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Palladium and Visible-Light Mediated Carbonylative Suzuki-Miyaura Coupling of Unactivated Alkyl Halides and Aryl Boronic Acids†

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Herein, a simple and efficient method for the palladium-catalyzed carbonylation of aryl boronic acids with unactivated alkyl iodides and bromides under visible-light irradiation, ambient temperature and low CO-pressure is presented. Notably, the procedure uses readily available equipment and an inexpensive palladium catalyst to generate the key alkyl radical intermediate. These mild conditions enabled the synthesis of a range of functionalized aryl alkyl ketones including the antiphyscotic drug, melperone.

The carbonylation reaction is one of the most versatile synthetic manifolds in modern organometallic chemistry and has found extensive application in the synthesis of numerous carbonyl containing compounds.[1] Despite the tremendous recent progress in this area, the electrophilic coupling partner substrate has largely been restricted to aryl, vinyl and benzyl (pseudo)-halides whereas engaging alkyl halides has been difficult. The slow oxidative addition to the metal center, made even more challenging by the π-acidic character of carbon monoxide, and the risk of β-elimination from the alkyl-metal oxidative addition complex has undoubtedly hampered the use of this valuable substrate class.[1,2]

Over the past decade, radical-mediated reactions have emerged as a powerful alternative approach to engage alkyl halides. These methods utilize an orthogonal mechanistic manifold, based on a single-electron transfer (SET) event, generating an alkyl radical, to circumvent the problems associated with the oxidative addition pathway. Generally these methods employ either intense UV/light irradiation[3] together with high pressures of CO[4] or elevated temperatures[5] to generate and functionalize the key radical intermediate, representing significant practical drawbacks.

Recently, visible-light photocatalysis has attracted considerable interest in the synthetic community as a simple and versatile platform for accessing radical chemistry. Importantly, these methods require only inexpensive equipment and allow radical generation under exceedingly mild and catalytic conditions. This approach has been elegantly applied to the functionalization of unactivated alkyl halides using cross-coupling[6], hydrodehalongenation[7] and aminocarbonylation[8] reactions. Herein we present the development of a visible-light mediated and palladium-catalyzed carbonylative Suzuki-Miyaura coupling for the preparation of unsymmetrical ketones from alkyl halides and aryl boronic acids. Importantly, the reaction is not burdened by the need for high-energy light irradiation, elevated temperatures or high CO-pressures, thereby overcoming the drawbacks associated with existing radical carbonylation procedures (Figure 1).

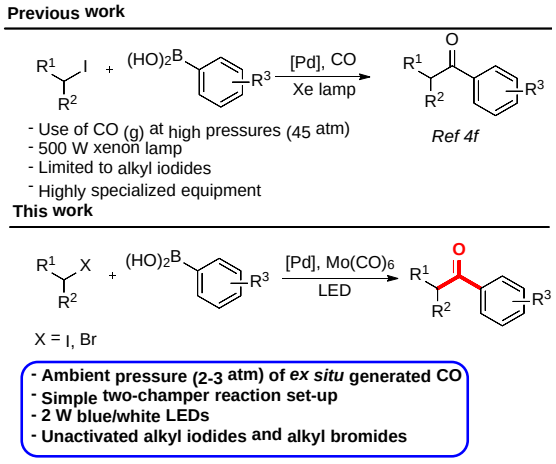

Figure 1. Palladium/light-mediated synthesis of aryl alkyl ketones.

The investigation began using a dual Ir/Pd catalytic system comprising of palladium(II)bis(triphenylphosphine) dichloride ($Pd(PPh_3)_2Cl_2$) and fac-Ir(ppy)$_3$ (**1**) with cyclohexyl iodide (**2**) and phenylboronic acid (**3**) as model substrates. To avoid the use of gaseous CO, molybdenum hexacarbonyl [$Mo(CO)_6$] was used as a solid CO-source together with a double-chamber reaction set-up.[9] Initially, irradiation with LEDs resulted in

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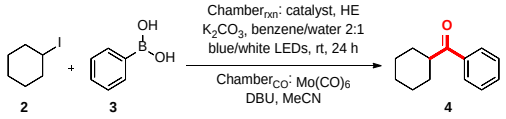
modest conversion to the desired product **4** and a NMR yield of 17% was obtained (Table 1, entry 1).[10] Changing the Pd catalyst to $Pd(PPh_3)_4$ gave a slight improvement in yield (24%, entry 2) as did heating the CO-releasing chamber (31% yield, entry 3).

