

# Palladium-Catalyzed Dehydrogenative $\beta$ -Arylation of Simple Saturated Carbonyls by Aryl Halides

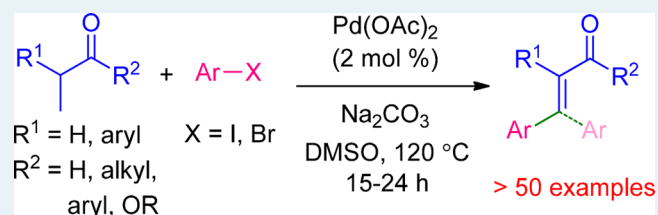
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**S** Supporting Information

**ABSTRACT:** A versatile palladium-catalyzed synthesis of highly substituted  $\alpha,\beta$ -unsaturated carbonyl compounds has been developed. In contrast to the known Heck-type coupling reaction of unsaturated carbonyl compounds with aryl halides, the present methodology allows the use of stable and readily available saturated carbonyl compounds as the alkene source. In addition, the reaction proceeds well with low catalyst loadings and does not require any expensive metal oxidants or ligands. A variety of saturated aldehydes, ketones, and esters are compatible for the reaction with aryl halides under the developed reaction conditions to afford  $\alpha,\beta$ -unsaturated carbonyl compounds in good to excellent yields. A possible reaction mechanism involves a palladium-catalyzed dehydrogenation followed by Heck-type cross couplings.

**KEYWORDS:** palladium, dehydrogenation, alkene, aryl halide, cross coupling

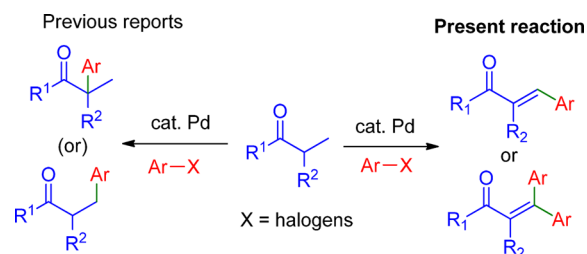


## INTRODUCTION

Highly substituted  $\alpha,\beta$ -unsaturated carbonyl compounds are an important class of organic compounds because of their ubiquitous presence in natural and bioactive molecules.<sup>1</sup> Moreover, they are also found to be potential intermediates in numerous organic and medicinal syntheses.<sup>2</sup> The classical methods of obtaining these compounds including Wittig, Horner–Wadsworth–Emmons, and Peterson olefination reactions are less attractive owing to their substrate unavailability, phosphorus byproduct, and sensitive reaction conditions.<sup>3</sup> Similarly, aldol and Claisen–Schmidt condensation reactions to synthesize  $\alpha,\beta$ -unsaturated carbonyl compounds are less appealing because of their basic and harsh reaction conditions.<sup>4</sup> In addition to these methods, several metal-mediated or -catalyzed reactions have been developed for the formation of  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>5,6</sup>

In recent years, the transition-metal-catalyzed dehydrogenation of saturated C–C bonds into unsaturated C=C bonds has emerged as an effective method in organic synthesis. In particular, the dehydrogenation of saturated carbonyl compounds into unsaturated or aromatic compounds provides a new effective synthesis approach.<sup>7</sup> In this context, dehydrogenative coupling reactions of saturated compounds with aryl nucleophiles (heteroarenes and aryl carboxylic acids) to form substituted unsaturated carbonyl compounds is limited to specific substrates and required expensive metal oxidants.<sup>8</sup> Alternatively, the use of simple and largely available aryl halides in the dehydrogenative coupling of saturated carbonyl compounds is very challenging because of the facile  $\alpha$ -arylation<sup>9</sup> or  $\beta$ -arylation<sup>10</sup> instead of dehydrogenation (Scheme 1). Our continuous interest in the development of new and efficient organic transformations using transition-metal catalysts<sup>11</sup> prompted us to tackle these problems. Herein, we report a straightforward route for the synthesis of

## Scheme 1. Pd-Catalyzed Reactions of Carbonyl Compounds with Aryl Halides



highly substituted  $\alpha,\beta$ -unsaturated carbonyl compounds via palladium-catalyzed dehydrogenative coupling of saturated carbonyl compounds with aryl halides.

