



# Palladium-catalysed reactions of conjugated enyne oxiranes with organoborons: A diastereoselective method of the synthesis of 2,4,5-trienol derivatives

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## ARTICLE INFO

### Article history:

Received 12 September 2017

Received in revised form

26 January 2018

Accepted 11 May 2018

Available online 12 May 2018

### Keywords:

Allene

Vinylallene

2,4,5-Trienol

Enyne oxirane

Organoboron

## ABSTRACT

A palladium-catalysed reaction of conjugated enyne oxiranes with organoboron reagents is described. This method allows aryl-substituted vinylallenes containing a hydroxyl group on the allylic position to be synthesized, with good diastereomeric ratios, under mild conditions.

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## 1. Introduction

Allenes are highly versatile reagents, with broad utility as building blocks to a diverse array of high-value products.<sup>1</sup> In addition, there are quite a number of biologically active natural products and pharmaceutical agents that contain an allene moiety.<sup>1a,b</sup> Therefore it is of interest to develop mild and selective methods to synthesise allenes with diverse substitution patterns<sup>2,3</sup> that can be elaborated into specific targets.<sup>1c,4</sup>

Our group has recently developed general palladium-catalysed methods to synthesise functionalized tetra-substituted allenes in a series of studies of conjugated enyne compounds.<sup>5</sup> This work was initiated with studies of enynes containing a carbonate-leaving group on the allylic carbon. These enynes react with CO/ROH combinations or organoboron reagents to afford esters and aryl- or alkenyl-substituted vinylallenes, respectively (Scheme 1).<sup>5a-c</sup>

We then extended the alkoxyacylation to conjugated enynes carrying an oxirane moiety to synthesise functionalized vinylallenes, thereby allowing the formation of 7-hydroxy-2,3,5-trienoates stereoselectively (Scheme 1).<sup>5d,6</sup>

We demonstrate in this study that enyne oxiranes are compliant reagents for Miyaura-Suzuki-type reactions<sup>7</sup> and thus produce aryl- or alkenyl-substituted vinylallenes bearing a hydroxyl group on the allylic position (Scheme 2).

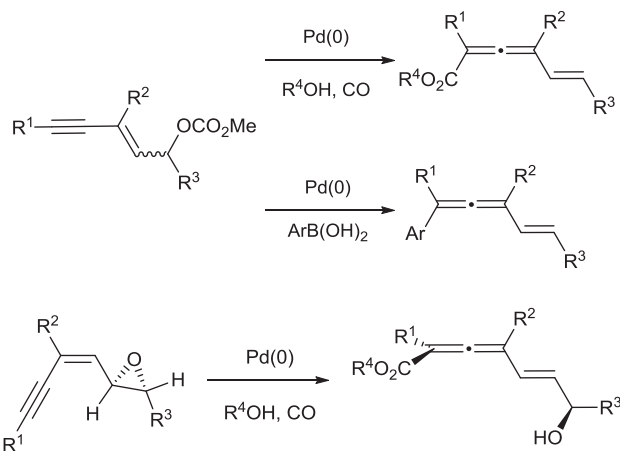
## 2. Results and discussion

A promising result was obtained in the reaction of the enyne oxirane **1a**, which had a dimethyl group on the oxirane terminus, with phenylboronic acid in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (3 mol%) in a THF/water (2:1) mixture at 50 °C. This reaction resulted in complete conversion in 1.5 h and furnished the phenyl-substituted vinylallene **3aa**, which had a hydroxyl group on the allylic position (Scheme 3).

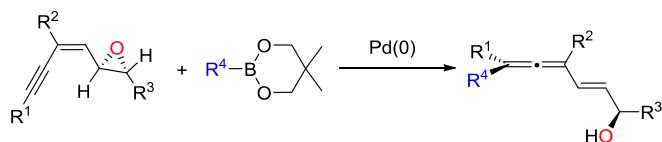
Based on this promising result, the optimization studies with the enyne oxirane **1b**, which had a disubstituted oxirane ring, were carried out so that the stereoselectivity of the process could be evaluated with respect to the relative configurations of the axially-chiral allenyl moiety and the hydroxyl-substituted chirality centre (Scheme 4). However, interestingly, the reaction of this substrate with phenylboronic acid under the aforementioned conditions led only to a condensation product. Other organoboron reagents, such as PhBF<sub>3</sub>K and (PhBO)<sub>3</sub> also shared the same fate.

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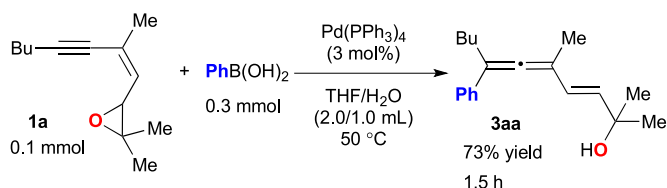
E-mail address: [leventartok@iyte.edu.tr](mailto:leventartok@iyte.edu.tr) (L. Artok).



