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Synthesis of Phenanthrone Derivatives from *sec*-Alkyl Aryl Ketones and Aryl Halides via a Palladium-Catalyzed Dual C–H Bond Activation and Enolate Cyclization

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Recently, palladium-catalyzed direct transformations of inactivated C-H bonds into various functional groups has emerged as a powerful method in organic synthesis. In particular, reactions involving directing-group-assisted activation of sp² or sp³ C-H bonds of ortho aromatic or alkenyl C-H bonds have been extensively investigated.¹ In general, this type of ortho C-H bond activation involves a five-membered cyclometalation reaction.² The directing groups frequently used in these C-H bond activation reactions include aldehyde, oxime, imine, alcohol, amine, carboxylic acid, phenol, and nitrile.^{1,2} The use of a ketone group as the directing group in the ortho aromatic C-H bond activation is also known. In this context, several examples of aromatic ketone-assisted addition of ortho C–H bonds to alkynes, $^{3a-c}$ alkenes, $^{3d-g}$ and CO/ alkenes^{3h} catalyzed by ruthenium complexes have been reported. In addition, a palladium-catalyzed multiple arylation of benzyl phenyl ketones with aryl bromides was reported by Miura and coworkers,⁴ and a ruthenium-catalyzed ortho arylation of aromatic ketones with aryl boronates was revealed by Kakiuchi et al.⁵ in 2003. Our continuous interest in metal-catalyzed dual C-H bond activation reactions⁶ via both five- and seven-membered metallacycles prompted us to explore the reaction of alkyl aromatic ketones with aryl iodides. Herein, we report an interesting synthesis of phenanthrone derivatives from sec-alkyl aryl ketones and aryl halides by a palladium-catalyzed dual C-H activation and enolate cyclization.

Since Pd(OAc)₂/Ag₂O is known to be an effective catalyst system for ortho C–H functionalization,^{1d–g} we employed this system for the reaction of acetophenone (**1a**) with iodobenzene (**2a**) in trifluoroacetic acid (TFA). The reaction at 120 °C for 20 h gave ortho-arylated product **3a** in 23% isolated yield (Table 1, entry 1). Similarly, 4-methoxyiodobenzene (**2b**) gave **3b** in 20% yield (Table 1, entry 2). Gratifyingly, the reaction of ethyl 4-iodobenzoate (**2c**) with **1a** gave the corresponding arylated product **3c** in 78% yield (Table 1, entry 3). Thus, it appears that aryl iodides with an electronwithdrawing substituent give higher yields of ortho-arylated products than those with an electron-donating group. The effects of various silver salts, oxidants, and solvents on the product yield were examined, and the results are shown in the Supporting Information.

Under the catalytic reaction conditions shown in Table 1, 4-methylacetophenone (**1b**) reacted smoothly with aryl iodides 2c-fhaving an electron-withdrawing substituent to give the corresponding ortho-arylated products 3d-g in 80, 71, 92 and 84% isolated yield, respectively (Table 1, entries 4–7). The palladium-catalyzed C–H activation is also compatible with acetophenones 1 having a chloro substituent on the aromatic ring. Treatment of 2-chloroacetophenone (**1c**) with **2f** gave **3h** in 52% yield (entry 8). The reaction of 3-chloroacetophenone (**1d**) with **2f** proceeded in a regioselective manner to give **3i** in 66% yield (entry 9). In this reaction, although there are two possible sites (C2 and C6 of 1d) for C-H bond activation, the activation occurred only at C6, likely as a result of the steric effect of the chloro group at C3. The reaction of 4-chloroacetophenone (1e) with 2c also proceeded smoothly to give the corresponding ortho-arylated product 3j in good yield (entry 10). Similarly, propiophenone (1f) reacted with 2f to give 3k in 68% yield (entry 11). Unlike the above results, benzophenone (1g) reacted efficiently with 2f to provide ortho-diarylated product 3A (Table 1 scheme) in 82% yield.

