

## Research Paper

## Two efficient pathways for the synthesis of aryl ketones catalyzed by phosphorus-free palladium catalysts

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## ARTICLE INFO

## Article history:

Received 28 August 2017

Received in revised form 10 October 2017

Accepted 17 October 2017

## Keywords:

Heck coupling

Allylic alcohols

Palladium

Ionic liquid

Aryl ketone

Isomerization

Nanoparticles

## ABSTRACT

Allylic alcohols, 1-buten-3-ol, 1-penten-3-ol and 1-octen-3-ol, reacted with aryl iodides (iodotoluene, 4-iodotoluene, 4-iodophenol and 4-iodanisole) under Heck reaction conditions to form corresponding saturated aryl ketones in one step. The same products were obtained in a two-step tandem reaction consisted of the Heck coupling of allylic alcohols with aryl iodides, followed by hydrogenation. Reactions were catalyzed by phosphorus-free palladium precursors modified with the menthol-substituted imidazolium chlorides. Formation of crystalline palladium nanoparticles, of the diameter up to 65 nm, in the reaction mixture was evidenced by TEM.

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## 1. Introduction

Aryl carbonyl compounds, aldehydes and ketones, have attracted considerable attention from synthetic chemists for many years. This is due to their properties, allowing them to be used as building blocks in the industrial production of pharmaceuticals, cosmetics, or agrochemicals [1–9]. In this context, particular attention has been paid to one group of aryl carbonyl compounds, 4-aryl-2-butanones. For example, raspberry ketone, 4-(4-hydroxyphenyl)-2-butanone, is a component of anti-cancer medicine and a dietary supplement [2–6]; nabumetone, 4-(6-methoxy-2-naphthalenyl)-2-butanone, is a non-steroidal anti-inflammatory drug, insecticide ingredient, and component in detergent preparation [22].

Aryl carbonyl compounds can be prepared by commonly known organic methods, such as Friedel–Crafts alkylation [10], Wittig olefination [11–13], or aldol condensation [14–17]. The main disadvantages of these procedures consist in the generation of large amounts of by-products and the need for expensive organophosphorus starting materials eventually forming environmentally unfriendly phosphorus waste. Therefore, the need to develop new

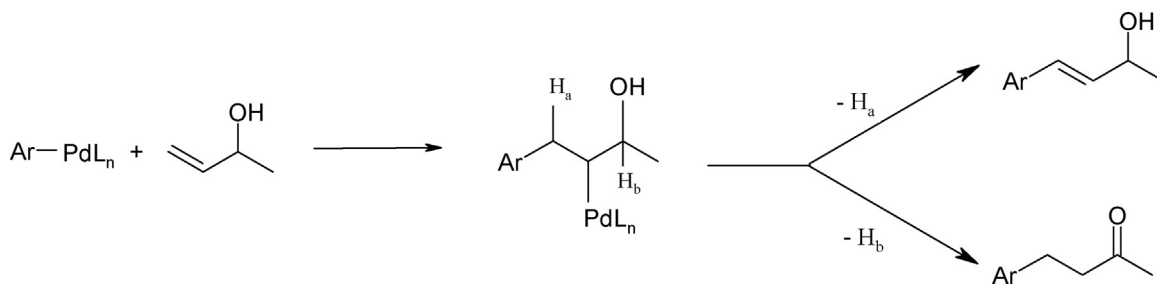
synthesis methods for aryl ketones is obvious. Among them, the palladium-catalyzed Heck arylation of unsaturated ketones could be considered. Thus, the Heck arylation of 3-buten-2-one with iodoanisole and iodophenol has been performed with homogeneous and heterogeneous palladium catalysts [13,18]. Palladium nanoparticles in ionic liquid media have been employed with good results in the arylation of 3-buten-2-one with iodobenzene, followed by the hydrogenation of 4-phenyl-3-buten-2-one to 4-phenyl-3-butan-2-one [19–21].

The Heck arylation of unsaturated allyl alcohols presents an alternative synthetic strategy leading to aryl ketones. In this very challenging process, high chemo- and regioselectivity can be achieved due to the efficiency of double bond isomerization [23–26]. The Heck arylation of different allylic substrates has been performed with PdCl<sub>2</sub> [27] and Pd(OAc)<sub>2</sub> [28–31] under homogeneous conditions or after the impregnation of palladium on the polymer [32]. Good results have been obtained employing palladium systems with phosphorus ligands [28,33–35] or palladacyclic compounds [36].

The unique reactivity of allylic alcohols has also been exploited in the preparation of aryl-substituted dicarbonyl compounds [37,38]. Carbonylative coupling between allylic alcohols and aryl iodides has resulted in the formation of 1,4-diketones in high yield [37]. Dicarbonyl compounds have been prepared by the palladium-

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**Scheme 1.** Hydrogen transfer in an  $\alpha$ -alkyl-palladium intermediate.

catalyzed Heck coupling of  $\beta$ -bromocarbonyl compounds with allylic alcohols [38].

In most cases,  $\beta$ -aryl ketone has been obtained as the main product of the Heck arylation of allylic alcohols. Although the interpretation of the selectivity of this reaction is still under debate [23–26], it can be assumed that  $\beta$ -hydride transfer ( $\beta$ -hydride elimination) is decisive for ketone formation. The rearrangement of an  $\alpha$ -alkyl-palladium intermediate, formed by migratory insertion, has led to an unsaturated alcohol or an saturated ketone. Thus, the selective catalyst should favor the transfer (elimination) of  $H_b$  over  $H_a$  (Scheme 1).

