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## Graphical Abstract

**Palladium-Catalyzed Carbonylative/Decarboxylative Cross-Coupling of *α*-Bromo-Ketones with Allylic Alcohols to *γ*,*δ*-Unsaturated Ketones**

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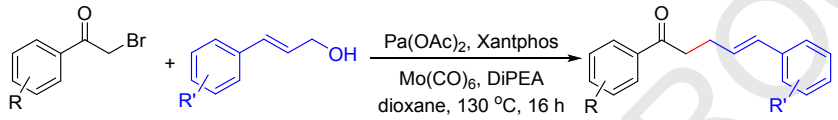

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# Palladium-Catalyzed Carbonylative/Decarboxylative Cross-Coupling of $\alpha$-Bromo-Ketones with Allylic Alcohols to $\gamma,\delta$-Unsaturated Ketones

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ABSTRACT

In this communication, a palladium-catalyzed carbonylative/decarboxylative cross-coupling of α-bromo-ketones with allylic alcohols has been developed. With $Mo(CO)_6$ as the CO source, γ,δ-unsaturated ketones were isolated in good yields. The release of $CO_2$ was confirmed as well.



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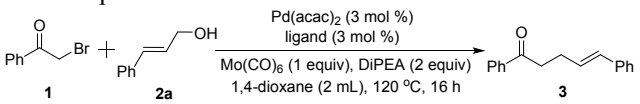
Palladium-catalyzed cross-coupling reactions, as recognized by 2010 Nobel Prize in Chemistry,[1] have now emerged as one of the most powerful methods for the formation of C-C bonds and have been widely applied in synthetic chemistry.[2] In general, organic halides reacted with different carbon nucleophiles under the catalysis of transition metals. Despite great efficiency and excellent functional group tolerance, organic metallic compounds were usually used as the coupling partner, thus reduced the total efficiency since the organometallics needed to be pre-prepared. Compared to the traditional coupling reactions, the reductive cross-coupling of two different electrophiles have recently attracted more and more attentions since the need for preformed carbon nucleophiles were avoided.[3-6]

On the other hand, transition metal-catalyzed carbonylation reaction has now been accepted as a powerful method for the synthesis of carbonyl-containing compounds.[7,8] However, examples on using carbon monoxide as deoxygen reagent in cross coupling reactions still rarely reported. Nevertheless, some related palladium-catalyzed decarboxylative carbonylation reaction were reported by Lee and then us.[9] Recently, we also developed a series of procedures for the carbonylative transformation of alcohols.[10] With our continuous interest in developing novel carbonylation based transformations, we were interested in realizing the cross-coupling of organic halides with alcohols via deoxygenation process. Notably, synthetically important γ,δ-unsaturated ketones can be produced as the terminal products.[11]

Initially, we chose 2-bromoacetophenone and cinnamyl alcohol as the model substrates to establish this catalytic system (Table 1). With $Pd(acac)_2$ as the catalyst and $PPh_3$ as the ligand, 12% of the desired 1,5-diphenylpent-4-en-1-one was formed in the presence of $Mo(CO)_6$ and DiPEA in 1,4-dioxane at 120 °C (Table 1, entry 1). Then different phosphine ligands were tested subsequently. Similar results were obtained when $BuPAd_2$, $PCy_3$, DPPP, DPPE or BINAP were used as the ligands (Table 1, entries 2-6). Large amount of acetophenone was formed due to the dehalogenation of 2-bromoacetophenone. To our delight, 55% of the target product was formed with Xantphos as the ligand (Table 1, entry 7). The reaction yield can be further improved when $Pd(OAc)_2$ or $Pd(TFA)_2$ was applied as the catalyst precursor (Table 1, entries 8-9). Finally, 73% isolated yield of 1,5-diphenylpent-4-en-1-one was achieved by performing the reaction at 130 °C using $Pd(OAc)_2$ as the catalyst (Table 1, entry 10). It's important to mention that no reaction occurred in the absence of $Mo(CO)_6$ or DiPEA.

