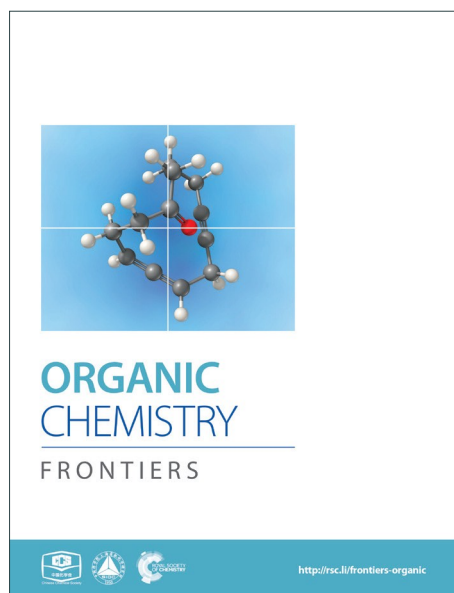
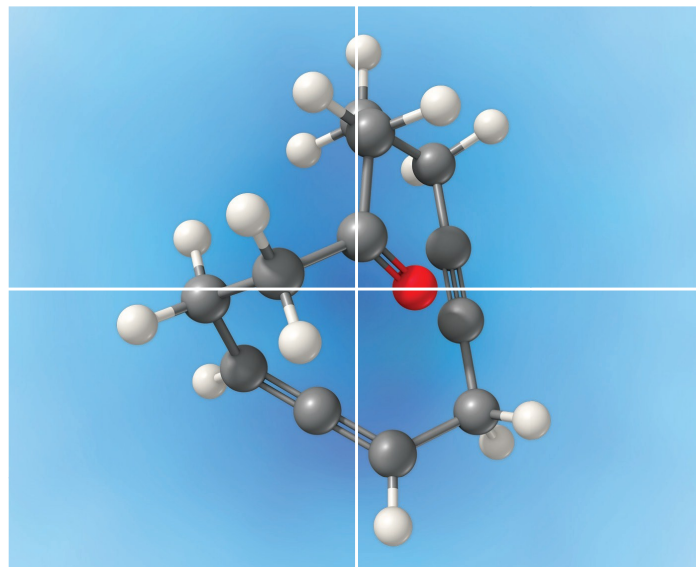


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Synthesis of Aromatic β -Keto Esters via a Carbonylative Suzuki-Miyaura Coupling Reaction of α -Iodo Esters with Arylboronic Acids

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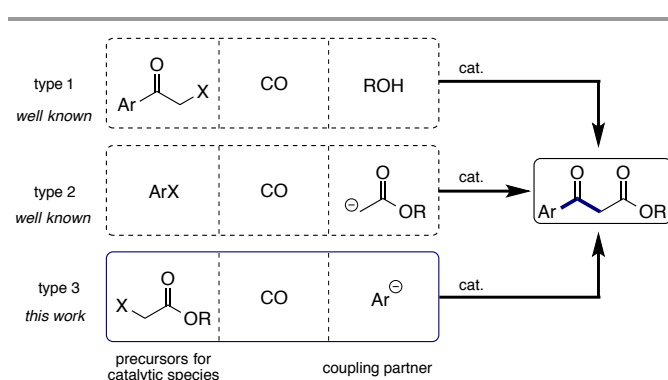
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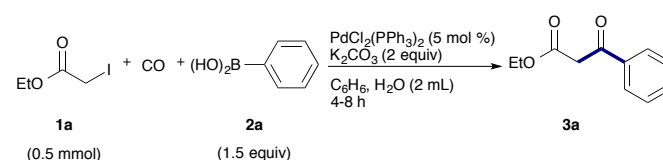
Abstract here. Aromatic β -keto esters were synthesized via a carbonylative cross-coupling reaction of alkyl iodides and arylboronic acids in the presence of a catalytic amount of Pd catalyst. A cooperative radical and Pd-catalyzed mechanism is proposed.

Carbonylation reactions with carbon monoxide are one of the most useful tools for the synthesis of carbonyl compounds.¹ Thus far, our group has focused on the potential of the Pd/light-induced system for the carbonylation of alkyl iodides,² and we previously reported that arylboronic acids can serve as a coupling reagent to modify the Pd/light-induced system to produce alkyl aryl ketones.³

β -Keto esters are a key species in basic organic reactions and are extensively used as building blocks for the synthesis of natural products.⁴ In principle the methods used for the synthesis of aromatic β -keto esters via carbonylation are categorized as 3 types (Scheme 1): metal catalyzed esterification of α -halo ketones using CO and alcohols (type 1);⁵ carbonylation of aryl halides in the presence of ester enolates (type 2);^{6,7} and, carbonylation of α -halo esters in the presence of aryl anions (type 3). Among them, to the best of our knowledge, the type 3 strategy has not been investigated so far. We recently reported that carbamoyl acetates could be synthesized using α -iodo acetates, CO, and amines with a Pd/light-induced system.⁸ We believed that the use of arylboronic acids instead of amines would lead to the synthesis of aryl β -keto esters, representing the type 3 reaction. Herein, we report that the envisaged reaction did proceed smoothly.

