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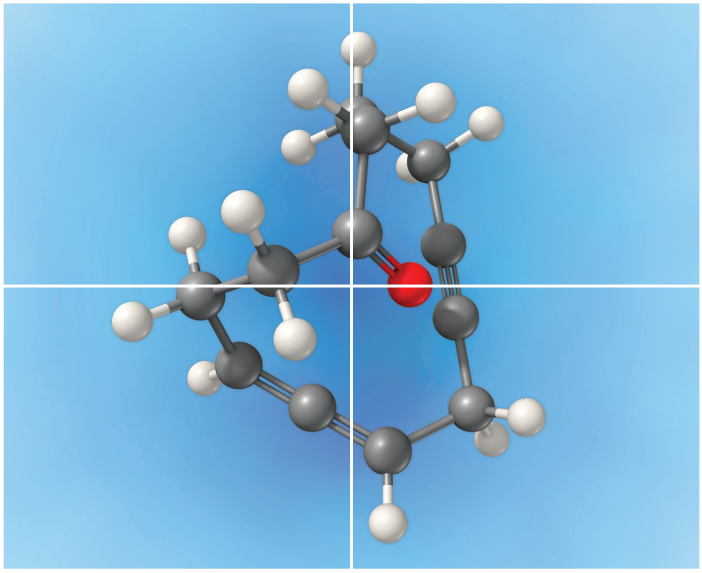

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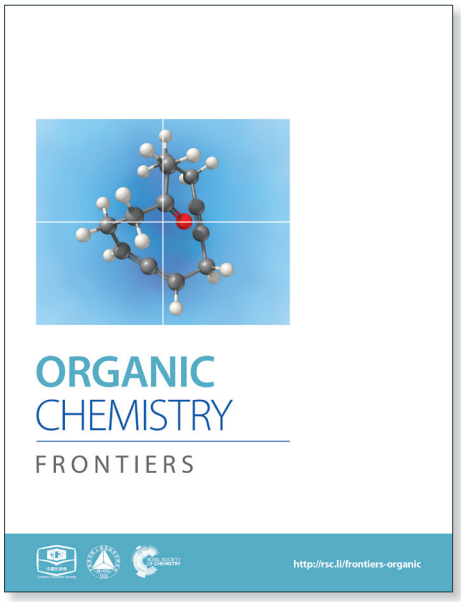

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ARTICLE TYPE

DDQ: the chlorinating reagent and oxidant for the ligand-directed *ortho*-chlorination of 2-arylpyridines

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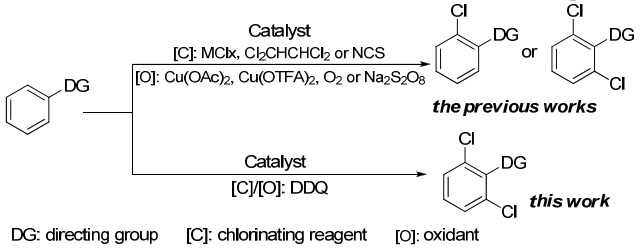
A new and simple protocol for palladium-catalyzed ligand-directed *ortho*-chlorination of 2-arylpyridines with DDQ was developed, generating the chlorinated products in good to excellent yields. Note that DDQ behaved dual roles as both the chlorinating reagent and oxidant in this reaction. Moreover, high regioselectivity was observed for 2-arylpyridines bearing a *meta*-substituent in the aryl ring moiety, and the chlorination could take place at less sterically hindered *ortho*-C–H bond.

Aryl halides are one type of the prominent coupling partners in transition metal-catalyzed C-C, C-N, C-O, and C-S bonds forming cross-coupling reactions, thereby becoming one of the most important organic intermediates and structural motifs in many natural products and synthetic drugs.[1,2] In particular, aryl chlorides are often much cheaper than aryl bromides or iodides, and 85% pharmaceuticals are manufactured using chlorides.[3] Nowadays, the most prevalent strategies for preparing aromatic chlorides are electrophilic aromatic substitution (EAS) or two-step directed ortho-lithiation/halogenation.[4] However, both of the two routes suffered from some disadvantages, including low regioselectivity as well as tedious and sometimes dangerous procedures.

