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# COMMUNICATION

## **Ligand-controlled C-O Bond Coupling of Carboxylic Acids and Aryl Iodides: Experimental and Computational Insights**

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**Abstract:** Palladium-catalyzed cross-coupling reactions between carboxylic acids and aryl halides have several possible competitive pathways. Decarboxylative C-C bond coupling and C-H arylation are well established in the literature. However, direct C-O bond coupling between carboxylic acids and aryl halides has received little success. In this report, we describe a protocol for exclusive C-O bond formation, enabled by a bidentate *N*,*N*-ligand such as 1,10-phenanthroline. The reaction is general for a broad range of carboxylic acids and iodoarenes. Experimental evidence and computational results suggest a high energy barrier for the alternative pathway of decarboxylative carbon-carbon bond coupling.

**Keywords:** C-O coupling; Palladium; Carboxylic acid; Aryl Iodides; Computational chemistry

Carbon-oxygen bond is one of the most common bonds in biomolecules, natural products and drugs.<sup>[1]</sup> In particular, O-aryl ethers and esters are privileged fragments in medicinal chemistry. Various synthetic routes for aryl esters have been disclosed. Most commonly, O-aryl ethers are synthesized from phenols and carboxylic acids using a stoichiometric amount of dehydrative agents. Recently, direct formation of O-aryl ethers from carboxylic acids and aryl iodonium salts were reported. This attractive protocol for C-O coupling can be accomplished by heating in the absence of a catalyst or using copper under milder conditions.<sup>[2]</sup> Transition-metal-catalyzed C-O bond formation using alcohols and aryl halides has been extensively studied.<sup>[3]</sup> Palladium has been demonstrated to be the most competent metal for this important transformation.<sup>[4]</sup> However, C-O coupling between carboxylic acids and aryl halides has received limited success and suffers a narrow substrate scope.<sup>[5]</sup> In 2017, MacMillan and co-workers reported an elegant photocatalytic strategy for O-aryl ester synthesis involving electron-deficient aryl bromides.<sup>[5a]</sup> More recently, Itami et al. reported Pd/NHC complexes as competent catalysts for C-O coupling of electron-rich aryl iodides and bulky tertiary aliphatic acids.<sup>[5b]</sup> Despite these advance, substrate scope of both phenol and carboxylic acids is limited. In case of Pd-catalyzed C-O coupling primary/secondary alkyl and aryl carboxylic acids, as well as electron-deficient aryl iodides resulted in very low conversion. Consequently, a general protocol for direct coupling of carboxylic acids and aryl halides is highly appreciated. Herein, we report that this transformation can be achieved by employing palladium with a substituted 1,10-phenanthroline ligand.



**Scheme 1.** Palladium-catalyzed reactions between benzoic acids and aryl halides.

Many C-O bond coupling reactions are mediated by palladium. The challenge associated with carboxylic acids in such reactions is a chemoselectivity issue involving decarboxylation and C-H palladation. There are numerous reports on palladium-catalyzed decarboxylative C-C bond coupling reactions involving carboxylic acids, a process often promoted by phosphine ligands (Scheme 1a).<sup>[6]</sup> Alternatively, both benzoic acids and aliphatic carboxylic acids have been shown to be excellent directing group in C-H arylation reactions, under ligand-free conditions or using amino acid derived ligands (Scheme 1b).<sup>[7]</sup> In order to dodge these two major alternative reaction pathways, we initially proposed a Pd(II)-Pd(IV)-Pd(II) catalytic cycle. Our previous studies demonstrated that oxidation of Pd(II) to Pd(IV) can be accelerated by N-heteroaryl ligands.<sup>[8]</sup> We envisioned that, with a proper nitrogen ligand, the oxidation of palladium might be accomplished prior to decarboxylation or C-H activation. Pd(IV) has been well documented to undergo facile reductive elimination to deliver desired C-O coupling products.<sup>[9]</sup>

We began our investigation by examining various bidentate N,N-ligands (Table 1). In the absence of a ligand, the C-O coupling product, using phenylpropanoic acid (1a) and 4-iodotoluene (2a), is observed in trace amounts. Bidentate phosphine L1 and diazafluorenone L2 failed to promote the desired reaction. Gratifyingly, a moderate yield of the product 3a was observed when the bipyridine L3 was Further used. survey showed that 1.10phenanthrolines are also competent ligands. The reaction is sensitive to the electron density of the ligand. The parent 1,10-phenanthroline L4 gives the ester product 3a in 23% yield. Electron-donating groups lead to higher conversion (L6 and L7). Increasing steric hindrance next to the nitrogen atoms (L8) shuts down the reaction. Cationic Pd(II) is most suited. Silver salts are essential and AgTFA appears to be the best additive (see Supplementary Information for more detail). Trifluoromethylbenzene is the most effective solvent for the reaction. Concentration of the reactants has a large impact on the yield of 3a. Under optimized conditions, the ester product 3a can be obtained in 85% yield.

