# Manganese(I)-Catalyzed $\alpha$ -Alkenylation of Ketones Using Primary Alcohols

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**Supporting Information** 

**ABSTRACT:** A simple protocol of manganese catalyzed selective  $\alpha$ -alkenylation of ketones using primary alcohols is reported. The reactions proceeded well with a low loading of catalyst (0.3 mol %). The overall transformation operates through O–H bond activation of primary alcohols via dearomatization—aromatization metal ligand cooperation in the catalyst to provide the corresponding aldehydes, which further undergo condensation with methylene ketones to deliver  $\alpha$ , $\beta$ -unsaturated ketones. This selective  $\alpha$ -alkenylation proceeds with the release of water and liberation of molecular hydrogen.



S ynthesis of  $\alpha,\beta$ -unsaturated ketones is one of the important reactions in organic synthesis due to the extensive applications of such unsaturated ketones in the synthesis of pharmaceuticals, biologically active compounds, pesticides, food additives, solar creams, and other functional materials.<sup>1</sup> In conventional synthesis, aldol condensation between ketones and aldehydes is employed for the preparation of  $\alpha_{,\beta}$ unsaturated ketones using a stoichiometric amount of strong base. In addition to the high cost, aldehydes are prone to air oxidation resulting in contamination with carboxylic acids, which creates a problem in storing these reactive compounds and requires purification before use.<sup>2</sup> These drawbacks urged the development of alternative methods for the synthesis of  $\alpha_{\beta}$ -unsaturated ketones. Rhodium-catalyzed direct  $\alpha$ -alkenylation of ketones using internal alkynes was reported recently; however, this method suffers from the requirement of high catalyst loading and use of bifunctional ligands in stoichiometric amounts (Scheme 1a).<sup>3</sup> Synthesis of  $\alpha,\beta$ -unsaturated ketones directly from the alcohols and ketones can result in synthetic brevity and circumvent the isolation and purification of intermediates. Thus, tandem synthetic methods are developed combining the oxidation of alcohols to aldehydes and condensation of aldehydes with ketones. Precious transition metals on alkaline solid supports, such as Pd/AlO(OH),<sup>4a</sup> Pd/MgO-Al<sub>2</sub>O<sub>3</sub>,<sup>4b</sup> Au/AlO(OH),<sup>4c</sup> and Pt/CeO<sub>2</sub>,<sup>4d</sup> containing active sites for oxidation of alcohols and condensation reactions were developed, which also required excess alkali additives.<sup>5</sup> Moreover, heterogeneous base metal catalysts such as TiN, NbN, and NbCN were also developed for the synthesis of  $\alpha_{,\beta}$ -unsaturated ketones, but the preparation of these catalysts requires tedious and harsh nitridation of the parent metal oxides.<sup>6a,b</sup> Recently, CrO<sub>3</sub> and CeO<sub>2</sub> catalysts have been reported, while the chromium is toxic, catalysis by cerium oxide is limited to chalcone synthesis (Scheme 1b).<sup>6c,o</sup>

Alternatively, acceptorless dehydrogenative coupling of  $alcohols^7$  and ketones is one of the most prominent synthetic

Scheme 1. Methods for the  $\alpha$ -Alkenylation of Ketones a) Synthesis of  $\alpha_{\beta}$ -unsaturated ketones using ketones & alkynes





b) Transition metal catalyzed coupling of alcohols with ketones



method for the preparation of  $\alpha$ , $\beta$ -unsaturated ketones, which produce water and H<sub>2</sub> as the only byproducts. Over the decades, homogeneous organometallic complexes have been developed as catalysts for the acceptorless dehydrogenation of alcohols followed by condensation of *in situ* generated aldehydes, with C–H acidic compounds to afford atom economical and sustainable chemical transformations.<sup>8</sup> Often hydrogen obtained from dehydrogenation of alcohols is

