



Palladium-catalyzed intramolecular vinylarylation of alkene: Access to spirocyclic scaffold

Longlei Hou, Yifan Wang, Xiaofeng Tong*

Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, 200237 Shanghai, China



ARTICLE INFO

Article history:

Received 16 January 2018

Revised 1 March 2018

Accepted 2 March 2018

Available online 3 March 2018

Keywords:

Palladium catalysis

Heck carbopalladation

C-H activation

Cascade reaction

Spirocycle

ABSTRACT

A Pd(0)-catalyzed cascade reaction of (Z)-1-iodo-1,6-diene bearing a N-heteroaryl ring, including indole, pyrrole as well as imidazole, is reported. The reaction proceeds via Heck-type carbopalladation, which is followed by C-H activation of the attached N-hetero ring, thus delivering 6,5-spirocycles in moderate to good yields. Furthermore, the preliminary attempt at asymmetric version was also conducted.

© 2018 Published by Elsevier Ltd.

Spirocyclic compounds¹ play an important role in medicinal chemistry and have been introduced as powerful building blocks for drug discovery due to their 3D-shaped structure with high fractions of sp³-hybridized carbon atoms,² which meet the rules of modern drug discovery, such as scaffold hopping,³ escape the flatland⁴ and conformational restriction.⁵ On the other hand, the indole is the major structural feature of a wide range of natural compounds and chemical drugs of biological interest.⁶ Thus, we believe that the spirocyclic indole scaffold with the combination of these two structural features may be useful for discovery of new drug candidates.

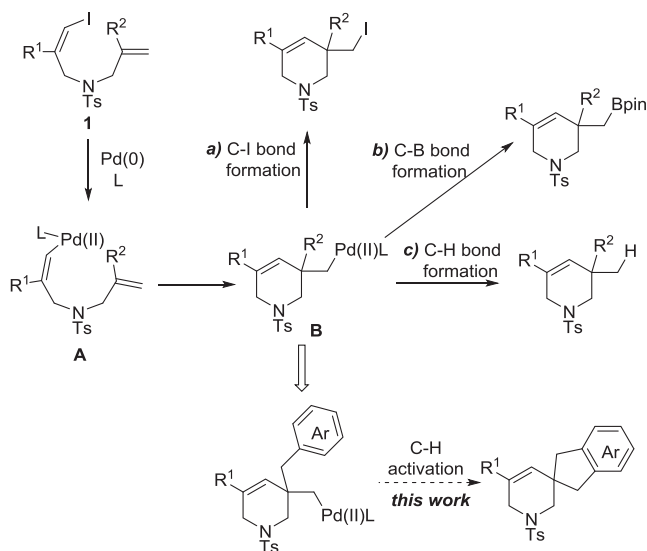
We have recently developed several palladium-catalyzed methods for the difunctionalization of alkene⁷ on the base of (Z)-1-iododienes **1** (Scheme 1).⁸ These reactions differentiate from distinct approaches of trapping the common alkyl-Pd(II) intermediate **B**, which was resulted from oxidative addition of Pd(0) to vinyl iodide and subsequent alkene insertion. For instance, without any additives, intermediate **B** is able to directly undergo reductive elimination to afford alkyl iodide products (Scheme 1a).^{8a} Moreover, intermediate **B** can also be trapped with either boron derivatives or hydride (Scheme 1b and c).^{8b,8c} Indeed, since the pioneering work for the group of Grigg,⁹ the related alkyl-Pd(II) without a β-hydrogen has been demonstrated to be an versatile intermediate for the development of a range of organic transformations by using various trapping steps.¹⁰ This interesting topic has attracted much

attention since these reactions are capable of constructing complex molecule from readily available starting materials in efficient manner, especially those involving C-H activation processes.¹¹ Inspired by these contributions and in connection with our continuing effort in the palladium-catalyzed difunctionalization of alkene, we envisioned that the resulting alkyl-Pd(II) species **B** would be able to promote C-H activation when an aromatic group was tethered in a proper position. This strategy would allow us to have general access to spirocyclic products.

To explore the feasibility of the designed Heck carbopalladation/C-H activation cascade process, we chose the diene substrate **1a** bearing an indole moiety which is widely-used for C-H activation.¹² When compound **1a** was subjected to our previous conditions for the vinylborylation,^{8b} the desired product **2a** was isolated albeit only in 9% yield (Table 1, entry 1). The structural assignment was initially supported by NMR and HRMS, and later corroborated by X-ray crystallography of product **4a** (Fig. 1).¹³ The yield of **2a** was increased to ca. 30% when either Pd₂(dba)₃ or Pd₂(MeO-dba)₃ was instead used (Table 1, entries 2 and 3). The released MeO-dba ligand has larger polarity, which is beneficial for product purification via column chromatography. Thus, Pd₂(MeO-dba)₃ was chose as the catalyst precursor in this study. Then, phosphine ligand was further investigated on the base of these results. However, other ligands, such as DPPP, BINAP as well as PPh₃, gave inferior results (Table 1, entries 4–6). During the course of the screening of base additive, we were delighted to find that the combination of Ag₂CO₃ (2.0 equiv) and K₂CO₃ (2.0 equiv) could significantly improve the reaction efficiency, delivering

* Corresponding author.

