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Synthesis of Alkyl Aryl Ketones by Pd/Light Induced Carbonylative Cross-Coupling of Alkyl Iodides and Arylboronic Acids

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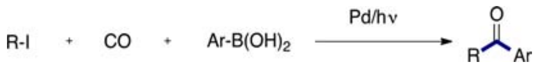
ABSTRACT



Alkyl aryl ketones were synthesized by the carbonylative cross-coupling reaction of alkyl iodides and arylboronic acids under combined Pd/light conditions. In this reaction, it is likely that an acylpalladium species would be formed via carbonylation of the alkyl radical, which would then undergo transmetalation of an arylboronic acid to give the corresponding acyl(aryl)palladium species, ready to undergo reductive elimination to yield the alkyl aryl ketone.

Carbonylation reactions with carbon monoxide have found magnificent applications in organic synthesis as a means for the synthesis of a wide variety of carbonyl compounds.[1] Transition-metal catalyzed carbonylative cross-coupling reaction of organo halides, such as aryl, vinyl, and allyl halides,[2–4] with organometallic species provides useful access to unsymmetrical ketones.[5] Alkyl aryl ketones are generally synthesized via the Type 1 strategy shown in Scheme 1, which involves the oxidative addition of aromatic halides to the metal center to give arylmetal complexes, CO insertion, and alkylation to form aroylalkylmetal species as a precursor to alkyl aryl ketones.[2] On the other hand, the Type 2 reaction based on the oxidative addition of alkyl halides to the metal center is relatively scarce in the literature.[6] This is presumably due to the fact that the resulting alkylmetal species would suffer from β-elimination and subsequent isomerization.[7,8]

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(5) For radical-mediated synthesis of unsymmetrical ketones, see: Kim, S. *Adv. Synth. Catal.* **2004**, *346*, 19. Also see refs 1e and 1f.

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(7) For efforts by ligand design, see: (a) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 384. (b) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099. (c) Neuschütz, M. R.; Dai, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 1945. (d) Kirchhoff, J. H.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910. (e) Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662. (f) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527. (g) Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Commun.* **2007**, 825. (h) Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *J. Org. Chem.* **2005**, *70*, 8503. (i) Hadei, N.; Kantchev, E. A. B.; O'Brie, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805. Also see rewiews: (j) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187. (k) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. *Adv. Synth. Catal.* **2004**, *346*, 346. (l) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (m) Terao, J.; Kambe, N. *Acc. Chem. Res.* **2008**, *41*, 1545. (n) Rudolph, A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656. (o) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417. (p) Hu, X. *Chem. Sci.* **2011**, *2*, 1867.

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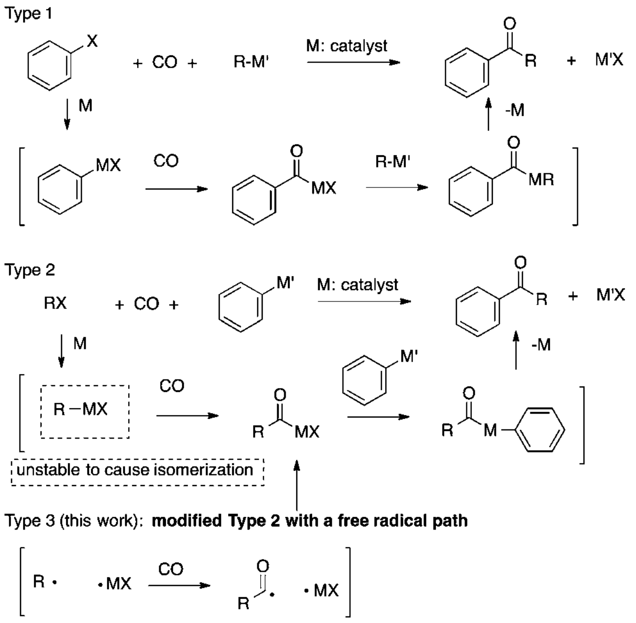
10.1021/ol401363t

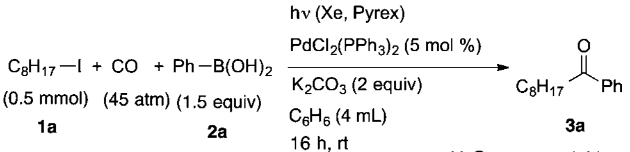
Scheme 1. Strategies for Alkyl Aryl Ketone Synthesis by Transition-Metal Catalyzed Carbonylation



