

# Studies on the zirconium-mediated alkyne–aldehyde coupling reactions: a facile synthesis of stereodefined allylic alcohols and (*Z*)-2-en-4-yn-1-ols

Shenghai Guo, Hao Zhang, Feijie Song and Yuanhong Liu\*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

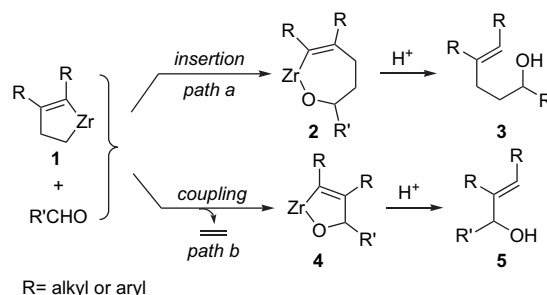
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**Abstract**—An improved zirconium-mediated alkyne–aldehyde cross-coupling reaction has been achieved to afford the stereodefined (*Z*)-allylic alcohols or 3-iodinated allylic alcohols selectively via protonolysis or iodinolysis of the corresponding five-membered oxazirconacycles. This method has also been successfully applied to the synthesis of (*Z*)-enynols through cross-coupling reactions of three different components involving alkyne, aldehyde, and alkynyl bromide in a one-pot procedure.  
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## 1. Introduction

The selective coupling of alkynes with unsaturated molecules such as alkynes, alkenes, ketones, aldehydes, nitriles, etc. by use of a low-valent zirconocene equivalent has been shown to lead to a variety of carbo- and heterometallacycles.<sup>1</sup> The in situ generated zirconacycles are important intermediates in a wide range of selective (including chemo-, regio-, and stereoselective) reactions.<sup>1</sup> Although much progress has been achieved in this area, there are only a limited number of reports on the alkyne coupling reactions with aldehydes to give five-membered oxazirconacycles.<sup>2</sup> The known procedures involve: (i) addition of aldehyde to zirconocene–alkyne complexes.<sup>2c–g</sup> The alkyne complexes used for this type of reaction are usually prepared by hydrozirconation of an alkyne followed by methylation with MeLi and elimination of methane from the alkenyl(methyl)zirconocene. The resulting alkyne complexes are trapped with trimethylphosphine.<sup>2c,f</sup> This method requires costly phosphine ligands and Cp<sub>2</sub>Zr(H)Cl. (ii) Reaction of zirconacyclopentenes with aldehydes as reported by Takahashi et al. (only one alkyne was tested to afford moderate NMR yields of oxazirconacycles).<sup>2a,b</sup> However, there is no systematic studies on this chemistry. In principle, two types of reactions of zirconacyclopentenes with aldehydes have been reported, one involves insertion of aldehydes at alkyl–zirconium bond (Scheme 1, path a)<sup>2b</sup> and the other involves the coupling of alkynes with aldehydes with concomitant extrusion of ethylene (path b).<sup>2a</sup> Negishi et al.

found that when the reaction was run at low temperature ( $\leq 25\text{ }^{\circ}\text{C}$ ), the insertion product **3** became the major product, while the formation of **5** was less than 2%. Recently, we have developed an efficient synthetic approach to stereodefined dihydrofurans or furans via gold-catalyzed cyclization of (*Z*)-2-en-4-yn-1-ols.<sup>3</sup> Within this program, (*Z*)-enynols derived from zirconium-mediated alkyne–aldehyde coupling reactions were substrates.



**Scheme 1.** Reaction patterns of aldehyde addition with metallacyclopentenes.

Initially, we applied the literature reaction conditions<sup>2a</sup> (addition of aldehyde to zirconacycle at 0 °C, then warmed up to 50 °C) for the alkyne–aldehyde coupling via zirconacyclopentenes. However, it was found that the byproducts of direct insertion reactions were always formed in comparable yields along with desired allylic alcohols. For example, the reaction between 1,2-dipropylzirconacyclopentene **1a** and benzaldehyde (1.5 equiv) afforded insertion product 1-phenyl-4-propyloct-4-en-1-ol **3a** and coupling product 1-phenyl-2-propylhex-2-en-1-ol **5a** in 98% combined NMR yield with

\* Corresponding author. E-mail: yhliu@mail.sioc.ac.cn

a ratio of 1:1 (determined by NMR). These unsatisfactory results prompted us to optimize the reaction conditions to enhance the selectivity of the desired cross-coupling reactions. In this paper, we describe the detailed studies on Zr-mediated alkyne–aldehyde coupling reactions under improved conditions, in which the above-mentioned insertion reactions are mostly suppressed. This reaction has also been applied to an efficient and one-pot synthesis of highly substituted, stereodefined allylic alcohols and (*Z*)-2-en-4-yn-1-ols.