Scheme 1. Synthesis of γ,δ-unsaturated ketones.

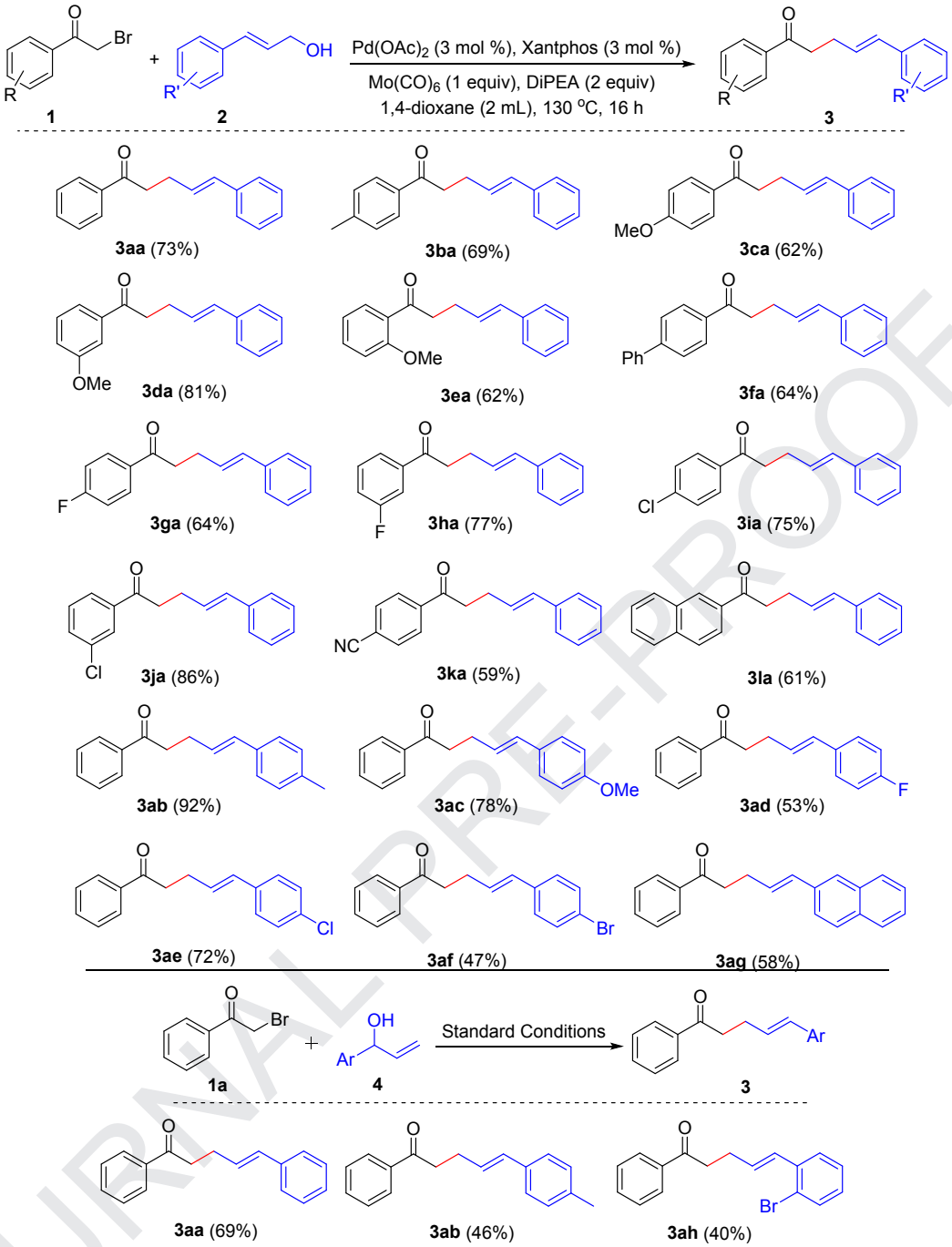
Table 1. Optimization of reaction conditions.[a]




