

Pd(II)-Catalyzed C–H Activation/Aryl–Aryl Coupling of Phenol Esters

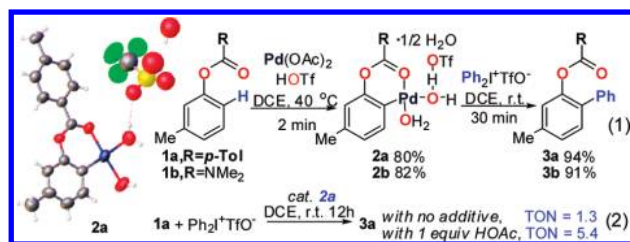
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Recently, Pd-catalyzed chelation-directed C–H activation/cross-coupling reactions have emerged as a promising set of synthetic reactions.¹ Nitrogen-containing directing groups such as amides,² N-heterocycles,³ imines,⁴ pyridine *N*-oxides,⁵ and amines⁶ are commonly used in these reactions, but the need for such groups restricts the general applicability and atom economy. Expanding the scope to include other types of substrates remains a critical challenge.⁷ Here we describe a practical Pd(II)-catalyzed ortho C–H arylation reaction of phenol esters under mild conditions. This reaction provides an example of acyloxy-directed Pd insertion into C–H bonds and a useful strategy for preparing 2-arylphenol derivatives. In comparison with the classical nitrogen-containing group-directed cyclopalladation,⁸ Pd(II) insertion into C–H bonds promoted by oxygen-only groups coordinating to the Pd remains rare. Recent studies^{9–11} have shown that hydroxy and carboxyl groups can be used as directing groups in Pd catalysis.¹² Nonetheless, a catalytic ortho arylation of phenol esters is still elusive.¹³

Our study began by attempting to synthesize a palladacycle of phenol esters. Related palladacycles of aromatic amides were made many years ago,^{8a} but there has not been any example of cyclopalladation mediated by an acyloxy group. As expected, our initial experiments with various phenol esters and Pd(II) salts failed to produce any stable complex. After extensive tests, we discovered that a crystalline compound (**2a**) could be obtained when **1a** reacted with 1:1 Pd(OAc)₂/HOTf in dichloroethane (DCE). X-ray analysis revealed that **2a** is the first example of acyloxy-directed Pd insertion into C–H bonds (eq 1).¹⁴ This indicates that the presence of HOTf to tune the electrophilicity of Pd(II) may constitute a simple but useful strategy to improve Pd-catalyzed C–H activation reactions. In addition, we successfully isolated the related *O*-phenylcarbamate palladacycle **2b**, as characterized by ¹H, ¹³C, and ¹⁹F NMR spectroscopy [see the Supporting Information (SI)].



It was next found that **2a** and **2b** can react stoichiometrically with Ph₂I⁺OTf⁻¹⁵ to produce the ortho-arylated phenol esters **3a** and **3b**. However, when **2a** was used as a catalyst in the reaction between **1a** and Ph₂I⁺OTf⁻, we could obtain a turnover number (TON) of only 1.3 (eq 2). Only after 1 equiv of HOAc was added to the reaction mixture did the TON increase to 5.4. This observation indicates that HOAc is important either for the C–H deprotonation step or for stabilizing some active Pd intermediates.

On the basis of the above findings, we proposed that using Pd(II) catalysts with both HOAc and HOTf additives would enable catalytic C–H activation/aryl–aryl coupling of phenol esters. Through systematic optimization of the reaction conditions (see the SI), we were delighted to find that stirring solutions of phenol esters **1a–i** with 1.2 equiv of Ph₂I⁺OTf⁻, 10 mol % Pd(OAc)₂, and 10 mol % HOTf in DCE at room temperature with no inert gas protection for 3 h afforded ortho-arylated products **3a–i** in 64–88% isolated yield (Table 1). Notably, 0.5 equiv of Ac₂O was added to the reaction mixture so the reaction would not be sensitive to moisture (see the SI).

Table 1. Ortho C–H Activation/Arylation of Phenol Esters^a

1a–1i		Yield ^a (%)		3a–3i	
R	Yield ^a (%)	R	Yield (%)	R	Yield (%)
R (3)	yield ^a (%)	R (3)	yield (%)	R (3)	yield (%)
4-Me-C ₆ H ₄ (3a)	83	Me (3d)	80	1-Ad (3g)	86
NMe ₂ (3b)	88	ⁿ C ₁₁ H ₂₃ (3e)	82	^t Bu (3h)	88 (94 ^b)
4-NO ₂ -C ₆ H ₄ (3c)	64	2-ethylhexyl (3f)	76	Ph (3i)	85

^a Isolated yield. ^b Pd(OPiv)₂ and Piv₂O (Piv = ^tBuCO) were used here.