E-mail address: tongxf@ecust.edu.cn (X. Tong).



Scheme 1. Pd(0)-catalyzed cyclizations of (Z)-1-iodo-diene **1**.

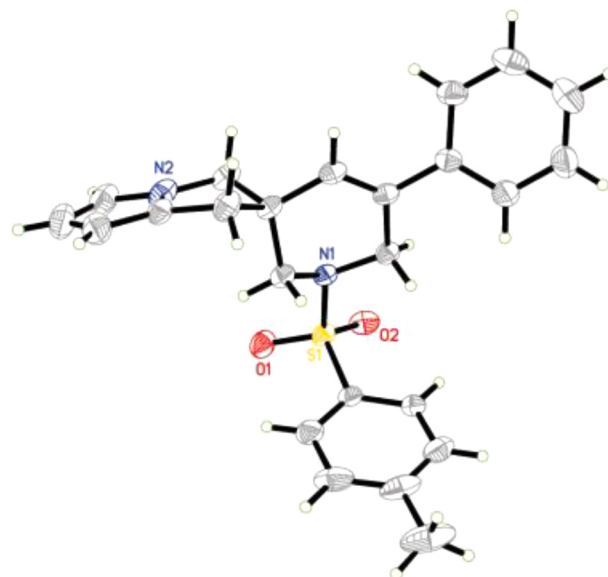


Fig. 1. The X-ray structure of compound **4a**.

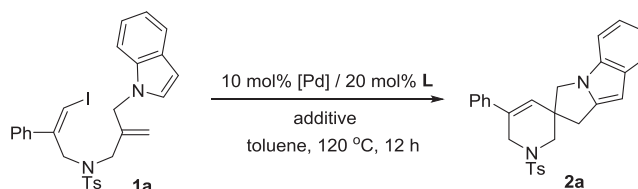
product **2a** in as high as 80% yield (Table 1, entry 7). While the role of base combination could not be clearly elucidated at this stage, its effect was further exemplified by the use of either Na_2CO_3 or Et_3N as an additional base additive (Table 1, entries 8 and 9). Furthermore, the yield of **2a** significantly dropped to 25% when only K_2CO_3 (2.0 equiv) was used as the base additive (Table 1, entry 10).

With the optimal conditions in hand, we next turned our attention to exploring the reaction scope and the results are summarized in Scheme 2. The reaction scope was firstly examined with respect to the substituent on the vinyl iodide moiety. It was delighted to find that both aryl and alkyl groups were well tolerated, giving the corresponding products **2a–2e** in good yields. Notably, the substrates **1b** and **1c** bearing an electron-rich aryl

group exhibited somewhat higher reactivity. However, the reaction of substrate **1f** was proven to be inferior, delivering product **2f** only in 50% yield. The substrates **1g** and **1h** with a NNs linkage showed similar activity. While the linkage could be extended to oxygen and $\text{C}(\text{CO}_2\text{Me})_2$, the corresponding reaction efficiency significantly dropped to ca. 50% yields (**2i–2k**). These results indicated that the linkage atom might be involved in the reaction likely via the coordination with metal center. Finally, the reaction was found to be compatible with more congested indole containing a methyl group at C3-position, giving product **2l** in 77% yield.

In addition to the indole skeleton, another N-heteroaryl groups could be readily incorporated by C–N bond connection, which would provide more diversified fragments. Due to the fact that

Table 1
Optimization of the reaction conditions.^a



Entry	[Pd]	L	Additive	Yield (%) ^c
1	$\text{Pd}(\text{OAc})_2$	DPPF	Ag_2CO_3^b	9
2 ^d	$\text{Pd}_2(\text{dba})_3$	DPPF	Ag_2CO_3	32
3 ^d	$\text{Pd}_2(\text{MeO-dba})_3$	DPPF	Ag_2CO_3	30
4	$\text{Pd}_2(\text{MeO-dba})_3$	BINAP	Ag_2CO_3	10
5	$\text{Pd}_2(\text{MeO-dba})_3$	DPPP	Ag_2CO_3	19
6 ^e	$\text{Pd}_2(\text{MeO-dba})_3$	PPh_3	Ag_2CO_3	Trace
7	$\text{Pd}_2(\text{MeO-dba})_3$	DPPF	Ag_2CO_3	80
8	$\text{Pd}_2(\text{MeO-dba})_3$	DPPF	Ag_2CO_3	50
9	$\text{Pd}_2(\text{MeO-dba})_3$	DPPF	Ag_2CO_3	56
10	$\text{Pd}_2(\text{MeO-dba})_3$	DPPF	–	25

^a Reaction conditions: see the Supporting Information for the detail.

^b 2.0 equiv. additive was used.

^c Yield of isolated product after column chromatography.

^d 5 mol% $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}_2(\text{MeO-dba})_3$ was used.

^e 40 mol% PPh_3 was used.

Download English Version:

<https://daneshyari.com/en/article/7829358>

Download Persian Version:

<https://daneshyari.com/article/7829358>

[Daneshyari.com](https://daneshyari.com)