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Palladium-catalyzed C–O bond formation: direct synthesis of phenols and aryl/alkyl ethers from activated aryl halides

Guoshu Chen,[a,b] Albert S. C. Chan[b] and Fuk Yee Kwong[b,*]

[a]*School of Chemistry and Chemical Engineering, Guangzhou University, 510402 Guangzhou, China*
[b]*State Key Laboratory of Chinese Medicine and Molecular Pharmacology, Shenzhen; Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong*

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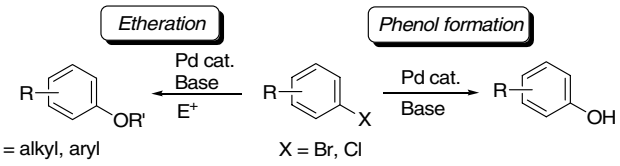
Abstract—A simple and efficient palladium-catalyzed carbon–oxygen bond formation is reported. The palladium-tri-*tert*-butylphosphine complex was found to be effective in converting haloarenes to corresponding substituted phenols. This methodology offers a direct transformation of aryl halides to phenols, as well as the straightforward application to generate a wide variety of diaryl or alkyl/aryl ethers.

1. Introduction

Phenols are important scaffolds for the preparation of a wide variety of pharmaceutically interesting and naturally occurring compounds.[1] They usually serve as a versatile intermediate in preparing oxygenated heterocycles.[2] The classical methods for affording phenols include[3] (1) nucleophilic substitution of activated aryl halides; (2) transformation of arene diazonium salts in the presence of copper complex; (3) anodic oxidation of arenes in trifluoroacetic acid;[4] (4) benzyne synthetic route, etc. Some drawbacks of the above protocol limit the applicability of these methodologies, such as nucleophilic aromatic substitution requires harsh reactions conditions, which is not compatible with base-sensitive functional groups. The presence of amino groups is necessary in a diazotization protocol. Besides, scrambling of phenolic products is observed in both anodic oxidation of arenes and benzyne methodology.

Catalysis is an important tool for the straightforward synthesis of various structurally diverse organic compounds. In the preparation of phenols, a recent advanced iridium-catalyzed aromatic C–H bond functionalization of arenes was reported.[5] This promising cascade borylation/oxidation protocol provides substituted phenols (non-*ortho*-substituted) directly in a good yield.[5] Additionally, the palladium-catalyzed C–O bond formation is an effective method for the construction of diaryl and alkyl aryl ethers from aryl halides and phenols or aliphatic alcohols.[6] However, the direct transformation of aryl halides to corresponding substituted phenols remains unprecedented.[7,8]

We have particular interest in the application of palladium-catalyzed coupling reactions.[9] In some of our catalytic C–C bond formation investigations, control experiments revealed that the 2-bromonitrobenzene electrophile could be partially converted to 2-nitrophenol in the absence of a nucleophile (such as boronic acid). This interesting result prompts us to explore the capability of using readily available palladium catalysts for the direct transformation of aryl hailde to corresponding substituted phenols, which to the best of our knowledge, has never been reported. We report herein that reactions with commercially available Pd-tri-*tert*-butylphosphine complex provide a simple and effective



Scheme 1. Pd-catalyzed direct transformation of aryl halides to phenols and ethers.

* Corresponding author. Tel.: +852 3400 8682; fax: +852 2364 9932; e-mail: bcfyk@inet.polyu.edu.hk

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Table 1. Initial screening of Pd-catalyzed formation of phenol from ArBr[a]

Entry	Ligand	Base	Solvent	Yield[b]
1	Nil[c]	$K_3PO_4{\cdot}H_2O$	Toluene	3
2	Ph_3P	$K_3PO_4{\cdot}H_2O$	Toluene	22
3	*t*-Bu_3P	$K_3PO_4{\cdot}H_2O$	Toluene	88
4	*t*-Bu_3P	K_3PO_4	Toluene	21
5	*t*-Bu_3P	Cs_2CO_3[d]	Toluene	44
6	*t*-Bu_3P	K_2O_3[d]	Toluene	38
7	*t*-Bu_3P	$K_3PO_4{\cdot}H_2O$	Dioxane	87

[a] *o*-Bromonitrobenzene (1.0 mmol), Pd_2dba_3 (0.5 mol %), ligand (2.0 mol %), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), solvent (2.0 mL) under N_2 at 30 °C for 20 h, after completion of reaction, dil HCl was added.
[b] GC yields of phenol were reported.
[c] Absence of Pd and L.
[d] Water (3.0 mmol) was added.

protocol for the preparation of phenols from aryl bromides/chlorides, as well as the one-pot procedure in the preparation of diaryl ethers or alkyl aryl ethers (Scheme 1).

