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New methods for copper-catalyzed decarboxylative C-H arylation reactions

Lijun Chen

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**NEW METHODS FOR COPPER-CATALYZED DECARBOXYLATIVE C-H ARYLATION
REACTIONS**

by

Lijun Chen

**Thesis submitted to the Eberly College of Arts and Science
at West Virginia University
in partial fulfillment of the requirements
for the degree of**

**Master of Science
in
Chemistry**

Approved by

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**Morgantown, West Virginia
2015**

Abstract

NEW METHODS FOR COPPER-CATALYZED DECARBOXYLATIVE C-H ARYLATION REACTIONS

by Lijun Chen

Metal-catalyzed cross-coupling reactions have become a powerful tool to construct unsymmetric biaryl structures. Traditional cross-coupling requires prefunctionalized coupling partners, resulting in poor atom- and step-economy. As an alternative, carboxylic acids are attractive coupling precursors after the release of carbon dioxide. Carboxylic acids are readily available in a wide scope and easily stored and handled. Over the past decade, work has been performed on developing new methods for metal catalyzed redox neutral decarboxylative coupling reactions with benzoic acids. However, redox neutral decarboxylative coupling reactions require a prefunctionalized aryl halide or aryl triflate coupling partner. Alternatively, oxidative decarboxylative cross-coupling enables direct C-H arylation, minimizing the possible halide waste. Current oxidative decarboxylative coupling systems suffer from few choices of metal catalyst and limitations of substrate scope. Because copper systems show a broad scope of both decarboxylation and C-H arylation reactions, copper salts might be potential for promoting oxidative decarboxylative cross-coupling reactions. During the past three years, I have been working on developing a new reaction of decarboxylative cross-coupling of arene C-H bonds with benzoic acids to construct biaryls using copper catalysts. Here in my thesis, I will report two classes of reactions I studied: (1) Copper-catalyzed reactions of 2-phenylpyridine and 2-nitrobenzoic acid; (2) Copper-catalyzed decarboxylative C-H arylation reactions of benzoxazoles with 2-nitrobenzoic acids.

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Lijun Chen

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I. CHAPTER 1: INTRODUCTION

1.1 Catalytic systems of decarboxylative coupling reactions

Metal-catalyzed cross-coupling reactions have become a powerful tool to construct unsymmetric biaryl structures¹. Traditional cross-coupling reactions (Scheme 1) require prefunctionalized coupling partners and separation of byproducts, resulting in poor atom- and step-economy. As an alternative, carboxylic acids, which are readily available in a wide scope and are easily stored and handled, can be employed as coupling reagents by the extrusion of carbon dioxide (CO₂).

Scheme 1. Traditional cross-coupling reactions to construct biaryls.

In 2006, Goossen et al. reported the first example of a palladium/copper-catalyzed redox neutral decarboxylative cross-coupling between benzoic acids and aryl bromides (Scheme 2).² In this system, palladium and copper are responsible for C-H arylation and decarboxylation, respectively, and the two catalytic cycles are connected by a transmetallation step. However, the substrate scope of benzoic acids is limited to 2-nitro substitution. Later in 2008, they developed a catalytic system with potassium benzoate salts as the decarboxylation partners. Instead of aryl bromides, they used less activated aryl chloride

substrates, and expanded the scope to 2-substituted benzoate salts, overcoming the need for a nitro group at the 2-position.³ Because of the thermodynamically unfavorable exchange of a halide for a non-*ortho*-substituted benzoate at the copper center,^{11a} they employed aryl triflates as the prefunctionalized precursors instead of aryl halides in another Pd/Cu catalytic system.⁴ As triflate is a weakly coordinating ion for coordination at the copper, the anion exchange step in copper-catalyzed decarboxylation cycle (Scheme 2) will not be hampered. In this system, they found a broader scope of benzoate salts, in which 2-substituents on the aromatic ring are no longer necessary.

Scheme 2. Redox neutral decarboxylative coupling of substituted 2-nitrobenzoic acids and aryl bromides.

In redox neutral decarboxylative coupling systems, prefunctionalized aryl halides or pseudohalides are still needed as one of the coupling partners. Alternatively, oxidative decarboxylative cross-coupling (ODC) enables the direct C-H arylation, minimizing the possible halide waste (Scheme 3). In 2009, Glorius' group first reported the Pd-catalyzed intramolecular decarboxylative C-H arylation of 2-phenoxy substituted benzoic acids to form biaryl furan structures.⁵ Then Greaney's group found that silver acetate was also able to catalyze the intramolecular ODC, though through a radical pathway.⁶ Pd and Ag catalyzed intermolecular ODC reactions have also been reported by Larrosa's group⁷ and Zhou's group⁸. In 2014, Hongjian Lu et al. successfully applied the first-row transition metal nickel as the ODC catalyst, providing efficient synthesis of 2-aryl-substituted azoles from azoles and *ortho*-nitro or -fluoro substituted benzoic acids.⁹ However, the reported Pd, Ag and Ni catalytic systems are all restricted to the use of *ortho* substituted benzoic acids, significantly narrowing the substrate scope. Recently, Weiping Su's group reported a silver-catalyzed oxidative decarboxylative arylation of arenes with aromatic carboxylic acids through a radical pathway.¹⁰ This system demonstrates a broad scope of aromatic benzoic acids, but the regioselectivity of C-H activation is not high and the reaction requires high loadings of arenes to get satisfactory yields.