Table 1. Results of the Reaction of Aryl Ketones with Aryl lodides^a







Surprisingly, the reaction of isopropyl phenyl ketone (1h) with ethyl 3-iodobenzoate (2d) under the same conditions as for the Pd(OAc)₂-catalyzed arylation of aryl ketones gave phenanthrone derivative 4a in 68% yield (see Table 2). This arylation and cyclization reaction was successfully extended to other *sec*-alkyl aryl ketones and aryl halides, and the results are shown in Table 2. Thus, the reaction of 1h with 3- and 4-nitro-1-iodobenzene (2e and 2f, respectively) afforded 10,10-dimethylphenanthrones 4b and 4c in 78 and 69% yield, respectively. The reaction of cyclic alkyl aryl

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ketones with aryl iodides also proceeded smoothly to give the corresponding spirophenanthrone derivative. Accordingly, cyclopentyl phenyl ketone (1i) reacted with 2f to give spirophenanthrone 4d in 76% yield. In a similar manner, various six- and seven-membered cyclic alkyl aryl ketones 1j-m reacted with aryl iodides efficiently under the same catalytic conditions to give the corresponding spirophenanthrones 4e-i in good yields. The structure of 4i was further confirmed by X-ray diffraction.

 $\ensuremath{\textit{Table 2.}}$ Results of the Reaction of $\ensuremath{\textit{sec}}\xspace\ensuremath{-}\xspace\ensuremath{\mathsf{Aryl}}\xspace$ Ketones with Aryl Iodides $\ensuremath{^a}\xspace$



^{*a*} Unless otherwise mentioned, all of the reactions were carried out using ketone **1** (1.00 mmol), aryl iodide **2** (3.00 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2O (1.0 mmol), and TFA (2.0 mL) at 120 °C for 20 h.

To account for the present catalytic reaction, a possible mechanism involving a palladium-catalyzed dual C–H activation and enolate cyclization is proposed (Scheme 1). The first step likely involves coordination of 1 to the Pd(II) species followed by ortho C–H activation to form five-membered palladacycle 5. Oxidative addition of aryl iodide to 5 to give Pd(IV) intermediate $6^{6c,d,7d}$ followed by reductive elimination affords 3-Pd. These two steps are evidenced by the isolation of palladacycle dimers 5a and 5k from the reactions of Pd(OAc)₂ with aryl ketones 1a and 1k, respectively, in TFA. The structure of 5k was determined by singlecrystal X-ray diffraction (see the Supporting Information). Moreover, 5a reacted with 2f to afford ortho-arylation product 3l in 83% yield, while 5k reacted with 2f to give cyclization product 4f in 86% yield (eq 1):



Further C-H activation of **3**-Pd gives seven-membered palladacycle **7**. Enolization of **7** and subsequent rearrangement (likely via a π -oxallyl intermediate **9**) affords **10**. It is expected that enolate **8** formed from a *sec*-alkyl ketone generally would be more stable than that from a primary alkyl ketone because tertiary C-H is weaker than primary C-H and because the enolate from a *sec*-alkyl ketone is stabilized to a greater extent by electron-withdrawing Pd(II) than that from a methyl ketone. Finally, reductive elimination of **10** affords product **4** and Pd(0). The latter is oxidized by silver ion to regenerate the active Pd(II) species.⁷

Scheme 1



To further support the proposed mechanism in Scheme 1, we prepared arylation intermediates **3m** and **3n** separately and examined their behavior under various conditions. Thus, treatment of **3m** and **3n** with 10 mol % Pd(OAc)₂ and 1 equiv of Ag₂O in TFA at 120 °C for 15 h gave the corresponding cyclization products **4j** and **4k** in 94–92% isolated yield (eq 2):



When the same reaction was carried out in the absence of Ag_2O , **4j** was obtained in 9% yield (see the Supporting Information). It is important to mention that methyl phenyl ketone **3a** did not give the expected cyclization product under the same catalytic conditions. These observations are in agreement with the results in Tables 1 and 2 that primary alkyl aryl ketones do not undergo further cyclization to give product **4**. The role of Ag_2O in the catalytic reaction is not entirely clear, but it likely acts as a halide scavenger, a base,^{7a} and an oxidant as observed previously.^{7b,c}

In conclusion, we have successfully developed a new and mechanistically interesting method for the synthesis of phenanthrone derivatives from *sec*-alkyl aryl ketones and aryl iodides catalyzed by palladium acetate in trifluoroacetic acid. The catalytic reaction appears to proceed via a dual C–H activation and enolate cyclization. Further studies directed toward the synthesis of various biaryl phenanthrone compounds and a detailed mechanistic investigation are in progress.

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Supporting Information Available: General experimental procedures and characterization details. This material is available free of charge via the Internet at http://pubs.acs.org.

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