## RESULTS AND DISCUSSION

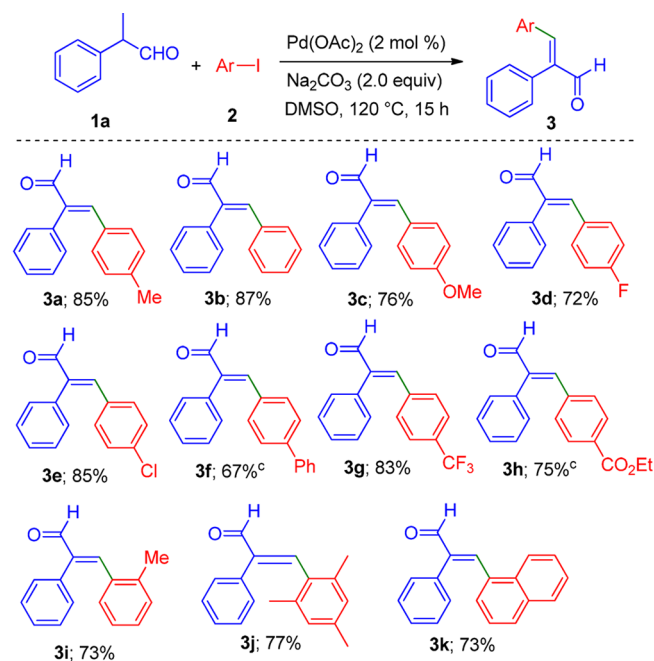
We started our investigations using 2-phenylpropanal (**1a**) and 4-iodotoluene (**2a**) as the substrates. After a series of systematic investigations, we found that the reaction of **1a** (0.50 mmol), **2a** (1.25 mmol),  $\text{Na}_2\text{CO}_3$  (1.0 mmol), and  $\text{Pd}(\text{OAc})_2$  (0.010 mmol, 2 mol %) in dimethyl sulfoxide (DMSO) at 120 °C for 15 h gave arylated product (*E*)-2-phenyl-3-(*p*-tolyl)acrylaldehyde (**3a**) in 85% isolated yield. (See the Supporting Information for the detailed optimization studies.) The present catalytic reaction conditions show excellent catalytic activity requiring low catalyst loading without the need for an external oxidant and ligand.

Next, we tested the generality of the reaction by using **1a** with various aryl iodides, and the results are presented in Table 1.

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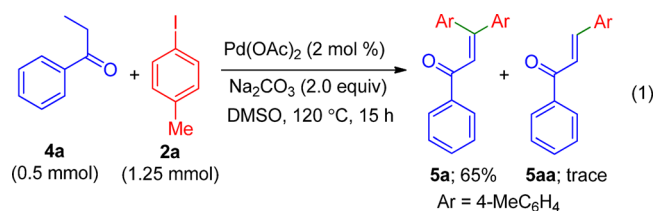
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**Table 1. Scope of Diarylacrylaldehyde Formation from 2-Phenylpropanal<sup>a,b,c</sup>**

<sup>a</sup>Unless otherwise mentioned, all reactions were carried out using **1a** (0.5 mmol), ArI (1.25 mmol), Pd(OAc)<sub>2</sub> (0.010 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol) in DMSO (2 mL) at 120 °C for 15 h. <sup>b</sup>Isolated yields. <sup>c</sup>PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.010 mmol) was used instead of Pd(OAc)<sub>2</sub> for **3f** and **3h**.

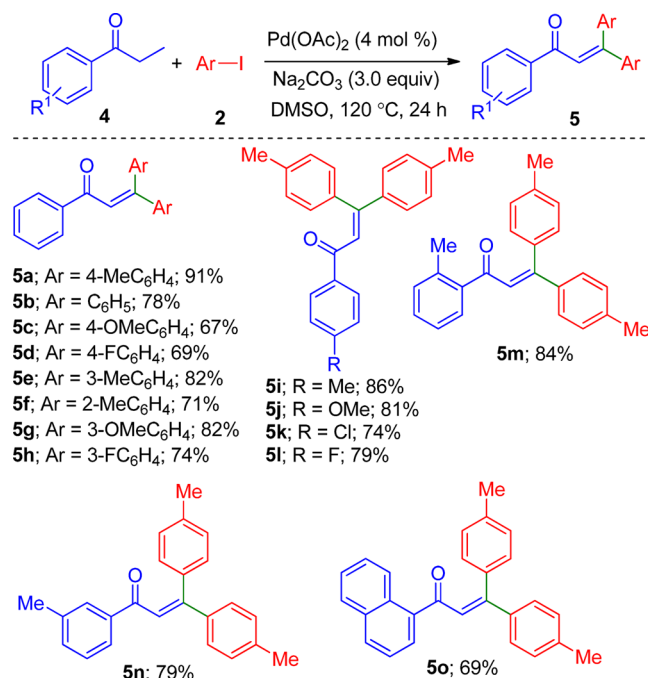
The catalytic reaction is compatible with both electron-donating and electron-withdrawing groups on the aryl iodides (Table 1). It is important to mention that there is no simple route to give unsymmetrical 1,2-diaryl acrylaldehydes.