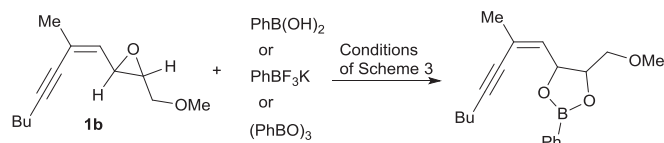
**Scheme 1.** Palladium-catalysed alkoxy carbonylation and Miyaura-Suzuki type reactions of enyne carbonates and enyne oxiranes.<sup>5</sup>



**Scheme 2.** This study: Palladium-catalysed arylation of enyne oxiranes.



**Scheme 3.** Palladium-catalysed reaction of **1a** and phenylboronic acid.



**Scheme 4.** Palladium-catalysed reaction of **1b** and organoborons.

Palladium-catalysed condensation of allylic oxiranes with organoboronic acids has been previously documented,<sup>8</sup> so the latter two reagents were probably also partially hydrolysed to phenylboronic acid under aqueous conditions. Encouragingly, the desired vinylallene product **3ba** could be obtained with a moderate yield (67%) and diastereomeric ratio (dr) of 79:21, as determined by <sup>1</sup>H NMR, with the use of the NaBPh<sub>4</sub> reagent (Table 1, entry 1). Increasing the THF/water ratio improved the reaction efficiency and dr to some extent (entry 2). However, lowering the reaction temperature to 25 °C resulted in a significant reduction in the yield and led to the formation of the allylic substitution product **4ba** (entry 3). The neopentyl glycol ester of phenylboronic acid (**2a**) was also compatible—when reacting with **1b** at 25 °C in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd<sub>2</sub>(dba)<sub>3</sub>-CHCl<sub>3</sub>/PPh<sub>3</sub> (3 mol% Pd; P/Pd = 4.5:1) catalyst systems, neither the condensation by-product formation nor **4ba** were observed to form and, thus, **3ba** could be obtained with a good yield, but with a non-satisfactory dr (entries 4 and 5).

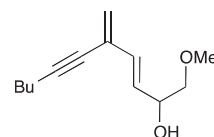
Several mono and bidentate ligands were surveyed in an attempt to improve the efficacy and stereoselectivity for the reaction of **1b** and **2a** (see the supporting file), among which the most promising ligands that provided dr levels greater than 80:20 are listed in Table 2.

The reactions in the presence of TFP, PPh<sub>2</sub>Me, AsPh<sub>3</sub>, dppe, dppp, and dppb ligands were either unaffordably slow or had unsatisfactory yields (entries 1–6). The best performance in terms of the **3ba** yield and reaction rate was achieved by the use of DPEPhos ligand, albeit with somewhat lessened stereoselectivity (entry 7).

Gratifyingly, the presence of a base additive has been found to be beneficial for the level of stereoselectivity (see the supporting file) and the organic bases usually performed better than inorganic bases (entries 8–10). The additive (*i*-Pr)<sub>2</sub>EtN was determined to be the most suitable base and even better diastereoselectivities were achieved by using larger amounts of the base (entries 11 and 12).

Having completed the optimization study, we surveyed the scope of the method against an array of neopentyl glycol esters of arylboronic acids with a variety of substitution patterns under the conditions of entry 11 of Table 2, which was judged to be sufficient for the selective formation of the desired product **3**. The palladium-catalysed reaction of **1b** and organoboron reagents (**2b–e**) substituted with an electron donating group gave the expected vinylallenes in good yields and stereoselectivities in relatively short reaction periods, regardless of the substitution pattern of **2** (Table 3, entries 1–4). However, the allylic substitution product **4bf** was the main product of the reaction carried out with the highly encumbered 2,6-dimethyl substituted organoboron **2f**, and therefore, yielded the desired **3bf** in low yield (entry 5).

Both electron-poor organoboron reagents (entries 6–8) and naphthylborons (entries 9 and 10) were competent reagents in terms of process efficiency and stereoselective formation of respective products. The reactions proceeded slower when the former organoboron reagents were used. The method was less stereoselective for alkenylboron reagents, whereas the structurally interesting divinylallene product **3bl** could be isolated with a synthetically useful dr (83:17) when using (*E*)-1-pentenylboronic ester (entry 11). On the other hand, the reaction with (*E*)-styrylboronic ester proceeded with remarkably low diastereomeric selectivity (entry 12). Interestingly, a β-hydride elimination product was the sole product of the reaction performed in the presence of 3-thienylboron (**2n**) (entry 13).



The enyne oxirane component of the reaction was also varied, usually with similar success (Table 4). The substrate **1a** showed a better performance under the optimized conditions. Hence, **3aa** could be obtained in high yield (entry 1). The method was also suitable to the synthesis of the vinylallene with a primary allylic alcohol portion (**3ca**), although it was obtained in a relatively lower yield (entry 2). While the pendant oxygen functionality within R<sup>3</sup> group could also be used in benzyl- or silyl-protected forms effectively, the protection of the hydroxyl functionality was not compulsory, although there was some reduction in yield without such protection (entries 3–5). The presence of a larger group in R<sup>3</sup>, such as 2-methoxypropan-2-yl group (**1g**), was also well-tolerated by the method (entry 6). However, the reaction was dramatically decelerated when there was only one methyl group at the oxirane terminus (**1h**) (entry 7).

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