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PII: S0040-4039(18)31425-4
DOI: https://doi.org/10.1016/j.tetlet.2018.11.071
Reference: TETL 50456

To appear in: *Tetrahedron Letters*

Received Date: 22 September 2018
Revised Date: 25 November 2018
Accepted Date: 27 November 2018

Please cite this article as: Botla, V., Akudari, A., Malapaka, C., Cu-Catalyzed Direct *ortho*-Chlorination/-Oxygenation of Aryls: Switching of Oxidant, Control the Diversity of Products, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.11.071

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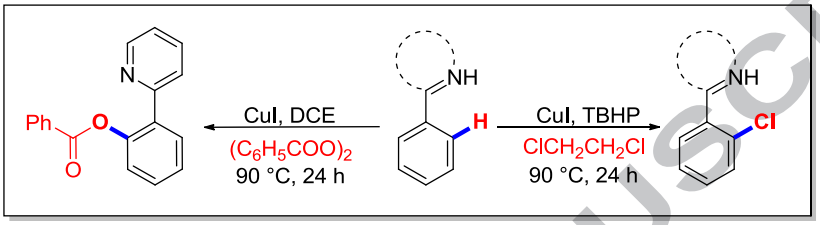

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Copper
Directing group
Phenyl pyridine
Chlorination
Benzoxylation

ABSTRACT

Highly regioselective copper catalyzed *ortho*-chlorination of aryl pyridines was achieved with TBHP as oxidant and 1,2-dichloroethane as chlorinating agent for the first time. Switching the oxidant from TBHP to benzoyl peroxide under identical reaction conditions effects *ortho*-oxygenation.

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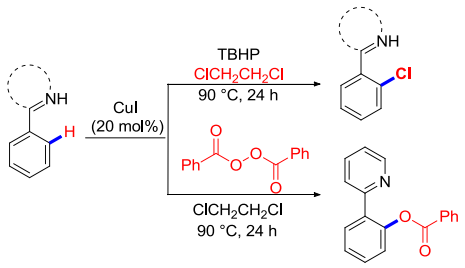
1. Introduction

Dense population of C-H bonds is present on the surface of organic and biomolecules and hence the construction of regioselective C-C and C-heteroatom bonds is attracting tremendous importance.[1] Control of site selectivity is a challenging task in C-H functionalization of arene derivatives due to the subtle differences among the C-H bonds present in the substrate.[2] Further formation of diverse products from the same substrate with site selectivity poses much bigger challenge. In this direction, several molecular architectures have been realized with a range of directing group (DG) assisted reactions (transient, traceless, easily removable, pharmacophorically significant, etc.,) that override innate reactivity and prevent prefunctinalization of the substrates.[3] However pyridine continues to occupy central position in these reactions, attributed mainly to its ability to selectively direct at *ortho*- or *meta*-positions depending on the transition metal/reaction conditions employed.[4] Many investigators reported efficient transition metal catalyzed *ortho*-halogenation and -benzoxylation of phenyl pyridines. However a common and simple reaction protocol that effects either *ortho*-chlorination or *ortho*-oxygenation would be a value added commodity in chemist's basket.[5] Chlorine is known to be a function by itself and a versatile functionality by virtue of its lability towards electrophilic aromatic substitution as well as in cross coupling reactions.[6] Further similar to fluorine and unlike bromine and iodine, many of the pharmaceutical compounds enhance their biological activity with the incorporation of chlorine in the molecule.[7] Construction of C-O bond via aryl benzoxylation is an important synthetic operation owing to the presence of oxygenated aryls in many natural products and pharmaceuticals.[8] Further benzoxylated aryls have potential applications as alternative electrophilic partners in palladium-free cross couplings and also as latent phenols.[9]

Scheme 1. *ortho*-chlorination and -benzoxylation of 2-aryl pyridine.