To extend the scope of the present reaction, we tested ethyl aryl ketones under the standard reaction conditions. Thus, the reaction of propiophenone (**4a**) and 4-iodotoluene (**2a**) gave β-diarylation product **5a** in 65% isolated yield with only a trace of monoarylation product **5aa** (eq 1). By increasing the amount of

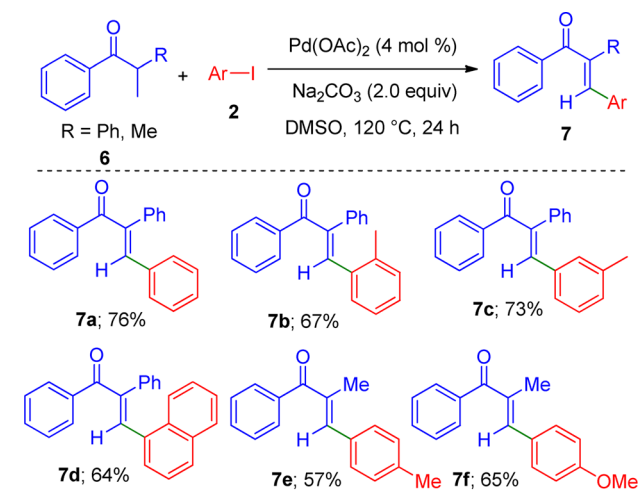


aryl iodide, base, reaction time, and catalyst loading, the reaction gave **5a** as the sole product in 91% isolated yield (Table 2). It is worth mentioning that the synthesis of trisubstituted alkenes via metal-catalyzed cross-coupling reactions is quite challenging.<sup>12</sup> Under these modified reaction conditions, the reaction of various substituted aryl ketones with aryl iodides to give trisubstituted alkenes was examined, and the results are shown in Table 2. The reaction worked well with diversely substituted ketones and aryl iodides to afford respectively substituted chalcones in very good yields.

Similar to the reaction of 2-phenylpropanal (**1a**) with aryl iodide **2**, α-aryl/alkyl substituted propiophenone **6** underwent dehydrogenative mono β-diarylation with aryl iodides to give various trisubstituted enone products **7a–f** (Table 3). In all cases, only E isomers were obtained. The stereochemistry of

**Table 2. Scope of the Dehydrogenative Arylation Reaction of Ethyl Aryl Ketones with Aryl Iodides<sup>a,b</sup>**

<sup>a</sup>Unless otherwise mentioned, all reactions were carried out using **4** (0.5 mmol), ArI (1.75 mmol), Pd(OAc)<sub>2</sub> (0.020 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in DMSO (2 mL) at 120 °C for 24 h. <sup>b</sup>Isolated yields.

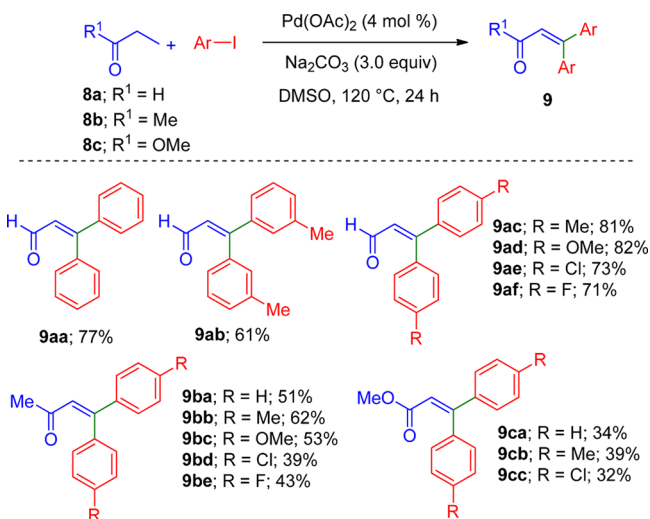
**Table 3. Scope of Dehydrogenative Arylation Reaction of α-Substituted Propiophenone **6** with Aryl Iodides<sup>a,b</sup>**

