Ru-catalyzed aerobic oxidative coupling of arylboronic acids with arenes†

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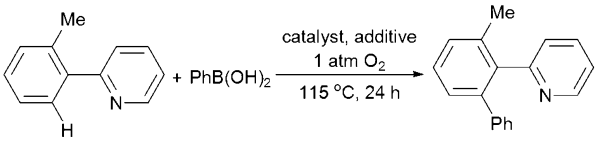
A Ru-catalyzed oxidative coupling of arenes with boronic acids using molecular oxygen *via* direct C–H activation is reported. Both the scope and the mechanism of the process are discussed.

The Suzuki-Miyaura reaction, cross coupling between aryl halide and boronic acid, was among the most powerful methodologies available for the construction of C–C bonds and has found widespread use in synthesis of pharmaceuticals, materials and fine-chemicals.[1] Recently, the oxidative coupling reaction of arenes with boronic reagents *via* direct C–H arylation is playing an increasingly important role in organic synthesis since it avoids the necessary pre-halogenation to make synthetic schemes shorter and more efficient.[2] Several transition-metal complexes based on palladium,[3] iron,[4] copper[5] and rhodium[6] have demonstrated high activity for such catalytic reactions. Although these are elegant methodologies, most of them required one or more equivalents of these often hazardous or toxic oxidizing agents. Notably, Kakiuchi *et al.*[7] and Sames *et al.*,[8] in their pioneering work, disclosed an efficient method for Ru-catalyzed C–H arylation with arylboronates. In these cases, Ru(0) species participate in a C–H bond cleavage step *via* oxidative addition. A shortcoming of this methodology was that aryl boronic acids were not suitable coupling partners. We describe here a direct arylation of arene with aryl boronic acids which employs molecular oxygen as the ultimate, stoichiometric oxidant.

Our investigation began by examining Ru-catalyzed coupling between 2-*o*-tolylpyridine (**1a**) and phenylboronic acid (**2a**).[9] With $[Ru(cymene)Cl_2]_2$ as a catalyst, the desired product (**3a**) was achieved in moderate yield (Table 1, entry 5). Interestingly, simple addition of $BiBr_3$ enhanced the conversion in a remarkable manner, resulting in the desired product in 78% yield (Table 1, entry 4).

Table 1 provided information on the impact of catalyst, oxidant, solvent and additive on the efficiency of this process. In the absence of $[Ru(cymene)Cl_2]_2$, no desired product **3a** was formed (Table 1, entry 6). When other Ru catalysts were used, product **3a** was achieved in moderate to good yield (Table 1, entries 1–3). Another feature of the transformation was that the use of molecular oxygen as the oxidant was essential for efficient conversion, as demonstrated by the fact that only trace amount of **3a** was observed when other common oxidants were employed (Table 1, entries 17–19). The effect of the solvent was dramatic. Among the various solvents examined, toluene was the most suitable for the reaction under the catalytic system (Table 1, entries 9–16). Replacement of toluene with other solvents led to decreased yield.

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Additive	Oxidant	Solvent	Yield[b]
1	$RuCl_3$	$BiBr_3$	O_2	Toluene	42%
2	$[Ru(C_6H_6)Cl_2]_2$	$BiBr_3$	O_2	Toluene	68%
3	$[Ru(PPh_6)Cl_2]_2$	$BiBr_3$	O_2	Toluene	72%
4	**$[Ru(cymene)Cl_2]_2$**	**$BiBr_3$**	**O_2**	**Toluene**	**78%**
5	$[Ru(cymene)Cl_2]_2$	—	O_2	Toluene	40%
6[c]	—	$BiBr_3$	O_2	Toluene	N.O.
7[d]	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	Toluene	56%
8[e]	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	Toluene	19%
9	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	Xylene	49%
10	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	CH_3NO_2	8%
11	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	Dioxane	34%
12	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	DCE	71%
13	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	DMF	Trace
14	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	PrOH	15%
15	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	THF	45%
16	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	O_2	MeCN	11%
17	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	Benzoquinone	Toluene	Trace
18	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	H_2O_2	Toluene	Trace
19	$[Ru(cymene)Cl_2]_2$	$BiBr_3$	NaClO	Toluene	Trace

[a] All reactions were carried out in the scale of 0.2 mmol in 2.0 mL of solvent in the presence of 3.0 equiv. $KHCO_3$, 5 mol% Ru catalyst and 20 mol% $BiBr_3$ under 1 atm molecular oxygen for 24 h unless noted otherwise. [b] Isolated yields. [c] Not observed. [d] In the absence of $KHCO_3$. [e] Under an argon atmosphere.

