DOI: 10.1002/adsc.201100782

C–X (X = Br, I) Bond-Tolerant Aerobic Oxidative Cross-Coupling: A Strategy to Selectively Construct β-Aryl Ketones and Aldehydes

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Received: October 8, 2011; Published online: February 9, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100782.

Abstract: Using moelcular oxygen as the terminal oxidant, various aryl halide-containing β-aryl ketones and aldehydes can be synthesized directly from readily available allyic alcohols and boronic acids *via* palladium-catalyzed oxidative cross-coupling reactions. The dual roles of copper, including electron-carrier and Lewis acid functions, are supposed to be critical for the high reactivity and selectivity of this aerobic oxidative coupling transformation.

Keywords: copper; cross-coupling; oxygen; palladium; selectivity

Functionalized ketones and aldehydes are among the most important organic motifs for chemical syntheses in the pharmaceutical, agrochemical, materials science fields etc. As an example, shown in Figure 1, the aryl halide-containing β-aryl ketones and aldehydes[1] are versatile synthetic building blocks. They not only contain traditional reactive positions, but also include aryl halides, which make these compounds more available than ever for further functionalizations due to the extensive development of cross-coupling reaction in the past few decades.

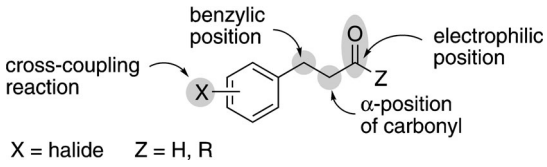


Figure 1. Aryl halide-containing β-aryl ketones and aldehydes.

Developments have been made to obtain β-aryl ketones and aldehydes *via* the traditional Heck reaction since 1970s.[2] Apart from special ligands, equivalent bases, additives, and high temperatures are often required to perform these transformations. They also lack generality and sometimes suffer from low selectivity. Moreover, since the aryl-halogen bond is the reactive position for oxidative addition, which is usually considered as the first step in cross-coupling (including Heck reactions), it is even more difficult to prepare aryl halide, especially iodide- and bromide-containing compounds *via* such a protocol. For the approach of an oxidative Heck reaction between aryl nucleophiles and allylic alcohols, there are only scarce methods existing in the literature.[3] Other strategies often require multiple-step operations from readily available allylic alcohols. For instance, both metal-catalyzed 1,4-addition[4] and oxidative Heck[5] reactions followed by reduction need the preparation of α,β-unsaturated carbonyl compounds as a first step.

To date, a general synthetic strategy toward aryl halide-tolerant compounds *via* cross-coupling is still elusive. The difficulty comes from the fact that the aryl halide bond itself is the reactive group in transition metal-catalyzed cross-coupling reaction (Figure 2, **A**). An oxidative cross-coupling reaction[6] of nucleophiles employs oxidants to recycle the metal catalyst, and thus the oxidative addition of the coupling partner is not involved in the catalytic cycle. We won-

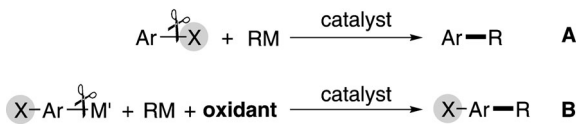
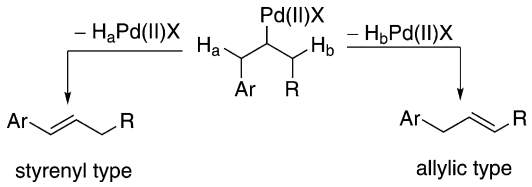


Figure 2. (**A**) Traditional cross-coupling reaction. (**B**) Oxidative cross-coupling reaction.

dered, therefore, if aryl halides would become fully compatible by choosing an appropriate oxidant, which has a higher reactivity with the metal catalyst than with the carbon-halide bond (Figure 2).

