2014

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Pereira, K. C., Porter, A. L., & DeBoef, B. (2014). Intramolecular arylation of benzimidazoles via Pd(II)/Cu(I) catalyzed cross-dehydrogenative coupling. *Tetrahedron Letters*, 55(10), 1729-1732. doi: 10.1016/j.tetlet.2014.01.103
Available at: <https://doi.org/10.1016/j.tetlet.2014.01.103>

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Published in final edited form as:

Tetrahedron Lett. 2014 March 5; 55(10): 1729–1732. doi:10.1016/j.tetlet.2014.01.103.

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.

Keywords

Cross-dehydrogenative coupling; Oxidative Coupling; Palladium; Dual catalysis; Biaryl

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-Miyaura² or Stille³ 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 substrates in CDC reactions. Mori and coworkers have shown an efficient homocoupling reaction for imidazoles,⁸ and the You group has found success coupling imidazoles to thiophenes,^{9–10} but CDC between imidazoles and benzenes has proved to be a challenging task. Dominguez and Dubois have

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Supplementary Material

Experimental procedures as well as characterization of previously unknown compounds.

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 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·H₂O 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·H₂O 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 C–H bond cleavage by forming Pd(OPiv)₂ prior to palladation.^{14–16} Fagnou and coworkers 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 was found to be 3 hours 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 equivalents 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, $\text{Na}_2\text{S}\cdot 9\text{H}_2\text{O}$ 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 moiety increased the coupling yield, as evidenced by comparing compounds **2**, **5**, **16** and **17**, and electron withdrawing functionalities on the benzimidazole (**9**) seemed to hinder coupling. When comparing electron rich and electron poor arene coupling partners, there didn't appear to be a significant trend in reactivity. The starting materials for products **8**, **9** and **13** were synthesized in inseparable mixtures, thus the cyclization reactions produced mixtures of isomers. The cyclization was successful in forming a new six-membered ring, compound **21**, but failed to couple compounds **19** and **20**, which would have produced seven membered rings. This indicated that the length of the tether highly influenced the success of the reaction.

Intramolecular coupling reactions between benzimidazole and other heterocycles, such as furan, imidazole, and the caffeine derivative, benzyl theophylline, were also tried under our optimized conditions; however, the attempts were unsuccessful (**12**, **14** and **22**, Table 2).

Kinetic isotope effects of the reaction were evaluated by carrying out competition studies. The first competition study employed equimolar amounts of *N*-benzylbenzimidazole and deuterated *N*-benzyl-*d*₇-benzimidazole, and subjected both substrates to the optimized coupling conditions. Relative amounts of the products were obtained from GC-MS analysis and a KIE of 1.03 was obtained (Scheme 2). This indicated that the metalation of the arene coupling partner was facile and not rate limiting.¹⁸ A second competition study was carried out with equimolar amounts of *N*-benzylbenzimidazole and *N*-benzyl-2-deuterobenzimidazole, but the KIE results of this test proved to be inconclusive due to H/D scrambling.

With the KIE studies in hand, we sought to propose a plausible mechanism for this unique intramolecular CDC reaction. Based on all data, it seemed that the coupling was taking place through a $\text{Pd}^{\text{II}}/\text{Cu}^{\text{I}}$ catalyzed system. Our reasoning behind the dual metal catalysis was supported by several factors. It was known from previous studies that Cu(I) was capable of enhancing azole coupling,^{8–11} so we speculated that Cu(I) was needed to activate the C2 position of the benzimidazole. Because the addition of Cu(I) only raised the percent yield slightly (Table 1, entry 10), we needed to be sure that the addition of Cu(I) was essential in the formation of the product. Since the $\text{Cu}(\text{OAc})_2$ oxidant could disproportionate into Cu(I), we theorized that there was perhaps some Cu(I) present to catalyze the reaction even in the absence of added CuOAc. This would explain why we did not see a significant raise in yield upon the addition of a Cu(I) source.

To further test whether Cu(I) was involved in the mechanism, we had to eliminate the use of $\text{Cu}(\text{OAc})_2$ as an oxidant (Scheme 3). A control reaction was carried out using AgOAc as an

oxidant and Pd(OAc)₂ as the only catalyst. The GC-MS results showed that there was low conversion of the starting material into a small amount of the acetoxyated product **3** and dimer **4**. None of the desired arylation product **2** was observed, though it is the presumed precursor of **3**. This indicated that the Pd(II) catalyst was capable of metallating both the C2 position of the benzimidazole and the ortho carbon of the tethered arene. However, the low conversion indicated that this process, involving two C–H palladations, was not likely the mechanism by which the reactions shown in Table 2 occurred.

We next ran a second control using only a Cu(I) catalyst and AgOAc as the oxidant. The GC-MS results showed there was a low conversion of the starting material into the dimer **4** (Scheme 3). Consequently, we concluded that Cu(I) could activate the benzimidazole moiety and form the benzimidazole dimer. This control reaction also indicated that Pd played a pivotal role in the activation of the arene for coupling.

Our proposed mechanism (Scheme 4) utilizes two independent metalation steps. First, Cu(I) inserts in the 2-position of benzimidazole, forming acetic acid and a Cu(I)-benzimidazole complex. Next, the arene is palladated, again producing acetic acid as a byproduct. At this point, a transmetalation could occur in which CuOAc is released and a biaryl Pd(II) complex is formed. The final step of the reaction would include a simple reductive elimination to form the coupled aryl-benzimidazole product and Pd(0). Subsequent oxidation of the Pd by the Cu(OAc)₂ oxidant would regenerate both the Pd(II) and Cu(I) catalysts. To our knowledge, two independent C–H activations by different metals followed by a transmetalation, is an intriguing mechanism, and would warrant future investigations.