Table 1. Optimization of reaction conditions



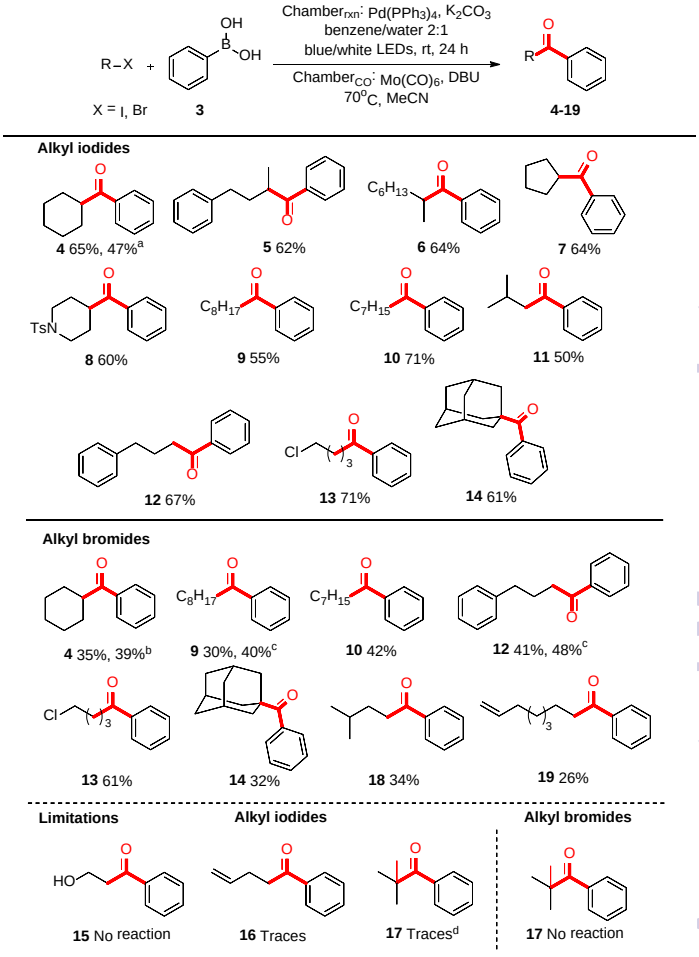
entry	catalyst	temperature C_{CO}	NMR yield[a]
1	$Pd(PPh_3)_2Cl_2$, **1**	rt	17%
2	$Pd(PPh_3)_4$, **1**	rt	24%
3	$Pd(PPh_3)_4$, **1**	70 °C	31%
4	$Pd(PPh_3)_4$, **1**[b]	70 °C	46%
5[c]	$Pd(PPh_3)_4$	70 °C	49%
6[c]	$Pd(PPh_3)_4$	70 °C	64%
7[c]	$Pd(PPh_3)_4$	70 °C	71% (65 %)
8[c,d]	$Pd(PPh_3)_4$	70 °C	70%
9[c,e]	$Pd(PPh_3)_4$	70 °C	(23 %)
10[c]	$Pd(PPh_3)_4$	50 °C[f]	71%

Conditions: **Chamber$_{rxn}$** 0.25 mmol **2** (entries 1-6), 0.3 mmol **2** (entries 7-10), 1.5 eq **3**, 5 mol% Pd-catalyst, 1 mol% **1**, 1 eq K_2CO_3, 2 eq Hantszch ester (HE), 2 mL solvent (entries 1-5) 4 mL solvent (entries 6-10) **Chamber$_{CO}$** 2.5 eq $Mo(CO)_6$ 5 eq DBU 2 mL MeCN (entries 1-5) 4 mL (entries 6-10). [a]Determined by ^{1}H NMR using an internal standard. Number in brackets represents isolated yield. [b]2 mol% **1**. [c]No HE. [d]Toluene instead of benzene. [e]Anisole instead of benzene. [f]C_{rxn} and C_{CO} were heated to 50 °C.

Increasing the amount of **1** to 2 mol%, in combination with reducing the amount of Hantzsch ester (HE) to 0.5 equivalents increased the yield to 46% (entry 4). Surprisingly, a control experiment omitting the photocatalyst **1** with the intent of investigating its role in the reaction, returned an increased yield of 49% (entry 5). When continuing without the expensive photocatalyst **1** and increasing the solvent volume to 4 mL to minimize the gas-phase volume,[11] the yield was further improved (64%, entry 6). Furthermore, increasing the amount of **2** to 0.3 mmol gave a yield of 71% (isolated yield 65%, entry 7). Screening of aromatic solvents that have been previously used in Suzuki-Miyaura couplings, revealed that toluene was equally efficient (70%, entry 8) whereas anisole gave **4** in 23% isolated yield (entry 9) due to a cumbersome purification.[12,13] To avoid the risk of side-reactions resulting from C-H functionalization of toluene,[14] we continued our studies using benzene. A final experiment, where both C_{rxn} and C_{CO} were heated to 50 °C, gave a yield of 71% (entry 10). However, for ease of handling the conditions in entry 7 were chosen for further evaluation.