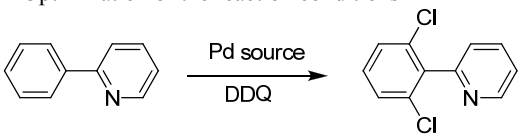
To address these limitations, transition metal-catalyzed ligand-directed ortho-halogenation has emerged as one of the most facile and efficient protocols within recent years.[3c,5] Especially, in 2003, the first palladium-catalyzed direct ortho-chlorination of C–H bond was introduced by Sanford and co-workers, who utilized NCS and air as the chlorinating reagent and oxidant, respectively.[5a] Then, significant efforts have been made towards such ortho-chlorination by the groups of Shi, Yu, Glorius, and others, employing MClx (M=Cu, Ca), $Cl_2CHCHCl_2$, or NCS as the chlorinating reagent and $Cu(OAc)_2$, $Cu(OTFA)_2$, O_2, or $Na_2S_2O_8$ as the oxidant (Scheme 1).[3c,5] Nevertheless, the reported procedures traditionally employed independent chlorinating and oxidative reagents, which would make the reaction conditions a little sophisticated and also did not conform to viewpoint of atom-economy. Thus, to simplify the reaction conditions and develop a simpler and more facile protocol for the regioselective *ortho*-chlorination would be urgent and highly desirable.



Scheme 1 Transition metal-catalyzed direct ortho-acylation

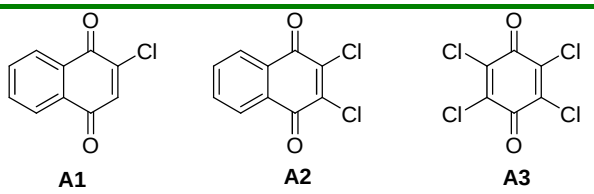
DDQ (2,3-Dichloro-5,6-dicyano-p-benzoquinone), as a one-electron oxidant to give a radical anion, has wide application in the oxidation of steroid ketones, hydroaromatic compounds, alcohols, phenols, and heterocycles.[6] Meantime, DDQ contains two chlorine atoms and may act as a potential chlorinating source. Therefore, we reasoned that DDQ would act as both the chlorinating reagent and the oxidant, thus providing a new, simple and efficient way to obtain highly regioselective *ortho*-chlorinated arenes.

Table 1 Optimization of the reaction conditions[a]



1a **2a**

Entry	Palladium Source (mol%)	T (^oC)	Solvent	Yield (%)[b]
1	$PdCl_2$ (5)	120	DMSO	10
2	$PdCl_2$ (5)	120	NMP	23
3	$PdCl_2$ (5)	reflux	H_2O	0
4	$PdCl_2$ (5)	120	HOAc	0
5	$PdCl_2$ (5)	reflux	toluene	56
6	$PdCl_2$ (5)	120	chlorobenzene	70
7	**$PdCl_2$ (5)**	**120**	**DMF**	**88**
8	$PdCl_2$ (5)	120	DMF/H_2O (1:1)	62
9[c]	$PdCl_2$ (5)	120	DMF	55
10	$PdCl_2$ (5)	100	DMF	56
11[d]	$PdCl_2$ (5)	120	DMF	89
12[e]	$PdCl_2$ (5)	120	DMF	77
13	$Pd(OAc)_2$ (5)	120	DMF	68
14	Pd_2dba_3 (2.5)	120	DMF	57
15[f]	$PdCl_2$ (5)	120	DMF	0
16[g]	$PdCl_2$ (5)	120	DMF	0
17[h]	$PdCl_2$ (5)	120	DMF	12

