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Copper(II)-Promoted Mono-Selective *ortho* C–H Chlorination of Arenes by Using Trimethyl(trichloromethyl)silane

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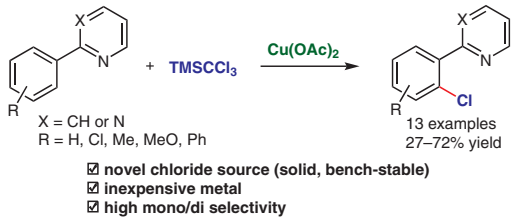

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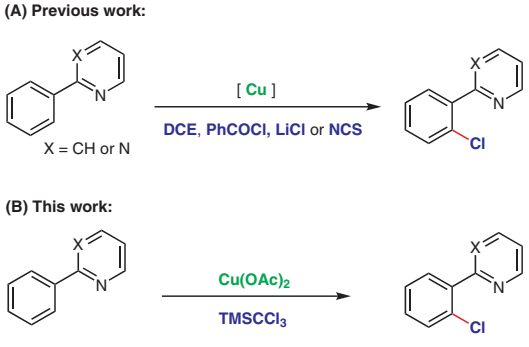
Abstract The first example of a Cu-promoted *ortho*-chlorination of aryl C–H bonds by using $TMSCCl_3$ as chlorinating agent is reported. This reaction features a high selectivity toward monochlorination over dichlorination, compatibility with a variety of functional groups, and gram-scale synthesis.

Key words C–H activation, copper, chlorination, trimethyltrichloromethylsilane

Aromatic chlorides are ubiquitous building blocks in chemical synthesis, as well as key structural motifs in numerous natural products and manufactured drugs.[1] They are usually obtained by direct electrophilic chlorination of electron-rich arenes,[2] Sandmeyer reactions of diazonium salts,[3] or directed *ortho*-metalation followed by chlorine quenching.[4] The first of these methods suffers mainly from poor regioselectivity and overchlorination of substrates, whereas the other methods involve laborious and/or hazardous reaction procedures, and show poor functional-group tolerance.

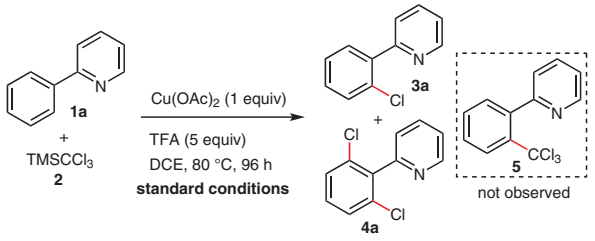
Transition-metal-catalyzed C–H activation has recently emerged as a promising technique for the step-economic preparation of functionalized molecules. In this context, significant achievements have been made in direct C–H chlorination catalyzed by transition metals[5] such as Pd,[6] Rh,[7] or Ni.[8] Although copper is one of the most abundant and inexpensive metals, Cu-catalyzed or Cu-mediated C–H chlorination has received relatively little attention.[9] In a pioneering work, Yu and co-workers reported a Cu-catalyzed direct C–H chlorination of 2-arylpyridines by using 1,2-dichloroethane (DCE) as a chlorine source.[10] Subsequently, a Cu-catalyzed *ortho*-chlorination of 2-arylpyridines with PhCOCl[11] or alkali-metal chlorides[12] was reported (Scheme 1, A). Unfortunately, the control of monochlorination/dichlorination selectivity was problematic in the above-mentioned cases. Recently, the groups of Carretero[13] and Shi[14] independently reported Cu-catalyzed C–H chlorinations of anilines and benzamides, respectively, bearing removable directing groups, with *N*-chlorosuccinimide (NCS). The Han group also achieved a Cu-mediated C–H mono- and dichlorination of 2-arylpyridines with NCS (Scheme 1, A).[15] Because of the important role of N-heterocyclic compounds in the pharmacy field, we developed a Cu-promoted mono-selective method for the *ortho*-chlorination of 2-arylpyridines and 2-arylpyrimidines by using the Ruppert–Prakash reagent (trichloromethyl)trimethylsilane ($TMSCCl_3$) as chlorinating agent (Scheme 1, B). $TMSCCl_3$ has previously been used as a trichloromethylating reagent for addition of CCl_3^- to aldehydes, ketones, imines, or Michael acceptors.[16] The present seminal work represents the first example of the use of $TMSCCl_3$ as a solid and bench-stable source of chlorine.



