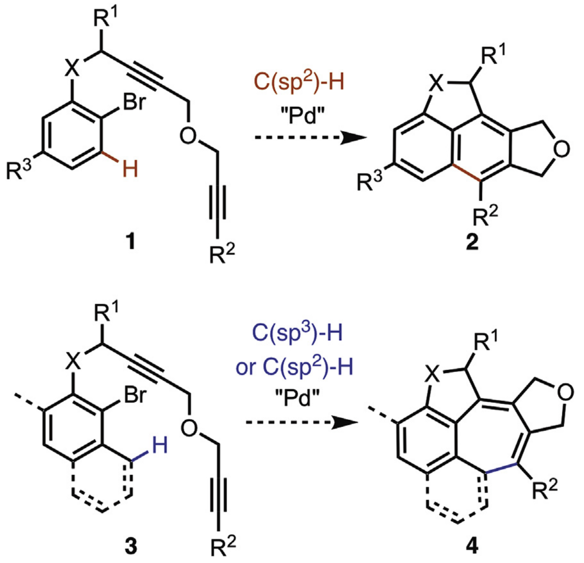
E-mail addresses: jean.suffert@unistra.fr (J. Suffert), gaelle.blond@unistra.fr (G. Blond).

http://dx.doi.org/10.1016/j.crci.2017.01.005

allow a succession of events that are triggered by well-placed functionalities in the structure of the starting material. In this direction, a useful transformation that has been extensively used is the intramolecular carbopalladation of alkynes [2] ended, for example, by a cross-coupling reaction such as Stille [3], Heck–Mizoroki [4], Suzuki–Miyaura [5], or Sonogashira reaction [5], a pericyclic reaction such as electrocyclization [6], or a CO insertion [7]. C–H activation has been also used after cyclocarbopalladations to end cascade reactions, C(sp^2)-H activation was the most common one [8], C(sp^3)-H activation is lightly described in the literature [9]. In this context, to develop novel cyclocarbopalladation/C–H activation cascade reactions, we have designed starting materials of types **1** and **3** (Scheme 1). Depending on the starting material, C(sp^2)-H or C(sp^3)-H activation should finish the cascade process leading to naphthalene derivatives (type **2**) and to original polycycles containing seven-membered rings (type **4**).

2. Carbopalladations/C(sp^2)-H activation cascade reactions

We started our investigations with the diyne **1a** to yield naphthalene derivatives. First, we decided to start our investigations with conditions that are classically used in our laboratory for such type of cascades, $Pd(PPh_3)_4/K_2CO_3$/PhH, at 100 °C under microwave irradiations (Table 1, entry 1). We were pleased to observe the formation of compound **5**, which represents the desilylated derivative of the desired product, in 33% yield. The protodesilylation is probably because of the proton source coming from the in situ formation of protonated base during the cascade process [10]. It is important to note that even if the desilylated compound **5** is obtained, the silyl group on the starting material is necessary to avoid degradation of the reaction mixture [11]. With an organic base, such as Et_3N and $^iPr_2NH$, the reaction was complete and a separable mixture of **2a** and **5** was obtained (entries 2 and 3). Yields were around 25% and 65% for **2a** and **5**, respectively. By decreasing the amount of base (1 equiv instead of 5), the yield of **5** was improved (80%, entry 4). Finally, the use of less amount of catalyst (5 mol % instead of 20 mol %), gave similar result in terms of yield and ratio between **2a** and **5** (entry 5). When the palladium diacetate/triphenylphosphine system was used, the quantity of compound **5** formed decreased and a large quantity of the starting material was recovered (entry 6). Eventually, the use of $Pd(PPh_3)_4$ (5 mol %) and diisopropylamine in benzene under microwave irradiation proved to be the conditions of choice to obtain **5** in good yield (72%, entry 5, Table 1).



Scheme 1. Synthesis of polycycles containing five- and seven-membered rings.

Table 1
Optimization of the cascade reaction.

Entry	Catalyst (mol %)	Base (equiv)	Time	**1a** (%)	**2a** (%)	**5** (%)
1	$Pd(PPh_3)_4$ (20)	K_2CO_3 (5)	2 h	34	–	33
2	$Pd(PPh_3)_4$ (20)	Et_3N (5)	30 min	–	24	65
3	$Pd(PPh_3)_4$ (20)	$^iPr_2NH$ (5)	30 min	–	25	64
4	$Pd(PPh_3)_4$ (20)	$^iPr_2NH$ (1)	30 min	–	15	80
5	$Pd(PPh_3)_4$ (5)	$^iPr_2NH$ (1)	30 min	–	19	72
6	$Pd(OAc)_2$ (5)/ PPh_3 (10)	$^iPr_2NH$ (1)	30 min	66	8	20

Concerning the formation of compound **5**, we propose the following mechanism (Scheme 2): after oxidative addition of the active palladium species into the C–Br bond of **1a**, a 5-*exo*-dig cyclocarbopalladation gives rise to intermediate **7** which undergoes a 5-*exo*-dig cyclocarbopalladation giving **8**. A C(sp^2)-H activation takes place to provide **9** followed by a reductive elimination leading to silylated compound **2a**. Finally, compound **5** was obtained by protodesilylation of **2a**.

A structural confirmation was obtained by an X-ray crystallographic analysis of compounds **2a** and **5** (Fig. 1).

The scope and limitations of this reaction were next investigated. As summarized in Scheme 3, substrates **1a**–**f** were treated under the optimized conditions to provide the naphthalene derivatives **2a**–**f** and **5** in 6–72% yields. With starting material **1b**, bearing a triethylsilyl group, the optimized conditions also induce a desilylation of the final product leading to a separable mixture of **2b** and **5** in, respectively, 12% and 54% yield. The use of propargyl alcohol derivative **1c** gave the naphthalene derivative **2c** in only poor yield. Almost the same result was observed with the ethyl or the phenyl starting materials **1d**–**f**.

The optimized conditions were applied on phenol derivative **10**, which was synthesized in three steps from the 2-bromophenol (Scheme 4). Only degradation of the starting material was observed. With the system $Pd(OAc)_2$/$P(OPh)_3$/Cs_2CO_3 in 1,4-dioxane, compound **10** underwent the desired cascade reaction ended by a protodesilylation to afford compound **11** in 65% yield.

To have an access to more challenging polycycles containing seven-membered rings, a similar starting material **3a** was designed in three steps in 69% yield starting from 1-bromonaphthalen-2-ol. Of note, because of the naphthalene moiety, the last step of the cascade reaction should as well be a C(sp^2)-H activation leading to the formation of a