Thus far our group has focused on the potential of the Pd/light-induced system for the carbonylation of alkyl iodides and we have previously reported the synthesis of aliphatic carboxylic acid derivatives[9] and alkyl alkynyl ketones.[10] A key to the success of this approach may lie in the employment of the free radical pathway[9c] which favors formation of the key acylmetal species. In this manner, the system can circumvent the problematic formation of the alkylmetal species prior to CO insertion. We believed that a similar approach should enable a Type 2 strategy for the synthesis of alkyl aryl ketones starting from alkyl halides as the substrate. We were pleased to discover that, with arylboronic acids coupling partners, alkyl aryl ketones could be synthesized effectively from alkyl iodides and CO under Pd/light induced reaction conditions.[11]

As a model reaction we chose the reaction of 1-iodooctane (**1a**) and phenylboronic acid (**2a**) (Scheme 2). When a mixture of **1a**, **2a**, K_2CO_3, and a catalytic amount of $PdCl_2(PPh_3)_2$ (5 mol %) was irradiated under 45 atm of CO using a xenon lamp (500 W) through a Pyrex filter, nonanophenone (**3a**) was obtained in 6% yield. Phenylboronic acid is sparingly soluble in benzene, and therefore we added water to increase its solubility. The addition of 0.1 mL of water to 4 mL of benzene dramatically increased the yield of **3a** up to 57%.[12] To our delight, when 2 mL of water were added to 4 mL of benzene, **3a** was obtained in 92% yield. The reaction in the absence of the Pd catalyst did not take place, and the use of thermal conditions (80 °C) in the dark gave **3a** in very low yield.

Scheme 2. Reaction of 1-Iodooctane (**1a**) and Phenylboronic Acid (**2a**) To Give Nonanophenone (**3a**)



	H_2O	yield
	—	6%
	0.1 mL	57%
	2 mL	92%
light irradiation without Pd cat.	2 mL	0%
80 °C without light irradiation	2 mL	2%

We then examined the generality of the carbonylative coupling reaction using a variety of alkyl iodides and arylboronic acids, whose results are summarized in Table 1. Similarly as in the case of **1a**, substituted primary alkyl iodides **1b**, **1c**, and **1d** gave the corresponding unsymmetrical ketones **3b**, **3c**, and **3d** in good yields (entries 2−4). Both cyclic and linear secondary alkyl iodides **1e** and **1f** gave the corresponding ketones **3e** and **3f** in good yields (entries 5 and 6). We also examined the reactivity of tertiary alkyl iodides **1g** and **1h**. The reaction of 1-adamantyl iodide (**1g**) with CO and **2a** gave adamantyl phenyl ketone (**3g**) in 78% yield, whereas the reaction of *tert*-butyl iodide (**1h**) gave only a modest yield of ketone **3h** (entries 7 and 8, respectively). A variety of boronic acids **2b**−**2h** were also shown to participate in the unsymmetrical ketone synthesis (entries 9−15). For example, the reaction of **1a** with 2-naphthylboronic acid (**2b**) and *p*-methoxyphenylboronic acid (**2c**) gave **3i** and **3j** in 80 and 92% yields, respectively. However, the reaction of *p*-trifluoromethyl-substituted phenylboronic acid **2d** gave the desired ketone **3k** in only 21% yield. In this reaction the anhydride of nonanoic acid was formed as the major carbonyalted product.[13] The use of a 5-fold excess of **1a** relative to **2d** resulted in an increase in the yield of **3k** to 63% (entry 11). F- and Br-substituted arylboronic acids **2f** and **2g** gave the corresponding ketones with the halogen remaining intact (entries 13 and 14). The reaction of cyclopropylmethyl iodide (**1i**) and **2a** gave the ring-opened ketone **3p**, generated by the cyclopropylcarbinyl radical to

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(9) (a) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812. (b) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383. (c) Fukuyama, T.; Inouye, T.; Ryu, I. *J. Organomet. Chem.* **2007**, *692*, 685. (d) Fusano, A.; Sumino, S.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2011**, *13*, 2114. (e) Fusano, A.; Sumino, S.; Nishitani, S.; Inouye, T.; Morimoto, K.; Fukuyama, T.; Ryu, I. *Chem.—Eur. J.* **2012**, *18*, 9415.

