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Intramolecular arylation of benzimidazoles via Pd(II)/Cu(I) catalyzed cross-dehydrogenative coupling

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ABSTRACT

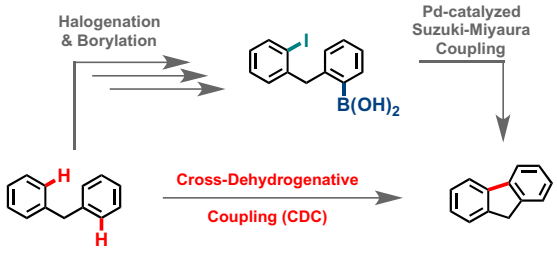
Electron poor benzimidazole substrates were arylated via an intramolecular cross-dehydrogenative coupling (CDC) reaction. These CDC reactions were catalyzed by a Pd(II)/Cu(I) catalyst system, capable of producing moderate yields on a large library of substrates. The substrate scope consisted of tethered arene-benzimidazoles that upon coupling, produced a fused polycyclic motif.

The biaryl motif is a prominent structure in many biologically active compounds, and green methods to synthesize these biaryl bonds are highly desired.[1] Conventional aryl coupling methods (i.e. Suzuki–Miyaura[2] or Stille[3] coupling) employ prefunctionalization steps to form activated C–metal or C–halogen bonds, which can readily undergo catalytic coupling. However, this prefunctionalization decreases the overall step economy of the synthesis and produces large amounts of waste. A far more advantageous coupling method would be cross-dehydrogenative coupling (CDC). It can be used to inter- and intramolecularly couple two aryl hydrocarbon bonds, requiring no prefunctionalization of substrates and affording high yields with minimal byproducts and waste (Scheme 1).

Much attention has been given to incorporating heterocycles into biaryl CDC reactions, since heterocyclic components are often found in nature and play a prominent role in pharmaceutical candidates.[1] The benzimidazole moiety alone has been shown to have many important uses including an antiviral for HIV,[4] antibacterials[5,6] and possible anticancer agents.[7] However, imidazoles are rarely found as a coupling substrate in CDC reactions. Mori and co-workers have shown an efficient homocoupling reaction for imidazoles,[8] and the You group has found success in coupling imidazoles to thiophenes,[9,10] but CDC between imidazoles and benzenes has proved to be a challenging task. Dominguez and Dubois have arylated imidazoles using aryl iodides,[11,12] but, to our knowledge, the only examples of coupling imidazoles with simple arenes via CDC are the recent examples of Bao and Guo.[13]

With this in mind, we decided to explore palladium catalyzed CDC reactions between benzimidazoles and arenes. To help overcome coupling difficulties, the arene was tethered to the benzimidazole prior to coupling by installing an *N*-benzyl substituent. The tether would help in the metalation of both coupling partners by keeping them in close proximity to each other, and at the same time reducing unwanted dimerization. CDC should cause this tethered substrate to cyclize into a fused polycyclic system.

The optimization studies for this reaction were performed on *N*-benzyl benzimidazole, substrate **1**, which was synthesized through a substitution reaction using deprotonated benzimidazole and benzyl chloride. Substrate **1** was then purified by column chromatography and afforded a 70% yield. Initially, we thought that a Cu(I) salt would be a beneficial catalyst since it has been shown that CuI



Scheme 1. The conventional Suzuki–Miyaura cross-coupling method versus CDC.

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can arylate the C2 position of azoles via intramolecular coupling with aryl iodides.[11] Since **1** did not contain a halogen, it was also theorized that a catalyst such as $Pd(OAc)_2$ would be needed to activate the aryl C–H bond. However both $Pd(OAc)_2$/CuI and $Pd(OAc)_2$/CuCl catalyst systems proved to be ineffective, since they both gave low conversion of starting materials and a mixture of byproducts. Next, a rhodium based catalyst, $[RhCl(coe)_2]_2$, was tried, but it suffered from low yields and dimerization. Simply using $Pd(OAc)_2$ as the catalyst with a $Cu(OAc)_2{\cdot}H_2O$ oxidant provided a superior system; therefore, further optimization reactions were run with this catalyst system (Table 1).

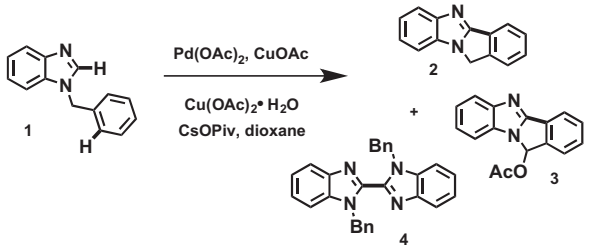
At the outset, undesired byproducts including the dimer **4** and the acetoxylated compound **3** plagued the reaction. It was found that lowering the amount of $Cu(OAc)_2{\cdot}H_2O$ oxidant helped reduce the amount of acetoxylated products since the amount of acetate anion was reduced. Also lowering the temperature and time of the reaction helped lower byproduct formation. Interestingly, the addition of CsOPiv (Table 1, entry 5) eliminated compound **3**, most likely due to the steric nature of the pivalate anion. It has been suggested by Fagnou that the addition of pivalate helps facilitate the C–H bond cleavage by forming $Pd(OPiv)_2$ prior to palladation.[14–16] Fagnou and co-workers also showed that reactions performed in pivalic acid instead of acetic acid greatly reduced unwanted oxidative byproducts including dimers.[14]

Upon doubling the amount of $Pd(OAc)_2$, compound **2** was recovered in a nearly double yield (Table 1, entry 6), suggesting that catalyst turnover was a problem in the reaction. After many trials, the optimal time and temperature for the coupling reaction were found to be 3 h at 150 °C using microwave heating (Table 1, entry 8). The longer reaction times led to a decrease in product yield, perhaps due to decomposition (Table 1, entry 9). Finally, we were excited to discover that the addition of 0.5 equiv of CuOAc improved the yield slightly, producing the best isolated yield of 58% (Table 1, entry 10).

