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Comparative study on the reactivity of propargyl and alkynyl sulfides in palladium-catalyzed domino reactions



Étude comparative de la réactivité des thioéthers propargyliques et acétyléniques dans les réactions domino pallado-catalysées

Thomas Castanheiro, Angèle Schoenfelder, Jean Suffert, Morgan Donnard*, Mihaela Gulea**

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

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ABSTRACT

Three types of sulfides bearing a propargyl or an alkynyl moiety have been studied in cyclocarbopalladation/cross-coupling domino palladium-catalyzed sequences. The reactivity of different types of sulfured starting materials has been compared as well as the difference in behavior of these compounds depending on the type of cross coupling ending the domino sequence. It appeared that these cascades were constantly more efficient on the propargyl benzyl thioether. In addition, it has been demonstrated that domino sequences ending with Stille, Suzuki–Miyaura, or Mizoroki–Heck lead efficiently and selectively to the desired cyclized products. Notably, when the introduction of an alkyne is targeted at the end of the cascade, it appeared that the Sonogashira coupling leads every time to the desired cyclic product in the mixture with the product resulting from the direct coupling between the aryl moiety of the substrate and the alkyne used as partner. Finishing the domino sequence with a Stille coupling instead of a Sonogashira one allowed improving significantly the ratio of the mixture in favor of the desired cyclized compound.

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R E S U M E

Divers substrats de type thioéther portant une partie propargylique ou acétylénique ont été étudiés dans des séquences domino pallado-catalysées de type cyclocarbopalladation/couplage croisé. La comparaison des différents types de composés soufrés en termes de réactivité a été réalisée ainsi que celle des comportements de ces mêmes substrats en fonction du type de couplage croisé terminant la séquence domino. Il est apparu que ces cascades réactionnelles sont systématiquement plus efficaces sur un précurseur de type benzyle propargyle thioether. De plus, il a été constaté que les réactions domino se terminant par un couplage de Stille, de Suzuki–Miyaura ou de Mizoroki–Heck conduisaient

* Corresponding author.

** Corresponding author.

E-mail addresses: donnard@unistra.fr (M. Donnard), gulea@unistra.fr (M. Gulea).

toutes, de manière efficace et sélective, au composé cyclique soufré. De manière notable, lorsque l'objectif était d'introduire un alcyne en fin de séquence réactionnelle, il est apparu que le couplage de Sonogashira conduisait systématiquement à un mélange du produit cyclisé désiré avec le produit issu du couplage direct entre l'alcyne utilisé et la partie aromatique du substrat. En finissant la séquence domino avec un couplage de Stille, il a été possible d'améliorer de manière significative le ratio du mélange en faveur du produit cyclique désiré.

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1. Introduction

Among metal-catalyzed cascade reactions, those initiated by palladium-based catalysts are undoubtedly the ones that have been the most intensively studied for more than the last 40 years [1]. Efficient processes have been developed to quickly synthesize valuable molecular scaffolds bearing various heteroatoms mostly including nitrogen [2] and oxygen [3]. In contrast to this intensive work, transformations involving organosulfur substrates have been far less studied, certainly because of the poisoning of the catalyst caused by the thiophilicity of palladium. However, in recent years, the number of palladium-catalyzed processes involving substrates bearing a sulfur functionality has significantly increased and elegant methodologies have emerged insuflating a real interest to the synthetic chemist community [4]. During the course of our studies on metal-mediated transformations of sulfur-containing substrates [5], we have recently reported a domino palladium-catalyzed access to original thiacycles, which are compounds of outstanding importance in particular for the pharmaceutical industry, starting from propargylic or alkyne sulfides [6]. This sequence involves an initial cyclizing carbopalladation step followed by a cross-coupling reaction between the resulting vinyl-palladium species and a coupling partner (stannylated or borylated) (Scheme 1).

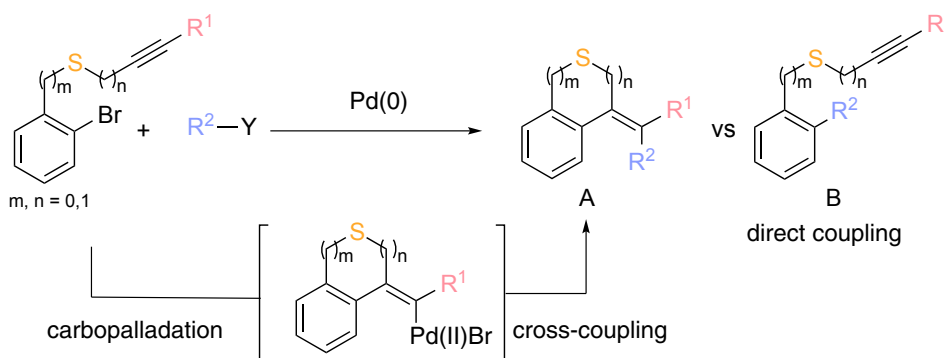
However, in this preliminary report, only the most efficient cross-coupling reactions, namely the Stille and the Suzuki couplings, have been investigated and an additional effort had to be made to rationalize the behavior of such substrates under different palladium-catalyzed domino transformations. To do so, we are reporting here a complete

study on the reactivity of three representative types of substrates (**1a**, **1b**, and **1c**) toward four distinct palladium-catalyzed domino reactions involving an initial cyclizing carbometalation step followed by the four most common cross-coupling reactions, respectively, the Stille reaction (organotin partner), the Suzuki–Miyaura reaction (organoboron partner), the Sonogashira reaction (alkyne partner), and the Mizoroki–Heck reaction (alkene partner) (Fig. 1).

2. Results and discussion

To rationalize the behavior of alkynyl and propargyl sulfides while submitted to these palladium-catalyzed domino transformations, we have first synthesized a set of three representative substrates namely propargyl aryl sulfide (**1a**), propargyl benzyl sulfide (**1b**), and alkynyl benzyl sulfide (**1c**). To access these three compounds, two different routes have been developed (Scheme 2).

The first route starts from 2-bromothiophenol and is based on a classical alkylation reaction using triethylamine as base and 3-(ethyl)propargyl bromide as an alkylating agent. After 4 h under reflux the desired aryl propargyl thioether **1a** was obtained almost quantitatively. The second route involves the in situ formation, by ethanolysis of a benzylic thioacetate, of a thiolate that can subsequently be alkylated. When 3-(ethyl)propargyl bromide is used as an alkylating agent, the thioether **1b** is obtained quantitatively. However, when propargyl bromide is used, the alkylation occurs to form the intermediary propargyl thioether that can then undergo a zip-type isomerization to reach the targeted ynethioether **1c** in a good 87% yield.



Scheme 1. General strategy of a palladium-catalyzed domino reaction of alkynyl and propargyl sulfides.

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