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COMMUNICATION

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Palladium-Catalyzed Direct β-C-H Arylation of Ketones with Arylboronic Acids in Water

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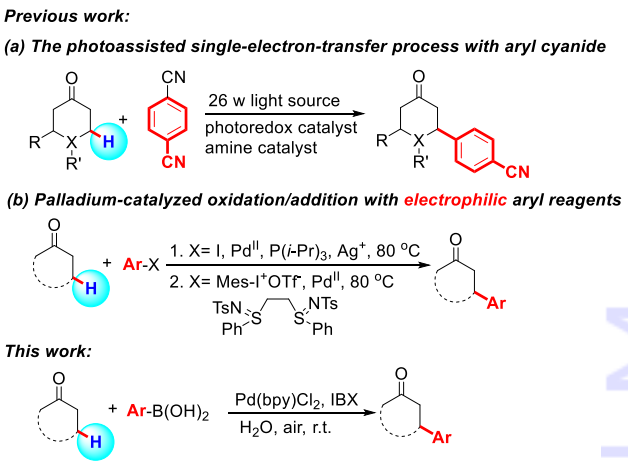
Abstract: A palladium-catalyzed direct β-C-H arylation of ketones was developed under mild conditions in water, featuring commercially available arylboronic acids as nucleophilic aryl sources and *o*-iodoxybenzoic acid as the oxidant. The method provides a concise route to access β-arylated ketones. Preliminary studies indicated that direct asymmetric β-C-H arylation of ketones could be achieved by this strategy.

Keywords: β-C-H arylation; arylboronic acids; *o*-iodoxybenzoic acid; β-arylated ketones; palladium



Scheme 1. Direct β-C-H arylation of ketones.

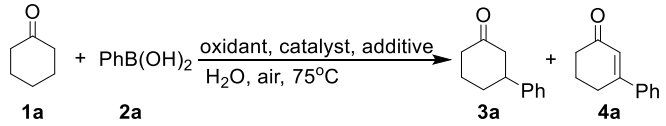
Functionalization of carbonyl compounds to form new C-C bonds is of vital importance in organic synthesis.[1] While carbonyl groups and their α-hydrogens are prone to functionalization due to their intrinsic electrophilicity and acidity, the direct β-functionalization of carbonyl compounds remains a challenging academic pursuit. Past decades have witnessed increasing synthetic efforts to address this challenge.[2] The β-C-H arylation of carbonyl derivatives, such as amides,[3] ester,[4] carboxylic acid[5] and 1,3-dicarbonyl compounds,[6] has been successfully developed. In contrast, little progress has been made in the direct β-C-H arylation of ketones until very recently. Classified by the mechanistic profile, the development in this direction includes the photo-initiated single electron transfer (SET) process, and the transition metal-catalyzed oxidation/conjugate addition sequence. The former method utilizes electron-deficient aryl cyanides as the aryl source (Scheme 1a).[7] In the latter case, electrophilic aryl iodides are employed in a palladium-catalyzed β-C-H arylation of ketones via a successive dehydrogenative oxidation and conjugate addition at elevated temperature (Scheme 1b-1).[8] To avoid the stoichiometric silver-based oxidant and air-sensitive P(*i*-Pr)$_3$ ligand, hypervalent diaryliodonium salts were proven effective alternatives as both the oxidant and the aryl source (Scheme 1b-2),[9] although additional steps are required to synthesize diaryliodonium salts from aryl iodides or arylboronic acids.[10]