In conclusion, we have developed an intramolecular coupling reaction between the 2-position of benzimidazole and a tethered arene to form fused polycyclic heterocycles. The use of cross-dehydrogenative coupling in this reaction makes it highly atom economical and cost efficient, since no prefunctionalization is required. Mechanistic investigations led us to propose that the reaction proceeds via a dual Pd^{II}/Cu^I catalyst system with a Cu(OAc)₂ oxidant. A large library of electron poor and electron rich arene-benzimidazoles were coupled in moderate yields, suggesting that this reaction could be a valuable tool in the synthesis of biologically useful heterocyclic compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was funded by the National Science Foundation (CAREER 0847222) and the National Institutes of Health (NIGMS, 1R15GM097708-01).

References and notes

1. Constable DJC, Dunn PJ, Hayler JD, Humphrey GR, Leazer JL Jr, Linderman RJ, Lorenz K, Manley J, Pearlman B, Wells A, Zaks A, Zhang TY. *Green Chem.* 2007; 9:411.
2. Miyaura N, Suzuki A. *J. Chem. Soc., Chem. Commun.* 1979; 1979:866–867.
3. Milstein D, Stille JK. *J. Am. Chem. Soc.* 1978; 100:3636.

4. Kim D, Wang L, Caldwell CG, Chen P, Finke PE, Oates B, MacCoss M, Mills SG, Malkowitz L, Gould SL, DeMartino JA, Springer MS, Hazuda D, Miller M, Kessler J, Danzeisen R, Carver G, Carella A, Holmes K, Lineberger J, Schleif WA, Emini EA. *Bioorg. Med. Chem. Lett.* 2001; 11:3103. [PubMed: 11720852]
5. Chaturvedi AK, Negi AS, Khare P. *RCS Adv.* 2013; 3:4500.
6. Sharma S, Gangal S, Rauf A. *Eur. J. Med. Chem.* 2009; 52:514.
7. Penning TD, Zhu G-D, Gandhi VB, Gong J, Liu X, Shi Y, Klinghofer V, Johnson EF, Donawho CK, Frost DJ, Bontcheva-Diaz V, Bouska JJ, Osterling DJ, Olson AM, Marsh KC, Luo Y, Giranda VL. *J. Med. Chem.* 2009; 52:514. [PubMed: 19143569]
8. Monguchi D, Yamamura A, Fujiwara T, Somete T, Mori A. *Tetrahedron Lett.* 2010; 51:850.
9. Wang Z, Li K, Zhao D, Lan J, You J. *Angew. Chem. Int. Ed.* 2011; 50:5365.
10. Xi P, Yang F, Qin S, Zhao D, Lan J, Gao G, Hu C, You J. *J. Am. Chem. Soc.* 2010; 132:1822. [PubMed: 20102197]
11. Barbero N, SanMartin R, Dominguez E. *Org. Biomol. Chem.* 2010; 8:841. [PubMed: 20135042]
12. De Figueiredo RM, Thoret S, Huet C, Dubois J. *Synthesis.* 2007; 2007:529.
13. These two communications were published while this manuscript was in preparation: Sun M, Wu H, Zheng J, Bao W. *Adv. Synth. Catal.* 2012; 354:835. Meng, Ge; Niu, H-Y.; Q, G-R.; Fossey, JS.; Li, J-P.; Guo, H-M. *Chem. Commun.* 2012; 48:9601.
14. Liegault B, Lee D, Huestis MP, Stuart DR, Fagnou K. *J. Org. Chem.* 2008; 73:5022. [PubMed: 18543991]
15. Stuart DR, Fagou K. *Science.* 2007; 316:1172. [PubMed: 17525334]
16. Lafrance M, Fagnou K. *J. Am. Chem. Soc.* 2006; 128:16496. [PubMed: 17177387]
17. Gamez P, van Harras J, Roubeau O, Driessen WL, Reedijk J. *Inorg. Chim. Acta.* 2001; 324:27.
18. Simmons EM, Hartwig JF. *Angew. Chem. Int. Ed.* 2012; 51:3066.
19. Reaction conditions are similar to those shown in Table 2.

Scheme 1.

The conventional Suzuki-Miyaura cross-coupling method vs. CDC

Scheme 2.KIE study of the intramolecular benzimidazolearene CDC¹⁹

Scheme 3.
Control reactions using AgOAc as an oxidant¹⁹

Scheme 4.

Proposed mechanism for the Pd(II)/Cu(I) catalyzed cyclization of N-benzylbenzimidazoles

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 Na₂S·9H₂O. See supporting information for a representative procedure.

Table 2

Scope of the Cyclization of *N*-benzylbenzimidazoles

^aReaction conditions: 0.384 mmol substrate, 20 mol % $\text{Pd}(\text{OAc})_2$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (0.768 mmol), CuOAc (0.192 mmol), CsOPiv (0.960 mmol) in 5 mL of 1,4-dioxane at 150 °C for 3 hr under microwave heating. Isolated yields following work-up with $\text{Na}_2\text{S} \cdot 9\text{H}_2\text{O}$. 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.