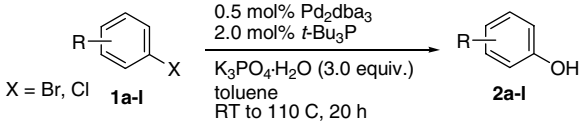
The initial screening of phenol formation was triggered as a function of the phosphine ligand, solvent and base (Table 1). The control experiment revealed that nearly no desired phenolic product was observed in the absence of palladium catalyst. Aryl phosphine was not as effective as the alkylphosphine ligands (Table 1, entries 2 and 3). K_3PO_4 monohydrate was the best base in this reaction (Table 1, entries 3–6). Anhydrous K_3PO_4 provides a lower product yield significantly. Toluene and dioxane gave similar results in these reactions (Table 1, entries 3 and 7). Thus, the preliminary optimized conditions are $K_3PO_4{\cdot}H_2O$ base and toluene solvent in the presence of the Pd-(*t*-$Bu_3P)_2$ complex.

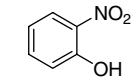
To test the effectiveness of this palladium-catalyzed phenol formation methodology, a range of aryl bromides and chlorides were examined (Table 2). *ortho*-Halonitroarenes were effectively converted to the corresponding substituted nitrophenols. These products are synthetically versatile intermediates for the preparation of benzoxazinones and the inhibitor of cathepsin, which are particularly useful in agricultural[10] and medicinal chemistry.[11] Notable mild reaction conditions in phenol formation are compatible with nitro, methoxy, nitrile, and ester functional groups. Sterically congested 2,6-disubstituted and 2-isopropyl aryl halides were viable substrates. It should be noted that a significant amount of diaryl ether was formed, such as substrate **1l**, from sterically non-hindered reactants. This possibly due to the in situ formed phenoxide ion serves as a nucleophile in this coupling reaction. Thus, diaryl ethers would form from the aryl halides without substituted groups at the *ortho*-position. These results offer an opportunity to explore a protocol for targeting symmetrical diaryl ethers.

The transformations of aryl halides to their corresponding symmetrical diaryl ethers are shown in Table 3. Good to excellent yields of the products were obtained in the presence of palladium-tri-*tert*-butylphosphine complex, tripotassium phosphate monohydrate and dioxane solvent.

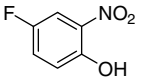
To further extend the scope of this methodology, we developed a one-pot procedure for the transformation

Table 2. Palladium-catalyzed formation of phenols from aryl halides[a]

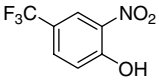




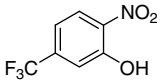
2a, X = Br (83%)[b]
X = Cl (91%)



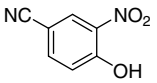
2b, X = Br (79%)[b]



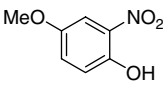
2c, X = Cl (75%)[c]



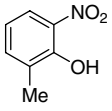
2d, X = Cl (78%)[c]



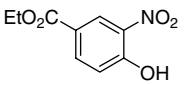
2e, X = Cl (51%)[c]



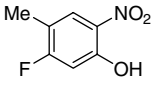
2f, X = Br (70%)[c]



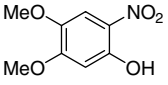
2g, X = Br (72%)[c]



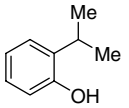
2h, X = Cl (65%)[c]



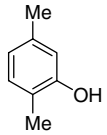
2i, X = Cl (73%)[c]



2j, X = Br (76%)[c]



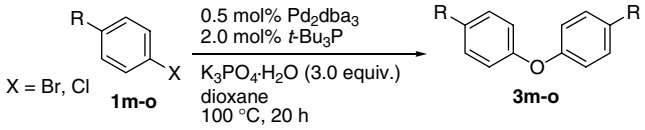
2k, X = Br (38%)[d]



2l, X = Cl (29%)[d]

[a] ArX (1.0 mmol), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), toluene (2.0 mL) under N_2 for 20 h, after completion of reaction, dil HCl was added; isolated yields.
[b] rt, 20 h.
[c] 50 °C, 22 h.
[d] 100 °C, 20 h.

Table 3. Palladium-catalyzed synthesis of diaryl ethers from aryl halides[a]



Entry	X	R	Yield[b]
1	Br	*p*-Me, **3m**	78
2	Cl	*p*-Me, **3m**	72
3	Br	*p*-*t*-Bu, **3n**	84
4	Br	*m*-OMe, **3o**	90

[a] ArX (1.0 mmol), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), dioxane (2.0 mL) under N_2 for 20 h.
[b] Isolated yields.

of aryl halides to alkyl aryl ethers.[12] The initially formed phenoxide was reacted with alkyl halides to afford the desired alkyl aryl ether products. This process is noteworthy since it requires two electrophilic components instead of one nucleophile and one electrophile in the coupling process.[13] It provide an alternative strategy for catalytic organic synthesis in etheration. The one-pot conversion of aryl halides to alkyl aryl ether is shown in Table 4. *o*-Halonitroarenes were efficiently converted to their corresponding methyl ethers in good yields. These mild reaction conditions allow methyl bromoacetate to react with in situ formed phenoxide ion in generating methyl phenoxyacetate (Table 4, entry 4).