Palladium(II) catalyst serves two purposes in the previous catalytic β-C-H arylation protocols: (1) to catalyze ketone dehydrogenation, and (2) to generate aryl nucleophiles from electrophilic aryl species by oxidative addition. The use of electrophilic aryl sources demands heating and the presence of the oxidant in these routes, likely due to the involvement of Pd(0)/Pd(II) cycle. To achieve direct β-C-H arylation of ketones under milder conditions, we envisioned an alternative oxidation/conjugate addition process without the involvement of Pd(0)/Pd(II) cycle, whereby nucleophilic aryl reagents replace the electrophilic aryl precursors. Among known nucleophilic reagents, commercially available arylboronic acids have been widely used due to their commercial availability and stability to heat, air and water, as well as the ease of handling and compatibility with a wide range of functional groups.[11] Herein we report a novel direct β-C-H arylation of ketones under very mild conditions in

aqueous solution,[12] in which readily available *o*-iodoxybenzoic acid (IBX)[13] is used as the oxidant and arylboronic acids as nucleophilic reagents.

To test our hypothesis, cyclohexanone **1a** and phenylboronic acid **2a** were used in the model study (Table 1). The choice of oxidant is very crucial for the success of this tandem oxidative transformation. It has to satisfy the following criteria: (a) be compatible with the conditions of conjugate addition reaction, (b) be able to selectively oxidize cyclohexanone **1a** in the presence of oxidative-coupling prone phenylboronic acid **2a**, and (c) be able to prevent the over-oxidation of **1a**. Examination of oxidants was initially conducted in the presence of Pd(II) complex bound to 2,2'-bipyridine (bpy) in water at 75 °C. Various common oxidants such as O_2, H_2O_2, ^{t}BuOOH and oxone failed to afford the desired β-arylated product (entries 1-4). When O_2 was used as an oxidant, most of **2a** was converted into biphenyl. IBX was found to be the preferred oxidant to promote this reaction, providing **3a** in 78% yield. The survey on reaction solvents showed that the reaction can proceed in neat water (entry 5), but the addition of a small amount of DMSO is favorable for forming **3a** in high yield (entry 6). Other palladium and rhodium catalysts were also tested (entries 7-10), and $Pd(bpy)Cl_2$ showed the best catalytic performance. Additionally, the effect of additives, such as pyrrolidine and *L*-proline, was also examined (entries 11-14). The absence of TFA or the addition of pyrrolidine led to low yield of **3a** and the formation of 10-15% the Heck-type product **4a**. Furthermore, it was observed that deboronation of **2a** occurred under the above conditions. Since there are two competing reactions for **2a**—nucleophilic addition and deboronation, this reaction was subjected to milder reaction conditions. To our delight, the reaction can proceed much better at room temperature (ca. 23 °C) and afforded **3a** in 87% yield in a prolonged reaction time (entry 14).

Table 1. Optimization of the reaction conditions[a].



Entry[a]	Oxidant	Catalyst	Additive	Yield of **3a** (%)[b]	**4a** (%)[b]
1[c]	O_2	$Pd(bpy)Cl_2$	-	-	-
2	H_2O_2	$Pd(bpy)Cl_2$	-	-	-
3	^{t}BuOOH	$Pd(bpy)Cl_2$	-	-	-
4	oxone	$Pd(bpy)Cl_2$	-	-	-
5[d]	IBX	$Pd(bpy)Cl_2$	TFA	66	trace
6	IBX	$Pd(bpy)Cl_2$	TFA/DMSO	78	trace
7	IBX	$Pd(OAc)_2$/bpy	TFA/DMSO	51	-
8	IBX	$Pd(OAc)_2$	TFA/DMSO	34	trace
9	IBX	$Pd(4,4'\text{-}(OMe)_2bpy)Cl_2$	TFA/DMSO	55	trace
10	IBX	$[RhCl(cod)]_2$	$NaHCO_3$/DMSO	-	-
11	IBX	$Pd(bpy)Cl_2$	DMSO	42	10
12[e]	IBX	$Pd(bpy)Cl_2$	*L*-proline/DMSO	trace	-
13[e]	IBX	$Pd(bpy)Cl_2$	Pyrrolidine/DMSO	31	15
14[e]	**IBX**	**$Pd(bpy)Cl_2$**	**TFA/DMSO**	**87**	**trace**

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), oxidant (1.5 equiv), catalyst (5 mol%), TFA (1.0 equiv) and DMSO (10 equiv) in 1.0 mL H_2O under atmospheric conditions for 16 h. [b] Yields were determined by ^{1}H-NMR spectroscopy using trimethoxybenzene as the internal standard. [c] Biphenyl was obtained. [d] 6 equiv TFA was used. [e] Reactions were carried out at r.t. for 72 h. TFA=trifluoroacetic acid.