Noteworthy are the reports by Sanford on the Pd catalysed C-H chlorination by NCS as terminal oxidant, and electrophilic *ortho*-chlorination of phenyl pyridine via C-Cl bond forming reductive elimination.[10]Chlorination of phenyl pyridine was also effected with the combination of $CuCl_2$ and tetrachloroethane solvent,[5a] and with Lithium halide in acetic acid.[5b] However both the methods produce dichlorinated products in addition to the desired mono *ortho*-chlorination product. Pd catalysed aryl chlorinations with acyl chlorides proceed at 140 °C under inert reaction conditions.[5c] Thus most of the reported reactions are plagued with either one or more of the following limitations 1. expensive catalyst, 2. high temperature conditions, 3. non-regioselectivity, 4. inert or oxygen atmosphere. We recently reported chlorination

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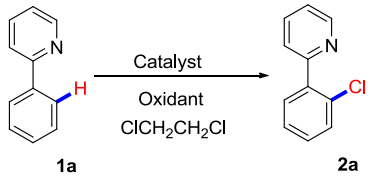
of aryls[11c], iron catalyzed benzoxylation of *N,N*-dialkylanilines[11d] and chelation assisted remote benzoxylation of 8-amidoquinolines.[11j] Inspired by recent literature on copper catalysed C-H functionalization[5a,12] and prompted by our interest on DG assisted iron or copper catalyzed C-H functionalization reactions, we investigated on the pyridine directed regioselective aryl C-H functionalisations. We herein report a typical example of an interesting and efficient transition metal catalysed *ortho*-selective mono-chlorination/benzoxylation of phenyl pyridines wherein switching of oxidant (TBHP/BPO) result in the divergence of products with inexpensive copper catalyst under otherwise identical mild and easy to operate reaction conditions (Scheme 1). DCE, a solvent in the benzoxylation reaction serves additionally as a new chlorine source in aryl chlorinations, a hither to unknown reaction. Our reaction protocol has several advantages such as, 1. inexpensive copper catalyst 2. DCE playing dual role as novel chlorination agent as well as solvent 3. highly regioselective mono *ortho*-chlorination 4. switching oxidant from TBHP to BPO produces regioselective oxygenated product 5. mild and easy to operate reaction conditions.