Scheme 3. General oxidative decarboxylative coupling reaction.

To summarize, current catalysts for decarboxylative C-H arylation are limited to Pd,^{5,7,8} Ag^{6,10} and Ni⁹ systems, and the substrate scope of benzoic acids is limited to 2-substituted benzoic acids for two-electron bond-forming pathways via organometallic intermediates.

1.2 C-H functionalization of 2-phenylpyridine catalyzed by copper

The 2-pyridyl group has been widely studied in metal-catalyzed directed C-H functionalization reactions.¹⁸ Aerobic copper-catalyzed C-H activation of 2-phenylpyridine has attracted significant attention because oxygen is a benign and abundant oxidant, and because copper is capable of effecting C-H activation reactions.^{12c}

In 2006, Yu's group developed a copper-catalyzed reaction of 2-pyridyl directed C-H chlorination with O₂ as the oxidant, and mono-chlorination of 2-phenylpyridine was obtained in 63% yield at 100°C while bis-*ortho*-chlorination product was formed in 92% yield at 130°C (Scheme 4).^{15b} The reaction was proposed to proceed through a radical pathway, in which the coordinated Cu(II) would react with the aryl ring via a single electron transfer (SET) to form the radical cation intermediate, which would then lead to *ortho*-functionalization.

Cu(OAc)₂ was reported to effectively catalyze the directed acetoxylation of 2-phenylpyridine under aerobic conditions by Yu's group.^{15b} With acetic anhydride (Ac₂O) and acetic acid (AcOH) as the solvent, a mixture of mono- and bis-*ortho*-acetoxylation products were obtained. Later in 2010, Cheng's group expanded the copper-catalyzed aerobic acetoxylation to acyloxylation of 2-phenylpyridine derivatives with anhydrides using toluene solvent (Scheme 5).²² Based upon the observations that the radical traps (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) did not suppress the oxidative acyloxylation, they proposed a two-electron bond-forming pathway via an aryl-copper(III) intermediate as shown in Scheme 5.

Copper catalysts have also been described to promote the amidation²³ and nitration²⁴ of 2-phenylpyridine at the *ortho* position under aerobic conditions. These examples demonstrate the diverse C-H

functionalizations of 2-phenylpyridine catalyzed by copper species with O₂ as an oxidant. As far as I know, no copper-catalyzed arylation reactions of 2-phenylpyridine have been developed.

Scheme 4. Copper-catalyzed directed chlorination of 2-phenylpyridine.^{15b}

Scheme 5. Copper-catalyzed directed acyloxylation of pyridylarenes.

1.3 Direct C-H functionalization of benzoxazoles catalyzed by copper

2-substituted benzoxazoles are important heterocyclic molecules of biological and pharmaceutical significance.²⁵ Copper-catalyzed direct C2-H amination of benzoxazoles with secondary or tertiary amines²⁶ have been reported independently by Mori^{26a}, Schrelber^{26b}, and Huang^{26c}. Interestingly, Duan and

coworkers developed an efficient and practical method for copper-catalyzed C-H amination of benzoxazoles with formamides as both the nitrogen source and the solvent.²⁷

Copper-catalyzed arylation of benzoxazoles is an attractive class of C-H functionalization because the corresponding biaryl products are important structures in natural products and medicinal compounds.²⁵ Several copper-catalyzed reactions have been developed for C-H arylation of benzoxazoles with aryl iodides.^{12a,28} One early example is Daugulis' catalytic copper system which enables the cross-coupling product in moderate to high yields within 10 minutes with LiOtBu included as a base (Scheme 6).^{12a}

Scheme 6. Copper-catalyzed direct arylation of benzoxazole with aryl iodides.

Scheme 7. General goal of ODC to construct biaryls with copper catalyst.

While copper systems show a broad scope of both decarboxylation¹¹ and C-H arylation¹² reactions, copper-catalyzed oxidative decarboxylative cross-coupling has not been developed. During my graduate education, I have been working on developing new decarboxylative C-H arylation reactions using catalytic copper (Scheme 7). Although our early attempts to enable directed ODC between 2-phenylpyridine and 2-nitrobenzoic acid were unsuccessful, we later developed a new copper-catalyzed C-H arylation reaction of benzoxazole with 2-nitrobenzoic acid. I will talk about the reactions of 2-phenylpyridine and 2-nitrobenzoic acid in Chapter 2, and the decarboxylative arylation of benzoxazoles with 2-nitrobenzoic acids in Chapter 3.

II. CHAPTER 2: REACTIONS BETWEEN PHENYLPYRIDINE AND NITROBENZOIC ACIDS

2.1 Overview

As mentioned in the introduction, our goal is to develop new methods of copper-catalyzed decarboxylative C-H arylation reactions.