Having established the optimized reaction conditions, we initiated investigations into the scope of the new C–H arylation. The transformation exhibits a broad scope and a high tolerance for a variety of functional groups, as shown in Table 2.

Both electron-rich and electron-poor arylboronic acids participated in this reaction. The arylboronic acids with electron-withdrawing substituents were somewhat more reactive than the arylboronic acids with electron-donating substituents. Substrates bearing halogen, F, Cl, Br, and I, were also efficiently converted into the corresponding products in high yields, without loss of halogen functions. Replacement of 2-*o*-tolylpyridine (**1a**) with 2-(2-fluorophenyl)pyridine and 2-(biphenyl-2-yl) pyridine also led to the desired products **3h** and **3o** in high yields respectively.

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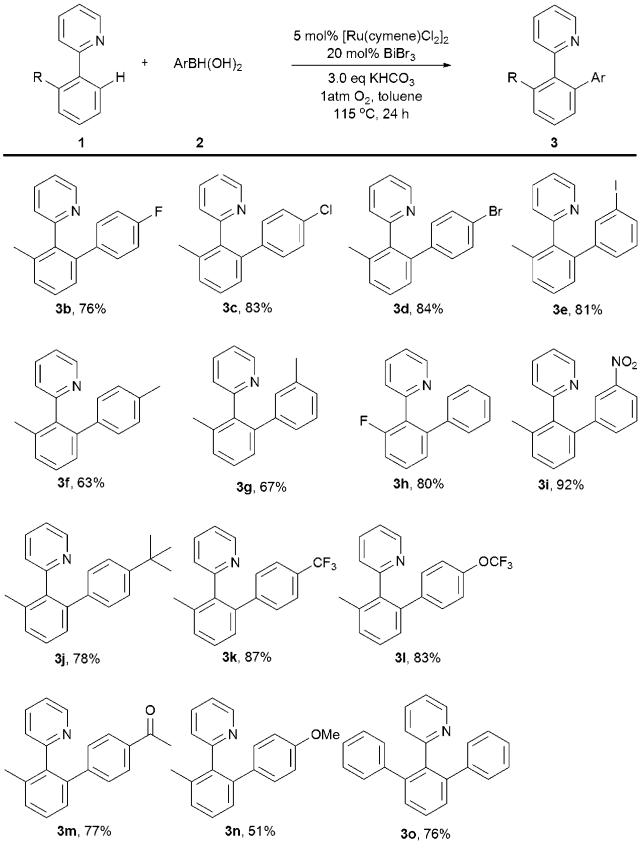
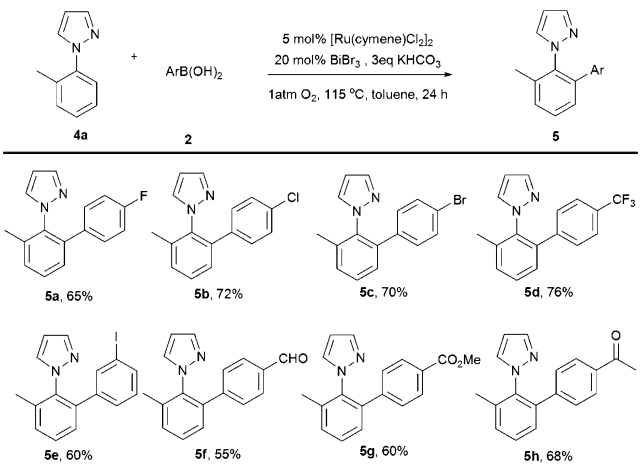
Table 2 Pyridine-directed C–H arylation with aryl boronic acids

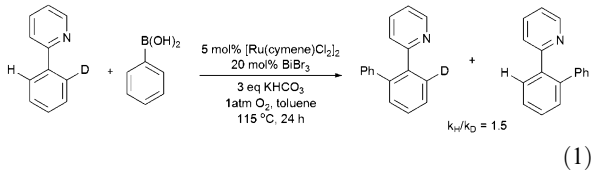


We envisioned expanding the scope of this reaction to include other useful nitrogen-containing directing groups. As shown in Table 3, 1-*o*-tolyl-1H-pyrazole (**4a**) and a variety of aryl boronic acids were subjected to the optimized conditions, leading to the corresponding products in moderate to good yields.