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utilized for the hydrogenation of condensation products, thus, resulting in the term "borrowing hydrogen methods",<sup>9</sup> which attracted increasing attention for the C–C and C–N bond formation reactions. The direct use of alcohols in dehydrogenative coupling reactions for the synthesis of  $\alpha,\beta$ -unsaturated ketones compound is challenging, because C==C double bonds undergo facile hydrogenation to deliver the  $\alpha$ -alkylated ketones or alcohols.<sup>10,11</sup> In this direction, Yus and co-workers reported the ruthenium-catalyzed  $\alpha$ -olefination of ketones by acceptorless dehydrogenative coupling alcohols. However, poor yields, limited substrate scope, and requirement of a stoichiometric base necessitate the need for an alternative protocol.<sup>12</sup>

In recent years, in order to attain sustainability in catalysis, replacement of precious noble-metal catalysts with economical and environmentally benign earth-abundant base-metal catalysts is in high demand. Thus, atom-economical dehydrogenative coupling of alcohols and ketones to  $\alpha$ .  $\beta$ -unsaturated ketones by base-metal catalysis is a desirable transformation. In this direction, Mn is one of the most earth-abundant transition metals, third only to Fe and Ti, and chemists have already developed excellent catalytic transformations using manganese complexes.<sup>13</sup> Encouraged by our recent results in developing atom economical and sustainable catalytic methods,<sup>14</sup> herein, we report a dehydrogenative coupling of alcohols and ketones catalyzed by Kempe's Mn PNP pincer complexes,<sup>15a,b</sup> which selectively produce the  $\alpha$ -alkenyl ketones, H<sub>2</sub>O and H<sub>2</sub>. To our knowledge, there is no literature report on  $\alpha$ -olefination of ketones catalyzed by Mn complexes.

Using 1-tetralone and benzyl alcohol as model substrates, extensive optimization studies were carried out to determine suitable experimental conditions for catalytic  $\alpha$ -alkenylation of ketones catalyzed by complexes 1 and 2 (see Table S1). Observations revealed that 4-methyl substituted catalyst 2 is better than catalyst 1 containing a phenyl group in the backbone. While catalyst 1 provided lower yields and selectivity, the catalytic reaction using 2 (0.3 mol %) and Cs<sub>2</sub>CO<sub>3</sub> (5 mol %) with 1-tetralone (0.5 mmol) and benzyl alcohol (0.6 mmol) provided a 97% conversion of 1-tetralone and the alkenyl and alkylated products 3a:3a' were isolated in 80% yield with 97:3 selectivity, respectively (Scheme 2). Use

Scheme 2. Mn(I)-Catalyzed  $\alpha$ -Alkenylation of 1-Tetralone Using Benzyl Alcohol



of other bases produced poor results. Control experiments with base alone (without catalyst) and without both base and catalyst proved that the combination of catalyst and base is essential for this transformation.

Using the optimized reaction conditions, a wide range of primary alcohols were subjected to manganese-catalyzed  $\alpha$ olefination of 1-tetralone (Scheme 3). In general, benzyl





<sup>*a*</sup>Reaction conditions: 1-tetralone (0.5 mmol), alcohol (0.6 mmol), *tert*-amyl alcohol (1.5 mL), catalyst **2** (0.3 mol %), and Cs<sub>2</sub>CO<sub>3</sub> (5 mol %) were heated at 135 °C under open conditions with an argon flow. Reported yields correspond to isolated pure compounds. Conversion of 1-tetralone is given within parentheses and determined by GC analysis using toluene as an internal standard. *α*-Alkylated ketone products were observed in less than 5% yield, in all reactions. <sup>*b*</sup>*α*-Alkylated ketone product was observed in 10% yield. <sup>*c*</sup>Reaction time of 20 h. <sup>*d*</sup>Using 0.5 mol % catalyst **2** and 5 mol % base.