| Entry | Palladium | Ligand | Yield (%) |
|---|---|---|---|
| 1 | $Pd(acac)_2$ | $PPh_3$ | 12 |
| 2 | $Pd(acac)_2$ | $BuPAd_2$ | 14 |
| 3 | $Pd(acac)_2$ | $PCy_3$ | 15 |
| 4 | $Pd(acac)_2$ | DPPP | 13 |
| 5 | $Pd(acac)_2$ | DPPE | 11 |
| 6 | $Pd(acac)_2$ | BINAP | 16 |
| 7 | $Pd(acac)_2$ | Xantphos | 55 |
| 8 | $Pd(OAc)_2$ | Xantphos | 63 |
| 9 | $Pd(TFA)_2$ | Xantphos | 62 |
| 10 | $Pd(OAc)_2$ | Xantphos | 75[b]; 73[b,c] |

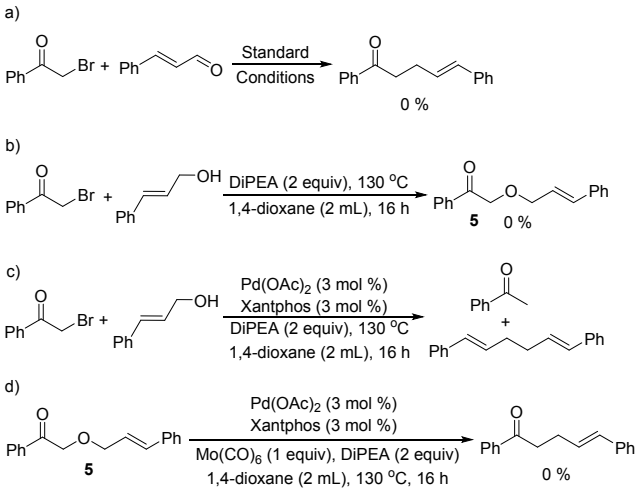
a. Reaction conditions: **1** (0.6 mmol), **2a** (0.5 mmol), palladium (3 mol%), ligand (3 mol% for bidentate ligand; 6 mol% for monophosphine), DiPEA (1.5 mmol), $Mo(CO)_6$ (0.5 mmol), 1.4-dioxane (2 mL), 120 °C, 16 h, yield was determined by GC. b. 130 °C. c. Isolated yield. DiPEA: *N*,*N*-diisopropylethylamine. $BuPAd_2$: di(1-adamantyl)-*n*-butylphosphine. DPPP: 1,3-bis(diphenylphosphino)propane. DPPE: 1,2-bis(diphenylphosphino)ethane. BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

With the optimized reaction conditions in hand, the scope of substrates was carried out subsequently (Scheme 1).[12] From the results we obtained, we can conclude that the substitution variation on α-bromo-ketones has very limited influence on the reaction yields (Scheme 1, **3ba**-**3la**; 59-86% yields). Then several allylic alcohols were tested with 2-bromoacetophenone under our standard conditions (Scheme 1, **3ab**-**3ag**). Moderate to excellent yields can be achieved in general (47-92%). Additionally, 1-aryl-2-propen-1-ols (**4**) were tested under our conditions as well. Moderate yields of the desired 1,5-diarylpent-4-en-1-ones can be successfully obtained as well. However, it is also important to mention that alcohols including 2-phenylbut-3-en-2-ol, 1,1-diphenylprop-2-en-1-ol, 3-(4-(dimethylamino)phenyl)prop-2-en-1-ol, 3-(furan-2-yl)prop-2-en-1-ol, 3-(thiophen-2-yl)prop-2-en-1-ol, 3-cyclohexylprop-2-en-1-ol, 3,7-dimethylocta-2,6-dien-1-ol, and 4,7-dimethylocta-2,6-dien-1-ol were also tested with 2-bromoacetophenone under our standard conditions, but no target product could be detected.




