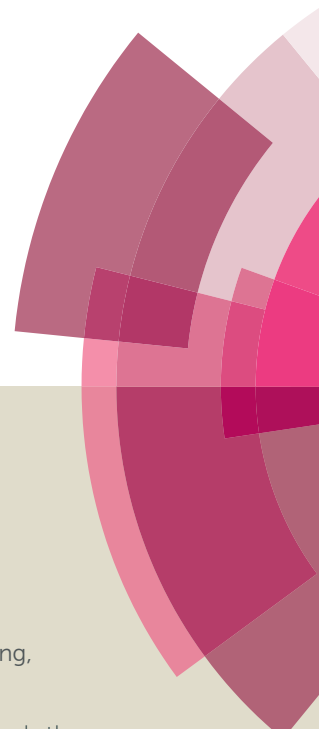
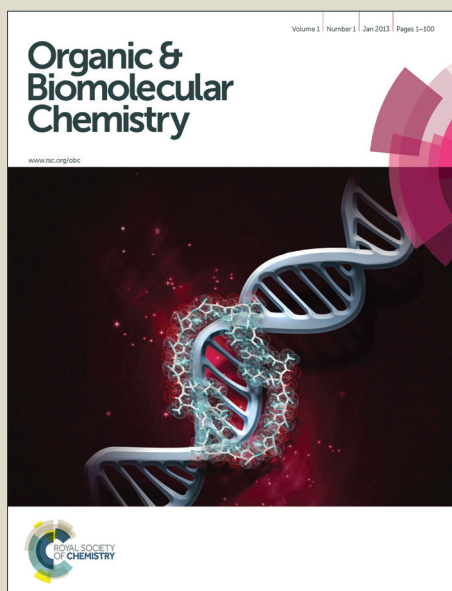


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Cu-Mediated Direct Regioselective C-2 Chlorination of Indoles

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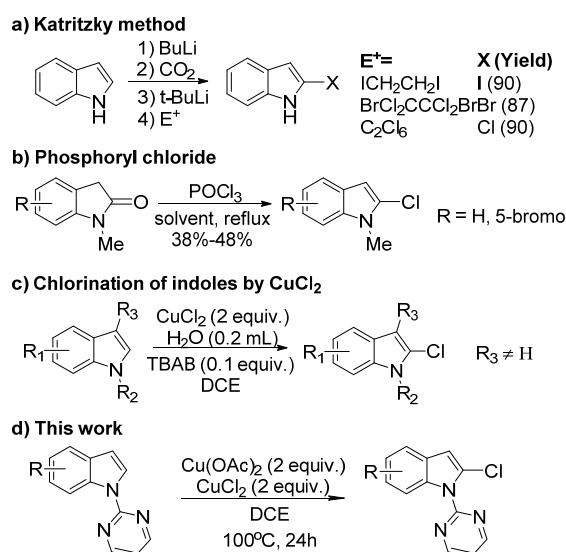
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Cu-mediated C-2 chlorination of indoles were accomplished with copper(II) chloride through the use of a directing pyrimidyl protection group. A highly regioselective manner can be achieved on a range of indole substrates with excellent functional group tolerance.

Transition-metal-catalyzed C-H halogenation of (hetero)arenes, in the past decade, has emerged rapidly as a straightforward and efficient synthetic protocol for halogenated (hetero)arenes, which are versatile building blocks in organic synthesis¹ and key structural motifs in numerous natural products and drugs.² However, the reported protocols generally depend on precious palladium catalysts.³ It is strongly desired to develop new reactions mediated by other economically sustainable transition metals.⁴ Thus, significant attention has recently been focused on copper catalysts as inexpensive and potentially effective alternatives.⁵ Since the first report on copper-catalyzed direct C-H halogenation of 2-arylpyridines by Yu and co-workers in 2006^{6a}, copper-catalyzed/mediated aryl C-H halogenation with different directing groups using various different halogen sources, such as acyl chlorides, lithium halides, and N-halosuccinimides (NXS), has been reported.⁶