alcohols bearing electron-donating substituents such as methyl, methoxy afforded the corresponding  $\alpha$ -alkenvl ketones in good yields with excellent conversion. Electron-rich benzyl alcohols substituted with an ortho and a meta methyl group were converted into 3b and 3c in excellent (90% and 89%, respectively) yields, whereas, para-methylbenzyl alcohol provided 3d in 81% yield. The  $\alpha$ -alkenylation of 1-tetralone with 4-methoxy, 4-isopropyl, and piperonyl benzyl alcohols afforded the corresponding products 3e-3g in 88%, 77%, and 65% yields, respectively. Notably, 4-methylthiolate substituted benzyl alcohol provided complete conversion under standard experimental conditions, and the corresponding product 3h was obtained in 96% yield. The presence of an electronwithdrawing substituent such as 3-chloro and 4-bromo on the aryl ring of benzyl alcohol required a longer reaction time (20 h) to provide good selectivity, and the  $\alpha$ -alkenyl ketones 3i and 3j were obtained in 54% and 78% yields, respectively. Importantly, heteroaryl methanols were tolerated in this catalytic direct  $\alpha$ -alkenvlation of ketones. 2-Thiophenemethanol and furfuryl alcohol provided  $\alpha$ -alkenylated products 3k and 31 in good yields with excellent conversion. Similarly, 1naphthalenemethanol performed well in this transformation and delivered 3m in 78% isolated yield. When  $\alpha$ -branched aliphatic alcohol such as 2-ethyl-1-butanol was subjected to

catalysis under standard experimental conditions,  $\alpha$ -alkenylated product **3n** was isolated in poor yields (37%). Thus, the catalyst load was increased to 0.5 mol %, which provided the product **3n** in 54% yield. In all these reactions,  $\alpha$ -alkylated ketone products were formed in less than 5% yield.

The scope of various aryl ketones with respect to the catalytic  $\alpha$ -alkenylation reaction using different alcohols was further investigated (Scheme 4). In general, a variety of





<sup>*a*</sup>Reaction conditions: ketone (0.5 mmol), alcohol (0.6 mmol), *tert*amyl alcohol (1.5 mL), catalyst **2** (0.3 mol %), and Cs<sub>2</sub>CO<sub>3</sub> (5 mol %) were heated at 135 °C under open conditions with an argon flow. Reported yields correspond to isolated pure compounds. Conversion of ketone is given within parentheses and determined by GC analysis using toluene as an internal standard. <sup>*b*</sup>Conversion determined from <sup>1</sup>H NMR analysis of reaction mixture using 1,2 dibromoethane as an internal standard. <sup>*c*</sup>Catalyst **2** (0.6 mol %) and base (10 mol %) were used. <sup>*d*</sup>α-Alkylated ketone product was observed in 35% yield.

primary alcohols can be employed under these reaction conditions to deliver  $\alpha$ -alkenylated products in moderate to good yields. Reaction of 4-methoxybenzyl alcohol with 0.3 mol % of 2 and 5 mol % base resulted in quantitative conversion of arylketone 5-methoxy-1-tetralone, and  $\alpha$ -alkenylated product 4a was isolated in 87% yield with 97% selectivity. The  $\alpha$ alkenyl ketone structure of 4a is also unequivocally corroborated using single-crystal X-ray analysis. When 6methoxy-1-tetralone and 7-methoxy-1-tetralone were reacted with 3,4-dimethoxybenzyl alcohol and 4-methylbenzyl alcohol, the corresponding  $\alpha$ -alkenyl ketones 4b and 4c, respectively, were isolated in good yields. Similarly, 4-(methylthio)benzyl alcohol and 2-thiophenemethanol showed very good reactivities in the  $\alpha$ -olefination of ketones and the products **4d** and 4e were obtained in 76% and 89% yields, respectively. When, 4-methyl-1-tetralone was reacted with 4-methylbenzyl alcohol and furfural alcohol, the corresponding alkenylated products 4f and 4g were formed in 71% and 86% yields, respectively. Notably, unactivated aliphatic alcohols are also amenable to this catalytic  $\alpha$ -alkenylation of ketones. 2-Ethyl-1-butanol was subjected to catalysis under standard experimental conditions,

which provided  $\alpha$ -alkenylated product **4h** in 59% yield. To expand the substrate scope beyond tetralones, 6,7,8,9tetrahydro-5*H*-benzo[7]annulen-5-one was reacted with benzyl alcohol, which delivered **4i** in 61% isolated yield. Remarkably, acyclic methylene ketone such as propiophenone was reacted with 2,3-dimethoxybenzyl alcohol and 4methoxybenzyl alcohol and the corresponding  $\alpha$ -alkenylated products **4j** and **4k** were obtained in 71% and 87% yields, respectively.