Reaction conditions: 1 (0.6 mmol), 2 or 4 (0.5 mmol), Pd(OAc) (3 mol %), Xantphos (3 mol %), DiPEA (1.5 mmol), $Mo(CO)_6$ (0.5 mmol), 1.4-dioxane (2 mL), 130 °C, 16 h, isolated yields.

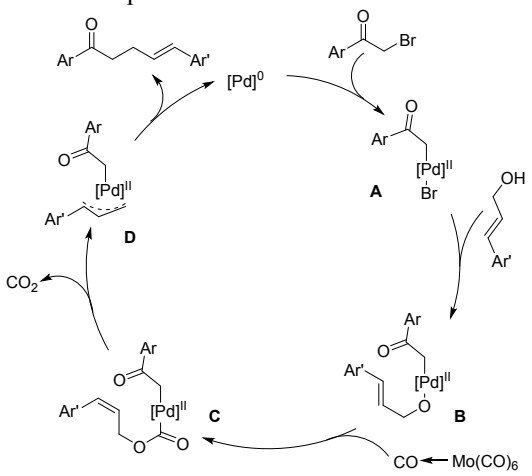
In order to understand the reaction pathway, several control experiments were performed (Scheme 2). Under the standard reaction conditions, no reaction occurred when we replace cinnamyl alcohol with cinnamaldehyde (Scheme 2, eq. a). No 2-(cinnamyloxy)-1-phenylethan-1-one (**5**) could be detected in the absence of palladium catalyst and $Mo(CO)_6$ (Scheme 2, eq. b). In the absence of $Mo(CO)_6$, only acetophenone and 1,6-diphenylhexa-1,5-diene could be detected (Scheme 2, eq. c). Then we prepared 2-(cinnamyloxy)-1-phenylethan-1-one (**5**) and applied as starting material under our standard conditions, no desired 1,5-diphenylpent-4-en-1-one could be detected (Scheme 2, eq. d). Additionally, we are also able to confirm the formation of $CO_2$ gas by releasing the gas of the model reaction into a clear solution of $Ca(OH)_2$ and white participate forms (see Supporting information).




Scheme 2 Control experiments.

With these information in hand and also inspired by literature,[3-7] a possible reaction mechanism is proposed (Scheme 3). Initially, Pd(0) complex will be generated and then do oxidative addition with 2-bromoacetophenone to produce complex **A**. After base assisted X-ligand exchanging with cinnamyl alcohol, complex **B** will be formed. Complex **C** will be produced after CO insertion which will subsequently release one molecular of $CO_2$ to give allylic palladium complex **D**. After reductive elimination, the terminal product will be eliminated and $Pd^0$ will be regenerated for the next catalytic cycle.

Scheme 3. Proposed reaction mechanism.




In summary, a palladium-catalyzed carbonylative/decarboxylative cross-coupling of α-bromo-ketones with allylic alcohols has been developed. With $Mo(CO)_6$ as the CO source, γ,δ-unsaturated ketones were isolated in moderate to good yields. The release of $CO_2$ was confirmed and a possible reaction pathway is proposed as well.

## Acknowledgments

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12. General Procedure: A 15 mL pressure tube containing **1** (0.6 mmol, 1.2 equiv.), **2a** (0.5 mmol), $Pd(OAc)_2$ (3 mol%), Xantphos (3 mol%), $Mo(CO)_6$ (0.5 mmol, 1 equiv.) was evacuated and purged with nitrogen gas three times. Then, DiPEA (1.5 mmol, 3 equiv.) and dioxane (2 mL) was added to the reaction tube by syringe. The tube was sealed and the mixture was stirred at 130 °C for 16 h. After the reaction was completed, the reaction mixture was filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel to afford the corresponding product **3**.

## Supplementary Material

General comments, optimization details, analytic data and NMR spectra.

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1. Carbonylative/decarboxylative cross-coupling reaction.
2. Good yields of γ,δ-unsaturated ketones with $Mo(CO)_6$ as the solid CO source.
3. Using α-bromo-ketones and allylic alcohols as readily available substrates.