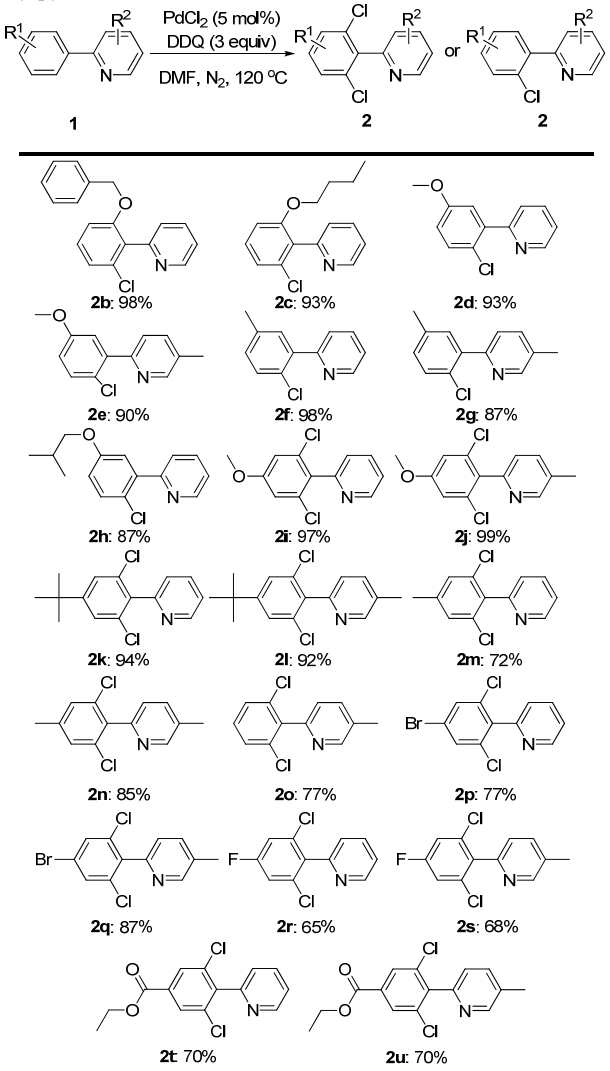


[a] Reaction conditions: **1a** (0.3 mmol), palladium catalyst, and DDQ (3 equiv) in 2 mL of solvent under a nitrogen atmosphere at 120 °C for 3 h. [b] Isolated yield. [c] DDQ (2 equiv). [d] For 5 h. [e] Under air. [f] 2-Chlorobenzoquinone (**A1**) (3 equiv)was used as the chlorinating reagent. [g] 2,3-Dichloro-1,4-naphthoquinone (**A2**) (3 equiv) was used as the chlorinating reagent. [h] chloranil (**A3**) (3 equiv) was used as the chlorinating reagent.

We started the optimization process by performing the chlorination of 2-phenylpyridine (**1a**) in DMSO under a nitrogen atmosphere at 120 °C for 3 h, and gratifyingly, the dichlorinated product was generated indeed albeit with a low yield of 10% (Table 1, entry 1). The solvent effect (e.g., NMP, H_2O, HOAc, toluene, chlorobenzene and DMF) was then screened, and to our delight, the DMF could deliver the dichlorinated product in up to 88% isolated yield (Table 1, entry 7). Some controlling experiments were also conducted such as adding water to the reaction, reducing the amount of DDQ to 2 equiv or reaction temperature to 100 °C, prolonging the reaction time to 5 h, and performing the reaction under air, but unfortunately, no better results were obtained (Table 1, entries 8–12). Other commercially available palladium source such as $Pd(OAc)_2$ and Pd_2dba_3 were also checked, and both of them did not exhibit higher catalytic activity (Table 1, entries 13 and 14). Finally, three DDQ analogues (e.g., 2-chlorobenzoquinone, 2,3-dichloro-1,4-naphthoquinone and chloranil) were prepared and applied to the chlorination of 2-phenylpyridine (**1a**), but the reactions did not afford the product in better yields, which may prove that DDQ played an irreplaceable role for the successful reaction (Table 1, entries 15–17).

Under the optimized reaction conditions, the scope of 2-arylpyridines was explored and summarized as Table 2. Generally, this chlorination could tolerate various functional groups (e.g., RO, F, Br and EtOOC), affording the desired products in moderate to excellent yields. Notably, the chlorination showed high regioselectivity for the substrates containing a meta-substituent in the benzene moiety, and the reaction could take place at less sterically hindered *ortho*-C–H bond, affording the monochlorinated products in good yields (Table 2, **2d**–**2h**). On the other hand, electronic effect has influence on this reaction and the substrates bearing an electron-donating group in the benzene moiety would give the desired products in slightly higher yields than those bearing an electron-neutral and electron-withdrawing group in the benzene moiety. For example, the substrate bearing an electron-donating group (MeO) in the benzene moiety could be converted to the dichlorinated product in a yield of up to 99% (Table 2, **2j**). Meanwhile, when the benzene moiety possessed a strong electron-withdrawing group (EtOCO), the desired products could be obtained in moderate yields (Table 2, **2t** and **2u**). The molecular structure of the dichlorinated product (**2j**) was unambiguously determined by the single crystal X-ray diffraction study (Fig. 1).[7]

Table 2 The palladium-catalyzed *ortho*-chlorination of 2-arylpyridines[a,b]



[a] Reaction conditions: 2-arylpyridine (0.3 mmol), $PdCl_2$ (5 mol%) and DDQ (0.9 mmol) in DMF (2 mL) under a nitrogen atmosphere at 120 °C for 3 h. [b] Isolated yield.