Literature precedents show that copper can facilitate decarboxylation of benzoic acids via a copper benzoate intermediate,¹¹ and catalytic copper can promote C-H functionalization of 2-phenylpyridine with an oxidant as discussed in the Introduction. Based on these examples, we predict three individual steps in the possible ODC catalytic cycle, namely anion exchange, decarboxylation and C-H functionalization (Scheme 8). Anion exchange from a copper salt and 2-nitrobenzoic acid would form a copper benzoate complex **I**. The following decarboxylation would lead to the formation of aryl copper intermediate **II**, which then reacts with 2-phenylpyridine in the presence of an oxidant to generate the desired product **A**, giving H₂Oxidant as a byproduct.

Scheme 8. Expected ODC reaction between 2-phenylpyridine and 2-nitrobenzoic acid.

2.2 Initial design of copper-catalyzed ODC system

Our initial conditions employed 10 mol% of a copper catalyst, combined with phen (1,10-phenanthroline) as the ligand, DMF (*N,N*-dimethylformamide) solvent, and air as the oxidant. According to what we have

outlined for the copper-catalyzed ODC cycle, the first challenge might be the decarboxylation step, and we began our reaction explorations by using phen and DMF because they have been shown to facilitate decarboxylation.^{11a} We would like to use air as an oxidant because that would be benign and generate water as the only byproduct.

We began our studies using these conditions (phen, DMF, air) and exploring a variety of copper salts for the ODC of phenylpyridine and 2-nitrobenzoic acid. We explored various copper salts including Cu(OAc)₂, CuCl₂, CuO, CuOAc, CuCl, and Cu₂O. However, the only products we observed were hydroxylated phenylpyridine and nitrobenzene formed from decarboxylation (Scheme 9a).

We hypothesized that the hydroxylated phenylpyridine was coming from trace water. In order to remove the water from the system, we tried including MS (molecular sieves) or adding a septum and a drying tube. However, the trace water was not sufficiently excluded with MS, and the hydroxylated phenylpyridine was still formed. With a drying tube, nitrobenzene was the only product and no C-H functionalization product was observed, probably due to the limited amount of air oxidant. We also explored the use of other oxidants under a rigorous nitrogen atmosphere, including benzoquinone (BQ), Ag₂CO₃, *tert*-butyl hydroperoxide (*t*BuOOH), and BQ combined with Ag₂CO₃. Unfortunately, these oxidants led to isolation of only nitrobenzene and recovered 2-phenylpyridine. Although the hydroxylated product was not formed, this system still did not give us the desired decarboxylative coupling product. From these data, we know that decarboxylation is happening, but there is no evidence for C-H arylation, and we think that the C-H arylation step is more challenging than decarboxylation in our designed system.

[Cu]: Cu(OAc)₂, CuCl₂, CuO, CuOAc, CuCl, Cu₂O

Scheme 9. Initial design of copper-catalyzed ODC of 2-phenylpyridine and 2-nitrobenzoic acid. (a) Exploration of copper salts. (b) Reaction without phen ligand. (c) Reactions with toluene or xylene solvent.

We hypothesize that there is competition between decarboxylation and C-H functionalization. Because the decarboxylation is too fast, it is difficult for the pyridyl group to coordinate at the copper center to facilitate C-H activation before the protodecarboxylation product is formed. As mentioned previously, the phen ligand and chelating DMF solvent will facilitate the decarboxylation, and copper-catalyzed decarboxylation is more effective for *ortho*-substituted benzoic acids than *para*- or *meta*-substituted benzoic acids.¹¹ To slow down the decarboxylation of 2-nitrobenzoic acid, we removed ligand (Scheme 9b), used non-amide solvents like toluene or xylene (Scheme 9c), and replaced 2-nitrobenzoic acid with more difficultly decarboxylated 3-nitrobenzoic acid, but none of these attempts were successful to generate the

desired cross-coupling product, and the decarboxylation reactivity was not influenced by applying 3-nitrobenzoic acid, given that nitrobenzene was obtained but no cross-coupling product was detected.

2.3 Conclusion

Early attempts to enable the decarboxylative direct C-H arylation of 2-phenylpyridine with nitrobenzoic acids were not successful. From our data, we hypothesized that the decarboxylation step might not be the difficult step under our catalytic reaction conditions. Instead, oxidative C-H arylation appears to be much more challenging. Thus, we think it might be a good idea to find an alternative arene.

III. CHAPTER 3: DECARBOXYLATIVE C-H ARYLATION OF BENZOXAZOLES WITH 2-NITROBENZOIC ACIDS

3.1 Overview

As our work shown in Chapter 2 suggests, C-H activation of 2-phenylpyridine does not proceed readily under our copper-catalyzed conditions. These results led us to search for an alternative arene for coupling. Benzoxazole has an acidic C2-H bond with an experimental pKa value of 24.8 in DMSO (dimethyl sulfoxide),²⁹ and stoichiometric copper is capable of effecting the regioselective C-H functionalization of azoles.¹⁷ We hypothesized that benzoxazole may be functionalized at the 2-position with 2-nitrobenzoic acid with a copper catalyst and the appropriate oxidant (Scheme 10).