<sup>a</sup>Unless otherwise mentioned, all reactions were carried out using **6** (0.50 mmol), ArI (1.25 mmol), Pd(OAc)<sub>2</sub> (0.020 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol) in DMSO (2 mL) at 120 °C for 24 h. <sup>b</sup>Isolated yields.

products **7c** and **7e** was further confirmed by single-crystal X-ray diffraction. The transition-metal-catalyzed hydroacylation of alkyne is a common strategy often employed to attain compound **7**. However, the use of unsymmetrical alkyne in the hydroacylation reaction produces inseparable regio- and stereoisomeric mixtures, which significantly limits their applicability.<sup>13</sup> The present reaction system overcomes the limitation and allows the synthesis of different substituted 2,3-diaryl vinyl ketones.

The present catalytic reaction can be further extended to the dehydrogenative coupling of alkyl carbonyl compounds such as propionaldehyde (**8a**), butan-2-one (**8b**), and methyl propionate (**8c**) with aryl iodides (Table 4). Thus, the reaction of **8a** with

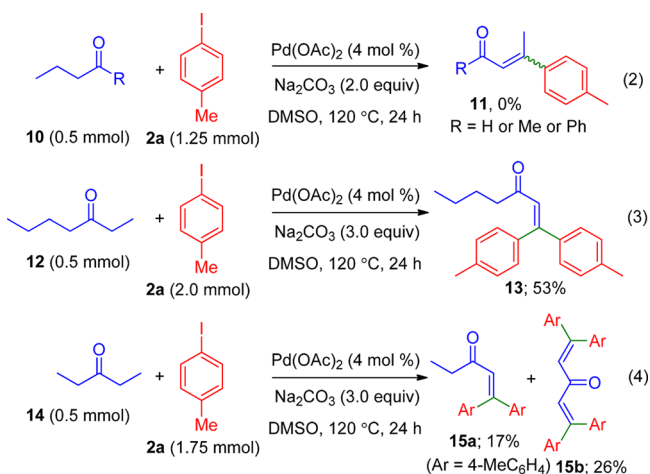
**Table 4. Scope of Dehydrogenative Arylation Reaction of Alkyl Carbonyl Compounds with Aryl Iodides<sup>a,b</sup>**



<sup>a</sup>Unless otherwise mentioned, all reactions were carried out using **8** (0.5 mmol), ArI (1.75 mmol), Pd(OAc)<sub>2</sub> (0.020 mmol), and Na<sub>2</sub>CO<sub>3</sub> (1.5 mmol) in DMSO (2 mL) at 120 °C for 24 h. <sup>b</sup>Isolated yields.

various aryl iodides afforded 3,3-diarylacrylaldehydes **9aa–af** in 61–82% yields. Likewise, ethyl methyl ketone **8b** underwent a dehydrogenative coupling reaction with different aryl iodides to give 4,4-diarylbut-3-en-2-one compounds **9ba–be** in moderate yields. The syntheses of compounds **9aa–af** and **9ba–be** from simple acrylaldehyde or methyl vinyl ketone are limited by facile polymerization.<sup>14</sup>

Surprisingly,  $\beta$ -substituted carbonyl compounds did not give dehydrogenative coupling products under similar reaction conditions (eq 2). The reaction of carbonyl compounds containing



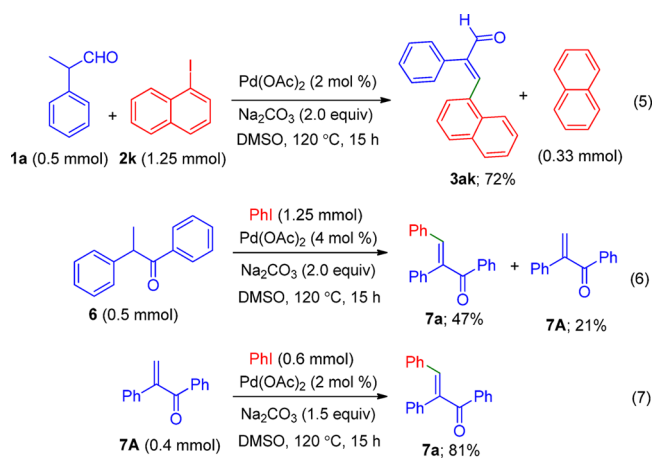
both substituted and unsubstituted  $\beta$ -carbons functionalized regioselectively at the unsubstituted  $\beta$ -carbon (eq 3) occurred. However, diethyl ketone reacted with 4-iodotoluene (**2a**) under similar reaction conditions to form 1,1-diarylation product **15a** in 17% yield and 1,1,5,5-tetraarylation product **15b** in 26% yield (eq 4).