To probe the mechanistic information, deuterated substrates have been synthesized and subjected to the standard conditions. A kinetic isotope effect (k_H/k_D = 1.5) was observed, which implied that C–H bond cleavage might be involved in the rate-limiting step (eqn (1)).[10]

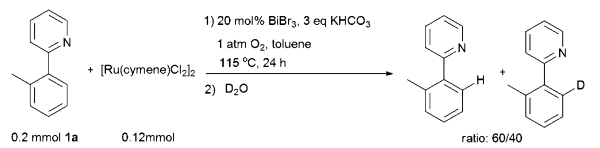
Table 3 Pyrazole-directed C–H arylation with aryl boronic acids



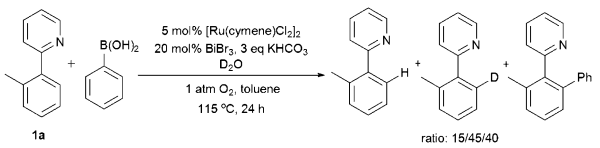


(1)

On addition of D_2O to the reaction system in the absence of boronic acid, deuterium was incorporated into the starting materials (eqn (2)). In the presence of boronic acid, both product and *D*-incorporated starting material were detected (eqn (3)). Based upon the above results, we reasoned that the initial C–H bond cleavage and subsequent transmetalation with boronic acid were involved in the catalytic cycle.

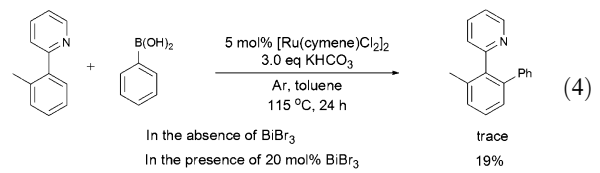


(2)

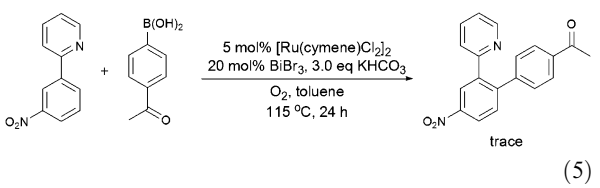


(3)

Next, further experiments were carried out to elucidate the role of the $BiBr_3$. Under an argon atmosphere, 19% yield was observed in the presence of 20 mol% $BiBr_3$. However, only trace amount of product was generated in the absence of $BiBr_3$ (eqn (4)).[11]



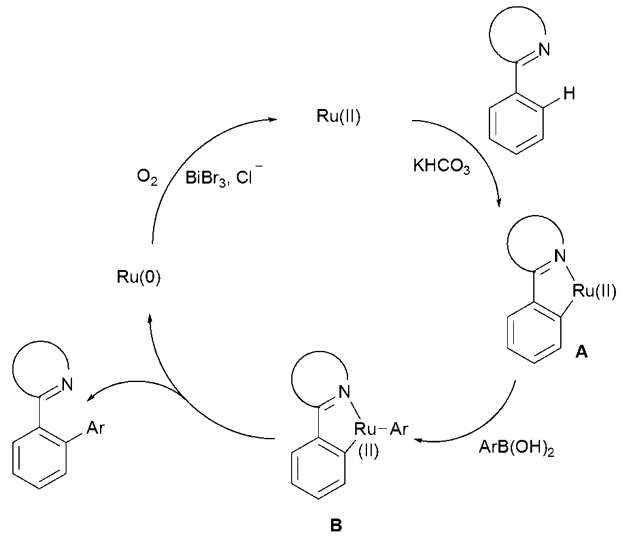
(4)



(5)

Pfeffer *et al.* reported C–H bond electrophilic activation between $[Ru(benzene)Cl_2]_2$ and 2-phenylpyridine.[12] Recently, several groups reported C–H activation by cooperative action of Ru(II) catalyst and base (concerted metalation-deprotonation pathway).[13] Notably, only moderate yield was observed in our transformation in the absence of base (Table 1, entry 7). For a substrate bearing a strong electron-withdrawing group, low conversion was observed (eqn (5)).

On the basis of the above results, we proposed a plausible mechanism given in Scheme 1 for the Ru-catalyzed aerobic arylation of arenes. Following initial C–H activation,



Scheme 1 Plausible reaction mechanism.

transmetalation with boronic acid produces the intermediate **B**. This intermediate subsequently generates the desired product and Ru(0) species *via* reductive elimination. Finally, the Ru(0) species is re-oxidized to Ru(II) species by cooperative action of molecular oxygen and $BiBr_3$.

In summary, we developed a novel Ru-catalyzed oxidative coupling of arylboronic acids with arenes *via* direct C–H arylation. Both pyridine and pyrazole can be used to mediate the direct C–H activation step. Notably, O_2 participates as the ideal oxidant under mild conditions. The transformation appeared to be highly compatible toward various functional groups. Further studies to elucidate the detailed mechanism as well as to expand the scope of the Ru-catalyzed C–H activation are underway in our lab.

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