Scheme 1 Directed copper-catalyzed or -mediated chlorination of C(sp^2)–H bonds of N-heteroarenes

Initially, we envisioned a reaction of 2-phenylpyridine (**1a**) with two equivalents of $TMSCCl_3$ in the presence of $Cu(OAc)_2$ and trifluoroacetic acid (TFA) under a nitrogen atmosphere. Unexpectedly, the monochlorinated product **3a** (72% yield) and a trace of the dichlorinated product **4a** were obtained, whereas the trichloromethylated product **5** was not observed after reaction in DCE at 80 °C for 96 hours (Table 1, entry 1). When $TMSCCl_3$ was removed from the reaction system, the reaction was completely shut down (entry 2). This control experiment indicated that the chlorine source was $TMSCCl_3$ rather than the solvent DCE;[10] this is probably due to the decomposition of CCl_3^- into dichlorocarbene and a chloride ion.[17] Note also that no reaction occurred in the absence of $Cu(OAc)_2$ (entry 3). Lowering the $Cu(OAc)_2$ loading to a catalytic amount led to the formation of traces of the product under a N_2 or air atmosphere (entry 4). Screening of other copper salts was also conducted, but none of them gave superior results (entries 5–9). The acid TFA was found to be essential for this transformation, and the reaction did not proceed in its absence (entry 10). A lower loading of TFA led to an increased amount of byproduct **4a**, whereas higher loadings of TFA led to the formation of monochlorinated product **3a** in slightly reduced yields (entries 11–12). The use of other additives such as acetic acid, pivalic acid (PivOH), or 3-nitrobenzoic acid gave inferior results (entries 13–15).

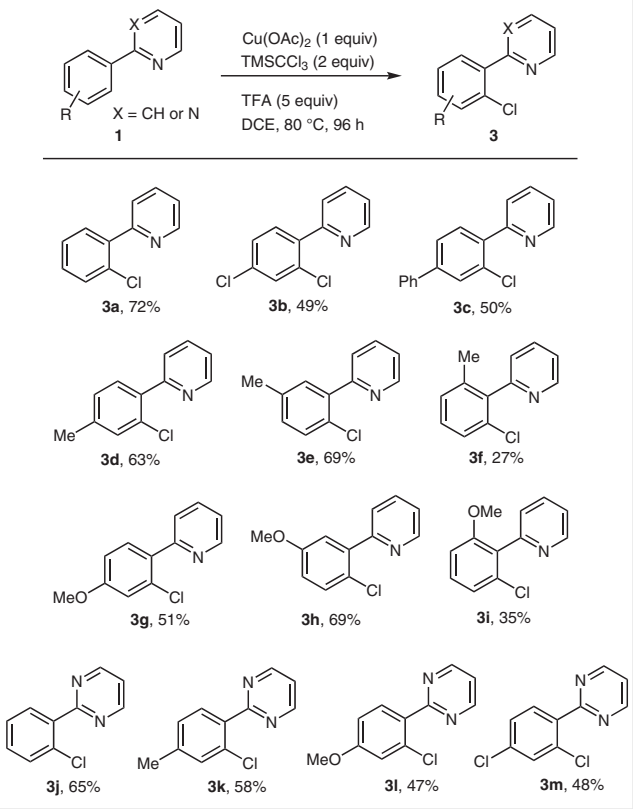
Table 1 Optimization of the Reaction Conditions[a]



Entry	Variation from standard conditions	Yield[b] (%)	
		3a	**4a**
1	none	72	5
2	no $TMSCCl_3$	0	0
3	no $Cu(OAc)_2$	0	0
4[c]	$Cu(OAc)_2$ (0.2 equiv)	trace	0
5	$CuCl_2$	40	0
6	CuCl	32	0
7	CuBr	trace	0
8	CuI	0	0
9	$Cu(OTf)_2$	0	0
10	no TFA	trace	0
11	TFA (3.0 equiv)	53	27
12	TFA (10.0 equiv)	60	2
13	AcOH	6	0
14	PivOH	23	0
15	$3\text{-}O_2NC_6H_4CO_2H$	54	12

[a] Standard conditions: **1a** (0.2 mmol), **2** (0.4 mmol), Cu salt (1.0 equiv), TFA (5.0 equiv), DCE (2.0 mL), 80 °C, 96 h, under N_2.
[b] Isolated yield.
[c] Under N_2 or air.