**Table 1.** Condition survey for C-O coupling of carboxylic acids<sup>[a]</sup>

	Ph 1a	H + Me 2a	Pd(TFA) <sub>2</sub> (10 mol%) L (20 mol%) AgTFA (2.0 equiv.) sovlent (0.2 M), 150 °C	Ph 3a Me
Ph <sub>2</sub> P	PPh <sub>2</sub>			R L4, R = H, R' = H L5, R = Me, R' = H L5, R = Me, R' = H L7, R = NMe <sub>2</sub> , R' = H R' L8, R = H, R' = Me
	entry	ligand	solvent	yield (%) <sup>[b]</sup>
	1	L1	PhCF <sub>3</sub>	0
	2	L2	PhCF <sub>3</sub>	0
	3	L3	PhCF <sub>3</sub>	34
	4	L4	PhCF <sub>3</sub>	23
	5	L4	PhMe	0
	6	L5	PhCF <sub>3</sub>	26
	7	L6	PhCF <sub>3</sub>	45
	8	L7	PhCF <sub>3</sub>	44

9	L8	PhCF <sub>3</sub>	0
10	L6	PhCF <sub>3</sub> (0.4 M)	65
11	L6	PhCF <sub>3</sub> (0.5 M)	85
12 <sup>[c]</sup>	L6	PhCF <sub>3</sub> (0.5 M)	0

[a] Standard reaction conditions: 1a (0.2 mmol), 2a (0.6 mmol), Pd(TFA)<sub>2</sub> (10 mol%), L (20 mol%), AgTFA (2.0 equiv.) in PhCF<sub>3</sub> (1 mL) at 150 °C for 15 h.

<sup>[b]</sup> Yields were determined by GC analysis using biphenyl as the internal standard.

<sup>[c]</sup> Without silver salt.

Having identified the optimal conditions, we examined the substrate scope of carboxylic acids (Scheme 2). Benzoic acids undergo the desired C-O bond formation smoothly. Groups of various electronic property and substitution patterns are well tolerated. It in worth noting that challenging electron-withdrawing functionalities, for example nitro, ester and ketone, do not interfere with the reaction. The desired ester products can be prepared in moderate to good yield (3b-3e). Benzoic acids bearing bromine or chlorine atoms also react smoothly (3e, 3i, 3j). Aliphatic carboxylic acids were tested and the reaction was found to proceed with similar efficiency regardless of the steric hindrance of the alkyl group. Despite being excellent substrates in decarboxylation, tertiary aliphatic acids undergoes the C-O coupling with no complications (3r).



**Scheme 2.** Scope of carboxylic acids.<sup>[a]</sup> <sup>[a]</sup> Isolated yield.

Subsequently, the scope of aryl iodides was investigated (**Scheme 3**). A series of *para*-substituted aryl iodides were tested and the reaction shows robust tolerance towards electronic modification of the aromatic ring, affording moderate to good yields in most cases (4b-4i). The C-O bond coupling process shows remarkable chemoselectivity towards iodides. Other halogen atoms, fluorine, chlorine and bromine, are unaffected (4j-4l). Substrates with substituents at *meta-* and *ortho-*positions show reactivity comparable to that of their *para*-counterparts. Significantly, sterically demanding groups at the *ortho*-position do not compromise the reaction rate or yield. 2-Isopropyl and 2-phenyl aryl iodides afford the desired O-aryl esters in 63% and 83% yield, respectively (4m and **4n**). Polycyclic aryl iodides also undergo smooth C-O coupling. This method therefore represents a stepeconomical approach to O-aryl ester derivatives. Compared to the conventional method of dehydrative coupling using carboxylic acids and phenols, our method is particularly attractive for late-stage functionalization of structural complexed arenes, in which a free hydroxy group is not present.



**Scheme 3.** Scope of aryl iodides.<sup>[a]</sup> <sup>[a]</sup> Isolated yield

Several control experiments were carried out to gain a better understanding of the unconventional chemoselectivity of the C-O coupling. When a 1:1 mixture of p-NO<sub>2</sub> and p-OMe benzoic acids was subjected to the standard reaction conditions, products **3b** and **3g** were isolated in similar yields, suggesting that the pKa of the carboxylic acid does not contribute to the overall reaction rate (Scheme 4a). In contrast, electron-rich p-iodoanisole produces much better yield than electron-poor p-CF<sub>3</sub> iodobenzene (Scheme 4b, 54% vs 10%). Besides direct C-O bond coupling, palladium-catalyzed hydroxylation of aryl iodides, followed by esterification, is an alternative reaction mechanism for this transformation. No phenol is detected by GCMS throughout the course of the reaction. Reacting phenol with benzoic acid under the standard conditions results in no formation of the Oaryl ester, ruling out the possibility of the hydroxylation/esterification pathway (Scheme 4c). Interestingly, decarboxylation is completely shut down during the reaction, as indicated by the lack of both decarboxylation and decarboxylative coupling products (Scheme 4d).