With the optimized reaction conditions in hand, the scope of arylboronic acids was explored (Table 2). In general, arylboronic acids bearing electron-donating or electron-withdrawing groups all reacted efficiently with **1a**. Various electron-rich arylboronic acids such as phenyl-, 4-tolyl-, 4-methoxylphenyl, 3-methoxylphenyl, 4-tert-butylphenyl and 2-naphthylboronic acids proceeded smoothly at room temperature to give the desired product in good to excellent yields (**3a**-**3f**). 4-Bromophenylboronic acid

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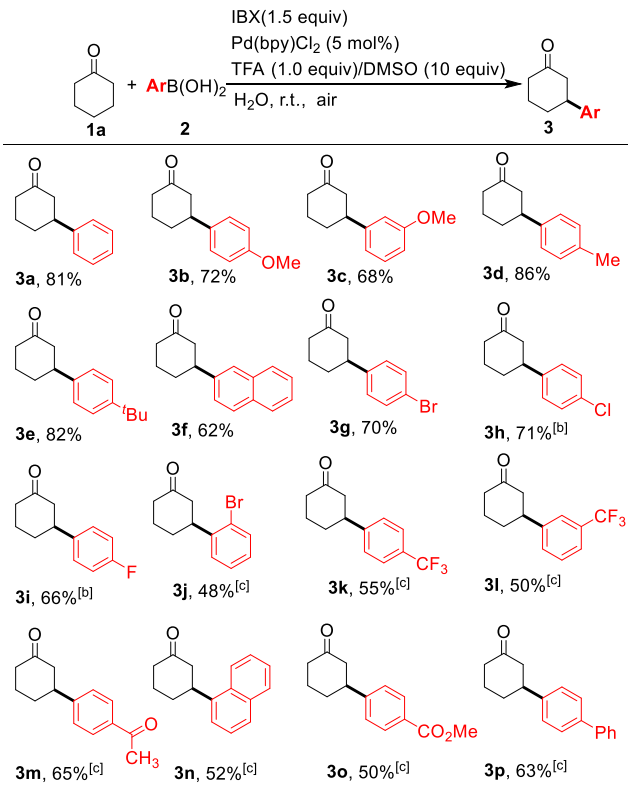
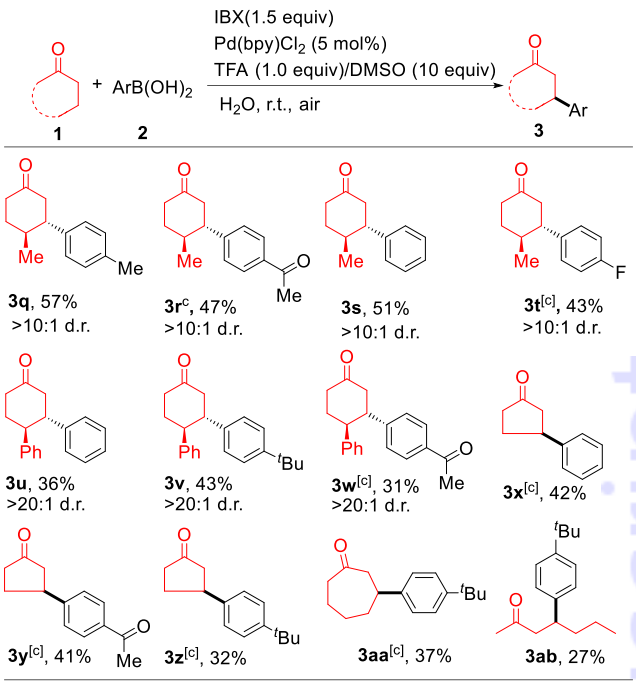
Table 2. Scope of arylboronic acids[a].



