



# Palladium-catalyzed reactions of cyclopropanols bearing oxazoline directing group

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## ABSTRACT

Cyclopropanols bearing oxazoline directing group were investigated in palladium-catalyzed reactions. When the directing group and cyclopropanol unit were bonded through two- or three-carbon spacer, formation of unusual products was observed. Oxidative ring opening proceeded with uncommon regioselectivity providing linear enones as main products. The reaction of such cyclopropanols with aryl iodides and silver acetate furnished diarylated  $\alpha$ -methylene ketones, which cannot be obtained from cyclopropanols lacking oxazoline ring under the same conditions.

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## 1. Introduction

Cyclopropanols are important synthetic intermediates with a strained ring, which is prone to regioselective cleavage under mild conditions.<sup>1</sup> Such reactions have been successfully used in syntheses of natural products and drugs.<sup>2</sup> Palladium complexes are known to catalyze diverse transformations of cyclopropanols **1** (Scheme 1) and these reactions proceed *via* intermediate homo-enolates **2**.<sup>1b</sup> Cha<sup>3</sup> and Okumoto<sup>4</sup> reported synthesis of  $\alpha$ -methylene ketones **3** *via*  $\beta$ -hydride elimination in **2**. Orellana,<sup>5</sup> Walsh<sup>6</sup> and Cha<sup>7</sup> disclosed palladium-catalyzed arylation,<sup>5a-b,d-e,6</sup> benzylation<sup>5c</sup> and alkenylation<sup>7</sup> of **1**. Dai developed an approach to oxaspirolactones **5** based on CO-insertion into intermediates **2**.<sup>8</sup> Moreover, Chen described a cascade of palladium-catalyzed reactions of 1-alkynylcyclopropanols **6** leading to diarylated dienone **8**.<sup>9</sup> The product was formed as a result of conversion of substrates **6** to dienones **7** followed by Mizoroki-Heck arylation of vinyl unit in the intermediate **7**. Selectivity and rate of reactions catalyzed by transition metals are strongly affected by directing groups which are present in the substrate.<sup>10</sup> However, directed transformations of cyclopropanols have never been investigated. In this article, we describe directed palladium catalyzed oxidative rearrangement of

hydroxycyclopropanes and directed palladium-catalyzed reaction of cyclopropanol moiety with aryl halides.

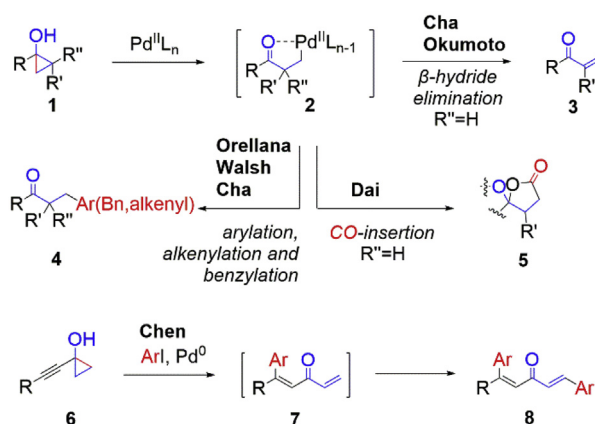
## 2. Results and discussion

Among numerous existing directing groups,<sup>10b</sup> we chose oxazoline heterocycle since in addition to its coordinative properties, it is stable under conditions of Kulinkovich reaction, which was applied for synthesis of substrates **9** and **10** from corresponding esters and alkenes (see SI).<sup>11</sup> First, we investigated cyclopropanols **9** in palladium-catalyzed synthesis of enones. To our delight, the reaction proceeded with unusual selectivity giving linear (*E*)-enones **11a-d** as the main products (Table 1). The highest 90:10 selectivity was achieved in the reaction of cyclopropanol **9b** bearing bulky isopropyl substituent. Primary chloride functionality is consistent with reaction conditions and enone **11d** was obtained without a significant loss in yield. In contrast, we failed to prepare product **11e**, which contains an alkenyl group. Gem-dimethyl group in aliphatic fragment of **9a-d** had an impact both on the selectivity and on the yield of the reaction. Cyclopropanol **9f** lacking methyl substituents gave a mixture of enones **11f** and **12f** with the lowest 64:36 selectivity and in a low 35% yield. Increase of the distance between the directing group and cyclopropanol moiety by only one carbon atom led to the disappearance of the directing effect. Only expected  $\alpha$ -methylene ketone **14** was obtained when cyclopropanol **10** was reacted. Preferential formation of the linear

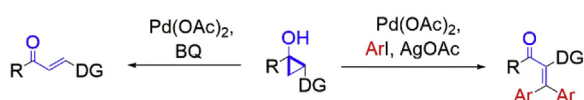
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## Previous work:



## This work:



Scheme 1. Palladium-catalyzed reactions of cyclopropanols.

