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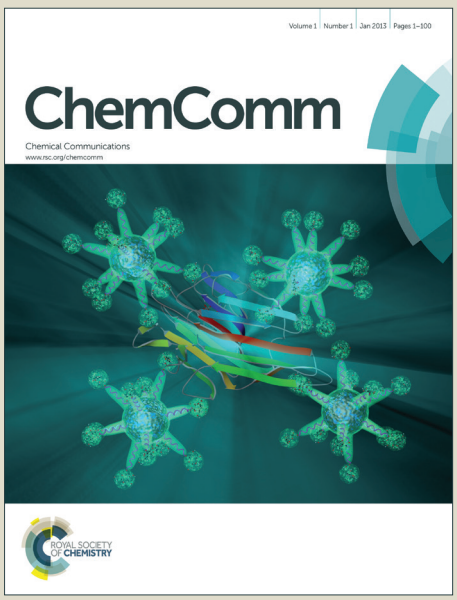

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Copper-Catalyzed Oxidative Decarboxylative C-H Arylation of Benzoxazoles with 2-Nitrobenzoic Acids

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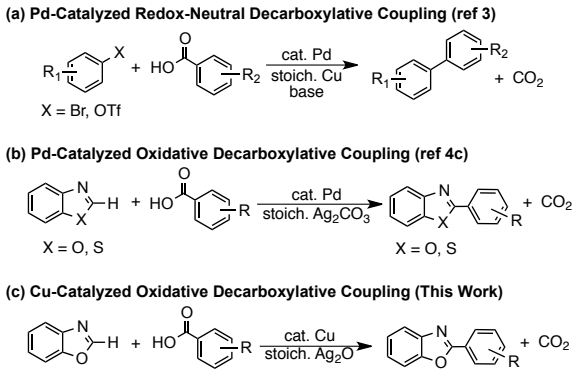
A copper-catalyzed oxidative decarboxylative coupling of benzoxazoles with 2-nitrobenzoic acids was developed. This methodology favors electron-rich benzoxazoles and electron-deficient benzoic acids and enables the preparation of a variety of arylated benzoxazoles in good yields. The trends in product yields suggest a delicate balance between the decarboxylation and C-H arylation steps.

Biaryl structures are common motifs in natural products and biologically relevant molecules.[1] Traditional transition-metal catalyzed cross-coupling methods to form biaryls involve the reaction of an electrophilic coupling partner (aryl halide) and a nucleophilic coupling partner (organometallic reagent). These redox-neutral cross-coupling methods have poor atom- and step-economy due to the requirement for prefunctionalized organometallic reagents, noble metal catalysts, and the separation of waste products. Carboxylic acids are attractive alternatives to traditional organometallic reagents, because they are commercially available, inexpensive, easily stored and handled, and available in a diverse scope.[2]

The redox-neutral decarboxylative couplings of benzoic acids with aryl halides and triflates to construct biaryl products (Scheme 1a) was pioneered by Goossen and coworkers.[3] These systems employ a Cu salt to decarboxylate the benzoic acid and a Pd catalyst to enable the cross-coupling with the aryl halide or aryl triflate substrate. As an alternative, the direct coupling of the metal aryl species with an arene C-H bond minimizes waste products and eliminates the need to pre-generate activated starting materials (Scheme 1b). There are, however, few examples of such decarboxylative direct arylation reactions,[4] and most current systems employ noble metal catalysts, are limited in substrate scope, and are not well understood.



Scheme 1. (a) Redox-neutral and (b) oxidative decarboxylative cross-coupling reactio catalyzed by Pd (c) The Cu-catalyzed oxidative decarboxylative cross-coupling reactio reported here.

Copper-promoted decarboxylations have been well studied[5] and recent work has shown Cu to enable a broa scope of redox-neutral decarboxylative couplings than other transition metal catalysts.[3c,6] Furthermore, Cu is capable of effecting C-H functionalization reactions.[7] It follows that copper-catalyzed decarboxylative direct arylation reaction ha the potential to show much broader scope than curre methodologies, yet to the best of our knowledge, copper has not been shown to catalyze such a reaction.[8] We report here the first copper-catalyzed decarboxylative C-H arylatio reaction.