Interestingly, tetraalkylammonium salts and ionic liquids significantly influence the reaction course [22,39,40]. For example, the application of TBAA (tetrabutylammonium acetate) in reactions of 1-octen-3-ol have resulted in the selective formation of  $\alpha$ -aryl alcohol, without isomerization to aryl ketone [40]. In contrast, TBAB (tetrabutylammonium bromide) has facilitated the formation of  $\beta$ -aryl ketone under similar conditions [40]. Aryl ketones have mainly been formed in the presence of TBAC (tetrabutylammonium chloride) [34,41], while alcohol has been obtained in the [bmim][BF<sub>4</sub>]/DMSO solution.

Our research aimed at the evaluation and comparison of two protocols leading to arylated ketones. In both procedures, a palladium catalyst was employed in a two-step tandem reaction. In the first method, unsaturated allylic alcohols were used as substrates, while in an alternative method, unsaturated ketones were employed. In both cases, the first step consisted of the Heck coupling, followed by hydrogen transfer (isomerization of unsaturated alcohol) or the hydrogenation of unsaturated ketone.

Considering literature examples that report the improvement of allylic alcohol reactions by ionic liquids, we decided to study the effect of menthol-modified imidazolium chlorides on the reaction course. Till now, these ionic liquids have not been used in catalytic reactions [42,43].

It was also expected that these ionic liquids would form *in situ* anionic palladates of the type [CA]<sub>2</sub>[PdX<sub>4</sub>] (CA = imidazolium cation) with attractive catalytic activity. In fact, the high catalytic activity of similar palladates has been evidenced in oxidative Heck reaction and in the functionalization of olefins by arylsilanes [44,45].

## 2. Results and discussion

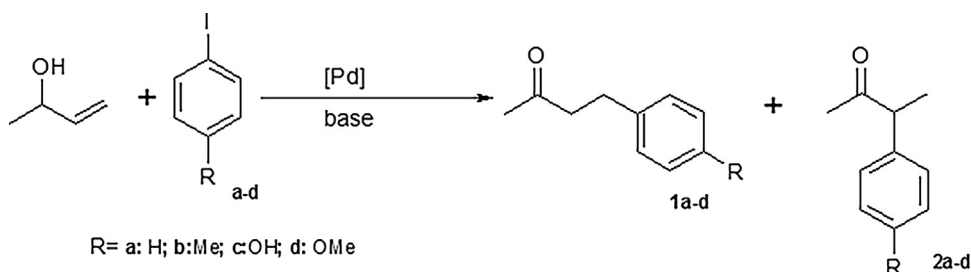
### 2.1. Arylation of allylic alcohols

Our investigations started from the studies of the arylation of 1-buten-3-ol with iodobenzene and its substituted derivatives. The formation of arylated ketone in this system was possible in two steps. First, the formation of unsaturated arylated alcohol was expected as a result of the Heck arylation at  $\beta$  (products 1a–d) and  $\alpha$  carbons (products 2a–d). According to the literature, in most systems arylation at the  $\beta$  position has been preferred [23–26]. The second step, involving the isomerization of unsaturated arylated allylic alcohol, leads to saturated ketone (Fig. 1). Thus, the palladium catalyst should be active in both steps, namely the Heck coupling and isomerization. As mentioned in the introduction, ketones 1a–d could be formed by the rearrangement of the  $\sigma$ -alkyl palladium intermediate without the isolation of unsaturated arylated alcohol.

Different palladium precursors were tested in this reaction, including simple PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> and anionic complexes [CA]<sub>2</sub>[PdCl<sub>4</sub>] containing an imidazolium cation with menthyl substituents (Table 1). These complexes were prepared in the reaction of PdCl<sub>2</sub>(cod) with imidazolium chlorides of the type [CA]Cl (Fig. 2)

In all reactions, the saturated ketone 1a was obtained as the main product. The yield of the second product, 2a, did not exceed 10%. It is worth noting that the isomerization reaction to 1a was very efficient under the applied conditions and, as a result, unsaturated alcohol was not found in the reaction mixture.

The highest conversion to 1a, 90%, was obtained for PdCl<sub>2</sub>(cod) in the DMF/H<sub>2</sub>O solvent mixture, while 82% of 1a was formed in DMF. The pre-treatment of the catalyst precursor with H<sub>2</sub> (1 atm) before the introduction of the substrates, in order to form Pd(0) *in situ*, only slightly changed the product composition, and 86% of 1a was formed. It can, therefore, be assumed that the Pd(II) precursor undergoes fast reduction *in situ* forming catalytically active Pd(0), similarly as was observed in other C–C bond forming reactions [46–49]. The *in situ* reduction is so efficient under the reaction conditions that the presence of H<sub>2</sub> has in fact no significant influence on the reaction course. Consequently, the pre-treatment of the catalyst is not needed to get high conversion. Interestingly, when a Pd(0) complex, Pd<sub>2</sub>dba<sub>3</sub>, was used, the yield of 1a was lower,



**Fig. 1.** Arylation of 1-buten-3-ol.

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