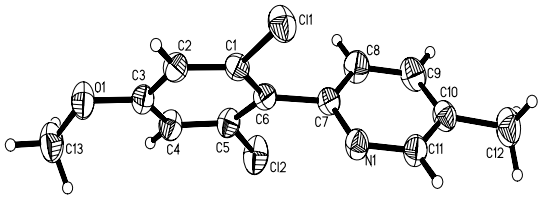
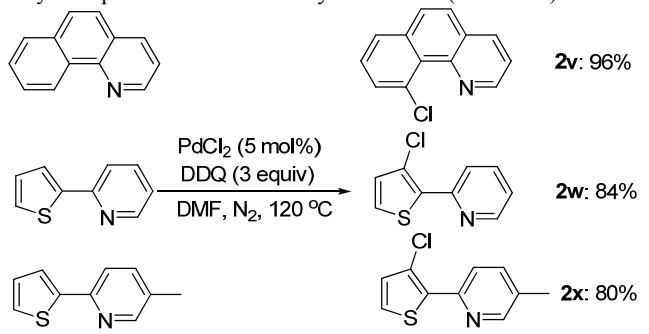


Figure 1 Molecular structure of **2j**

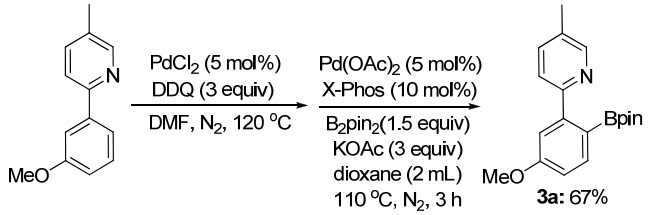
The scope of this *ortho*-chlorination could also be extended to heterocycles such as benzo[h]quinoline and 2-thienylpyridine derivatives, and all of them could provide the corresponding products in good to excellent yields (Scheme 3).

In addition, arylboronates are valuable and robust organic intermediate, since they can be utilized as the coupling partners in many catalytic reactions.[8] An alternative and elegant synthesis of arylboronates could be fulfilled via a two-step reaction of ligand-directed *ortho*-chlorination/borylation to afford the *ortho*-

borylated product in a moderate yield of 67% (Scheme 4).

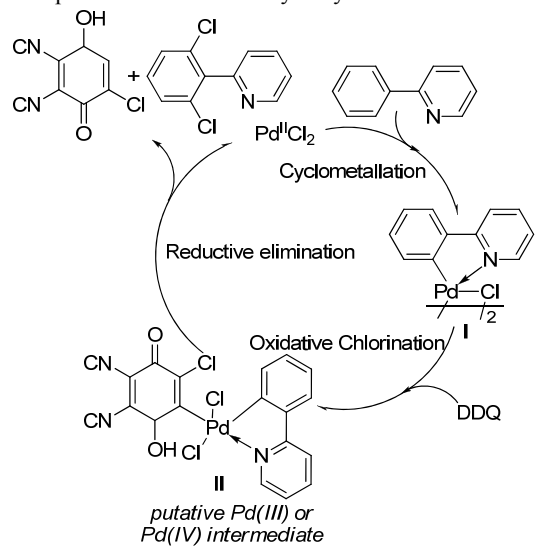


Scheme 3 The palladium-catalyzed *ortho*-chlorination of heterocycles



Scheme 4 The new synthetic strategy for ligand-directed *ortho*-borylation.

A tentative mechanism for the palladium-catalyzed ligand-directed *ortho*-C–H chlorination is depicted in Scheme 2. The reaction would be initiated by *ortho*-cyclometalation of the substrate with $PdCl_2$ to form the palladacycle **I**. Then, the reaction of DDQ with the intermediate **I** (the chlorinating step) took place, affording the oxidative addition product as intermediate **II**. Finally, the reductive elimination of intermediate **II** would lead to the desired product and the reductive product of DDQ determined by GC-MS (see ESI), regenerating the active palladium species to fulfil the catalytic cycle.