Scheme 10. Targeted copper-catalyzed arylation of benzoxazole by decarboxylative coupling with 2-nitrobenzoic acids.

3.2 Condition optimization of catalyzed ODC of benzoxazoles with 2-nitrobenzoic acid.

With the goal of achieving decarboxylative C-H arylation of benzoxazoles with 2-nitrobenzoic acid in the presence of copper and oxidant, we initially designed the reaction as shown in Scheme 11a. To test if copper is able to mediate both decarboxylation and C-H arylation in this system, we started with stoichiometric loadings of copper chloride. To aid the decarboxylation, we included 1,10-phenanthroline as the ligand and used DMF, a chelating amide solvent. KO^tBu was used as base because it is effective in

other couplings of benzoxazole^{12a} and because we hypothesized that CuO^tBu would be formed, which we believed would then be transformed into (phen)Cu(O₂CAr) species in the presence of phen and aromatic carboxylic acids. We then started our studies using Ag₂CO₃ as the oxidant. The reaction was run under nitrogen gas for 23 hours, and we were pleased to find that the targeted cross-coupling product 2-(2-nitrophenyl)-benzo[d]oxazole was achieved in 15% yield. However, there were five undesired byproducts and the cross-coupling was not the dominant product (Scheme 11a).

To test if the ODC reaction between benzoxazole and 2-nitrobenzoic acid will proceed under catalytic loadings of copper, the copper loading was reduced to 20 mol%. We were delighted to find that under these reaction conditions the desired product was obtained in 17% yield (Scheme 11b). Lower reaction temperature (under 90°C) led to lower yields (less than 10%) of the desired cross-coupling. At 95°C, 16% yield of cross-coupling product was obtained at 95°C, and a lower yield (4%) of homocoupling of benzoxazole was achieved than at 110°C (27%). This suggests that 95°C was sufficient under these reaction conditions, because lower temperatures afford lower yields of cross-coupling and higher temperatures provide higher yields of homocoupling but no higher yields of desired cross-coupling.

According to the results of product distribution (cross-coupling versus homocoupling) shown in Scheme 11b, we thought that the challenge was to promote cross-coupling and meanwhile suppress homocoupling. The use of Ag₂CO₃ as a base instead of an oxidant has been reported in a copper/silver-catalyzed oxidative dimerization of azoles system with O₂ as the oxidant.³⁰ The choice of oxidant might have a significant effect on the ODC system, especially if the oxidant is not just reoxidizing copper(I) to copper(II), but also involved in the C-H activation step. If this is the case, the oxidant would greatly affect the product distribution between cross-coupling and homocoupling.

(a) Stoichiometric loading of Cu:

(b) Catalytic loading of Cu:

temperature	^a yield 1	yield 2	yield 3
80 °C	5%	7%	3%
90 °C	8%	16%	2%
95 °C	16%	26%	4%
110 °C	17%	13%	27%

^aYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

Scheme 11. Reaction of benzoxazole and 2-nitrobenzoic acid with (a) stoichiometric copper and (b) catalytic copper with varying temperatures.

We tried various commonly used oxidants (Table 1), and found that non-silver oxidants like air, K₂S₂O₈, ^tBuOOH (*tert*-butyl hydroperoxide), ^tBuOO^tBu (*tert*-butyl peroxide), BzOOBz (benzoyl peroxide), and I₂ did not give the desired cross-coupling product (entries 1-6). We then tried Ag₂O and 10% yield of the desired product was obtained (entry 8). Although the yield was lower than the 16% obtained with Ag₂CO₃, the reaction showed favored selectivity of cross-coupling over homocoupling, so we decided that Ag₂O would be our choice of oxidant for further optimization of ODC reaction conditions. We decreased the loading of

CuCl from 20 mol% to 10 mol%, and then got a higher yield of 43% by increasing the temperature to 110°C (entry 9).

entry	oxidant	^a yield 1	yield 2	yield 3
1	air	ND	ND	ND
2	K ₂ S ₂ O ₈	ND	ND	ND
3	^t BuOOH	ND	ND	ND
4	^t BuOO ^t Bu	ND	ND	ND
5	BzOOBz	ND	ND	ND
6	I ₂	ND	ND	ND
7	Ag ₂ CO ₃	16%	26%	4%
8	Ag ₂ O	10%	9%	7%
^b 9	Ag ₂ O	43%	9%	8%
^c 10	none	ND	ND	ND

^aYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

^b10 mol% CuCl, 10 mol% phen, 110 °C. ^cNo decarboxylation was observed.

Table 1. Exploration of oxidants in the ODC of benzoxazole and 2-nitrobenzoic acid.