Because 1,10-phenanthroline (phen) ligated copper speci s are known to promote the decarboxylation of benzoic acids in amide solvents at elevated temperatures,[3c] our studies be an by exploring related conditions for the copper-catal ed decarboxylative C-H arylation using benzoxazole (**1a**) and 2-nitrobenzoic acid (**2a**) as model substrates (Table 1).

We were pleased to find that our initial reaction conditio s employing a Ag_2CO_3 oxidant and KO*t*Bu base afforded the desired decarboxylative arylation product **3aa**, although moderate yields (Table 1, entry 1). Under these reaction conditions a number of byproducts also formed, including th protodecarboxylation product nitrobenzene **4a**, a

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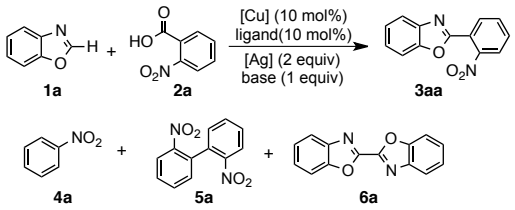
† Electronic Supplementary Information (ESI) available: experimental procedures, details on reaction development, characterization data for starting materials and reaction products and ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of the reaction conditions for the copper-catalyzed decarboxylative arylation of benzoxazole with 2-nitrobenzoic acid[a]



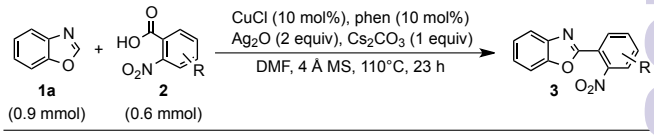
entry	[Cu]	[Ag]	base	ligand	**3aa** (%)[b]
1[c]	CuCl	Ag_2CO_3	KO*t*Bu	phen	55
2[c]	CuCl	Ag_2CO_3	Cs_2CO_3	phen	6
3[c]	CuCl	Ag_2O	KO*t*Bu	phen	39
4[c]	CuCl	Ag_2O	Cs_2CO_3	phen	67
5	**CuCl**	**Ag_2O**	**Cs_2CO_3**	**phen**	**71**
6	$CuCl_2$	Ag_2O	Cs_2CO_3	phen	13
7	$CuBr_2$	Ag_2O	Cs_2CO_3	phen	26
8	CuBr	Ag_2O	Cs_2CO_3	phen	48
9	CuI	Ag_2O	Cs_2CO_3	phen	55
10	Cu_2O	Ag_2O	Cs_2CO_3	phen	26
11	CuCl	Ag_2O	Cs_2CO_3	bpy	25
12	CuCl	Ag_2O	Cs_2CO_3	py	9
13	CuCl	Ag_2O	Cs_2CO_3	none	12
14	CuCl	none	Cs_2CO_3	phen	22
15	none	Ag_2O	Cs_2CO_3	phen	ND[d]

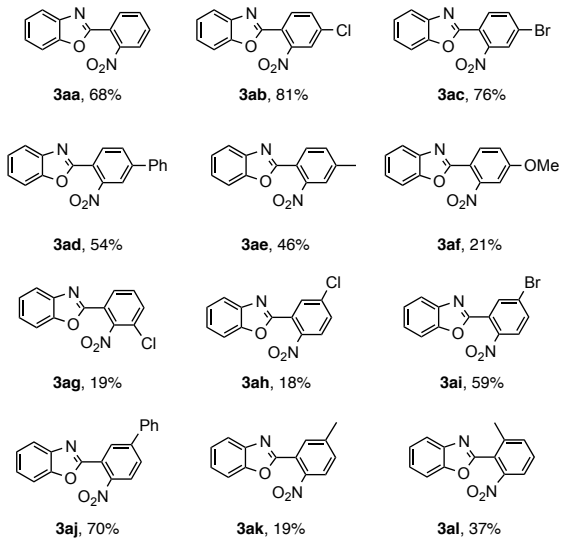
[a] All reactions were carried out using 0.3 mmol benzoxazole and 0.2 mmol 2-nitrobenzoic acid in 2 mL DMF for 23 h at 110°C. [b] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using hexamethylbenzene as internal standard. [c] 0.2 mmol benzoxazole. [d] None detected.