As an example, we are interested in accessing the aryl halide-containing β-aryl ketones and aldehydes *via* oxidative Heck coupling from readily available allylic alcohols. In fact, to accomplish this transformation, the difficulty of achieving high regioselectivity, as shown in Scheme 1, is another challenge that has to be addressed. In 2008 and 2010, the groups of White[5l] and Sigman[5k] respectively reported selective oxidative Heck reactions between arylboronic acids and allylic compounds. In both examples, conjugated styrene derivatives (Scheme 1, styrenyl type) generated *via* β-H_a elimination were afforded favorably. However, the exclusive formation of molecules (of the allylic type) *via* β-H_b elimination was rarely reported in the oxidative Heck process.

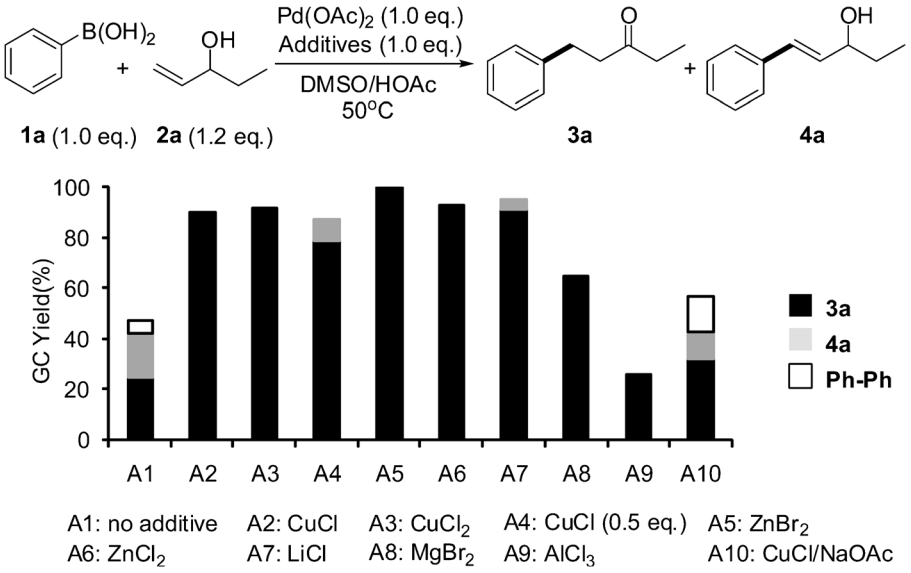
To assess the selectivity, we investigated the cross-coupling between phenylboronic acid **1a** and 1-penten-3-ol **2a** using stoichiometric Pd(II) (1.0 equiv.) in the absence of oxidant (Scheme 2, A1; please see the Supporting Information for details). It was observed that the total yield was less than 50% and the regioselectivity between **3a** and **4a** was poor. This demonstrated that the β-H elimination between H_a and H_b (Scheme 1) was inherently not distinguishable enough in this coupling reaction as expected. To our delight, when 1.0 equivalent of CuCl or $CuCl_2$ was added (Scheme 2, A2 and A3), **3a** was produced exclusively in above 90% GC yield. Moreover, when 0.5 equivalent of CuCl was used, an improvement in the regioselectivity was also observed. When 1.0 equivalent of CuCl was used in combination with 0.5 equivalent of $Pd(OAc)_2$ in the absence of oxidant, **3a** was afforded in 48% yield as the only product. These results strongly supported the assumption that copper played a critical role in the selectivity.



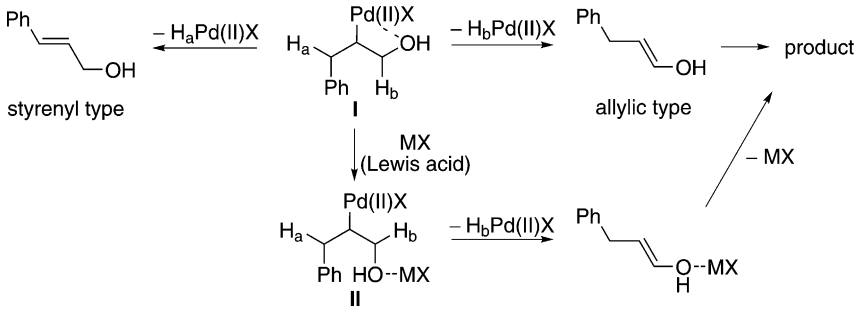
Scheme 1. Two directions of β-H elimination.