Potassium *tert*-butoxide can act as a ligand to copper as well as a base. It was noticed that the reaction yield was significantly decreased in the absence of a base (Table 2, entry 7). Based upon this observation, we explored several bases including Cs₂CO₃, K₂CO₃, Na₂CO₃, NaOAc, and NaHCO₃ (Table 2). By looking into these bases, we found carbonate salts are ideal (entry 2-4), and among them, Cs₂CO₃ gave the highest yield of cross-coupling product, which is 52%.

entry	base	^a yield 1	yield 2	yield 3
1	KOtBu	43%	9%	8%
2	Cs ₂ CO ₃	52%	14%	9%
3	K ₂ CO ₃	43%	7%	8%
4	Na ₂ CO ₃	45%	11%	8%
5	NaOAc	10%	ND	14%
6	NaHCO ₃	34%	27%	19%
7	none	20%	23%	12%

^aYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

Table 2. Exploration of bases in the ODC of benzoxazole and 2-nitrobenzoic acid.

entry	copper salt	ligand	^a yield
1	CuCl	phen	70%
2	Cu(OTf) ₂	phen	44%
3	CuCl ₂	phen	45%
4	CuI	phen	60%
5	CuCl	OMebpy	61%
6	CuCl	^t Bubpy	68%
7	CuCl	bathophen	69%
^b 8	none	phen	ND

^aYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

^bNitrobenzene obtained as the only product in 48% yield.

Table 3. Exploration of copper salts and ligands in the ODC of benzoxazole and 2-nitrobenzoic acid.

To our delight, increasing the loading of benzoxazole to 1.5 equiv led to a good yield of cross-coupling product, which is 70% (Table 3 entry 1).

We further explored different copper species and different ligands, but none of them gave a higher yield of the desired coupling product than CuCl paired with phen (Table 3). Notably, without copper, silver(I) oxide gave only nitrobenzene via protodecarboxylation, but no cross-coupling product was observed (entry 8), confirming the importance of copper in this system.

The screening data discussed above led us to the optimized reaction conditions shown in Scheme 12. 2-nitrobenzoic acid and benzoxazole are combined in a 1:1.5 ratio, and 10 mol% CuCl catalyst paired with

phen ligand, 2 equiv Ag₂O oxidant and 1 equiv Cs₂CO₃ base are included. The isolated yield of the desired 2-(2-nitrophenyl)-benzo[d]oxazole product in the scale of 0.6 mmol 2-nitrobenzoic acid and 0.9 mmol benzoxazole was 68%.

Scheme 12. Optimized conditions for copper-catalyzed ODC of benzoxazole and 2-nitrobenzoic acid.

3.3 Exploration of the substrate scope

Before we identified the optimized reaction conditions, we performed some preliminary tests on the tolerance of substituents on the benzoic acid with 1 equiv benzoxazole (Table 4). The product of homocoupling of benzoxazole was formed without exception with each evaluated benzoic acid. We examined benzoic acids with a nitro group *meta* (entry 3) or *para* (entry 4) to the carboxylic acid, and the reactions showed no evidence for decarboxylation at 110°C. Although nitrobenzene, formed from protodecarboxylation was obtained after increasing the temperature to 160°C, the cross-coupling product was still not observed. 2-fluorobenzoic acid showed similar decarboxylation reactivity as 3-nitro and 4-nitrobenzoic acids (entry 5) in that fluorobenzene was formed only at high temperatures. The other substituents including 2-methoxy (entry 6), 2-phenoxy (entry 7), 2-chloro-4-nitro (entry 8) groups yielded protodecarboxylation products and the product of dimerization of benzoxazole. Meanwhile, the decarboxylative homocoupling product of 2-chloro-4-nitrobenzoic acid was also observed. Fortunately, the desired cross-coupling products were achieved with 4-bromo-2-nitrobenzoic acid (entry 1) and 5-chloro-2-nitrobenzoic acid (entry 2) in 42% and 54% yields respectively. These results show that only benzoic acids with *ortho* nitro groups would lead to the desired ODC product under our reaction conditions. Because without *ortho* nitro group, we were able to see decarboxylation but no cross-coupling, we thought that the nitro group at the 2-position might not only influence the decarboxylation, but also play an important role in the C-H arylation step.

entry	product	yield	entry	product	yield
1		42%	2		54%
3		ND ^c	4		ND ^c
5		ND ^c	6		ND ^b
7		ND ^b	8		ND ^b

^aYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

^bProtodecarboxylation product observed at 110 °C. ^cBoth protodecarboxylation and homocoupling of benzoxazole observed when increasing the temperature to 160 °C.

Table 4. Tests of scope of benzoic acids under copper-catalyzed ODC reaction conditions.

Since we have found the importance of 2-nitro substitution of benzoic acids under our conditions, we examined a variety of substituted 2-nitrobenzoic acids under our optimized reaction conditions (Table 5). We were glad to see that both electron-donating and -withdrawing groups at different positions afford the desired cross-coupling products under our conditions, although some gave unsatisfactory yields. As shown in Table 5, electron rich methyl group on the 2-nitrobenzoic acid will decrease the yield, regardless of the

substitution position, affording the desired products in yields ranging from 19% to 46%. 4-substituted-2-nitrobenzoic acids generally gave higher yields of corresponding biaryl products, presumably due to the decreased steric hindrance relative to any other positions. It is notable that arylbromide (entry 2) is well tolerated under our new system, surviving the possible redox neutral cross-coupling to afford the ODC product in 76% yield.

