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Efficient Microwave-Assisted Pd-Catalyzed Hydroxylation of Aryl Chlorides in the Presence of Carbonate

Chao-Wu Yu,[†] Grace S. Chen,[‡] Chen-Wei Huang,[†] and Ji-Wang Chern*[,†,§]

School of Pharmacy, College of Medicine, National Taiwan University, Taipei, 10051, Taiwan, Republic of China, Department of Applied Chemistry, Providence University, Taichung 43301, Taiwan, Republic of China, and Department of Life Science, College of Life Science, National Taiwan University, Taipei 10617, Taiwan, Republic of China

jwchern@ntu.edu.tw

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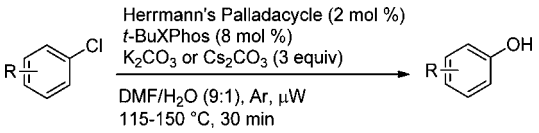
ABSTRACT



An efficient microwave-assisted, palladium-catalyzed hydroxylation of aryl chlorides in the presence of a weak base carbonate was developed, which rapidly converts aryl and heteroaryl chlorides to phenols, and can be used when the aryl chloride is functionalized with a ketone, aldehyde, ester, nitrile, or amide.

Phenols are important moieties of various pharmaceuticals, polymers, and natural products and serve as useful intermediates.[1] Their preparations by nonoxidative methods include nucleophilic substitution of activated aryl halides, copper-catalyzed conversion of diazoarenes, and addition of benzyne.[2] These methods are hampered by harsh conditions and limited availablility of starting materials. Copper-catalyzed hydroxylation of aryl halides with various ligands was reported recently,[3] as was the transformation of aryl iodides and bromides into phenols under aqueous conditions using $FeCl_3$ as the catalyst.[4] However, a much longer reaction time was required for copper- or iron-catalyzed reactions when compared to palladium. Additionally, palladium is the most efficient catalyst for the synthesis of phenols from aryl halides as shown by the palladium-catalyzed hydroxylation of aryl halides with bulky dialkyl or trialkylphosphine ligands,[5] even though the reactions required several hours to 2 days. However, none of the aforementioned studies[5] used an amide-derivatized aryl halide, and only one example of a substrate containing an ethyl ester has been reported, which used $K_3PO_4 \cdot H_2O$ as a base affording a phenol product in moderate yield. To shorten the reaction time, microwave (μW) irradiation has been widely applied to the

[†] School of Pharmacy, National Taiwan University.
[‡] Department of Applied Chemistry, Providence University.
[§] Department of Life Science, National Taiwan University.

(1) Tyman, J. H. P. *Synthetic and Natural Phenols*; Elsevier: New York, 1996.

(2) (a) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585. (b) Cohen, T.; Dietz, A. G.; Miser, J. R. *J. Org. Chem.* **1977**, *42*, 2053. (c) Agnello, L.; Williams, W. *Ind. Eng. Chem.* **1960**, *52*, 894.

(3) (a) Tlili, A.; Xia, N.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725. (b) Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8729. (c) Paul, R.; Ali, M. A.; Punniyamurthy, T. *Synthesis* **2010**, *2010*, 4268. (d) Maurer, S.; Liu, W.; Zhang, X.; Jiang, Y.; Ma, D. *Synlett* **2010**, *2010*, 976. (e) Yang, D.; Fu, H. *Chem.—Eur. J.* **2010**, *16*, 2366. (f) Jing, L.; Wei, J.; Zhou, L.; Huang, Z.; Li, Z.; Zhou, X. *Chem. Commun.* **2010**, *46*, 4767. (g) Thakur, K. G.; Sekar, G. *Chem. Commun.* **2011**, *47*, 6692. (h) Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 4340. (i) Xu, H.-J.; Liang, Y.-F.; Cai, Z.-Y.; Qi, H.-X.; Yang, C.-Y.; Feng, Y.-S. *J. Org. Chem.* **2011**, *76*, 2296. (j) Chen, J.; Yuan, T.; Hao, W.; Cai, M. *Catal. Commun.* **2011**, *12*, 1463.

(4) Ren, Y.; Cheng, L.; Tian, X.; Zhao, S.; Wang, J.; Hou, C. *Tetrahedron Lett.* **2010**, *51*, 43.