As shown in Scheme 3, during the transformation without copper, the free alcohol group could possibly coordinate to the Pd(II) center, and lead to the intermediate **I**, which would induce a β-H_a elimination and produce styrenyl derivatives. When the unstable four-member ring was opened, β-aryl carbonyl products *via* β-H_b elimination could be generated meanwhile. We propose that Cu salts might act as Lewis acids, and could coordinate with the free alcohol group. This coordination would undoubtedly interrupt the interaction between the Pd center and OH group, and generate another intermediate **II**. Benefitting from this interaction, the irreversible formation of β-aryl carbonyl molecules *via* β-H_b elimination would be favorable.

To examine the role of Cu salts, other Lewis acids such as ZnX_2, LiCl, $MgBr_2$, $AlCl_3$ were subjected to the same reaction conditions (Scheme 2, A5–A9). Similar enhancements in the yield and regioselectivity were also observed. When the reactions were treated with an additional Brønsted base (Scheme 2, A10), the intereaction between Cu and OH was possibly influenced, which afforded a decreased yield and selectiviy. These results strongly support the assumption



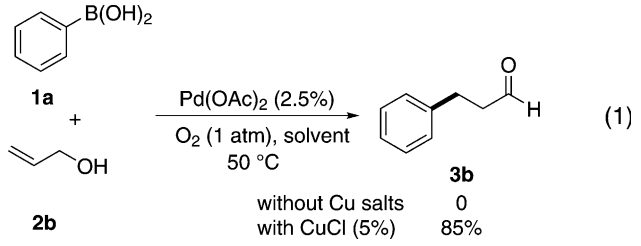
Scheme 2. Stoichiometric reactions between phenylboronic acid and allylic alcohol **2a** in the presence of different additives.



Scheme 3. Two directions of β-H elimination of intermediate **I**.

that copper salts played the role of a Lewis acid in this reaction.

When the reactions were conducted with catalytic amounts of $Pd(OAc)_2$ in the presence of an oxygen atmosphere under conditions with or without copper salts, the total chemical yields of the products were disparate [Eq. (1)]. Adding a catalytic amount of



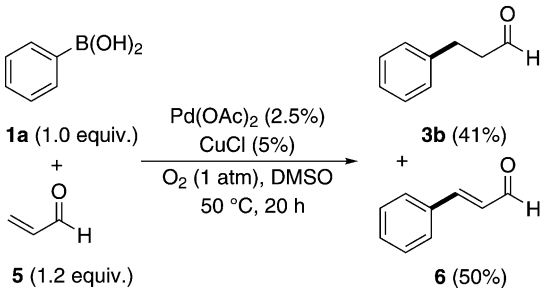
(1)

copper under the same conditions could increase the yield of the target product to 85%. While the oxygenation of a Pd center by the triplet-state O_2 is formally a spin-forbidden process,[7] electron-transfer mediators (ETMs) are often required to reoxidize the palladium and to prevent the precipitation of inactive bulk metal.[6b] Among many ETMs, copper salts, which have been supposed to have a close interaction with reduced Pd,[8] are one of the most widely accepted options. Moreover, Cu(I) can be directly oxidized by O_2 under mild conditions.[9] Based on our observation, copper also played another important role of an ETM in this aerobic oxidative coupling.

It is noteworthy that, as shown in Table 1, high levels of chemoselectivity were observed within this oxidative coupling process. As the functional groups bromide and iodide are often incompatible in conventional cross-coupling reactions, this oxidative coupling process leaves such halides intact, making them available for many further functionalizations *via* conventional cross-coupling technique. With this oxidative coupling protocol, both halide-substituted β-aryl ketones and aldehydes can be afforded in good yields.

As shown in Table 2, under our conditions, a variety of β-aryl ketones and aldehydes could be synthesized in satisfactory yields. With different substituents on the arylboronic acids, these reactions were all regioselective, and the steric hindrance showed little influence on the reactivity.