<chem>c1ccc2c(c1)oc[nH]2</chem> + <chem>O=C(O)c1ccc(R)cc1[N+](=O)[O-]</chem> $\xrightarrow[\text{4Å MS, DMF, 110 °C, 23 h}]{\text{CuCl (10 mol\%), phen (10 mol\%)}$ $\text{Ag}_2\text{O (2 equiv), Cs}_2\text{CO}_3 \text{ (1 equiv)}$					
entry	product	^a yield	entry	product	yield
1		68%	9		37%
2		76%	10		19%
3		72%	11		28%
4		30%	12		19%
5		46%	13		^b 34% (NMR)
6		61%	14		^b 54% (NMR)
7		20%	15		^b 55% (NMR)
8		42%	16		^b 27% (NMR)

^aIsolate yields. 0.9 mmol benzoxazole, 0.6 mmol acid, 6 mL DMF. ^bYields determined by ¹H NMR analysis of the crude reaction mixture using a hexamethylbenzene internal standard.

Table 5. Scope of 2-nitrobenzoic acids in the copper-catalyzed ODC of benzoxazoles and 2-nitrobenzoic acids.

$ \begin{array}{c} \text{R} \text{---} \text{benzoxazole} + \text{HOOC} \text{---} \text{2-nitrophenyl} \\ \xrightarrow[\text{4\AA MS, DMF, 110 } ^\circ\text{C, 23 h}]{\text{CuCl (10 mol\%), phen (10 mol\%)}, \text{Ag}_2\text{O (2 equiv), Cs}_2\text{CO}_3 \text{ (1 equiv)}} \\ \text{R} \text{---} \text{benzoxazole} \text{---} \text{2-nitrophenyl} \end{array} $			
entry	substrate	product	yield ^a
1			68%
2			62%
3			70%
4			33%
5			28%
6			48%
7			60%

^aIsolate yields. 0.9 mmol benzoxazole, 0.6 mmol acid, 6 mL DMF

Table 6. Scope of benzoxazoles in the copper-catalyzed ODC of benzoxazoles and 2-nitrobenzoic acids.

Next, the generality of the reaction for substituted benzoxazoles was examined (Table 6). Benzoxazoles with different substituents including methyl, methoxy, phenyl, chloro and bromo were treated with 2-nitrobenzoic acid under our reaction conditions. As shown in Table 6, functional groups such as methyl (entry 1), methoxy (entry 2) and phenyl (entry 3) groups at the C5 position are compatible with the reaction conditions, affording good yields of cross-coupling products. Halide substituted benzoxazoles, such as chloro (entries 4 and 6) and bromo (entry 5) substituted benzoxazoles are also fair substrates, giving synthetically useful yields of desired products ranging from 28% to 48%.

3.4 Conclusion

In summary, we have developed a new method for copper-catalyzed oxidative decarboxylative arylation reactions. In this method, using CuCl paired with 1,10-phenanthroline as the catalyst, Ag₂CO₃ as the oxidant and Cs₂CO₃ as the base, substituted 2-nitrobenzoic acids can be used to arylate benzoxazoles by the extrusion of carbon dioxide. This method provides a new approach to synthesize 2-aryl-substituted benzoxazole derivatives. However, there are limitations for this method: (1) The 2-nitro group was necessary to obtain the cross-coupling product, while the reason is not clear yet. (2) Silver species were the only oxidants capable of promoting the oxidative decarboxylative coupling under our conditions, and the function of silver in this class of reaction has not been discovered. Literature reports^{11b,20} and our results of control reactions without copper show that silver salts can also promote the decarboxylation of benzoic acids. It is not known yet if the silver just serves as an oxidant to reoxidize Cu(I) to Cu(II), or if it is also involved in the decarboxylation step. Investigations to answer these questions would be interesting future work to perform.

EXPERIMENTAL SECTION

1. General considerations.

^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were recorded on a Varian 400 MHz spectrometer. Chemical shifts (δ) are given in parts per million and referenced to the residual solvent signal¹; all coupling constants are reported in Hz. Melting points were taken on a Mel-II melting point apparatus. Column chromatography was performed using Silicycle 60 silica gel. All commercial reagents were used without further purification unless otherwise noted.

2. Representative procedure for direct arylation of benzoxazoles with benzoic acids.

2-nitrobenzoic acid (0.6 mmol, 99 mg), CuCl (10 mol%, 6 mg), 1,10-phenanthroline (10 mol %, 11 mg), Cs_2CO_3 (1 equiv, 195 mg), Ag_2O (2 equiv, 279 mg) and 4Å MS (1500 mg) were combined in a 50 mL Schlenk tube fitted with a septum and a stir bar. The tube was evacuated and backfilled with N_2 three times before a solution of benzoxazole (1.5 equiv, 108 mg) in DMF (6 mL, 0.15 M) was added. The reaction mixture was stirred under N_2 at 110°C for 23 h, then cooled to room temperature and diluted with ethyl acetate. The mixture was filtered through celite and the solvent removed under vacuum. The crude mixture was purified by silica column chromatography to yield the title compound.