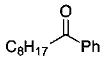
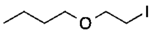
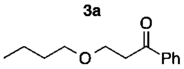
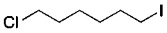
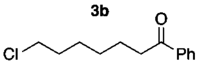
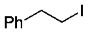
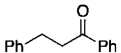
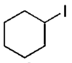
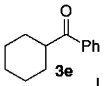
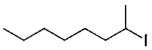
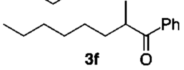
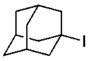
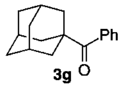
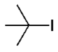
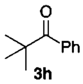
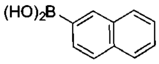
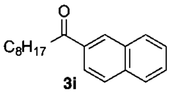
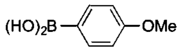
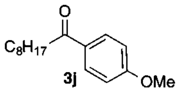
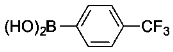
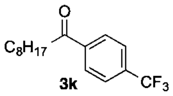
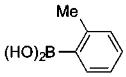
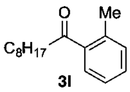
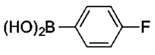
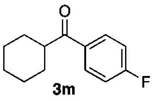
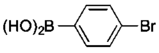
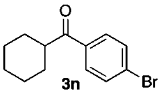
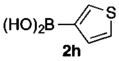
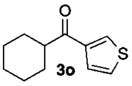
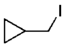
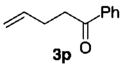
(10) Fusano, A.; Fukuyama, T.; Nishitani, S.; Inouye, T.; Ryu, I. *Org. Lett.* **2010**, *12*, 2410.

(11) For the synthesis of unsymmetrical ketones using 9-BBN derived reagents, see: (a) Ishiyama, T.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1991**, *32*, 6923. (b) Ishiyama, T.; Murata, M.; Suzuki, A.; Miyaura, N. *J. Chem. Soc., Chem. Commun.* **1995**, 295.

(12) While the Suzuki−Miyaura coupling product was not formed, nonanoic acid anhydride was formed as the byproduct.

(13) Acid anhydrides are formed as byproducts in the cases where the yields of ketones are not high. For a similar observation, see ref 10.

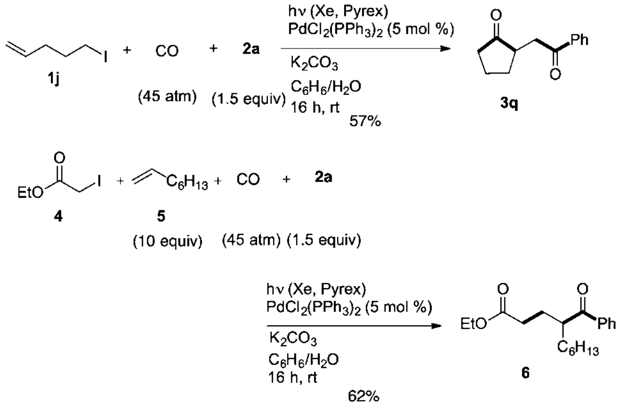
Table 1. Synthesis of Alkyl Aryl Ketones **3** by Carbonylative Coupling of Alkyl Iodides **1** and Arylboronic Acids **2**[a]

entry	RI **1**	ArB(OH)$_2$ **2**	RCOAr **3**	yield (%)[b]
1	C_8H_{17}—I **1a**	$(HO)_2B$−Ph **2a**	 **3a**	92
2	 **1b**	**2a**	 **3b**	81
3	 **1c**	**2a**	 **3c**	83
4	 **1d**	**2a**	 **3d**	87
5	 **1e**	**2a**	 **3e**	81
6	 **1f**	**2a**	 **3f**	71
7	 **1g**	**2a**	 **3g**	78
8	 **1h**	**2a**	 **3h**	48
9	**1a**	 **2b**	 **3i**	80
10	**1a**	 **2c**	 **3j**	92
11	**1a**	 **2d**	 **3k**	21 (63)[c]
12	**1a**	 **2e**	 **3l**	95
13	**1e**	 **2f**	 **3m**	82
14	**1e**	 **2g**	 **3n**	57
15	**1e**	 **2h**	 **3o**	82
16	 **1i**	**2a**	 **3p**	64