decarboxylative homocoupling product **5a**, and a benzoxazole dimer **6a**. The use of Cs_2CO_3 as a basic additive and Ag_2O as the oxidant decreased the yields of the dimeric products **5a** and **6a** and increased selectivity for the desired decarboxylative arylation product **3aa** (Table S1, entries 1-4). Evaluation of other oxidants, including air, $K_2S_2O_8$, and peroxides, revealed the reaction to be specific to silver-based oxidants (Table S2).[9,10] A further increase in yield was obtained by altering the ratio of starting materials (entries 4 and 5). A survey of copper salts (entries 5-10) and ligands (entries 5, 11, and 12 and Table S1) revealed CuCl and phen to produce the highest yield for this transformation. The optimized conditions employ 10 mol% CuCl, 10 mol% phen, 1 equiv Cs_2CO_3, and 2 equiv Ag_2O to yield 71% of the desired decarboxylative arylation product, **3aa** (entry 5). In the absence of silver, only small amounts of product **3aa** are formed. Alternatively, in the absence of copper no coupling product **3aa** is observed, instead only nitrobenzene **4a** is formed (entry 15 and Table S1), indicating that copper is required for the formation of the decarboxylative arylation product **3aa**.

Following the identification of the optimized reaction conditions, we explored the scope of benzoic acids (Table 2). For the decarboxylative arylation reaction to proceed smoothly a nitro group is needed *ortho* to the carboxylic acid (Chart S1). Similar limitations have been observed under Pd-catalyzed decarboxylation conditions[4b-e,11] and in redox-neutral Cu-catalyzed decarboxylative coupling reactions.[3b, 6a, 12]

Table 2. The scope of 2-nitrobenzoic acids in the copper-catalyzed decarboxylative arylation of benzoxazole.[a]





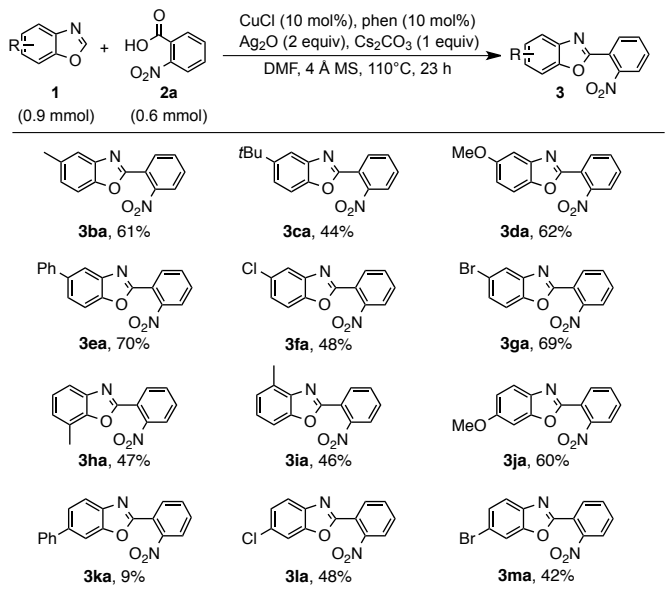
[a] Yields given are isolated yields. All reactions were carried out using 0.9 mmol benzoxazole and 0.6 mmol 2-nitrobenzoic acid in 6 mL DMF for 23 h at 110°C.

Within the class of 2-nitro-subtituted benzoic acids, the reaction is compatible with both electron-rich and electron-deficient substituents on the benzoic acid. Benzoic acids bearing electron-deficient substituents lead to higher yields (such as **3ab** and **3ac**). Electron-rich substituents on the benzoic acid result in lower yields (such as **3af** and **3ak**). These substituent trends are consistent with a decarboxylation step that favors electron-deficient benzoic acids, such as the mechanism proposed by Goossen and coworkers for Cu- and Ag-catalyzed protodecarboxylations.[5] Notably, this copper catalyst tolerates both aryl bromides and aryl chlorides and operates at lower temperatures than most current Ni- and Pd-catalyzed decarboxylative arylation reactions.[4]

Subsequently, the scope of substituted benzoxazoles was explored (Table 3).[13] Although both electron-rich and electron-deficient substituents are tolerated, in general, electron-rich substituents give higher yields (such as **3da** and **3ja**). These substituent trends are surprising because they are inconsistent with deprotonation[7c] or organometallic C-H functionalization pathways,[14] yet a single electron transfer C-H activation pathway is unlikely for benzoxazoles. We are currently exploring the possibility that these substrate trends are due to competitive decarboxylation and transmetallation steps.