Scheme 1 Possible Strategies for Aromatic β -Keto Esters via Carbonylation Reactions

As a model, we chose the reaction of ethyl iodoacetate (**1a**) and phenylboronic acid (**2a**) (Table 1). When a mixture of **1a**, **2a**, K_2CO_3 , and a catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol %) was irradiated under 10 atm of CO using a xenon lamp (500 W) through a Pyrex filter, ethyl benzoylacetate (**3a**) was obtained in 65% yield (entry 1). The reaction with atmospheric CO gave only 16% yield of **3a** (entry 2). The use of a black light (15 W \times 2) instead of a xenon lamp increased the yield 76-78% (entries 3 and 4). We noticed that even under ambient temperature and dark conditions, 40% yield of **3a** was formed (entry 5). The reaction conducted at 40 °C gave **3a** in 58% yield (entry 6). When we extended the reaction time to 8 h, **3a** was obtained in 69% yield (entry 7).

Table 1. Reaction of Ethyl Iodoacetate (**1a**) and Phenylboronic Acid (**2a**) to Give Ethyl Benzoylacetate (**3a**)^a

entry	conditions	CO (atm)	C ₆ H ₆ (mL)	Yield ^b (%)
1	hv (Xe, Pyrex), 4 h	10	4	65
2	hv (Xe, Pyrex), 4 h	1	4	16

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3	hv (black light ^c , Pyrex), 5 h	10	4	76
4	hv (black light ^c , Pyrex), 5 h	10	2	78 (72)
5	r.t., 5 h	10	2	40
6	40 °C, 5 h	10	2	58
7	40 °C, 8 h	10	2	69 (65)

^a Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), PdCl₂(PPh₃)₂ (5 mol %), K₂CO₃ (2 equiv), C₆H₆ (2 or 4 mL), H₂O (2 mL), CO (1 or 10 atm), 4-8 h. ^b NMR (isolated) yield. ^c Black light (peak wavelength at 352 nm).

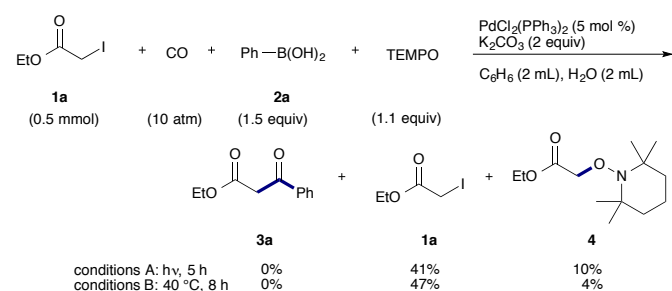
We then examined the generality of the carbonylative coupling reaction using a variety of α -iodo esters **1** and arylboronic acids **2**. Both black light irradiated conditions (conditions A) and heated conditions (conditions B) were examined, and the results are summarized in Table 2. The reaction of **1a** with 2- and 4-substituted arylboronic acids **2b-2d** gave the corresponding β -keto esters **3a-d** in good yields irrespective of the reaction conditions (entries 2-4). The reaction of **1a** with (3,5-dimethylphenyl)boronic acid (**2e**) gave the corresponding product **3e** in 61% yield (entry 5). When **1a** was reacted with arylboronic acids **2f** and **2g** having a fluorine or chlorine atom, **3e** and **3f** were obtained in modest yields (entries 6 and 7). The reaction of bromo-substituted phenyl boronic acid **2e** with **1a** gave **3h** remaining the carbon-bromine intact. The reaction was sluggish (31%, after 5 h), however the extended reaction time of 20 h gave **3h** in 95% yield (entry 8). The reactions worked well for 2-naphthaleneboronic acid (**2g**) and 3-methoxyphenylboronic acid (**2h**) although the yields were moderate (entries 9 and 10). α -Iodo benzyl ester **1b** reacted with **2a** to give **3i** in good yields under both conditions (entry 11). We then examined α -alkyl substituted iodo esters **1c** and **1d**, whose results were contrasting. The reaction of α -iodo- γ -butyrolactone (**1c**) with **2a** was smooth under either conditions **A** or **B** to give the corresponding acylated product **3j** in a good yield (entry 12). By contrast, only thermal conditions gave keto ester **3k** in reactions with ethyl 2-iodooctanoate (**1d**) and **2a** (entry 13). The failure of the reaction under photoirradiation conditions may be ascribed to the facile E2 elimination of linear iodide **1d**. The carbonylative Suzuki-Miyaura coupling reaction can be successfully extended to iodomethyl phenyl sulfone (**1e**), which gave α -sulfonyl acetophenone **3k** (entry 14).⁹ Whereas the reaction under photoirradiation conditions gave **3l** in a moderate yield due to slow reaction, heated conditions (80 °C) gave **3l** in 91% yield.¹⁰