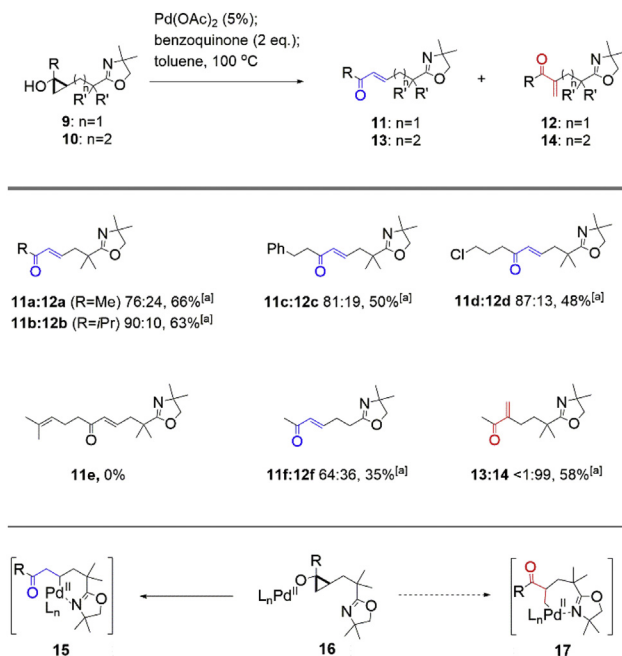
enones **11a–f** from cyclopropanols **9** could be explained by considering two possible intermediates **15** and **17** in which Pd(II) center is coordinated by the directing group.  $\beta$ -Hydride elimination in **15** would lead to major linear enones **11**, while intermediate **17** would give the minor product **12**. Six-membered palladacyclic intermediate **15** is considered to be more favorable than **17** bearing

larger seven-membered ring.

Next, cyclopropanols bearing oxazoline group were engaged in palladium-catalyzed arylation. We expected that this reaction would also proceed with unusual selectivity but when the cyclopropanol **9a** was arylated under the Orellana's conditions,<sup>5b</sup> only conventional  $\alpha$ -benzyl ketone **4** was formed together with  $\alpha$ -methylene ketone **12a**. Unexpected transformation of **9a** was observed when it reacted with an excess of iodobenzene in the absence of phosphine ligands but in the presence of silver acetate at 100 °C in toluene (Table 2, entry 1). The reaction furnished the bis-arylated  $\alpha$ -methylene ketone **18aa** in a 36% yield. Presumably, **18aa** was formed as a result of conversion of the cyclopropanol **9a** to  $\alpha$ -methylene ketone **12a** followed by its Mizoroki–Heck bis-arylation.<sup>12</sup> Previously, application of cyclopropanols as synthetic equivalents of enones in Mizoroki–Heck reaction was reported only for 1-alkynyl substituted cyclopropanols.<sup>9</sup> The presence of the directing group in the disclosed transformation was found to be essential. When 1-pentyl-2-ethylcyclopropanol lacking directing substituents was reacted under the same conditions, decomposition of the starting material occurred. To improve the yield of **18aa**, we started screening of the reaction conditions (Table 2). Attempts to change silver acetate for cesium or sodium salts resulted in dramatic decrease of the yield (entries 2–3). Replacement of silver acetate with silver carbonate reduced efficiency of the reaction providing a mixture of mono- and diarylated products (entry 4). The yield of **18aa** was improved to 55% when the temperature was lowered to 60 °C and the solvent was changed to THF (entries 5–10). Variation in the amount of the catalyst, silver acetate or iodobenzene resulted in only negligible effect on the yield (entries 11–14). Our attempts to synthesize enone **19aa** bearing only one aryl substituent were less successful. Reaction of the cyclopropanol **9a** with one equivalent of iodobenzene led to a mixture of **18aa** and **19aa** in which the diarylated product **18aa** still predominated

Table 1

Oxazoline directed palladium-catalyzed synthesis of enones from cyclopropanols.



<sup>a</sup> Isolated yields of enones. Ratio of isomers was determined by <sup>1</sup>H NMR analysis.

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