(5) (a) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (b) Chen, G.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2007**, *48*, 473. (c) Gallon, B. J.; Kojima, R. W.; Kaner, R. B.; Diaconescu, P. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 7251. (d) Schulz, T.; Torborg, C.; Schäffner, B.; Huang, J.; Zapf, A.; Kadyrov, R.; Börner, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 918. (e) Sergeev, A. G.; Schulz, T.; Torborg, C.; Spannenberg, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7595. (f) Dumrath, A.; Wu, X.-F.; Neumann, H.; Spannenberg, A.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8988.

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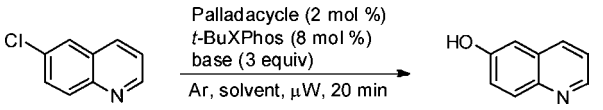
Table 1. Optimization of Pd-Catalyzed Hydroxylation of 6-Chloroquinoline[a]



entry	solvent	concn (M)	temp (°C)	base	heating mode	yield (%)[b]
1	DMF/H_2O (1:1)	0.2	125	K_2CO_3	CV[c]	37
2	DMF/H_2O (3:1)	0.2	125	K_2CO_3	CV	68
3	DMF/H_2O (9:1)	0.2	125	K_2CO_3	CV	87
4	DMF/H_2O (24:1)	0.2	125	K_2CO_3	CV	81
5	DMF/H_2O (9:1)	0.4	125	K_2CO_3	CV	85 (82)[d]
6	DMF/H_2O (9:1)	0.4	125	Cs_2CO_3	CV	79
7	DMF/H_2O (9:1)	0.4	100	K_2CO_3	CV	81
8	DMA/H_2O (9:1)	0.2	125	K_2CO_3	CV	89
9	DMF/H_2O (9:1)	0.2	115	K_2CO_3	OV[e]	99
10	DMF/H_2O (9:1)	0.2	100	K_2CO_3	OV	51
11	dioxane/H_2O (9:1)	0.2	100	K_2CO_3	OV	trace[f]
12	MeCN/H_2O (9:1)	0.2	100	K_2CO_3	OV	trace
13	DMF/H_2O (9:1)	0.2	115	K_2CO_3	Oil bath	91[g]
14	DMF/H_2O (9:1)	0.2	100	KOH	OV	trace
15	DMF	0.2	115	$K_3PO_4 \cdot H_2O$	OV	66
16	DMF	0.2	100	$Na_2CO_3 \cdot H_2O$	OV	trace
17	DMF	0.2	125	$Na_2CO_3 \cdot H_2O$	OV	trace
18	H_2O	0.4	120	K_2CO_3	CV	36

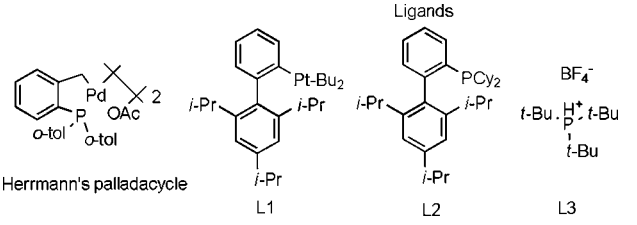
[a] 6-Chloroquinoline (1.0 mmol), 2 mol % Herrmann's palladacycle, 8 mol % *t*-BuXPhos, base (3.0 mmol), solvent (2.5 mL for 0.4 M and 5 mL for 0.2 M), Ar, μW, 20 min. [b] Determined by ^{1}H NMR of crude product using dibromomethane as an internal standard. [c] CV: Close vessel. [d] Isolated yield. [e] OV: Open vessel. [f] Monitored by TLC. [g] 11 h.

organic synthesis. Leadbeater et al.[6] reported that the copper-catalyzed conversion of aryl halides to phenols between 180 and 300 °C proceeded more rapidly with μW irradiation.

With the ultimate goal of shortening the reaction time and increasing the types of substrates that can be used, we report herein that the use of a weak base and μW is suitable for the Pd-catalyzed hydroxylation of 6-chloroquinoline. Moreover, although aryl chlorides are less expensive, they are less reactive substrates[5b] than aryl iodides and bromides. We report an efficient process for hydroxylation of aryl chlorides catalyzed by palladium using dialkylphosphine ligands in DMF/H_2O (9:1) in the presence of potassium or cesium carbonate under μW irradiation.