Halogenated indoles are found in nature⁷ and used as starting materials for the synthesis of a large number of alkaloids.⁸ They are also present in biologically active compounds, for example, 2-chloro-4-fluoroindole nucleoside was designed as shape mimics of 8-oxopurines and used as mechanistic probes of cellular responses to DNA damage.⁹ A series of trichlorinated indole nucleosides exhibit potent and selective activity against human cytomegalovirus (HCMV).¹⁰ Thus, C-H halogenation, especially chlorination of indoles has received great attention from synthetic chemists. Due to the

electron-rich character of indoles, 3-haloindoles are mainly obtained in electrophilic halogenation reactions.¹¹ Development of selective halogenation protocols for the synthesis of 2-haloindoles is still highly challenging.¹² One early example is the Katritzky method that involves lithiation at C-2 position, followed by trapping with halogenating agents (Scheme 1a).¹³ Another common procedure comes from the conversion of *N*-substituted oxindole derivatives to 2-haloindoles using phosphoryl chloride (Scheme 1b).¹⁴ Although C-2 chlorination of indole by copper(II) chloride was reported, it required the presence of a substitution at the C-3 position (Scheme 1c).¹⁵ Thus, it is significant to develop an efficient and selective approach toward 2-chloroindoles with mild condition, simple operations and good yields. Herein, we introduce a copper-mediated C-2 chlorination of indoles with excellent regioselectivity, inexpensive and low-toxin copper(II) chloride as the chlorine source. In order to alter the regioselectivity from C-3 to C-2 C-H bonds, a removable pyrimidyl directing group is introduced to the indole nitrogen atom (Scheme 1d). To the best of our knowledge, direct C-



Scheme 1. The synthesis of 2-chloroindoles

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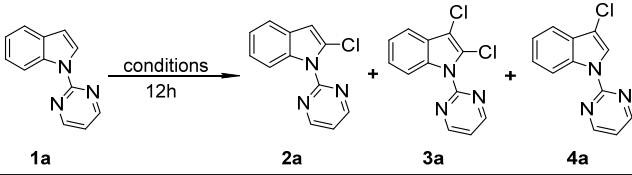
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Table 1. Optimization studies for C-2 chlorination of indole