In the presence of oxygen and palladium catalysts, allylic alcohols could be oxidized to α,β-unsaturated carbonyl compounds.[6c] Conjugate additions of arylboronic acids to these α,β-unsaturated carbonyl compounds were also reported.[11] To examine whether our reaction was a cascade oxidation/1,4-addition, the oxidation and addition were investigated separately. Under the optimized conditions, we found that the allylic alcohol was hardly converted to carbonyl compounds (only 5% of oct-1-en-3-ol was converted to ketone after 24 h). When acrolein **5** was subjected to our oxidative coupling conditions, **3b** and cinnamaldehyde **6** were formed in 91% total yields with a ratio of 4:5 [Eq. (2)]. The selectivity was not in accordance

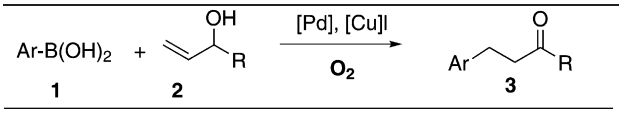


(2)

with that observed in the oxidative cross-coupling of **1a** and allylic alcohol (85% **3b**, no **6**). Therefore, the cascade oxidation/1,4-addition path was unambiguously ruled out.

In conclusion, we have reported the first palladium-catalyzed aerobic oxidative cross-coupling reaction between arylboronic acids and allylic alcohols. Within this transformation, the dual roles of Cu, functioning as a Lewis acid and as an ETM, were supposed to be critical for the high regioselectivity and reactivity in this process. It revealed that the effect of Cu could be more than an electron-carrier in many oxidative transformations. Using this oxidative coupling method, various aryl halide-containing β-aryl ketones

Table 1. Palladium-catalyzed aerobic oxidative cross-coupling reactions of halide-containing arylboronic acids with allylic alcohols.[a]



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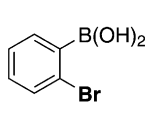
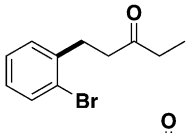
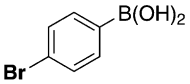
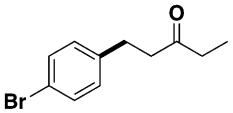
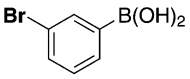
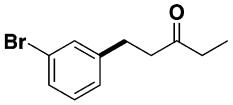
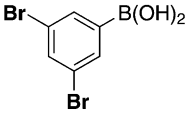
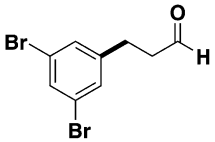
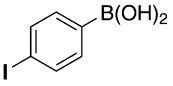
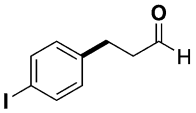
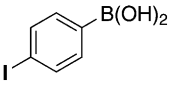
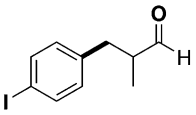
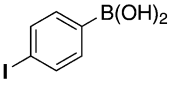
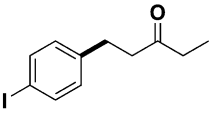
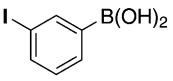
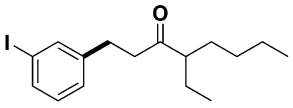
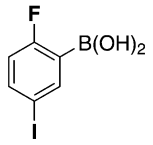
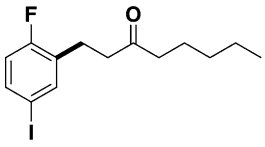
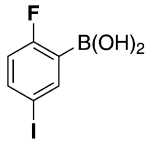
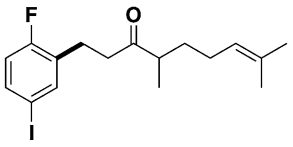
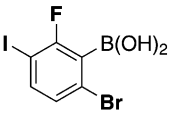
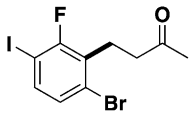
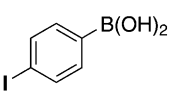
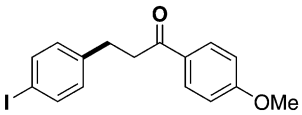
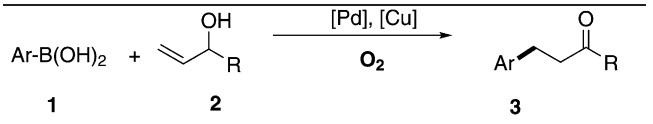
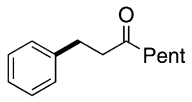
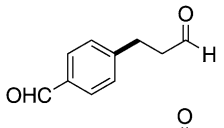
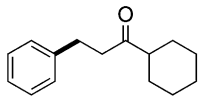
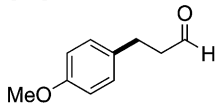
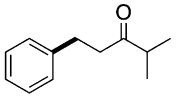
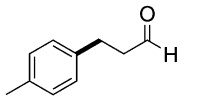
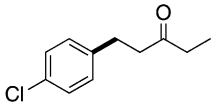
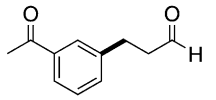
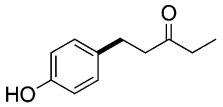
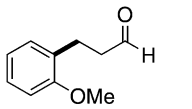
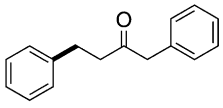
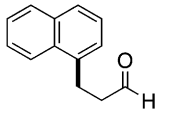
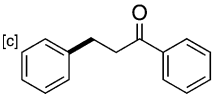
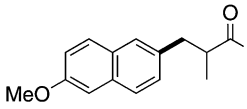
1			76
2			81
3			82
4[c]			83
5			78
6			79
7			80
8			81
9[d]			73
10[d]			63
11[d]			56
12[c]			75