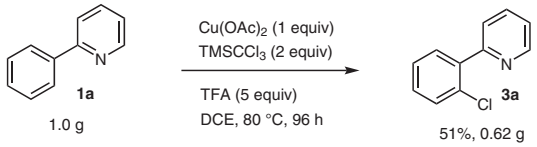
By using the optimized conditions, we then examined the substrate scope of this chlorination reaction.[18] As shown in Scheme 2, a variety of phenylpyridines bearing various substituents, such as chloro (**1b**), phenyl (**1c**), methyl (**1d** and **1e**), or methoxy (**1g** and **1h**) in the *para*- or *meta*-positions of the aromatic ring provided the desired monochlorinated products in good yields. However, with the *ortho*-methyl-substituted substrate **1f** and the *ortho*-methoxy-substituted substrates **1i**, lower yields were obtained due to the steric effect, and large quantities of the starting materials were recovered. Notably, this chlorination reaction showed a high regioselectivity toward substrates containing a *meta*-substituent in the phenyl ring. It also proceeded with less sterically hindered *ortho*-C–H bonds, giving the monochlorinated products **3e** and **3h** in good yield. When pyrimidine was employed as a directing group, the reaction proceeded smoothly to afford the corre-



Scheme 2 Copper-mediated chlorination of aromatic C–H bonds with $TMSCCl_3$

sponding monochlorinated products **3j–m** in moderate yields. Both electron-deficient (**1b** and **1m**) and electron-rich arenes (**1d**, **1g**, **1k**, and **1l**) showed comparable reactivities under the optimized conditions. A high selectivity toward monochlorination over dichlorination was maintained in all cases, with only traces of dichlorinated products were detected by TLC analysis.

To demonstrate the practicability of this method, we conducted a gram-scale experiment. Gratifyingly, the monochlorinated product **3a** was obtained in 51% isolated yield with recovery of the 48% of the starting material **1a** after 96 hours in DCE at 80 °C; the dichlorinated product **4a** was not detected (Scheme 3).



Scheme 3 Gram-scale experiment for chlorination of 2-phenylpyridine

In summary, we have developed the first copper-mediated *ortho*-chlorination of aromatic C–H bonds by using $TMSCCl_3$ as a chlorine source. This reaction showed a high selectivity toward monochlorination over dichlorination in all cases, and a high regioselectivity toward substrates bearing a *meta*-substituent in the benzene ring. Moreover, the reaction is compatible with a variety of functionalities and is amenable to be scaled up to a gram scale.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591542.

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(18) **Copper-Promoted Monochlorination of 2-Arylpyridines or 2-Arylpyrimidines 1 with $TMSCCl_3$; General Procedure**
A solution of **1** (0.2 mmol), $Cu(OAc)_2$ (0.2 mmol), $TMSCCl_3$ (0.4 mmol), and TFA (1.0 mmol) in DCE (2.0 mL) was stirred in a reaction tube under N_2 (1 atm) at 80 °C for 96 h, then cooled to r.t. A 2 M aq solution of NaOH (8.0 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10.0 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under vacuum. The crude product was purified by chromatography [silica gel, PE–EtOAc (20:1)].
2-(2-Chlorophenyl)pyridine (3a)
Yellow oil; yield: 27.2 mg (72%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.32 (m, 1 H), 7.32–7.39 (m, 2 H), 7.48 (dd, *J* = 1.6, 7.2 Hz, 1 H), 7.60 (dd, *J* = 2.0, 7.6 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.77 (td, *J* = 1.6, 7.6 Hz, 1 H), 8.73 (d, *J* = 4.8 Hz, 1 H).
2-(2,6-Dichlorophenyl) pyridine (4a)
Yellow oil; yield: 2.2 mg (5%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.28 (m, 1 H), 7.34–7.37 (m, 2 H), 7.41 (d, *J* = 8.8 Hz, 2 H), 7.82 (td, *J* = 2.0, 8.0 Hz, 1 H), 8.76–8.75 (m, 1 H).