These results suggest that the dehydrogenation step is slower than the Heck reaction step.

The reaction of aryl bromides with **1a** or **4a** under the above reaction conditions did not give the expected dehydrogenative coupling products. However, the reaction of 2-phenylpropanal (**1a**) and 4-bromotoluene (**16a**) proceeded smoothly in the presence of bidentate phosphine ligand 1,4-bis(diphenylphosphino)butane (dppb) in dimethylformamide (DMF) instead of DMSO. Unlike the reaction of **1a** with aryl iodide, aryl bromide gave both mono- and diarylated products in good yields (Scheme 2). Under similar reaction conditions, propiophenone (**4a**) also reacted with aryl bromides **16** to give diarylation products **5** in moderate to good yields (Scheme 2).

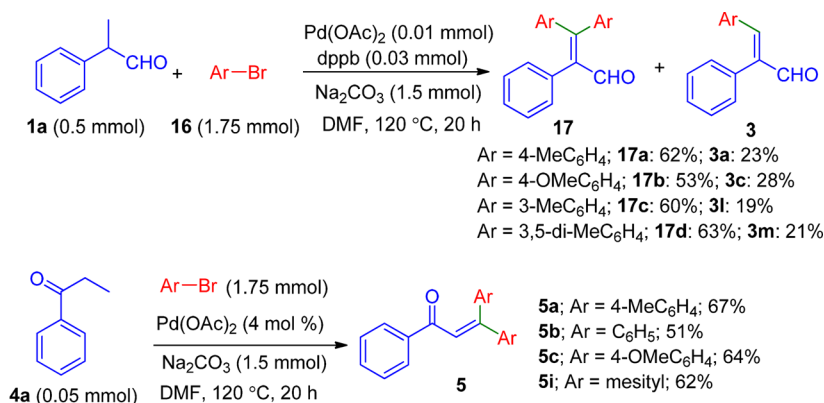
To understand the nature of the present catalytic reaction, we carried out a deuterium scrambling reaction for substrates **1a** and **4a** by the addition of 10 equiv of CD<sub>3</sub>OD under standard reactions in the absence of aryl halides (Scheme 3). Both substrates showed 50% deuterium exchange at the  $\alpha$ -carbon after 5 h of reaction, whereas no deuterium scrambling was observed at  $\beta$ -carbon or aromatic hydrogens.

On the basis of these experimental results and the existing literature, a possible catalytic cycle is depicted in Scheme 4. The catalytic cycle is initiated by the oxidative addition of aryl iodide to palladium(0) to form Ar–Pd<sup>II</sup>–I. Then, the substitution of I<sup>–</sup> into arylpalladium iodide species by carbonyl compound **1a** in the presence of Na<sub>2</sub>CO<sub>3</sub> affords intermediate **I**. Pd<sup>II</sup>-enolate **I** could exist as either an O-bound or C-bound complex. In general, late transition metals favor C-bound over O-bound enolates, and thus palladium favors the formation of intermediate **I**. Facile  $\beta$ -hydride elimination<sup>7,8</sup> of intermediate **I** under the reaction conditions gave unsaturated carbonyl compound **II** and Ar–Pd–H, which then underwent reductive elimination to form Pd(0) and ArH. The classical Heck reaction of intermediate **II** with ArI in the presence of Pd(0) and base gave final product **3** and Pd(0). In contrast to the known palladium-catalyzed dehydrogenation reactions, the present reaction proceeds well without expensive metal oxidants. ArX indirectly acts as an oxidant of palladium under this catalytic reaction. The formation of ArH from ArX under our reaction conditions is evidenced by the isolation of naphthalene in the synthesis of **3ak** from **1a** (eq 5). Furthermore,