During our study of quinazoline derivatives,[7] 6-chloroquinoline served as a model reactant when optimizing hydroxylation conditions. For the present study, initially the catalyst Herrmann's palladacycle was used in a closed microwave vessel, and the solvent and base were varied. The mixed solvent DMF/H_2O (9:1) provided a satisfactory yield (87%; Table 1, entry 3). Neither an increased 6-chloroquinoline concentration nor the use of Cs_2CO_3 improved the yield (Table 1, entries 5 and 6). A comparable yield was obtained with DMA/H_2O as the solvent (89%; Table 1, entry 8). To avoid carbonylation or other possible side reactions induced by high pressure,[8] some of the reactions were carried out in open vessels, which, interestingly, improved the yield when the reaction was run at a lower

Table 2. Pd-Catalyzed Hydroxylation of 6-Chloroquinoline with Different Pd-Catalysts and Ligands[a]



entry	cat. (mol %)	yield[b]
1	Herrmann's palladacycle (2 mol %)/**L1** (8 mol %)	99%
2	$Pd_2(dba)_3$ (2 mol %)/**L1** (8 mol %)	82%
3	$Pd(OAc)_2$ (2 mol %)/**L1** (8 mol %)	94%
4	$Pd(OAc)_2$ (2 mol %)/**L2** (8 mol %)	27%
5	$Pd(OAc)_2$ (2 mol %)/**L3** (8 mol %)	trace[c]
6	Herrmann's palladacycle (2 mol %)	no reaction

[a] 6-Chloroquinoline (1.0 mmol), K_2CO_3 (3.0 mmol), solvent (5 mL), Ar, μW, 115 °C, 20 min. [b] Determined by ^{1}H NMR of crude product using dibromomethane as an internal standard. [c] Monitored by TLC.

(6) (a) Kormos, C. M.; Leadbeater, N. E. *Tetrahedron* **2006**, *62*, 4728. (b) Mehmood, A.; Leadbeater, N. E. *Catal. Commun.* **2010**, *12*, 64.

(7) Deore, R. R.; Chen, G. S.; Chen, C.-S.; Chang, P.-T.; Chuang, M.-H.; Chern, T.-R.; Wang, H.-C.; Chern, J.-W. *Curr. Med. Chem.* **2012**, *19*, 603–614.

(8) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232.

Table 3. Pd-Catalyzed Synthesis of Phenols from Aryl Chlorides[a]

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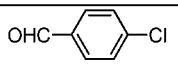
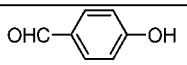
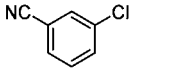
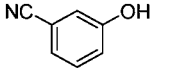
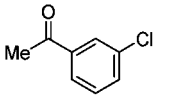
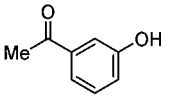
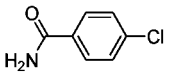
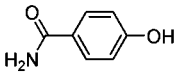
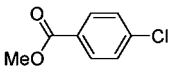
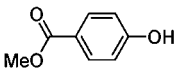
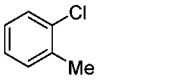
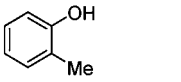
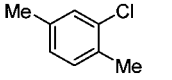
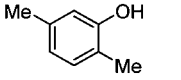
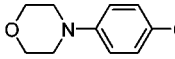
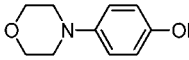
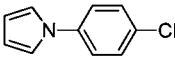
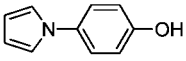
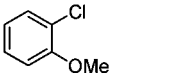
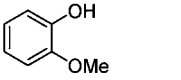
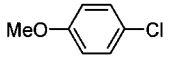
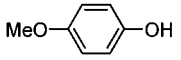
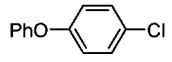
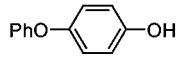
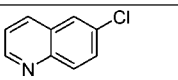
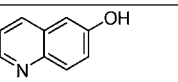
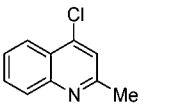
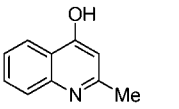
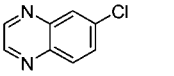
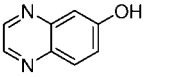
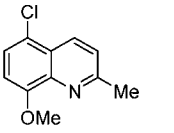
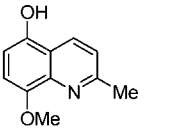
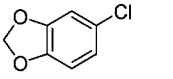
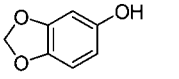
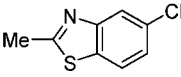
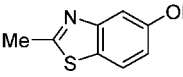
1			93
2			90
3			81
4			58
5			92
6			63(89)[c, d]
7			89
8			84[e]
9			87[e]
10			60
11			55[f]
12			67