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), IBX (1.5 equiv), Pd(bpy)Cl_2 (5 mol%), TFA (1.0 equiv) and DMSO (10 equiv) in H_2O (1.0 mL) under atmospheric conditions for 72 h. [b]50 °C, 24 h. [c] 2.0 equiv **2**, 75 °C, 16 h.

Table 3. Scope of ketones[a,b].



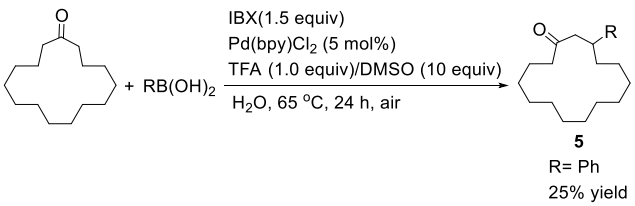
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), IBX (1.5 equiv), Pd(bpy)Cl_2 (5 mol%), TFA (1.0 equiv) and DMSO (10 equiv) in H_2O (1.0 mL) under atmospheric conditions for 72 h. [b] The d.r. values were determined by GC analysis. [c] Reactions were carried out at 75 °C for 16 h.

was also reactive in this reaction, affording the desired product in 70% yield (**3g**). However, the reaction proceeded less efficiently when 4-chlorophenyl- and 4-fluorophenylboronic acids were used at room temperature. By increasing the reaction temperature to 50 °C, the corresponding β-arylated ketones were obtained in good yields (**3h**, **3i**). For arylboronic acids with electron-withdrawing or sterically hindered groups such as 2-bromophenyl, 4-triflurometylphenyl, 3-triflurometylphenyl, 4-methoxy carboxyphenyl, 4-acetylphenyl, 4-biphenyl and 1-naphthyl, a higher temperature was typically required. By elevating the temperature to 75 °C, the desired β-C-H arylated products were also obtained in moderate to good yields (**3j**-**3p**).

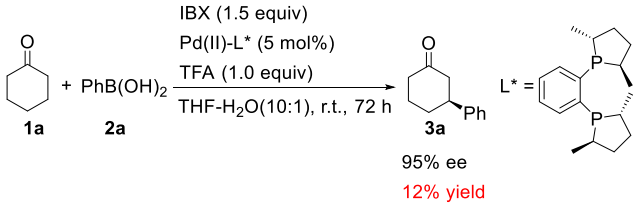
Furthermore, different ketones reacted with phenyl-, 4-tolyl, 4-fluorophenyl, 4-acetylphenyl- and 4-*tert*-butylphenylboronic acids to afford the corresponding β-arylated ketones in moderate to good yields (Table 3). Substituents at the γ-position of cyclohexanone caused a negative effect on the reaction efficiency. Direct β-C-H arylation of 4-methylcyclohexan-1-one proceeded smoothly with electron-rich arylboronic acids at room temperature, and with electron-withdrawing arylboronic acids at higher temperature to afford relatively satisfying yields (**3q**-**3t**). However, the presence of a phenyl group at C4-position gave the *trans* products with excellent diastereoselectivity (> 20:1) (**3u**-**3w**), albeit in low yields. Linear as well as five- and seven-membered ring cyclic ketones were also successfully arylated with arylboronic acids (**3x**-**3ab**).

