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ARTICLE TYPE

Palladium-catalyzed synthesis of primary benzamides from aryl bromides *via* cyanation and hydration sequence**

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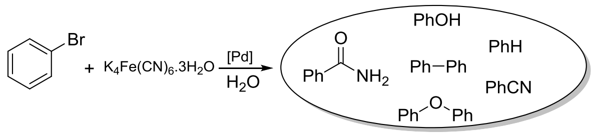
An interesting and effective procedure for the synthesis of benzamides from aryl bromides has been developed. In the presence of palladium catalyst, various primary benzamides have been produced in moderate to excellent yields in one-pot one-step manner.

Benzamides are important intermediates in organic synthesis and have been applied as starting materials for engineering plastics, detergents, lubricants and etc.[1] Although several procedures have been established for their preparation, there is still continuing demand in the development of new, improved and effective methodologies for benzamides synthesis. Among the known transformations, primary benzamides are commonly synthesized either by hydration of the corresponding aromatic nitrile,[2] or by conversion of benzoic acids or acid chlorides with ammonia.[3] Less common synthetic strategies including the transformation of benzaldehydes or benzaldoximes,[4] or the oxidation of primary benzyl amines or alcohols.[5] More recently, palladium-catalyzed aminocarbonylations have also been applied in primary aromatic amides synthesis.[6] In these cases, aryl halides were applied as substrates and carbon monoxide and ammonia gas were needed as the source of amide group. However, the usage of cyanation and *in situ* hydration sequence for the synthesis of primary benzamides from aryl bromides have not reported until nowadays.[7]

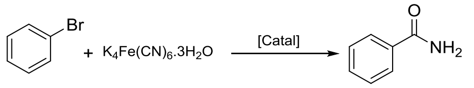
Theoretically, as shown in Scheme 1, the synthesis of benzamide from bromobenzene *via* cyanation and hydration sequence has non-avoidable side reactions. Detailly, phenol can be produced from bromobenzene *via* hydroxylation,[8] benzonitrile will exist becasue of non-complete hydration, and several other reactions.



Scheme 1. Synthesis of benzamide from bromobenzene.

Initially, the first set of reactions were carried out with bases testing in the mixture of DMSO and water with $Pd(OAc)_2$ and Xantphos as the catalytic system. Among the tested bases (NEt_3, DBU, DiPEA, K_3PO_4, K_2CO_3, Na_2CO_3, NaO*t*Bu, LiO*t*Bu), K_3PO_4 gave the best yield of benzamide (Table 1, entries 1-7). Then solvents variations were performed. As the compulsory demand of water for nitrile hydration, we tested the ratio of DMSO and H_2O and then the combination of H_2O with other organic solvents (1,4-dioxane, DMF, MeCN, NMP). The 1:1 ratio combination of DMSO and H_2O was still found to be the best. After ligands ($BuPAd_2$, PPh_3, PCy_3, Binap, DPEPhos) testing, the best yield of benzamide was achieved (65%; Table 1, entry 4). In this procedure, the inhibiting of hydroxylation of bromobenzene is the most challenge step.

Table 1. Palladium-catalyzed benzamide synthesis.[a]

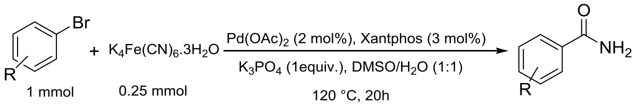


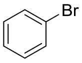
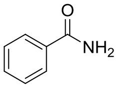
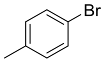
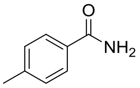
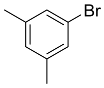
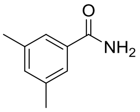
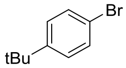
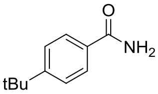
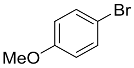
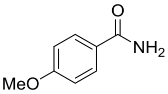
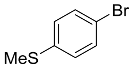
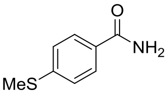
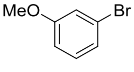
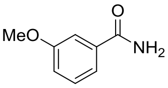
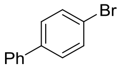
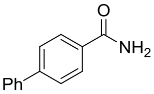
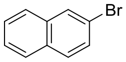
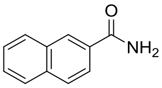
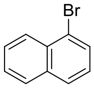
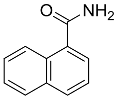
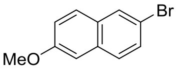
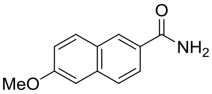
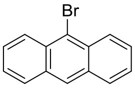
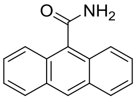
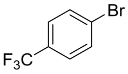
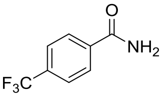
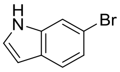
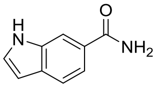
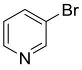
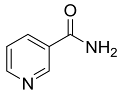
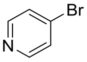
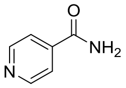
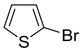
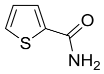
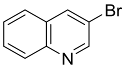
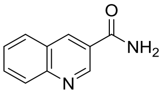
Entry	Base	Solvent	Ligand	Yield[b]
1	NEt_3	DMSO	Xantphos	<2%
2	DBU	DMSO	Xantphos	<2%
3	DiPEA	DMSO	Xantphos	<2%
4	K_3PO_4	DMSO	Xantphos	71%(65%)[c]
5	Na_2CO_3	DMSO	Xantphos	35%
6	NaOtBu	DMSO	Xantphos	11%
7	LiOtBu	DMSO	Xantphos	9%
8	K_3PO_4	1,4-Dioxane	Xantphos	23%
9	K_3PO_4	DMF	Xantphos	56%
10	K_3PO_4	MeCN	Xantphos	29%
11	K_3PO_4	NMP	Xantphos	61%
12	K_3PO_4	DMSO	$BuPAd_2$	30%
13	K_3PO_4	DMSO	PPh_3	16%
14	K_3PO_4	DMSO	PCy_3	5%
15	K_3PO_4	DMSO	BINAP	66%
16	K_3PO_4	DMSO	DPEPhos	65%