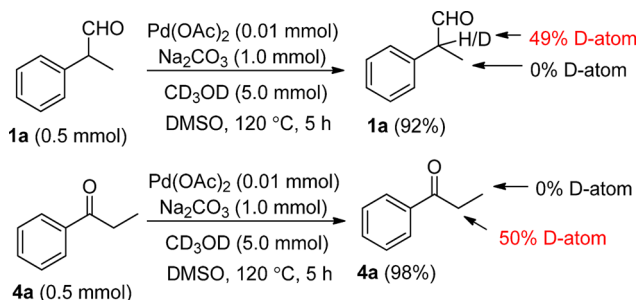


the formation of intermediate **II** was evidenced by the isolation of 1,2-diphenylprop-2-en-1-one (**7A**) from the reaction of 1,2-diphenylpropan-1-one (**6**) and iodobenzene with a shorter reaction time (eq 6). The reaction of **7A** with iodobenzene under the standard catalytic reaction conditions affords (*E*)-1,2,3-triphenylprop-2-en-1-one **7a** in 81% isolated yield (eq 7). The results

Scheme 2. Pd-Catalyzed Dehydrogenative Coupling Reaction Using Aryl Bromides



Scheme 3. Deuterium Exchange Studies



obtained from eqs 5–7 strongly support the proposed reaction mechanism in Scheme 4.

The selective formation of unsaturated compound **II** over the other possible  $\alpha$ - or  $\beta$ -arylations from **1a** (Scheme 3) is the success of the present catalyst system. It is known that  $\beta$ -hydrogen elimination from  $\alpha$ -metal carbonyl compound **I** has an activation energy that is lower than their reductive elimination.<sup>10a,15</sup> Furthermore, the general criteria for  $\beta$ -hydrogen elimination is the presence of a vacant site in a metal complex. Under the present reaction condition, intermediate **I** has four coordination sites, from which two are filled by alkyl and aryl groups and the other two ligands most probably are filled by DMSO. It has been reported that DMSO can coordinate to Pd very weakly and in a reversible manner.<sup>16</sup> Thus, the reaction

system supports  $\beta$ -hydrogen elimination over reductive elimination.

## CONCLUSIONS

We have successfully demonstrated a versatile method for the synthesis of highly substituted  $\alpha,\beta$ -unsaturated carbonyl compounds by the palladium-catalyzed dehydrogenative coupling reaction of saturated carbonyl compounds with aryl halides. The reaction proceeds with broad substrate scope and good to excellent yields. The present catalytic system does not require expensive metal oxidants. A possible mechanism of the catalytic reaction is proposed, and key intermediates were isolated to support the proposed reaction mechanism.

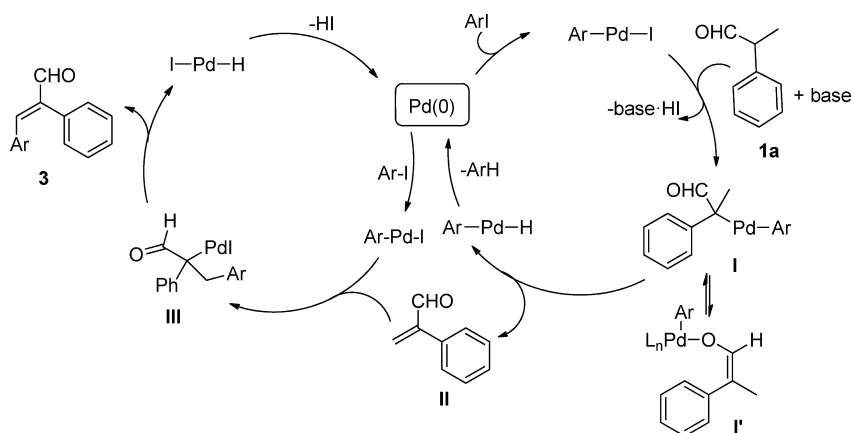
## ASSOCIATED CONTENT

### Supporting Information

The following files are available free of charge on the ACS Publications website at DOI: 10.1021/cs501326p.

General experimental procedures, characterization details, and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of new compounds (PDF).  
 Crystallographic data file data\_121035lt\_0m (CIF).  
 Crystallographic data file data\_mo\_140935lt\_0m (CIF).  
 Crystallographic data file data\_140936LT\_0m (CIF).

Scheme 4. Proposed Catalytic Cycle



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## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

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