This method was applied to synthesize β-substituted cyclopentadecanone, the main component of musk.[14] As illustrated in Scheme 2, with this direct β-C-H arylation method, ketone **5** was obtained in a single step from cyclopentadecanone, while five steps were generally required previously for preparing β-substituted cyclopentadecanone from the same ketones.[15]

Our attempt to carry out an enantioselective β-C-H arylation of ketones based on this strategy was successful by combining a chiral diphosphine ligand[16] with Pd(II), providing chiral 3a with excellent enantioselectivity (up to 95% ee) (Scheme 3), although with a low conversion at this stage. Efforts towards developing highly efficient and enantioselective transformations are ongoing.



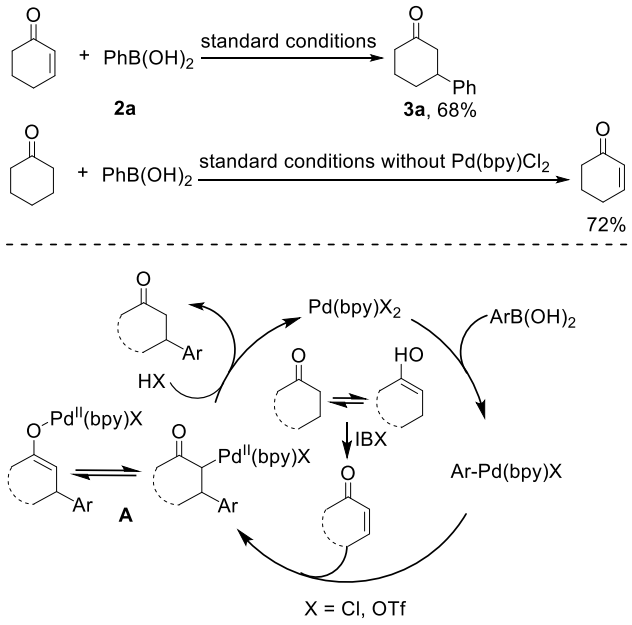
Scheme 2. Direct β-C-H arylation of cyclopentadecanone.



Scheme 3. Preliminary examination of asymmetric direct β-C-H arylation of **1a**.

To better understand this chemistry, two control experiments were conducted (Scheme 4). The results showed that 2-cyclohexen-1-one could also afford the β-C-H arylated product **3a** in 68% yield under the standard reaction conditions; whereas in the absence of $Pd(bpy)Cl_2$, the reaction only furnished 2-cyclohexen-1-one in 72% yield, and compound **3a** was not observed. Based on the previous report[17] on Pd(II)-catalyzed conjugate addition and our mechanistic studies, a tentative mechanism is proposed for this reaction (Scheme 4). Firstly, enolization of ketones catalyzed by acids occurred, and the enol reacted with IBX to generate α,β-unsaturated ketones.[13g] Then, Ar-[Pd] formed via transmetalation of the aryl group from arylboronic acids to the palladium reacted with the C=C bond of α,β-unsaturated ketones to give a palladium enolate **A**. Finally, protonolysis of **A** furnished the desired β-arylated ketone with regeneration of the Pd catalyst.

In conclusion, we have developed a simple and efficient protocol for direct β-C-H arylation of ketones with arylboronic acids under mild conditions in water. The use of commercially available arylboronic acids as aryl source would make this method more practical and popular due to their



Scheme 4. A tentative mechanism for the direct β-C-H arylation of ketones.

stability towards air and water, as well as compatibility with a wide range of functional groups. Additionally, the very mild conditions in aqueous solution make this method more user-friendly and more promising to obtain asymmetric β-C-H arylation products.

Experimental Section

General procedure for the direct β-C-H arylation of ketones with aryboronic acids

In a 10 mL microwave vial were combined ketone (0.20 mmol), arylboronic acid (0.30 mmol), $Pd(bpy)Cl_2$ (3.3 mg, 5 mol%), IBX (0.3 mmol), DMSO (2.0 mmol) and TFA (0.20 mmol) in water (1.0 mL). The mixture was then stirred at r.t. under atmospheric conditions for the time specified in Table 2 and 3. The mixture was then extracted with ethyl acetate (3 × 3 mL). Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

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