Table 1. Optimization of the *ortho*-chlorination

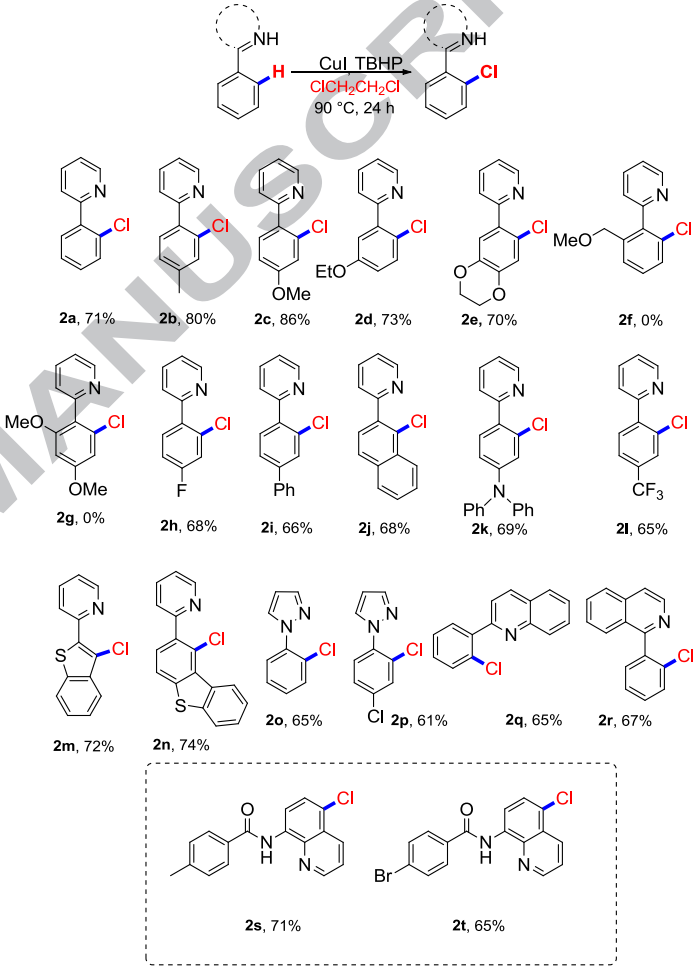


S.No	Catalyst	Oxidant (5.0 equiv)	Temp °C	Yield[b](%)
1	CuI	TBHP	Rt	-
2	CuI	TBHP	60	-
3	**CuI**	**TBHP**	**90**	**71**
4	CuI	Aq. TBHP	90	32
5	CuI	DTBP	90	46
6	CuI	$PhI(OAc)_2$	90	36
7	CuI	$K_2S_2O_8$	90	-
8	CuI	DDQ	90	18
9	CuI	BP	90	Trace
10	CuI	Oxone	90	-
11	CuI	H_2O_2	90	20
12	$Cu(OAc)_2$	TBHP	90	48
13	$CuCl_2$	TBHP	90	62
14	CuBr	TBHP	90	26
15	$CuBr_2$	TBHP	90	33
16	$Cu(OTf)_2$	TBHP	90	55
17	$FeCl_3$	TBHP	90	-
18	$FeCl_2$	TBHP	90	-
19	$Pd(OAc)_2$	TBHP	90	-
20	[Ru(*p*-cymene)Cl_2]$_2$	TBHP	90	-
21	-	TBHP	90	-
22[c]	CuI	TBHP	90	59
23[d]	CuI	TBHP	90	68
24[e]	CuI	TBHP	90	73
25[f]	CuI	TBHP	90	69
26[g]	CuI	TBHP	90	65
27[h]	CuI	TBHP	90	71

[a]Reaction Conditions: 1a (1.0 equiv), catalyst (20 mol %), oxidant (5.0 equiv), in 2 mL of 1,2-DCE stirred the reaction for 24 h. [b]all are isolated yields, [c]CuI (10 mol %), [d]CuI (40 mol %) [e]dry 1,2-DCE, [f]under N_2 atmosphere, [g]under O_2 atmosphere, [h]in the presence of additive (4 A° Molecular Sieves).

Initially, 2-phenyl pyridine **1a** was chosen as a model substrate to examine the *ortho*-chlorination of aryls with various catalysts, oxidants and solvents (Table 1). When the substrate 1a (1.0 equiv.), was stirred at room temperature in presence of the catalyst CuI (20 mol %) and the oxidant TBHP (2.0 equiv.) in 1,2-DCE, the starting material was recovered unreacted. The reaction did not progress even when conducted at 60 °C, (Entry 1, 2 Table 1) however further increase of the reaction temperature to 90 °C resulted in the formation of the desired product **2a**, in 71% yield. Increased loading of the oxidant, TBHP (5-6 M in decane) further improved the yield to 32%. To our delight, 5.0 equiv. of TBHP significantly improved the yield of the desired product to 71% (Entry 3, Table 1). Other oxidants i.e., aq. TBHP, DTBP, $PhI(OAc)_2$, $K_2S_2O_8$, DDQ, Benzoyl peroxide, oxone and H_2O_2 were also screened to check the efficacy of the aryl chlorination reaction (Entries 4-11, Table 1).

Scheme 2. Substrate scope of DG-assisted *ortho*-chlorination of 2-aryl pyridines.[a]



[a]The reaction was performed with 1a (1.0 equiv), CuI (20 mol %), TBHP (5.0 equiv) in 1,2 DCE(2 mL) the mixture was heated in an oil bath at 90 °C for 24 h in a sealed tubetightly closed with screw cap.