In summary, we have developed a simple and efficient catalytic system for the straightforward synthesis of functionalized phenols from aryl halides employing commercially available palladium complex. Notably, we have demonstrated that the initially formed phenols can be directly transformed to alkyl aryl ether via a one-pot protocol. This new method provides an alternative route in etheration when compared with the existing Pd-catalyzed coupling reactions of aryl halides and aliphatic alcohols (electrophile and nucleophile manner).

2. Experimental

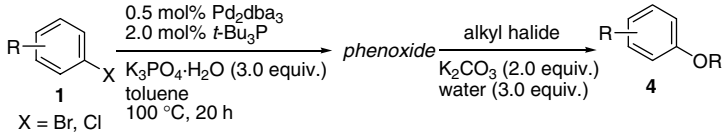
2.1. General consideration

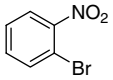
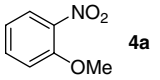
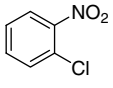
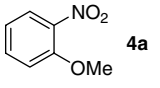
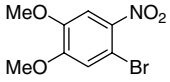
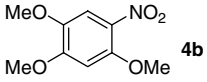
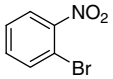
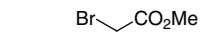
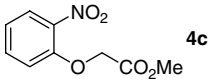
Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All catalytic reactions were performed in Rotaflo® (England) HP-6 resealable screw cap Schlenk flask (approximately 20 mL volume) with oil bath heating and magnetical stirring. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Commercially available aryl bromides/chlorides (liquid form only) were purified by passing through a short plug (0.5 cm width × 4 cm height) of neutral alumina or distillation under reduced pressure. GC analysis was conducted on an HP G1800C GCD system using an HP5MS column (30 m × 0.25 mm). Known products were characterized by NMR and mass spectroscopy and compared to literature data or authentic sample analysis. **2d**,[14] **2i**,[15] **2j**,[16] **3n**,[17] **3o**,[18] **4c**.[19] Compounds **2a–c**, **2e–h**, **2k–l**, **3m** and **4a–b** are commercially available. The products described in GC yield accorded to the authentic samples/dodecane calibration standard.

2.2. General procedure of Table 2

ArX (1.0 mmol, if solid), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %) and $K_3PO_4{\cdot}H_2O$ were charged to a Schlenk tube equipped with a magnetic stirbar. The tube was evacuated and backfilled with nitrogen (3 cycles). Toluene (2.0 mL) and ArX (1.0 mmol, if liquid) were added. The tube was placed in a preheated oil bath with mag-

Table 4. Palladium-catalyzed etheration of aryl halides[a]



Entry	ArX	Alkyl halide	Product	Yield[b]
1		MeI	 **4a**	88
2		MeI	 **4a**	81
3		MeI	 **4b**	78
4			 **4c**	69

[a] Step 1: ArX (1.0 mmol), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %), $K_3PO_4{\cdot}H_2O$ (3.0 mmol), toluene (2.0 mL) under N_2 for 20 h; Step 2: K_2CO_3 (2.0 mmol), degassed water (3.0 mmol), DMF (3.0 equiv), alkyl halide (2.0 mmol) were added, 100 °C, 3 h.
[b] Isolated yields.

netic stirring. The consumption of ArX was judged by TLC or GC analysis. The reaction was allowed to reach room temperature, and dil HCl was carefully added. The reaction mixture was extracted with diethyl ether and purified by column chromatography on silica gel using hexane/ethyl acetate as the solvent system.

2.3. General procedure of Table 3

ArX (1.0 mmol, if solid), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %) and $K_3PO_4{\cdot}H_2O$ were charged to a Schlenk tube equipped with a magnetic stirbar. The tube was evacuated and backfilled with nitrogen (3 cycles). Dioxane (2.0 mL) and ArX (1.0 mmol, if liquid) were added. The tube was placed in a preheated oil bath with magnetic stirring. The consumption of ArX was judged by TLC or GC analysis. To the crude reaction mixtures was added water (~5 mL) and extracted with diethyl ether. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate as the solvent mixture.

2.4. General procedure of Table 4

ArX (1.0 mmol, if solid), Pd_2dba_3 (0.5 mol %), *t*-Bu_3P (2.0 mol %) and $K_3PO_4{\cdot}H_2O$ were charged into a Schlenk tube equipped with a magnetic stirbar. The tube was evacuated and backfilled with nitrogen (3 cycles). Toluene (2.0 mL) and ArX (1.0 mmol, if liquid) were added. The tube was placed in a preheated oil bath with magnetic stirring. The consumption of ArX was judged by TLC or GC analysis. The reaction was allowed to reach room temperature. K_2CO_3 (2.0 mmol), water (3.0 mmol), DMF (3.0 mmol) and alkyl halide (2.0 mmol) were added. The reaction tube was re-sealed and heated to 100 °C for 3 h. The tube was cooled to room temperature, and water (~5 mL) was added. The crude mixture was extracted with diethyl ether and purified by column chromatography on silica gel.

Acknowledgments

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