A combined mass spectrometry (MS) and density functional theory (DFT)<sup>[10]</sup> analysis was performed. Two conventional catalytic cycles, involving Pd(0)/Pd(II)<sup>[11]</sup> or Pd(II)/Pd(IV)<sup>[9,12]</sup> mechanisms respectively, were evaluated (Scheme 5). The free energy profiles are uniformly composed of three key steps: oxidative addition, carboxylate exchange and reductive elimination. The competitive decarboxylation process prior to the reductive elimination was also considered. For the Pd(0)/Pd(II) catalytic cycle, the DFT calculation suggests that the decarboxylative C-C bond coupling is preferred over C-O coupling, which is contradicted by the experimental data (SI, Figure S1). In the absence of a strong oxidant or other factor to stabilize a Pd(IV) species, the Pd(II)/Pd(IV) catalytic cycle appears unlikely to occur. The activation barrier (51.6 kcal/mol) for the oxidation of Pd(II) to Pd(IV) is very high (SI, Figure S2). Therefore, conventional mechanisms do not account for either the chemoselectivity or the reactivity observed experimentally. We decided to search for potential active species, using HRMS, responsible for the observed selectivity.



Scheme4. Control experiments.



**Scheme 5.** Plausible mechanisms involving Pd(0)/Pd(II) or Pd(II)/Pd(IV) catalytic cycles.

A mixture of Pd(TFA)<sub>2</sub> and **L6** (in a ratio of 1:2) in methanol was analyzed by electrospray ionization MS (ESI-MS). Besides the signals for **L6**-bounded Pd(II)-TFA complex **1** (Scheme 6, Figure S3), the spectra showed significant peaks at higher m/z value. Based on the isotope pattern and fragmentation analysis *via* collision-induced dissociation (CID), a TFAbridged dinuclear Pd(I)-Pd(I) complex **2** attenatively assigned (Figure S4-6).<sup>[13]</sup> Isolation of dimeric palladium species was unsuccessful. At this stage, it is premature to claim complex **2** is crtically involved in the catalytic cycle without further experimental evidence.



Scheme 6. CID mass spectrum.

Mechanistic details of palladium with +1 oxidation state has been reported in cross-coupling reactions.<sup>[15]</sup> In 2013, Schoenebeck reported Pd(I) bimetallic species might be operative in a Br/I halogen exchange reaction.<sup>[16]</sup> The remarkable activity of the dinuclear Pd(I)-Pd(I) species was proposed as a key intermediate for carbon-heteroatom bond formation.<sup>[17]</sup> Although lack of experimental evidence, we did carry out preliminary DFT calculation considering involvement of a dinuclear Pd(I)-Pd(I) species.<sup>[18]</sup> Detailed energy profiles for is enclosed in SI (Figure S7). The competitive decarboxylation pathway is also calculated (red line in Figure S7 and S8). The energy barrier required for decarboxylation is significantly higher than direct reductive elimination (10.4 kcal/mol higher), consistent with the experimental data. We acknowledge that this speculative reaction pathway is one out of of several possible scienarios. Further experiments and theoretical studies are currently underway to identify active Pd species and evaluate alternative reaction pathways.

In conclusion, we developed a general, palladiumcatalyzed cross-coupling reaction between carboxylic acids and aryl iodides. The reaction proceeds with exclusive chemoselectivity towards C-O bond formation. Various benzoic acids, primary, secondary and tertiary aliphatic acids are tolerated, as well as challenging electron-deficient iodobenzenes. DFT calculation revealed that the intriguing chemoselectivity can not be explained by common pathways involving Pd(0)/Pd(II) and Pd(II)/Pd(IV). A spectulative intemediate involving a dinuclear Pd complex is briefly studied.

#### **Experimental Section**

General methods for cross-coupling: An oven-dried 15 mL schlenk tube was charged with carboxylic acid substrate (1, 0.2 mmol), iodobenzene (2, 0.6 mmol), Pd(TFA)<sub>2</sub> (6.7 mg, 0.02 mmol), L6 (9.6 mg, 0.04 mmol), AgTFA (88.0 mg, 0.4 mmol) and deoxygenated benzotrifluoride (0.4 mL, 0.5 M) in a glove box. The schlenk tube was capped with a rubber septum, then the reaction vessel was heated at 150 °C for 15 h. The solvent was removed under vacuum and the product was purified through column chromatography.

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#### COMMUNICATION

Ligand-controlled C-O Bond Coupling of Carboxylic Acids and Aryl Iodides: Experimental and Computational Insights

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