We next turned our attention on catalytic activities of various copper (Entries 12-16, Table 1), iron salts (Entries 17, 18, Table 1), palladium and ruthenium catalysts (Entries 19, 20, Table 1). The reaction did not proceed in the absence of any catalyst and CuI proved to be the best when loaded 20 mol% quantity for the *ortho*-chlorination reaction. However with 10 mol% and 40 mol% of the catalyst loading, the reaction is not efficient (Entries 22, 23, Table 1). Among various halogen containing solvents employed, 1,2-DCE proved to be the best, playing a duel role as chlorine source and also as solvent for this directing group assisted *ortho*-chlorination(See ESI for chlorinating solvent optimization). Further it was found that excess quantity of 1,2-DCE is required for the reaction to proceed (ESI). In our hands, tetrachloroethane could not affect the chlorination under standard reaction conditions (ESI). When dry 1,2-DCE was used, the product was obtained in 73% yield (Entry 24, Table 1). When

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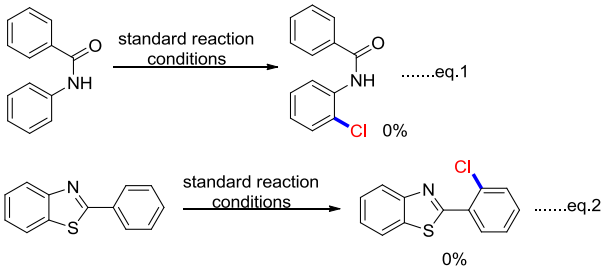
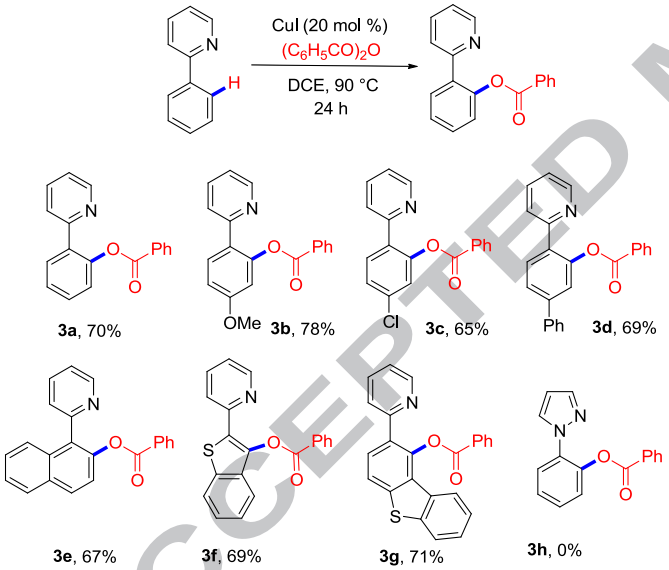
the reaction was performed under N_2 or O_2 atmosphere, the yields were comparable with air atmosphere conditions, indicating that oxygen does not play significant role to improve the yield (Entries 25, 26, Table 1). Neither the presence of additive (4 A° Molecular Sieves) affected the yield of the reaction (Entry 27, Table 1).

Scheme 3. Other DG-assisted o*rtho*-chlorination.



However, interestingly when TBHP is replaced with benzoyl peroxide as the oxidant, we observed the formation of *ortho*-benzoxylation product instead of *ortho*-chlorination under otherwise identical conditions. Portion wise addition of 2.5 equiv. (5×0.5 equiv./0.5 h) of benzoyl peroxide was found to be adequate for the successful benzoxylation in good yields.

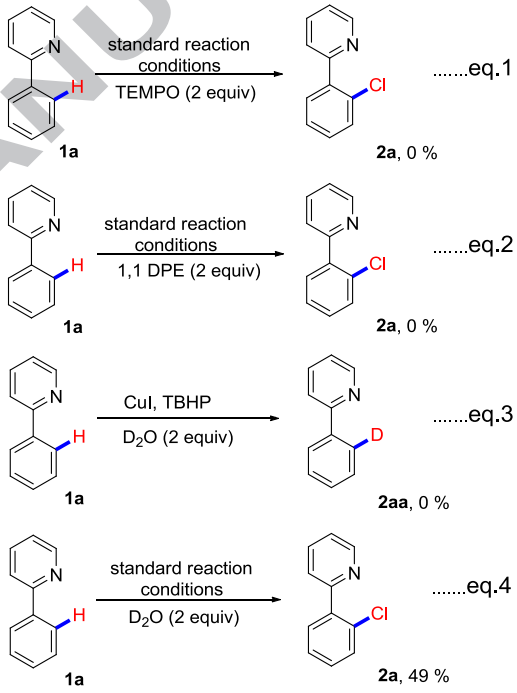
Scheme 4. Substrate scope of DG-assisted o*rtho*-benzoxylation of 2-aryl pyridines.[a]