[a] *Reaction conditions:* All reactions were performed with **1** (0.5 mmol), allylic alcohol (0.6 mmol), $Pd(OAc)_2$ (2.5 mol%), CuCl (5 mol%) and DMSO/HOAc[10] (1.5 mL, v/v = 1/1), 50 °C, 12–24 h, O_2 (1 atm).
[b] Yield of isolated product.
[c] 2 mL DMSO were used as solvent.
[d] **1** (0.65 mmol) and allylic alcohol (0.5 mmol) were used.

Table 2. Palladium-catalyzed aerobic oxidative cross-coupling reactions of arylboronic acids with allylic alcohols.[a]



1 2 3

Entry	Product **3**	Yield [%] [b]	Entry [d]	Product **3**	Yield [%] [b]
1		94	8		71
2		89	9		90
3		75	10		86
4		84	11		79
5		82	12		83
6		66	13		85
7[c]		73	14		83

[a] *Reaction conditions:* All reactions were performed with **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2.5 mol%), CuCl (5 mol%) and DMSO/HOAc[10] (3 mL, v/v = 1/1), 50 °C, 20 h, O_2 (1 atm).
[b] Yield of isolated product.
[c] 3 mL DMSO were used.
[d] $Pd(OAc)_2$ (2.5 mol%), CuI (5 mol%), DMSO (3 mL), 50 °C, 20 h, O_2 (1 atm).

and aldehydes can be prepared in good yields under mild conditions with no need of base and ligand. This method is a successful example to demonstrate that the oxidative coupling reaction can be employed as

an important complementary method to prepare the aryl halide-containing compounds, which are still elusive *via* traditional coupling protocols.

Experimental Section

Typical Procedure

4-Iodophenylboronic acid (124.0 mg, 0.5 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), and CuCl (2.5 mg, 0.025 mmol) were combined in a dry Schlenk tube containing 1.5 mL dry solvent (DMSO/HOAc = 1/1, v/v). 1.2 equivalents of 1-penten-3-ol (60 μL, 0.6 mmol) were then added at room temperature. Subsequently, the tube was purged with a balloon pressure of oxygen for 3 times. The reaction mixture was stirred at 50 °C for 20 h. After the reaction was stopped, the solution was diluted with 5 mL saturated NaCl solution. The mixture was extracted with Et_2O (150 mL), washed with saturated $NaHCO_3$ (3 × 10 mL), saturated NaCl (2 × 10 mL) and dried over Na_2SO_4. The solvent was removed, and the residue was subjected to flash column chromatography with petroleum/Et_2O (100/1) as eluent to obtain the desired product 1-(4-iodophenyl)pentan-3-one; yield: 115.8 mg (80%).

Acknowledgements

We thank the generous support from the National Natural Science Foundation of China (20702040, 20832003, 20972118).

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