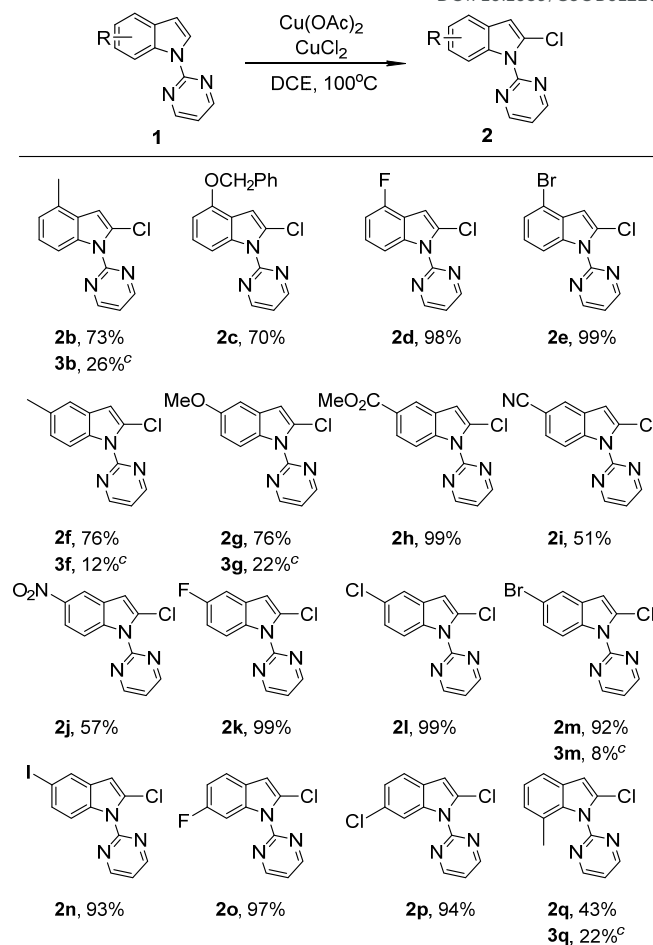
Entry	Conditions ^a	Yield(%) ^b of 2a/3a/4a
1	Pd(OAc) ₂ (5 %), NCS (1.1 eq), AcOH, 120°C	0/3/92
2	Pd(OAc) ₂ (10 %), NCS (1.1 eq), DCE, 100°C	0/12/75
3	Pd(OAc) ₂ (10 %), NCS (1.1 eq), MeCN, 100°C	0/7/77
4	Pd(OAc) ₂ (10 %), LiCl (2 eq), K ₂ S ₂ O ₈ (2 eq), AcOH, 120°C	0/15/0
5	Pd(OAc) ₂ (10 %), LiCl (2 eq), NaIO ₃ (2 eq), AcOH, 120°C	0/5/14
6	Pd(OAc) ₂ (10 %), LiCl (2 eq), PIDA (2 eq), AcOH, 120°C	0/8/25
7	Pd(OAc) ₂ (10 %), CuCl ₂ (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	70/12/0
8	CuCl₂ (2 eq), Cu(OAc)₂ (2 eq), DCE, 100°C	79/10/0
9	CuCl ₂ (2 eq), DCE, 100°C	0/18/46
10	NaCl (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	n.r.
11	KCl (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	n.r.
12	CsCl (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	n.r.
13	NH ₄ Cl (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	21/0/0
14	Bu ₄ NCl (2 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	36/0/0
15	CuCl ₂ (2 eq), Cu(OAc) ₂ (1.5 eq), DCE, 100°C	73/14/0
16	CuCl ₂ (2 eq), Cu(OAc) ₂ (1 eq), DCE, 100°C	62/23/0
17	CuCl ₂ (1.5 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	65/7/0
18	CuCl ₂ (1 eq), Cu(OAc) ₂ (2 eq), DCE, 100°C	53/6/0

^a Reaction conditions: **1a** (0.2 mmol), catalyst, chloride and additives as specified, solvent (0.2 M), 12h. ^b Determined by ¹H NMR spectroscopy. n.r. = no reaction.

2 chlorination of indoles is not disclosed in the literature.

Initially, we examined the reaction of *N*-pyrimidyl indole **1a** with *N*-chlorosuccinimide (NCS) using Pd(OAc)₂ as the catalyst¹⁶ (Table 1). However, only trace amount of desired product **2a** was detected with different solvents, and the major product **4a** came from the direct electrophilic addition of NCS (Entries 1-3). Then, non-electrophilic chlorine source LiCl in combination with an oxidant was used in place of NCS in the reaction, but the results were not improved (Entries 4-6). Subsequently, inspired by Shi's work^{3e}, we investigated the reaction using Pd(OAc)₂ in DCE with CuCl₂ as the chlorinating reagent and Cu(OAc)₂ as the oxidant. Gratifyingly, the reaction gave the desired product in 70% yield (Entry 7). Then we conducted the reaction in the absence of Pd(OAc)₂, to our delight, the chlorinated product **2a** was observed in 79% yield together with 10% of double chlorination product **3a** (Entry 8). Further investigation revealed that Cu(OAc)₂ is necessary to obtain product **2a** in good yield (Entry 9). Remarkably, we also attempted to employ other chlorine sources, such as metal chlorides or organic chlorides, but no further success was achieved (Entries 10-14). Lowering the Cu(OAc)₂ loading decreased the ratio of **2a/3a** (Entries 15-16) and lowering the CuCl₂ loading led to the decrease of the conversion (Entries 17-18). Hence, the optimal conditions involve 2.0 equivalents of Cu(OAc)₂ and 2.0 equivalents of CuCl₂ in DCE at 100 °C for 12h (Entry 8).