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), $PdCl_2(PPh_3)_2$ (5.0 mol %), K_2CO_3 (1.0 mmol), C_6H_6 (4 mL), H_2O (2 mL), hν (Xe lamp, Pyrex), 16 h, rt. [b] Isolated yield. [c] **1a** (2.5 mmol), **2d** (0.5 mmol), $PdCl_2(PPh_3)_2$ (5.0 mol %), K_2CO_3 (1.0 mmol), C_6H_6 (4 mL), H_2O (2 mL), hν (Xe lamp, Pyrex), 40 h, rt.

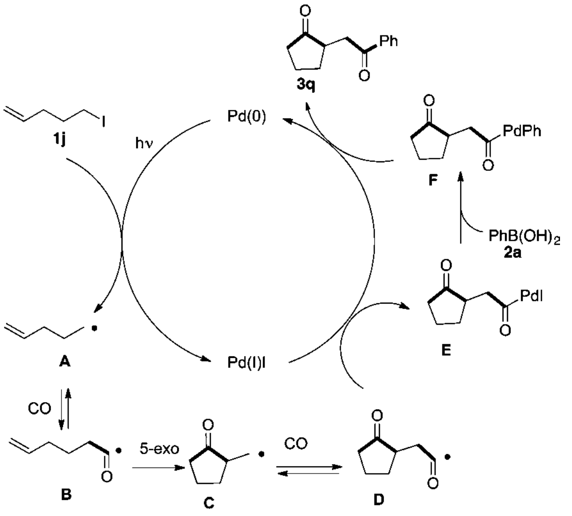
undergo a homoallyl radical ring-opening reaction (entry 16).[14]

Scheme 3. Four-Component Cascade Carbonylation Reactions



We then examined four-component cascade reactions (Scheme 3). When the reaction of 5-iodo-1-pentene (**1j**) and **2a** was carried out, double carbonylation accompanied with cyclization took place to give aryl ketone **3q** bearing a cyclopentanone scaffold, in 57% yield. The four-component reaction comprising ethyl iodoacetate (**4**), 1-octene (**5**), CO, and **2a** also proceeded smoothly to give the expected functionalized ketone **6** in 62% yield. These results demonstrated that the present Pd/light-induced carbonylative cross-coupling reactions can be readily combined with radical cascade reactions.

Scheme 4. Radical/Metal Relay Mechanism



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(15) For examples of an electron transfer from low valent palladium or platinum complexes to iodoalkanes, see: (a) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832. (b) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145. (c) Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205. Also see ref 9e.

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The proposed mechanism for the Pd/light carbonylation reaction is shown in Scheme 4, taking the conversion of **1j** to **3q** as an example. In the first step, **1j** would react with Pd(0) under irradiation conditions to afford alkyl radical **A** and Pd(I)I by a one-electron transfer.[15,16] Under the employed pressurized CO conditions, the resulting alkyl radical **A** would be quickly converted to acyl radical **B**[17] which then undergoes 5-exo cyclization to give alkyl radical **C**. Then, the alkyl radical **C** would add to a second molecule of CO to form acyl radical **D**. Acyl radical **D** would couple with Pd(I)I to form acylpalladium intermediate **E**. Transmetalation of **2a** with **E** would give **F**, which undergoes reductive elimination to give the product **3q** with accompanying liberation of Pd(0).

In summary, we have demonstrated that the carbonylative coupling reaction of alkyl iodides, CO, and arylboronic acids proceeds effectively in a combined Pd/light reaction system to give good yields of alkyl aryl ketones. Extension of this methodology to four-component coupling reactions is also possible. Unlike typical organometallic reagents, arylboronic acids are readily available and easily handled in air, and this presents an attractive feature of the carbonylation method reported herein.

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Supporting Information Available. Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The primary alkyl radical adds to CO at the rate constant of $2.1 \times 10^5\ s^{-1}$ at 60 °C. See: Nagahara, K.; Ryu, I.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 7384 and references cited therein.

The authors declare no competing financial interest.