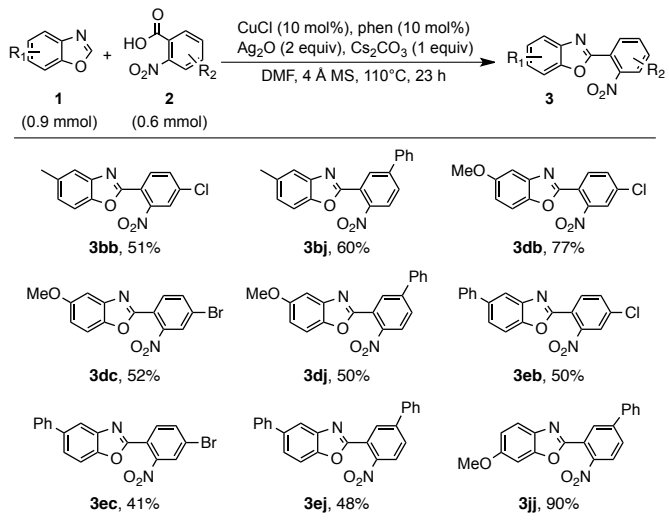
Finally, the substituent trends shown in Tables 2 and 3 allowed us to apply our decarboxylative arylation conditions to a broader scope of electron-deficient 2-nitrobenzoic acids and electron-rich benzoxazoles (Table 4).

Table 3. The scope of substituted benzoxazoles in the copper-catalyzed decarboxylative arylation with 2-nitrobenzoic acid.[a]



[a] Yields given are isolated yields. All reactions were carried out using 0.9 mmol benzoxazole and 0.6 mmol 2-nitrobenzoic acid in 6 mL DMF for 23 h at 110°C.

Table 4. The scope of the copper-catalyzed decarboxylative arylation of substituted benzoxazoles with substituted 2-nitrobenzoic acids.[a]



[a] Yields given are isolated yields. All reactions were carried out using 0.9 mmol benzoxazole and 0.6 mmol 2-nitrobenzoic acid in 6 mL DMF for 23 h at 110°C.

Under our reaction conditions, benzoic acids lacking the *ortho*-nitro group do not undergo decarboxylative cross-coupling to generate product **3** (Chart S1). To gain some insight into the requirement for the 2-nitro substituent, the product distribution for unreactive benzoic acids was evaluated. Treating 2-methoxybenzoic acid and 2-fluorobenzoic acid under our standard reaction conditions in the presence of benzoxazole **1a** generates only anisole and fluorobenzene, respectively. Alternatively, subjecting 4-nitrobenzoic acid to the same reaction conditions results in no reaction, and only the carboxylic acid starting material is recovered. These data indicate that the coordinating substituent in the *ortho*-position facilitates decarboxylation, however the nitro group is needed to facilitate coupling to generate **3**. We believe that the *ortho*-nitro group may play a key role in a transmetallation step and current work is exploring this possibility.

In summary, we have identified a copper-catalyzed decarboxylative C-H arylation of benzoxazoles with 2-nitrobenzoic acids to generate substituted heterobiaryl products. These reactions are the first example of a copper-catalyzed decarboxylative arylation and operate under relatively mild conditions. We are currently exploring methods to broaden the substrate scope and mechanistic studies are underway to understand the role of the 2-nitro substituent in this decarboxylative arylation reaction.

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Notes and references

§ General procedure for catalytic reactions: 2-nitrobenzoic acid (0.6 mmol), CuCl (0.06 mmol), phen (0.06 mmol), Cs_2CO_3 (0.6 mmol), Ag_2O (1.2 mmol), and 4Å molecular sieves (600 mg) were combined in a 50 mL Schlenk tube fitted with a stir bar. The tube was evacuated and backfilled with N_2 three times before a solution of benzoxazole (0.9 mmol) in dry DMF (6.0 mL, 0.15 M) was added. The reaction mixture was stirred under N_2 at 110°C for 23 h. Upon completion, the mixture was cooled to room temperature and diluted with ethyl acetate (40 mL), filtered through celite and the solvent removed. The crude product was purified by silica gel column chromatography (ethyl acetate in hexanes) to yield the decarboxylative arylation product.

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