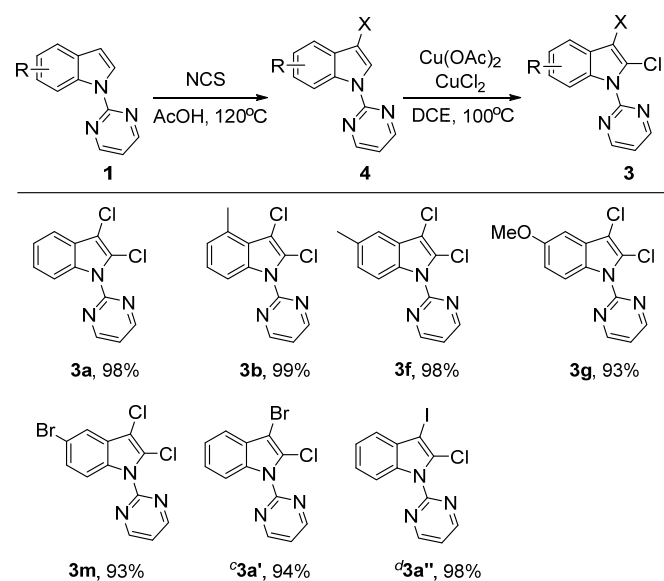
With the optimized reaction conditions in hand, we then extended the reaction with a range of substrates. As illustrated in Table 2, this reaction was compatible with different substitutions at C4-, C5-, C6- or C7-positions, and afforded 2-chloroindoles in good

Table 2. The scope of C-2 chlorination of indoles^{a,b}View Article Online
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^a Reaction conditions: substrate (0.2 mmol), Cu(OAc)₂ (2.0 equiv), CuCl₂ (2.0 equiv), DCE (1 mL), 100°C, 24h (to ensure the completion). ^b Isolated yield. ^c Isolated yield of the double chlorination product **3**.

to excellent yields with high regioselectivity. *N*-Pyrimidyl indoles containing both electron-donating groups (methyl, **2b**, **2f** and **2q**; benzyloxy, **2c**; methoxy, **2g**) and electron-withdrawing groups (ester, **2h**; cyano, **2i**; nitro, **2j**) afforded 2-chlorinated products predominately. Indoles with electron-donating methyl, benzyloxy and methoxy groups usually gave better yields than those with electron-withdrawing cyano and nitro groups, however, significant amount of 2,3-dichloroindole (**3b**, **3f**, **3g** and **3q**) were also obtained in the reaction. Notably, the indoles possessing halogen groups (chloro, **2l** and **2p**; bromo, **2e** and **2m**; fluoro, **2d**, **2k** and **2o**; iodo, **2n**) tend to give much higher yields than other groups.

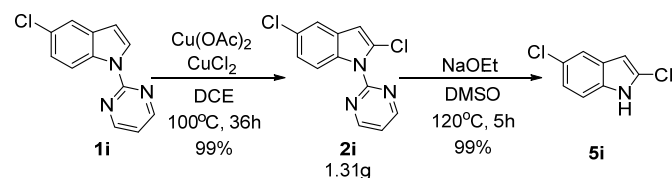
2,3-Dichloroindole motifs have been recognized as a highly valuable building block as evidenced by their presence in many pharmaceutical candidates.¹⁷ Our chlorination protocol could also be applied to the efficient synthesis of 2,3-dichloroindoles^{11a, 18} (Table 3). The two-step sequence started with the direct C-3 chlorination of **1** with NCS in AcOH. Then the resulting 3-chloroindoles **4** could be converted into 2,3-dichloroindoles **3** under our optimized condition with excellent yields. It is worth noting 2,3-dichloroindoles could not be prepared in good yields by simply over-