¹ Gottlieb, H. E.; Kotlyar, V.; Abraham, N. *J. Org. Chem.* **1997**, *62*, 7512-7515.

3. Characterization of oxidative decarboxylative cross-coupling products.

2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 97.9 mg (68% y) of the title compound as a white solid (mp = 102.2-102.8°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.12 (dd, *J* = 8, 2, 1H), 7.87 (dd, *J* = 8, 1H, 1H), 7.79 (m, 1H), 7.69 (m, 2H), 7.56 (m, 1H), 7.37 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 158.63, 150.85, 149.01, 141.41, 132.24, 131.76, 131.23, 125.87, 124.83, 124.00, 121.23, 120.54, 110.81.

2-(4-bromo-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 145.5 mg (76% y) of the title compound as a yellow solid (mp = 159.9-161.6°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.01 (d, *J* = 9, 1H), 7.96 (d, *J* = 2, 1H), 7.83 (dd, *J* = 8, 2, 1H), 7.78 (m, 1H), 7.54 (m, 1H), 7.38 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 162.38, 157.61, 150.89, 141.16, 135.06, 132.28, 127.10, 126.07, 125.35, 125.05, 120.58, 119.86, 110.76.

2-(4-chloro-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 137.0 mg (72% y) of the title compound as a white solid (mp = 142.3-143.2°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.10 (d, *J* = 8, 1H), 7.82 (d, *J* = 2, 1H), 7.78 (m, 1H), 7.68 (dd, *J* = 8, 2, 1H), 7.54 (m, 1H), 7.38 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 162.34, 157.73, 150.95, 141.45, 137.96, 132.40, 132.25, 126.26, 125.10, 124.46, 120.78, 119.62, 110.96.

2-(4-fluoro-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 47.0 mg (30% y) of the title compound as a white solid (mp = 102.3-103.9°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.15 (dd, *J* = 9, 5, 1H), 7.78 (m, 1H), 7.58 (dd, *J* = 10, 3, 1H), 7.55 (m, 1H), 7.43 (ddd, *J* = 9, 7, 3, 1H), 7.38 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 164.67, 162.11, 150.93, 141.40, 133.24, 126.07, 124.99, 120.64, 119.75, 119.53, 112.46, 112.18, 110.87.

2-(4-methyl-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 70.5 mg (46% y) of the title compound as a yellow solid (mp = 110.6-112.2°C). ¹H NMR (CDCl₃, 400 MHz): δ 7.98 (d, *J* = 8, 1H), 7.77 (m, 1H), 7.79 (m, 1H), 7.63 (d, *J* = 1, 1H), 7.50 (m, 2H), 7.35 (m, 2H), 2.48 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): 158.85, 150.76, 148.95, 143.10, 141.44, 132.79, 130.96, 125.68, 124.71, 124.40, 120.39, 118.30, 110.71, 21.18.

2-(4-phenyl-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield the title compound 146.8 mg (61%) as a yellow solid (mp = 96.3-97.1°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.20 (d, *J* = 8, 1H), 8.03 (d, *J* = 2, 1H), 7.90 (dd, *J* = 8, 2, 1H), 7.80 (m, 1H), 7.63 (m, 2H), 7.56 (m, 1H), 7.47 (m, 3H), 7.37 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 158.63, 150.97, 149.63, 145.166, 141.61, 137.53, 131.67, 130.27, 129.32, 129.24, 127.13, 125.98, 124.93, 122.44, 120.65, 119.49, 110.90.

2-(4-methoxy-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 34.1 mg (21% y) of the title compound as a yellow solid (mp = 113.5-116.2°C). ¹H NMR (CDCl₃, 400 MHz): δ 7.97 (d, *J* = 8, 1H), 7.76 (m, 1H), 7.75 (m, 1H), 7.63 (d, *J* = 1, 1H), 7.50 (m, 2H), 7.35 (m, 2H), 3.55 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): 161.97, 158.93, 150.86, 141.61, 132.54, 132.28, 125.59, 124.74, 123.96, 120.37, 113.32, 110.75, 109.72, 56.16

2-(5-phenyl-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 100.7 mg (42% y) of the title compound as a light yellow solid (mp = 98.3-101.4°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.28 (d, *J* = 2, 1H), 7.97 (d, *J* = 7, 1H), 7.84 (dd, *J* = 7, 2, 1H), 7.82 (m, 1H), 7.65 (m, 2H), 7.58 (m, 1H), 7.6 (m, 3H), 7.38 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 158.63, 151.84, 148.92, 145.80, 141.88, 137.80, 130.07, 129.93, 129.23, 129.17, 127.35, 126.02, 124.99, 124.93, 122.28, 120.67, 120.96, 110.96.