[a]The reaction was performed with 1a (1.0 equiv), CuI (20 mol %), Benzoyl peroxide (2.5equiv) in 1,2 DCE (2 mL) the mixture was heated in an oil bath at 90 °C for 24 h in a sealed tube tightly closed with screw cap.

With the optimal conditions for chlorination reactions in hand, the substrate scope of the reaction was investigated (Scheme 2). A moderate, 71% yield of the *ortho*-chlorination product was obtained with the substrate **2a** and excellent yields were often achieved when electron-donating moieties including 4-methyl, 4-methoxy, 3-ethoxy and 4,5-ethylenedioxy groups were present on the aromatic ring (Scheme 2, **2b–2e**, 70-86%). However *o*-subistituted, *o*- and *p*- disubstituted motifs suffered from steric crowding which inhibited the desired product formation (scheme 2, **2f** and **2g**). The yields were moderate with, 4-fluoro, 4-phenyl, naphthyl, 4-*N*,*N*-diphenyl substitutions (Scheme 2, **2h**–**2k**, 66-69%). Under the optimal reaction conditions, good yields of the *ortho*-chlorinated products were obtained with electron withdrawing group present on *para*-position of aryl ring (Scheme 2, **2l** 65%). In addition, substrates with heterocyclic motifs also showed good to moderate reactivity towards *ortho*-chlorination under standard reaction conditions and furnished 72, 74% of yields (Scheme 2, **2m**, **2n**). Substrates bearing a pyrazole directing group underwent *ortho*-chlorination smoothly with good yields of the products in 65%, 61% respectively (Scheme 2, **2o**, **2p**). Quinolone and isoquinoline directing groups also effected the *ortho*-chlorination producing the desired products in good yields 65%, 67% respectively (Scheme 2, **2q**, **2r**). The chlorination reaction works for bidentate directing groups as well. The reaction proceeded smoothly on the subistituted 8-amidoquinolines under standard reaction conditions and the chlorination occurred at remote C5-position with good yields 71%, 65% (scheme 2, **2s** and **2t**) demonstrating the efficacy of the chlorination protocol. However other directing groups i.e., benzamide and 2-aryl benzothiazoles failed to effect the chlorination under standard reaction conditions (Scheme 3).

Scheme 5. Mechanistic insights.



Interestingly, highly selective mono *ortho*-benzoxylation of 2-phenyl pyridine was achieved successfully under the same set of reaction conditions when benzoyl peroxide was employed instead of TBHP as an oxidant (Scheme 4). The benzoxylation of phenyl pyridine produced the desired product in 70% yield (Scheme 4, **3a**), while 4-methoxy, 4-chloro, 4-phenyl and 1-naphthyl substituted aryl pyridines also underwent selective *ortho*-benzoxylation and afforded 65%-78% yields of the benzoxylated products (Scheme 4, **3b**-**3e**) Heteroaryl moieties, benzothiophene and dibenzothiophene also proved to be suitable substrates for the selective benzoxylation under standard reaction conditions producing 69%, 71% yields of the products respectively (Scheme 4, **3f**, **3g**). However *ortho*-benzoxylation was not observed with the substrate bearing a pyrazole directing group (Scheme 4, **3h**). For *ortho*-oxygenation the detailed mechanistic studies and plausible mechanism was studied (ESI).