Table 3. The two step synthesis of 2,3-dichloroindoles and 2-chloro-3-bromo/iodo-indoles^{a,b}

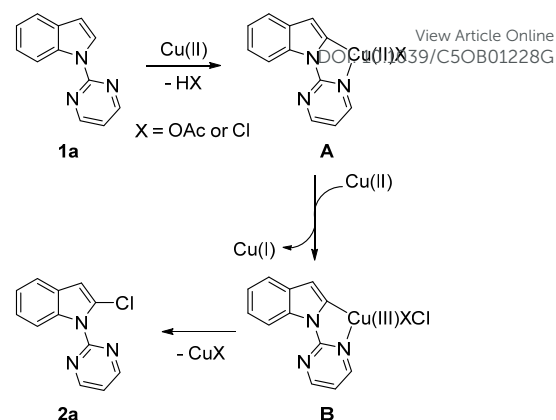
^a Step 1, reaction conditions: substrate **1** (0.4 mmol), NCS (1.1 equiv), AcOH (1 mL), 120°C, 5h. Step 2, reaction conditions: **4** (0.2 mmol), Cu(OAc)₂ (2.0 equiv), CuCl₂ (2.0 equiv), DCE (1 mL), 100°C, 12h. ^b Isolated yield. ^{c,d} The synthesis of **4a'** and **4a''** were different from step 1 (see supporting information).

recharging NCS (3.0 equivalents) in the first step (see supporting information). Furthermore, with 3-bromoindole and 3-iodoindole in hand, 2-chloro-3-bromoindole **3a'** and 2-chloro-3-iodoindole **3a''** could be obtained efficiently. The two-step sequence can only be applied to the electron-rich indole substrates and certain halogen substituted indoles.

Under the optimal conditions, the C-2 chlorination reaction can be carried out on a gram scale without a decrease in yield and selectivity, as illustrated by the preparation of product **2i** to demonstrate the robustness of this strategy (Scheme 2). The gram scale synthesis was achieved with increased reaction time to ensure its completion. Moreover, upon treatment of **2i** with NaOEt in DMSO at 120 °C for 5h, 2,5-chloro-1*H*-indole was isolated with excellent yield.

**Scheme 2.** Gram scale synthesis and deprotection.

Meanwhile, control experiments using 1*H*-indole and 1-phenylindole as starting material were conducted under the optimized conditions. The former turned into a complex mixture and the latter turned into 3-chloro-1-phenylindole in 60% yield (see supporting information). These results suggested the important role of pyrimidyl group in the C-2 chlorination protocol. Based on these

**Scheme 3.** Proposed mechanism for the C-H chlorination

results and recent progress on high-valent organometallic copper in catalysis,¹⁹ a possible mechanism was proposed as shown in Scheme 3. First, the coordination of pyrimidyl group of compound **1a** to copper(II) is followed by ortho-C-H bond activation which gives the cyclometalated Cu(II) intermediate **A**. Disproportionation of Cu(II) species lead to the Cu(III) intermediate **B**. Subsequently, the reductive elimination of Cu(III) intermediate **B** can provide the corresponding chlorinated product **2a**. Nonetheless, a single electron transfer (SET) process couldn't be excluded.^{6a}

Conclusions

In conclusion, we have demonstrated a versatile and highly efficient Cu-mediated direct C-2 chlorination strategy for indoles with excellent regioselectivity and functional group tolerance. This C-H chlorination protocol strongly exploits the easily removable *N*-(2-pyrimidyl) motif as the metal-directing group. It serves as a novel and alternative route for preparation of 2-chloro-1*H*-indoles. Further understanding of the reaction mechanism and application expansion of this approach to other synthetically useful substrates are ongoing in our laboratory.

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