Table 2. Catalytic Ortho Arylation of Substituted Phenol Esters^a

25 °C, 12 h, 90%	25 °C, 6 h, 96%	25 °C, 6 h, 92%	25 °C, 6 h, 75%
40 °C, 12 h, 82%	40 °C, 6 h, 88%	40 °C, 6 h, 94%	40 °C, 12 h, 85%
40 °C, 24 h, 62%	60 °C, 24 h, 24% ^b	40 °C, 24 h, 42%	40 °C, 24 h, 40% ^c
40 °C, 6 h, 95%	60 °C, 24 h, 86%	25 °C, 12 h, 4o 55% and 4o' 14%	60 °C, 24 h, 4o 10% and 4o' 63% ^{cd}
60 °C, 48 h, 70% ^e	60 °C, 48 h, 74% ^e	60 °C, 48 h, 55% ^e	60 °C, 48 h, 70% ^e

^a Isolated yields are given. Detailed reaction conditions can be found in the SI. ^b With 71% starting material recovered. ^c Isolated after hydroxylation by ^tBuONa/MeOH at room temperature. ^d Only the monoarylated product could be readily hydrolyzed, making the separation easy. ^e The reaction was conducted with the dimethylcarbamate as the substrate. Pd(OAc)₂ was used instead of Pd(OPiv)₂. Piv₂O was not added. Products were hydrolyzed during the reaction process.

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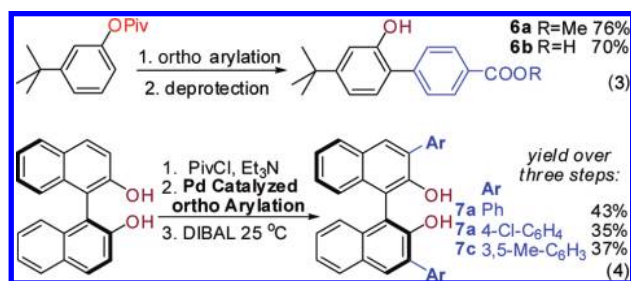
^{*} Tsinghua University.

Replacing Pd(OAc)₂ with Pd(OPiv)₂ (Piv = ^tBuCO) further improved the yield (Table 1, footnote *b*). Under the Pd(OPiv)₂/HOTf/Piv₂O conditions, ortho arylation occurred smoothly with phenol esters carrying various substituents (Table 2). Importantly, the iodo, bromo, and chloro substitutions (**4e–h,j**) were tolerated, making possible additional modification reactions at the halogenated positions. For substrates containing strong electron-withdrawing groups (**4r, 4s**), the corresponding dimethylcarbamates were used because their esters are relatively unstable. Even so, the ortho-arylated products were already hydrolyzed into phenols during the reaction. Notably, the selectivity of mono- versus diarylation could be controlled by tuning the reaction temperature and reactant ratio (**4o** vs **4o'**). Moreover, the scope of the reaction with respect to the arylation reagent is presented in Table 3. Both electron-rich and electron-deficient phenyl groups could be incorporated into the phenol esters. However, ortho substituents on the arylation reagents reduced the coupling yields.

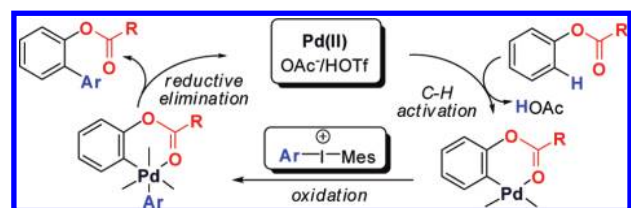
Table 3. Reaction Scope with Respect to the Arylation Reagent

	R	Yield
	5a 4-Cl	90%
	5b 4-Me	86%
	5c 4-CO ₂ Et	84%
	5d 3,5-Me	92%
	5e 3-CF ₃	96%
5f 2-F	21%	
5g 2-Me	trace	

Further examination of the utility of the reaction for the synthesis of useful organic intermediates was conducted. Equation 3 describes a more efficient synthesis of hydroxybiphenyl inhibitors of EGF-stimulated cellular proliferation,¹⁶ and eq 4 describes a new and practical method for 3,3'-bisarylation of BINOL. HPLC analysis indicated that the chirality of BINOL is fully maintained during the transformations. The resulting 3,3'-bisarylated BINOLs provide key intermediates in the development of ligands for transition-metal-catalyzed asymmetric synthesis.¹⁷ In comparison with previous approaches for the synthesis of these phenol derivatives, the key advantage of the new method is that the transformation is not sensitive to moisture or air and does not require flammable reagents such as BuLi.



Scheme 1. Proposed Mechanism



The mechanism of the arylation reaction most likely involves an acyloxy-directed Pd insertion into the C–H bond and subsequent oxidation of the Pd(II) complex to a Pd(IV) intermediate by Ar₂I⁺OTf[–]

(Scheme 1).⁷ Reductive elimination from the Pd(IV) complex then occurs, affording the desired product. An intramolecular isotope effect ($k_H/k_D = 5.7$) was observed (eq 5), indicating that the cleavage of the C–H bond is involved in the rate-determining step.



In summary, we have characterized by X-ray crystallography the first cyclopalladation complex formed from a simple phenol ester. A promising protocol for the ortho C–H activation/aryl–aryl coupling of phenol esters that is not sensitive to moisture or air has been established. Because substituted phenols are important organic intermediates, this reaction is likely to find broad synthetic utility.

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Supporting Information Available: Experimental details and compound characterizations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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