2-(2-methyl-6-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 56.5 mg (37% y) of the title compound as a yellow solid (mp = 56.8-58.3°C). ¹H NMR (CDCl₃, 400 MHz): δ 7.97 (dd, *J* = 8, 1, 1H), 7.80 (m, *J* = 8, 1H), 7.58 (m, 3H), 7.39 (m, 2H), 2.39 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): 158.56, 150.79, 149.48, 141.47, 141.34, 135.32, 130.97, 125.58, 124.64, 122.85, 122.19, 120.45, 110.85, 19.92.

2-(5-methyl-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 29.6 mg (19% y) of the title compound as a white solid (mp = 115.2-116.3°C). ¹H NMR (CDCl₃, 400 MHz): δ 7.88 (d, *J* = 1, 1H), 7.83 (d, *J* = 8, 1H), 7.79 (m, 1H), 7.55 (m, 1H), 7.45 (dd, *J* = 8, 1, 1H), 7.37 (m, 2H), 2.51 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz): 159.35, 151.05, 143.81, 141.48, 132.21, 132.06, 125.89, 124.86, 124.46, 121.74, 120.58, 110.91, 21.32

2-(3-fluoro-2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 43.6 mg (28% y) of the title compound as a white solid (mp = 102.2-102.8°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.09 (dt, *J* = 8, 1, 1H), 7.78 (m, 1H), 7.61 (td, *J* = 8, 5, 1H), 7.56 (m, 1H), 7.43 (dd, *J* = 9, 1, 1H), 7.40 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 152.67, 150.68, 141.47, 131.80, 131.73, 126.53, 125.24, 125.20, 121.17, 121.03, 119.74, 119.55, 110.95.

2-(2-chloro-6-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 36.9 mg (19% y) of the title compound as a yellow solid (mp = 126.5-128.5°C). ¹H NMR (CDCl₃, 400 MHz): δ 8.25 (dd, *J* = 8, 1, 1H), 7.80 (dd, *J* = 8, 1, 1H), 7.65 (dd, *J* = 8, 1, 1H), 7.56 (m, 2H), 7.40 (m, 2H). ¹³C NMR (CDCl₃, 100 MHz): 163.01, 156.54, 150.61, 141.46, 132.93, 130.87, 128.13, 126.67, 126.50, 125.21, 121.03, 120.77, 110.89.

5-methyl-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 103.0 mg (68% y) of the title compound as a white solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.10 (dd, J = 8, 1, 1H), 7.85 (dd, J = 8, 1, 1H), 7.67 (m, 2H), 7.57 (d, J = 1, 1H), 7.41 (d, J = 8, 1H), 7.18 (dt, J = 8, 1, 1H), 2.47 (s, 3H). ^{13}C NMR (CDCl_3 , 100 MHz): 158.78, 149.28, 141.72, 134.84, 132.26, 131.67, 131.32, 127.16, 125.66, 124.12, 121.58, 120.48, 110.26, 21.47.

5-methoxy-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 100.4 mg (62% y) of the title compound as a white solid. ^1H NMR (Acetone-d_6 , 400 MHz): δ 8.19 (dd, J = 8, 2, 1H), 8.01 (dd, J = 8, 2, 1H), 7.86 (m, 2H), 7.55 (d, J = 8, 1H), 7.27 (d, J = 8, 1H), 7.02 (dt, J = 8, 2, 1H), 3.87 (s, 3H).

5-phenyl-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 132.9 mg (70% y) of the title compound as a light yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.15 (dd, J = 8, 2, 1H), 7.99 (dd, J = 8, 2, 1H), 7.89 (dd, J = 8, 2, 1H), 7.69 (m, 2H), 7.46 (m, 2H), 7.36 (m, 1H).

5-chloro-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 54.3 mg (33% y) of the title compound as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.11 (dd, J = 8, 2, 1H), 7.89 (dd, J = 8, 2, 1H), 7.78 (d, J = 2, 1H), 7.71 (m, 1H), 7.47 (d, J = 8, 1H), 7.37 (dd, J = 8, 2, 1H).

5-bromo-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 61.8 mg (28% y) of the title compound as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.12 (dd, J = 8, 2, 1H), 7.97 (d, J = 2, 1H), 7.93 (dd, J = 8, 2, 1H), 7.70 (m, 2H), 7.52 (dd, J = 8, 2, 1H), 7.45 (d, J = 8, 1H).

6-chloro-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 79.0 mg (48% y) of the title compound as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.13 (dd, J = 8, 2, 1H), 8.11 (dd, J = 8, 2, 1H), 7.96 (d, J = 8, 1H), 7.88 (dd, J = 8, 2, 2H), 7.83 (d, 1H), 7.44 (dd, J = 8, 2, 1H).

6-methoxy-2-(2-nitrophenyl)-benzo[d]oxazole

The crude material was purified by silica column chromatography to yield 96.8 mg (60% y) of the title compound as a yellow solid. ^1H NMR (CDCl_3 , 400 MHz): δ 8.10 (dd, $J = 8, 1$, 1H), 7.82 (dd, $J = 8, 1$, 1H), 7.70 (m, 3H), 7.06 (d, $J = 2$, 1H), 6.97 (dd, $J = 8, 2$ Hz, 1H), 3.85 (s, 3H).

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