Table 2. Synthesis of Ketones **3** by Carbonylative Coupling of Alkyl Iodides **1** and Arylboronic Acids **2**^a

entry	1	2	3	yield (%)
1				3a 72 (A) 65 (B)
2	1a			3b 85 (A) 60 (B)
3	1a			3c 78 (A) 86 (B)
4	1a			3d 92 (A) 89 (B)
5	1a			3e 61 (B)
6	1a			3f 50 (A) ^c 46 (B)
7	1a			3g 32 (A) 37 (B)
8	1a			3h 95 (A) ^d 63 (B)
9	1a			3i 60 (A) 47 (B)
10	1a			3j 39 (A) 34 (B)
11		2a		3k 72 (A) 82 (B)
12		2a		3l 85 (A) 70 (B)
13		2a		3m <1 (A) 34 (B) ^e
14		2a		3n 51 (A) 91 (B) ^e

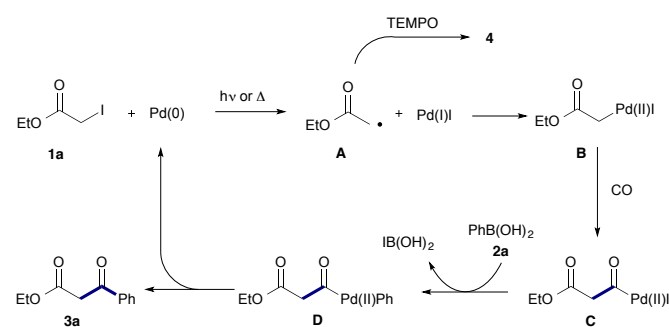
^a Reaction conditions: conditions A: **1** (0.5 mmol), **2** (0.75 mmol), PdCl₂(PPh₃)₂ (5 mol %), K₂CO₃ (1.0 mmol), C₆H₆ (2 mL), H₂O (2 mL), CO (10 atm), hv (black light, Pyrex), 5 h. conditions B: **1** (0.5 mmol), **2** (0.75 mmol), PdCl₂(PPh₃)₂ (5 mol %), K₂CO₃ (1.0 mmol), C₆H₆ (2 mL), H₂O (2 mL), CO (10 atm), 40 °C, 8 h. ^b Isolated yield. ^c **1** (1.0 mmol), **2** (1.5 mmol), PdCl₂(PPh₃)₂ (5 mol %), K₂CO₃ (4.0 mmol), C₆H₆ (2 mL), H₂O (2 mL), CO (10 atm), hv (black light, Pyrex), 8 h. ^d 20 h. ^e 80 °C.

To examine the participation of radical species, we conducted the reaction in the presence of TEMPO (2,2,6,6-tetramethylpiperidinoxy) as a radical scavenger (Scheme 2). Under both conditions, the desired reaction stopped and TEMPO adduct **4** was produced together with a largely recovered **1a**.



Scheme 2. TEMPO-Trapping Experiment

Based on the above results, we can propose a reaction mechanism involving an α -ester radical (Scheme 3). In the first step, **1a** reacts with Pd(0) to afford acetate radical **A** and Pd(I)I via a single-electron transfer.^{11,12} The resultant acetate radical **A** would couple with Pd(I)I to form α -pallado ester **B**.¹³ Then, insertion of CO into the C-Pd bond of **B** takes place to give acylpalladium species **C**. Transmetalation of **C** with phenylboronic acid (**2a**) followed by reductive elimination gives the product **3a** with an accompanying liberation of Pd(0). An alternative path based on carbonylation of radical is highly unlikely because of ready backward decarbonylation.¹⁴



Scheme 3. A Cooperative Radical and Pd-Catalyzed Mechanism

Conclusions

In summary, we have demonstrated that the carbonylative coupling reaction of readily available α -iodo esters, CO, and arylboronic acids proceeds effectively under either a combined Pd/light reaction system or Pd/thermal conditions. This method constitutes a valuable repertoire for the synthesis of aromatic β -keto esters. We proposed a reaction mechanism whereby radical reactions would lead to the effective formation of a key organopalladium species for carbonylation.

Acknowledgements

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