a) Bromobenzene (1 mmol), $K_4Fe(CN)_6.3H_2O$ (0.25 equiv.), $Pd(OAc)_2$ (2 mol%), ligand, base, H_2O (1 mL), solvent (1 mL), 120 °C, 20h. b) GC yield, with hexadecane as the internal standard. c) Isolated yield.

With the best reaction conditions in hand, we performed the substrates scope of this transformation (Table 2). Alkyl substituted primary benzamides were produced in 45-87% yields from the corresponding aryl bromides (Table 2, entries 2-4). Methoxy- and methylthio-substituted aryl bromides can be applied as substrates successfully, and provide the desired amides in moderate to good yields (Table 2, entries 5-7). Additionally, phenyl-, trifluoromethyl- and naphthyl- substituted aryl bromides and 9-bromoanthracene can all be tolerated and provide the corresponding benzamides in low to moderate yields (Table 2, entries 9-13).

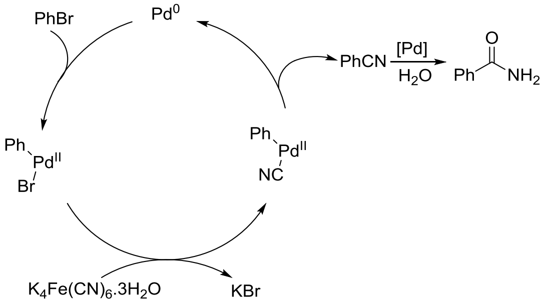
Table 2. Synthesis of benzamides from aryl bromides.[a]



Entry	Substrate	Product	Yield[b]
1			65%
2			67%
3			87%
4			45%
5			83%
6			54%
7			86%
8			46%
9			35%
10			58%
11			35%
12			27%
13			58%
14			87%
15			92%
16			94%
17			47%
18			95%

[a] Bromobenzenes (1 mmol), $K_4Fe(CN)_6.3H_2O$ (0.25 equiv.), $Pd(OAc)_2$ (2 mol%), Xantphos (3 mol%), K_3PO_4 (1 equiv.), DMSO/H_2O (1 mL/1 mL), 120 °C, 20h. [b] Isolated yield.

To our delight, several types of heteroaryl bromides can also be successfully applied. Nitrogen and sulfur containing primary amides were formed in moderate to excellent yields (Table 2, entries 14-18; 47-95%). Based on previous studies, as shown in Scheme 2, a most possible reaction pathway has been proposed. Firstly, the reaction started with palladium-catalyzed cyanation reaction and followed by subsequently hydration of the in situ formed nitrile group (Scheme 2).



Scheme 2. Proposed reaction pathway.

In conclusion, an interesting and effective procedure for the synthesis of primary benzamides from aryl bromides has been developed. Under the assistant of palladium catalyst, various primary benzamides were produced in moderate to excellent yields in one-pot one-step manner.

Experimental Section

General comments:

All the products are commercially available. NMR spectra were recorded on 300 MHz spectrometer at 295 K in $CDCl_3$ or DMSO. Chemical shifts (ppm) are given relative to solvent: references for $CDCl_3$ were 7.26 ppm (^1H-NMR) and 77.00 ppm (^{13}C-NMR); references for d6-DMSO were 2.50 ppm (^1H-NMR) and 40.00 ppm (^{13}C-NMR). The products were isolated from the reaction mixture by column chromatography on silica gel 60, 0.063-0.2 mm, 70-230 mesh.

General procedure:

In a Argon filled pressure tube, $Pd(OAc)_2$ (2 mol%), Xantphos (3 mol%), K_3PO_4 (1 equiv.) and $K_4Fe(CN)_6.3H_2O$ (0.25 equiv.) were weighted and transferred. Then bromobenzene (1 mmol), DMSO (1 mL) and H_2O (1 mL) were injected via syringe. The pressure tube was sealed and transfer to oil bath at 120 °C for 20 hours. After the reaction finished, the tube was cool down to room temperature. Purifications were carried out by column chromatography using pentane (PE)/ethyl acetate (EA) as the eluent.

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Notes and references

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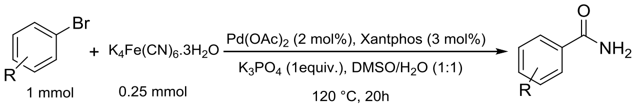

An interesting and effective procedure for the synthesis of primary benzamides from aryl bromides *via* cyanation and *in situ* hydration sequence has been developed. Under the assistant of palladium catalyst, various primary benzamides were produced in moderate to excellent yields in one-pot one-step manner