## 2. Results and discussion

### 2.1. Zirconium-mediated alkyne–aldehyde coupling reactions

Zirconacyclopentenes are known to undergo cross-coupling reaction with unsaturated compounds through facile  $\beta,\beta'$ -carbon–carbon bond cleavage reaction along with elimination of one ethylene molecule.<sup>4</sup> It seems that once the system is ‘preactivated’, the behavior of ethylene ligand should be more labile and easy to be eliminated from the metal center. Thus this system is expected to be feasible to perform the desired alkyne–aldehyde cross-coupling reactions, and minimize the possibility of direct insertion reactions. Consequently, we found that simply heating the reaction mixture of zirconacycle **1a** up to 50 °C for a few minutes followed by slow addition of benzaldehyde, the desired coupling product **5a** was formed in 82% NMR yield with high isomeric purity (>99%) as shown in Scheme 2. The amount of **3a**, which is the major product at 0 °C, was <1%. Interestingly, when the reaction mixture of **4a** was quenched with 3 N HCl for overnight, the stereodefined product **6** could be generated in 38% isolated yield through acid-induced allylic isomerization.<sup>5</sup> The (*E*)-configuration of C=C bond in **6** was determined by the <sup>1</sup>H–<sup>1</sup>H NOESY spectrum.

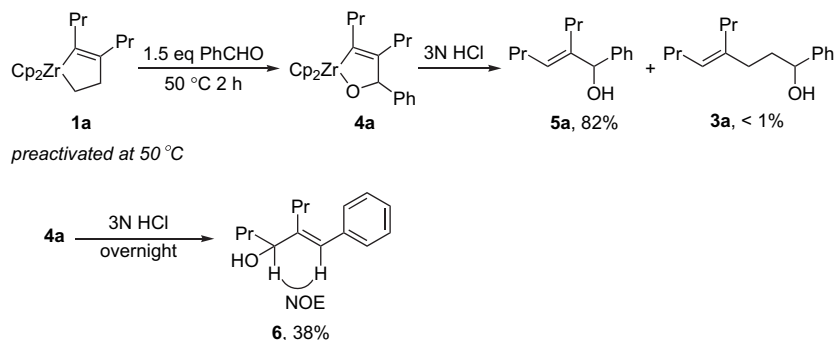
The results of the preparation of allylic alcohols from alkynes and aldehydes are summarized in Table 1. As shown in Table 1, alkyl, aryl, and heteroaryl aldehydes are all compatible with coupling conditions. The corresponding allylic alcohols were formed in good to high yields. For alkyl-substituted alkyne, addition of aldehyde at 0 °C (then warmed up to 50 °C) always resulted in the formation of byproducts of type **3**. The ratio of **3/5** is varied from 0.6:1 to 2.5:1.<sup>6</sup> However, under the ‘preactivated’ conditions, the selectivity was significantly improved to more than 89%, implying the undesired formation of **3** was mostly suppressed

(Table 1, entry 1–4). We checked two cases of the reaction with aryl-substituted alkyne, the results indicated that there was no significant difference in product yields and selectivity under the above two reaction conditions.<sup>6,7</sup> The coupling product **5** was formed predominantly with >98% selectivity (entry 5–10). When bis(thienyl)alkyne was employed, the corresponding alcohol **5h** was formed in a good yield of 72% (entry 8). Substitution at C-1 with a thienyl group resulted in a quick allylic isomerization during the acidic quenching, and the two products of **5i** were obtained in a ratio of 3:1 with a combined yield of 88% (entry 9). When the aldehyde tethered with an alkyne moiety such as 4-(phenylethynyl)benzaldehyde was used, the coupling reaction selectively occurred at the carbonyl moiety, furnishing the product **5j** in 90% yield, while the triple bond in the substrate remained intact (entry 10). Interestingly, with 1-trimethylsilyl-1-hexyne, two regioisomers of **5k** and **5l** were formed in 22% and 33% yields, respectively (entry 11). The regioselectivity is lower than that observed in the coupling reaction of silylated alkynes with nitriles,<sup>4a</sup> in which only one regioisomer (silyl group substituted at the  $\alpha$ -position in azazirconacycles) was observed.

### 2.2. Iodination of oxazirconacycles **4**

The oxazirconacycles **4** produced by this method are versatile synthetic intermediates, which can be trapped with electrophiles to afford tetrasubstituted olefins with high stereoselectivity. We found that iodination of zirconacycle **4a** with 3 equiv of iodine at room temperature proceeded at the alkenyl-zirconium moiety to afford stereodefined (*Z*)-3-iodo-1-phenyl-2-propylhex-2-en-1-ol **7a**<sup>8</sup> in 59% yield (Scheme 3). The use of 1.5 equiv of I<sub>2</sub> resulted in a prolonged reaction time (55% for 5 h).

Takahashi et al. had reported that addition of copper salt is effective for the iodination of C(sp<sup>2</sup>)-Zr bond in zirconacyclopentadienes and zirconacyclopentenes.<sup>9</sup> With the use of 20% CuI, the amount of iodination reagent (I<sub>2</sub>) could be reduced to 1.2 equiv, and the product **7a** was formed in 56% yield but prolonged reaction time (8 h) was required. The results of iodination are summarized in Table 2. ICl could also be used as an effective iodination reagent (Table 2, entries 2, 4–7). It should be noted that in most cases, ICl was more effective than I<sub>2</sub>. Interestingly, when diphenyl-substituted zirconacycle **4b** was subjected to CuI-mediated iodination condition, the product was formed as a mixture of *Z* and *E* isomers in 76% yield with the ratio



Scheme 2. Alkyne–aldehyde coupling reaction through a preactivated zirconacyclopentene.

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