With the optimized conditions in hand, the scope of the reaction with respect to the alkyl halide component was explored (Scheme 1). A range of unactivated secondary alkyl iodides, including acyclic and cyclic derivatives, were efficiently transformed into the desired products **4**-**8** in good yields. Notably, the protected piperidine derivative **8** was isolated in 60% yield and is readily amenable for further modifications.

Scheme 1. Alkyl halide scope and limitations



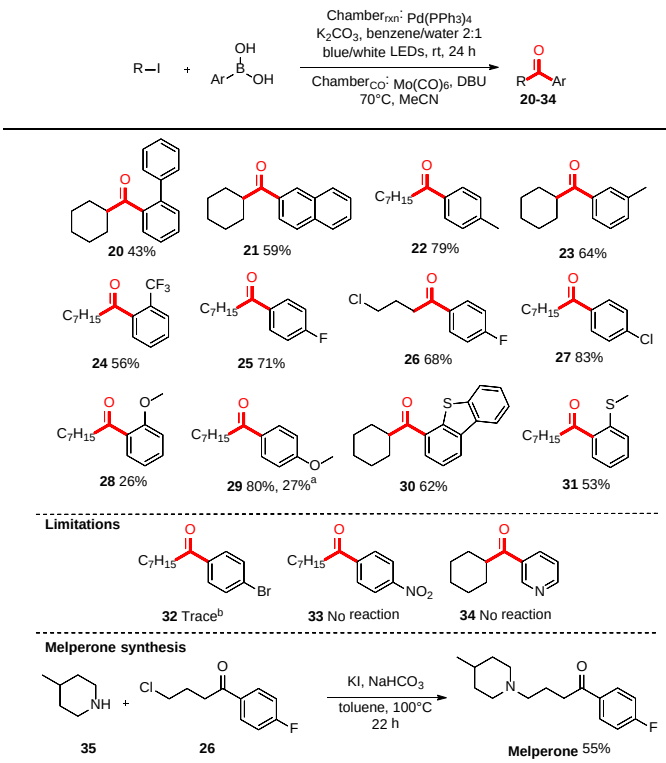
Conditions from entry 7, Table 1. [a]1 mmol scale. [b]C_{rxn} and C_{CO} heated to 50 °C. [c]Reaction time 55 h. [d]Reaction time 72 h.

Primary iodides performed equally well as substrates, giving products **9**-**13,** in yields ranging from 50%-71%. Excellent chemoselectivity for the iodide center was observed in the synthesis of **13**, with no detection of side-products arising from substitution of the chlorine atom (GC/MS). Finally, the tertiary iodide 1-iodoadamantane returned the desired product **14** in 61% yield. Unfortunately, *tert*-butyl iodide furnished only trace amounts of **17**, even after prolonged reaction time (72 h) presumably due to high radical stability and slow carbonylation rate.[15]

To further extend the scope of this carbonylative process, we set about exploring even more challenging alkyl bromide substrates. Gratifyingly, a range of unsymmetrical aryl alkyl ketone products (**4, 9**-**10**, **12**-**14** and **18**-**19**) were isolated in up to 61% yield from the respective alkyl bromide (Scheme 1). Not surprisingly, the alkyl bromides were found to be less reactive than their iodide counterparts and, in some instances, the reactions did not go to completion after 24h. Heating both chambers to 50 °C led to a slight improvement in yield (e.g. **4**) whereas when irradiating the reaction for 55h, the yields of **9**

and **12** increased from 30% and 41% to 40% and 48%, respectively. The reactivity trend was the same as for the alkyl iodides, with primary and secondary alkyl bromides performing equally well. The chlorinated derivative **13** was also isolated in 61% yield, another demonstration of high reaction selectivity and, in **19**, no competing reaction with the pendent olefin was noted.[7,16] Here, the ring-size of the putative cyclized product probably disfavored the intramolecular reaction.

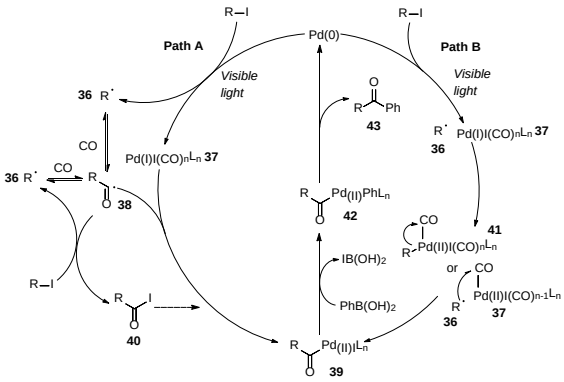
Scheme 2. Boronic acid scope and limitations



Conditions from entry 7, Table 1. [a]HCO_2H/H_2SO_4 used instead of $Mo(CO)_6$. [b]Reaction time 48 h.