A mercury-poisoning experiment was performed to examine the involvement of any metal nanoparticles formed from complex 2. The catalytic reaction of 1-tetralone with benzyl alcohol was carried out in the presence of mercury (5 equiv, relative to 1-tetralone), which provided the corresponding alkenylated ketone 3a in 73% isolated yield (against the 80% yield in the absence of mercury; see Scheme 2), indicating that the reaction proceeds with involvement of molecular intermediates (Scheme 5a). To probe whether the  $PN_5P$ -





Mn complex 2 is also involved in the C–C bond formation in the aldol reaction, reaction of benzaldehyde with 1-tetralone in the presence and absence of the catalyst were performed, which resulted in formation of 80% and 70% of 3a, respectively (Scheme 5b and 5c). This enhanced formation of 3a is an indication that the catalyst might have moderate involvement in the key C–C bond formation process. Upon reaction of  $\alpha$ deuterated benzyl alcohol-d<sub>3</sub>, product 3a-D was obtained in which incorporation of 80% deuterium was observed at the vinyl position (Scheme 5d).

On the basis of these experimental observations and the previous studies involving the PN<sub>5</sub>P manganese pincer catalyst,<sup>15</sup> the plausible reaction mechanism for acceptorless dehydrogenative coupling of alcohols and ketones is proposed in Scheme 6. Complex 2 reacts with a catalytic amount of base to generate the dearomatized coordinatively unsaturated

Scheme 6. Proposed Reaction Mechanism for Dehydrogenative α-Alkenylation of Ketones Catalyzed by Manganese Pincer Complex 2



intermediate I. Further this intermediate I reacts with alcohol to provide alkoxy-ligated manganese complex II, through O– H activation of alcohols. Similar manganese alkoxy complexes have been isolated previously by Milstein,<sup>16</sup> Yu,<sup>17a</sup> and Liu.<sup>17b</sup>  $\beta$ -Hydride elimination of manganese-ligated alkoxy ligand with saturated intermediate II provides the corresponding aldehyde and Mn-hydride complex III. The liberated aldehyde then undergoes aldol condensation with ketone to provide the  $\alpha$ -alkenylated ketone and water as the byproduct. Intermediate III liberates H<sub>2</sub> to attain dearomatized intermediate I, completing one loop in a catalytic cycle. The aromatization and dearomatization metal–ligand cooperation in manganese intermediates I–III maintains the same oxidation state (+1) in all intermediate complexes and plays an important role in this transformation.

In conclusion, a manganese pincer complex catalyzed selective synthesis of  $\alpha$ -alkenyl ketones by acceptorless dehydrogenative coupling of primary alcohol with ketones is demonstrated. Notably, using a minimal base metalmanganese catalyst (0.3 mol %) and a mild base  $Cs_2CO_3$  (5 mol %), an assortment of cyclic and acyclic benzylic ketones can be efficiently and selectively  $\alpha$ -alkenylated with primary alcohols in moderate to excellent yields. Notably, under these catalytic conditions, heteroaryl, aliphatic, and benzylic primary alcohols containing methoxy, thiomethyl, chloro, and bromo functionalities are well tolerated. Mechanistic studies confirm the involvement of an aldehyde intermediate. The acceptorless dehydrogenative coupling of alcohols and ketones proceeds via dearomatization-aromatization metal ligand cooperation. Overall, 1 equiv of water and molecular hydrogen are liberated from the reaction as the only byproducts in this environmentally benign transformation.

## ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b01327.

Experimental procedures, spectral data, crystal data of compounds **3g** and **4a**, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of the products (PDF)

#### **Accession Codes**

CCDC 1905606–1905607 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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