[a] ArCl (1.0 mmol), palladacycle (2 mol %), **L1** (8 mol %), K_2CO_3 (3.0 equiv), DMF/H_2O (9:1, 5 mL), μW, 115 °C, 30 min. [b] Isolated yield. [c] Yield in parentheses was determined by ^{1}H NMR of crude product using dibromomethane as an internal standard. [d] Volatile compound. [e] With Cs_2CO_3 (3 equiv) at 150 °C. [f] With K_3PO_4 at 130 °C.

temperature of 115 °C (99%; Table 1, entry 9). However, at 100 °C with DMF/H_2O, dioxane/H_2O, or MeCN/H_2O as the solvent, the yield dramatically decreased (Table 1, entries 10–12). Conventional heating at 115 °C also produced a high yield, but a longer reaction time (11 h) was needed (Table 1, entry 13) when compared to μW irradiation (20 min) under the same reaction conditions (Table 1, entriy 9). A significant amount of Pd-black was formed with the use of KOH, and the catalytic efficiency was decreased with the use of **L1** and KOH because the palladium catalyst was not stable (entry 14).[5a] A decreased yield might also have resulted from DMF instability in the presence of KOH.[9] Lower yields were obtained when the hydrate of a base was used rather than the cosolvent H_2O (DMF/H_2O (9:1); Table 1, entries 15–17). With the K_2CO_3/H_2O system, the yield was only 36% (Table 1, entry 18).

(9) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th ed.; Butterworth-Heinemann: Oxford, 2009; p 130.

Table 4. Pd-Catalyzed Synthesis of Phenols from Heteroaryl Chlorides[a]

entry	ArCl	ArOH	yield (%)[b]
1			95
2			98
3			86
4			66[c]
5			51[d]
6			59

[a] ArCl (1.0 mmol), palladacycle (2 mol %), **L1** (8 mol %), K_2CO_3 (3.0 equiv), DMF/H_2O (9:1, 5 mL), μW, 115 °C, 30 min. [b] Isolated yield. [c] With Cs_2CO_3 (3 equiv) at 150 °C. [d] With Cs_2CO_3 at 130 °C.

Different palladium sources and ligands were also screened with the use of K_2CO_3 (Table 2). In addition to Herrmann's palladacycle, $Pd_2(dba)_3$ and $Pd(OAc)_2$ provided satisfactory yields in combination with **L1** (entries 2 and 3). Additionally, a ratio of 1:2 or 1:4 of palladium to ligand gave comparable results (entries 1–3). The catalytic activity decreased substantially with the use of dicyclohexylphosphine (**L2**, entry 4) or [(*t*-Bu)$_3$PH]BF$_4$ (**L3**, entry 5). The reaction did not occur in the absence of ligand (entry 6).

Having established reaction conditions that produced a substantial yield of 6-hydroxyquinoline, different electron-poor and electron-rich aryl chlorides were used as substrates to explore the scope of the reaction (Table 3). Aldehyde, nitrile, methyl ketone, and amide were tolerated under the reaction conditions (entries 1–4). To our knowledge, hydroxylation of an aryl chloride bearing a free amide group has not been reported. Additionally, the vulnerable methyl ester derivative gave a high yield without hydrolysis (entry 5). Aryl chlorides containing a substituent at the *ortho* position reacted smoothly (entries 6 and 7). The deactivated aryl chlorides gave lower yields (entries 8, 9, 11, and 12), and therefore the reaction required a higher temperature. In general, Cs_2CO_3 provided better results than did K_2CO_3. For example, Cs_2CO_3 was needed for the deactivated *para* nitrogen-substituted substrates (entries 8 and 9) since the substrates could not be completely converted by K_2CO_3 within 30 min. K_3PO_4 also provided a moderate yield with 4-chloroanisole as the substrate (entry 11).

Microwave irradiation/Pd catalysis was also applied to heteroaryl chlorides (Table 4). The chloro-substituted quinoline and quinoxaline derivatives were converted to the corresponding hydroxy derivatives in high yield (entries 1−3). Again, introduction of a *para* electron-donating group gave lower yields (entries 4−6) as for aryl chlorides (entries 8, 9, 11, and 12, Table 3). 2-Methyl benzothiazole stayed intact during the hydroxylation (entry 6).

In summary, an efficient protocol for palladium-catalyzed hydroxylation of aryl and heteroaryl chlorides was developed. To our knowledge, carbonate has not been reported as an efficient base for either copper- or palladium-catalyzed hydroxylation. The present catalytic system does not substantially hydrolyze potentially vulnerable functional groups and can be used with either conventional heating or microwave irradiation.

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

The authors declare no competing financial interest.