Next, the scope of boronic acid component was explored and the reaction was found to be compatible with a range of electronically diverse coupling partners affording products **20-31** in moderate to very good yields (Scheme 2). Notably, bulky or potentially coordinating *ortho*-substituents were well tolerated (e.g. **20**, **24** and **31**) as was an electron rich heterocycle (**30**). Halogenated boronic acids were also suitable substrates (**24**-**27**), however the bromosubstituted analog **32** was formed in trace amounts, even after prolonged irradiation time (55 h). Product **29** was also synthesized using formic acid as a CO-source albeit in an unoptimized yield of 27%. Product **26** is a precursor in the synthesis of the atypical antipsychotic drug melperone, and has been previously synthesized in two steps using sequential palladium and gold catalysis.[17] Further elaboration via a nucleophilic substitution with 4-methylpiperidine (**35**) gave melperone in 55% yield (Scheme 2) in an overall step-efficient process.

To delineate whether the reaction presented herein proceeds via S_N2 or SET pathways[18], a set of control experiments were performed using cyclohexyl- iodide (**2**) or bromide.[10] In both cases, removal of the catalyst was deleterious for conversion and conducting the reaction in the absence of light, or under ambient light conditions, resulted in only traces of the ketone product. Furthermore, the addition of TEMPO completely abolished product formation and the cyclohexyl-TEMPO adduct could be detected by LC/MS analysis. Based on these results, a tentative reaction mechanism is depicted in Scheme 3. A SET between Pd(0) and the alkyl halide, here an alkyl iodide, initiates the reaction by forming alkyl radical **36** and $L_n(CO)_nPd(I)I$ **37**. The exact role of the visible light in this process is yet to be elucidated and the Pd-catalyst may act either as a photosensitizer, to promote radical formation[19], or as a photocatalyst through a SET from an excited state species.[18a,b] The need for irradiation supports a radical mechanism, as does the formation of a TEMPO-adduct. The alkyl radical can then react via two different pathways (path A or B).



Scheme 3. Plausible reaction mechanism.

In path A, the alkyl radical traps CO to form acyl radical **38**, which after addition to **37** gives acyl-palladium complex **39**. Radical **38** can also propagate the alkyl radical formation by iodine transfer, whereby acyl iodide **40** is formed which can enter the catalytic cycle after addition to a palladium species. This pathway is favored for carbonylation of alkyl iodides performed under high CO-pressures (> 45 bar)[4b,c,e,f,20] and the maximum CO-pressure here was measured to 2.5 bar.[10] In path B, **36** and **37** form a caged radical pair which can collapse to a Pd(II)-complex **41** in which the alkyl group can migrate to Pd-coordinated CO. Alternatively **36**, formed either through path A or after escaping the radical cage,[21] can add directly to a bound CO on **37**. Both pathways converge on **39**, which can undergo transmetallation with the aryl boronic acid to give complex **42**. A reductive cleavage regenerates Pd(0) and liberates the ketone product **43**. Path B has been proposed to operate in conditions with low CO-pressures, where increasing the CO-pressure had a detrimental effect on the yield.[3a,5b,22] The lower yield obtained for **29** using formic acid as CO-source may be partly attributed to this phenomenon as a higher CO-pressure is reached (3.5 bar).[8] As for the pathway under operation here, two lines of evidence support a reaction via path A namely, the addition of TEMPO completely abolishes product formation and the removal of CO results only in

unreacted starting material. This suggests the intermediacy of a discreet radical intermediate rather than a caged radical pair[5b] and that acyl radical **38** may be required for efficient radical propagation. However, further studies are needed to fully elucidate the reaction mechanism.

In summary, a carbonylative Suzuki-Miyaura coupling of unactivated alkyl halides with aryl boronic acids has been presented. By using visible-light irradiation, alkyl halides were coupled with aryl boronic acids under ambient temperature and low CO-pressure in moderate to very good yields. In general, the isolated yields were in the same range as previously reported using elevated CO-pressures and high energy irradiation. Notably, a SET or photosensitization event between $Pd(PPh_3)_4$ and the alkyl halide substrate circumvents the need for an expensive photocatalyst. Furthermore, the application of challenging alkyl bromides as substrates has been realized for the first time. Additional improvements to related methods are the use of a solid CO-source instead of gaseous CO and use of cheap and readily available LED lights that together with the double-chamber system constitutes a convenient reaction set-up. Moreover, the discovery that the combination of a simple palladium catalyst and visible-light irradiation can promote efficient radical generation from challenging alkyl halide substrates opens up an exciting new dimension in both palladium and photocatalysis chemistry. Further studies to explore the scope of this process are currently underway in our laboratory and will be reported in due course.

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