Scheme 2 Proposed mechanism for catalytic *ortho*-C–H chlorination

In summary, we have developed a new and simple protocol for palladium-catalyzed *ortho*-C–H chlorination of 2-arylpyridines and some heterocycles. Notably, DDQ played a dual role of the chlorinating reagent and oxidant for the successful reaction. Moreover, this reaction showed high regioselectivity for the substrates bearing a *meta*-substituent in the benzene moiety. Further application of this synthetic methodology is currently underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) D. Prim, J. M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041; (b) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (c) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; (d) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (e) G. Bringmann, R. Walter and R. Weirich, *Angew. Chem., Int. Ed.*, 1990, **29**, 977; (f) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125.

2 (a) D. A. Evans, J. L. Katz, G. S. Peterson and T. Hintermann, *J. Am. Chem. Soc.*, 2001, **123**, 12411; (b) A. Butler and J. V. Walker, *Chem. Rev.*, 1993, **93**, 1937.

3 (a) K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4442; (b) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (c) X. Y. Sun, G. Shan, Y. H. Sun and Y. Rao, *Angew. Chem., Int. Ed.*, 2013, **52**, 4440.

4 (a) R. Taylor, *Electrophilic Aromatic Substitution*, John Wiley, New York, 1990; (b) H. H. Hodgson, *Chem. Rev.*, 1947, **40**, 251; (c) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879; (d) D. W. Young and D. L.Comins, *Org. Lett.*, 2005, **7**, 5661.

5 (a) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004, **126**, 2300; (b) X. B. Wan, Z. X. Ma, B. J. Li, K. Y. Zhang, S. K. Cao, S. W. Zhang and Z. J. Shi, *J. Am. Chem. Soc.*, 2006, **128**, 7416; (c) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Org. Lett.*, 2006, **8**, 2523; (d) X. Chen, X. S. Hao, C. E. Goodhue and J. Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (e) R. B. Bedford, M. F. Haddow, C. J. Mitchell and R. L. Webster, *Angew. Chem., Int. Ed.*, 2011, **50**, 5524; (f) B. R. Song, X. J. Zheng, J. Mo and B. Xu, *Adv. Synth. Catal.*, 2010, **352**, 329; (g) N. Schröder, J. Wencel-Delord and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 8298; (h) J. M. Murphy, X. B. Liao and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 15434.

6 (a) Y. H. Zhang and C. J. Li, *Angew. Chem., Int. Ed.*, 2006, **45**, 1949; (b) W. Y. Tu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2009, **48**, 4567; (c) L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2010, **49**, 3069; (d) C. Guo, J. Song, S. W. Luo and L. Z. Gong, *Angew. Chem., Int. Ed.*, 2010, **49**, 5558; (e) L. Liu and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2010, **49**, 5894; (f) Y. Hayashi, T. Itoh and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2011, **50**, 3920; (g) D. Walker and J. D. Hiebert, *Chem. Rev.*, 1967, **67**, 153; (h) L. Minuti, A. Taticchi, A. Marrocchi, D. Lanari, E. Gacs-Baitz and A. Gomory, *Tetrahedron Lett.*, 2005, **46**, 949.

7 CCDC 917218 contains the supplementary crystallographic data for **2j**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* https://www.ccdc.cam.ac.uk/datarequest/cif, and are in the ESI. Crystal, data for compound **2j**: $C_{13}H_{11}Cl_2NO$, M = 268.13, Triclinic, a = 6.2427(4) Å, α = 74.492(6)°, b = 8.5337(6) Å, β = 77.526(6)°, c = 12.7695(10) Å, γ = 81.552(5)°, V = 637.16(8) Å^3, T = 291.15 K, space group = P$\bar{1}$, Z = 2, Number of reflections = 4499, Independent reflections = 2279, [R(int) = 0.0212], Final R indices [I>2σ (I)] R_1 = 0.0389, wR_2 = 0.1078, R indices (all data) R_1 = 0.0443, wR_2 = 0.1131.

8 (a) J. Yan, H. Fang and B. H. Wang, *Med. Res. Rev.*, 2005, **25**, 490; (b) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (c) T. Ishiyama and N. Miyaura, *Chem. Rec.*, 2004, **3**, 271; (d) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.