From the observations that, failure to produce the desired product in the absence of CuI (Table 1; entry17) and also the

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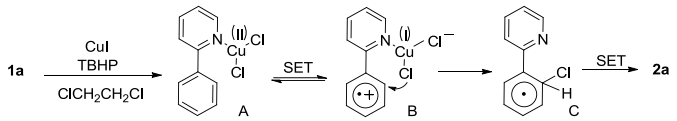
ineffectiveness of Ru(*p*-cymene) catalyst (Table 1, entry 18) indicates the key role of copper salt in the directing group assisted *ortho*-chlorination of 2-phenyl pyridine. Further to understand the mechanism, when the reaction was conducted in the presence of TEMPO/ 1,1Diphenylethene (Scheme 5, eq. 1 &2) as radical scavengers, no desired product was observed and instead, only the starting material was recovered. Addition of 2 equiv. of D_2O to the reaction mixture in the absence as well as in the presence of 1,2-DCE, under otherwise standard reaction conditions did not produce the deuterium incorporated products (Scheme 5, eq. 3& 4)[13a] indicating that the reaction may follow a radical process.

Scheme 6. Plausible mechanism.



From the above observations and the literature reports, a plausible mechanism involving single electron-transfer (SET) pathway for the copper-catalyzed direct *ortho*-chlorination of 2-phenylpyridine is presented (Scheme 6).[13, 5a] The in situ generated $Cu(II)Cl_2$ from TBHP and 1,2-dicholoroethane reacts with 2-phenylpyridine (**1a)** to form complex **A**. The complex **B** is then formed by single electron transfer (SET) followed by intramolecular chlorine transfer results in the formation of complex **C**. Another SET event occurs that transforms complex **C** into the target product **2a**. Investigations on the detailed mechanistic pathway are under way in our laboratory.

Conclusions

Copper-catalyzed Directing group assisted highly regioselective *ortho*-chlorination and -benzoxylation was achieved by switching the oxidant under relatively mild conditions. DCE played dual role as novel chlorination reagent as well as solvent and TBHP as oxidant for the C-H activation reaction effecting *ortho*-chlorination of aryl pyridines. *Otho*-aryl C-H oxygenation takes place under the same reaction conditions with simply switching the oxidant from TBHP to benzoyl peroxide. The synthesis of divergent products arising from Csp^2-Cl and Csp^2-O bond formations by C-H activation reaction on aryls is successfully demonstrated with high regioselectivity and under easy to operate reaction conditions.

Acknowledgments

VinayakBotla thanks the University Grant Commission (UGC), New Delhi for the award of Senior Research Fellowship (SRF).

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Cu-Catalyzed Direct *ortho*-Chlorination/-Oxygenation of Aryls: Switching of Oxidant, Control the Diversity of Products.

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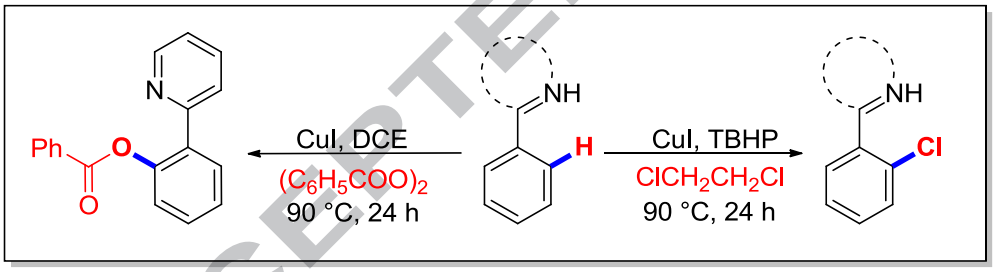
Copper-catalyzed divergent products via Csp^2-Cl and Csp^2-O bond formations, by switching of oxidant (TBHP/Benzoyl peroxide) is demonstrated. DCE played dual role as novel chlorination reagent as well as solvent. The highly regioselective *ortho*-chlorination/-oxygenation is affected under easy to operate reaction conditions



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Our reaction protocol has several advantages such as,

- Inexpensive copper catalyst
- DCE playing dual role as novel chlorination agent as well as solvent
- Highly regioselective mono *ortho*-chlorination
- Switching oxidant from TBHP to BPO produces regioselective oxygenated product
- Mild and easy to operate reaction conditions.

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