Another interesting observation during the optimization of this reaction was the copper color present in the organic layer while extracting the product. Cu(II) has been known to coordinate to pyrazole ligands in isolatable complexes;[17] thus we speculated that copper was forming a complex with our benzimidazole products, and therefore lowering the isolated yield. A stronger ligand was perhaps needed to coordinate to the copper and liberate the final product. Immediately following the coupling reaction, $Na_2S{\cdot}9H_2O$ was added to the reaction and stirred at room temperature for an hour. This removed all copper color from the organic extract, and simultaneously increased the yields of the coupled product.

Next, an array of substrates was screened with the optimized conditions to determine the scope of the reaction (Table 2). The presence of an electron donating group on the benzimidazole

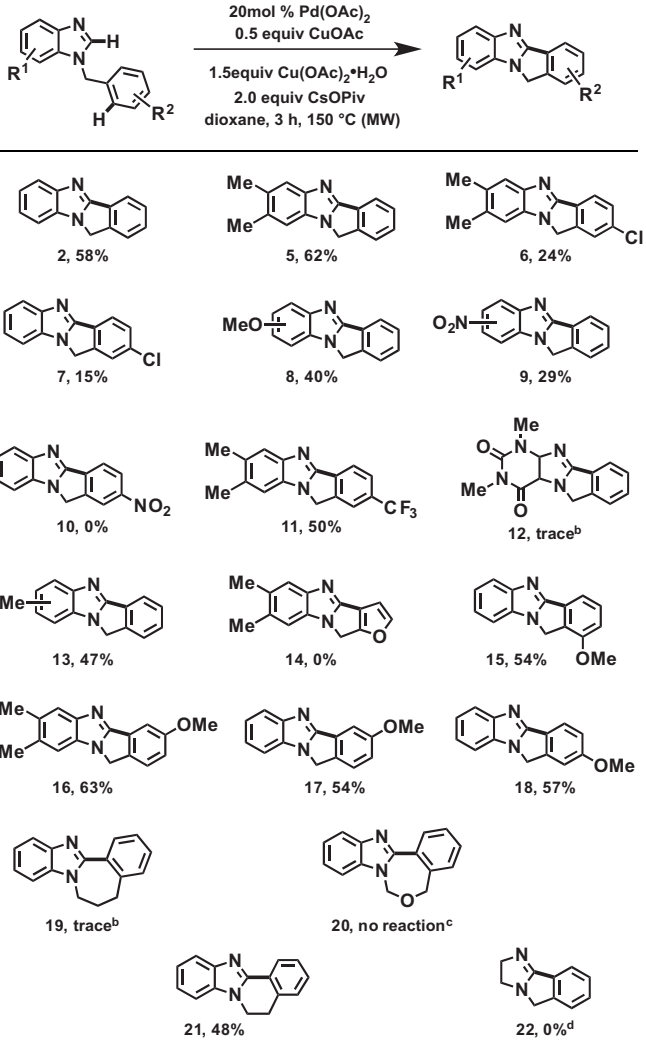
Table 1
Optimization of the reaction conditions



	$Pd(OAc)_2$ (mol %)	$Cu(OAc)_2$ (equiv)	CsOPIv (mol %)	CuOAc (equiv)	Temp. (Time)	% Yield 2:3:4[a]
1	10	4	0	0	160 °C (1 h)	0:21:11
2	10	2	0	0	120 °C (1 h)	19:0:<1
3	10	2	0	0	120 °C (8 h)	31:0:<1
4	10	2	0	0	120 °C (4 h)	23:12:<1
5	10	2	2.5	0	120 °C (4 h)	28:0:0
6	20	2	2.5	0	120 °C (4 h)	47:0:0
7	20	1.5	2	0	120 °C (6 h)	41:0:<1
8	20	2	2	0	150 °C (3 h)	56:0:0
9	20	2	2	0	150 °C (4 h)	46:0:0
10	20	1.5	2	0.5	150 °C (3 h)	58:0:0

[a] Isolated yield following a work-up with $Na_2S{\cdot}9H_2O$. See Supporting information for a representative procedure.

Table 2
Scope of the cyclization of *N*-benzylbenzimidazoles[a]



[a] Reaction conditions: 0.384 mmol substrate, 20 mol % $Pd(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$ (0.768 mmol), CuOAc (0.192 mmol), CsOPiv (0.960 mmol) in 5 mL of 1,4-dioxane at 150 °C for 3 h under microwave heating. Isolated yields following work-up with $Na_2S{\cdot}9H_2O$. See Supporting information for a representative procedure.
[b] A small amount of the desired product was detected by GC–MS.
[c] Only starting materials were observed by GC–MS.
[d] The starting material was completely consumed, but the desired product was not observed.