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Rhodium-Catalyzed Regioselective C−H Chlorination of 7-Azaindoles Using 1,2-Dichloroethane

Guangyin Qian,[†] Xiaohu Hong,[†] Bingxin Liu,*[,†] Hong Mao,[†] and Bin Xu*[,†,‡,§]

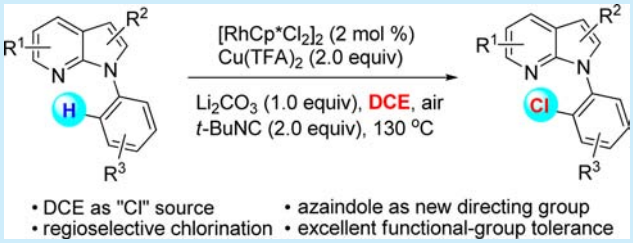
[†]Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai 200444, China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

[§]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, Shanghai 200062, China

Supporting Information

ABSTRACT: An unexpected rhodium-catalyzed regioselective C−H chlorination of 7-azaindoles was developed using 1,2-dichloroethane (DCE) as a chlorinating agent and 7-azaindole as the directing group. This protocol provides an efficient access to *ortho*-chlorinated azaindoles with operational simplicity, good functional group tolerance, and a wide substrate scope.



The azaindole skeleton is one of the most attractive frameworks as a bioisostere for indoles with a wide range of biological and pharmacological activities, and has been found in numerous biologically active natural products and marketed drugs.[1] Due to their ability to act as both hydrogen-bond donor and acceptor, azaindoles have exhibited a broad spectrum of biological activities such as antitumor,[2] antibacterial,[3] and anti-inflammatory activity.[4] The structural feature of electron-rich azole and electron-deficient azine rings in the 7-azaindoles makes them a unique structure in many therapeutic agents, such as marketed anticancer drug Vemurafenib,[5] hNK1 receptor,[6] and potent antimelanoma agent PLX4720.[7] Given the broad utilities of 7-azaindoles in medicinal chemistry, efficient functional group modifications at the C2 or C3 position of azaindoles with the aid of transition metals have been described.[8] A site-selective direct arylation of the 7-azaindole core was also developed by making use of both the *N*-oxide activation strategy and the Larrosa arylation protocol to achieve the 6- and 2-arylation products, respectively.[9]

In recent decades, transition metal catalyzed direct C−H bond functionalization has achieved great success in the formation of C−C, C−N, and C−heteroatom bonds, which provides efficient protocols to construct many useful molecules.[10] Among them, the ligand-directed C−H activation approach has emerged as one of the most important processes in organic synthesis to simplify the preparation of functionalized building blocks and intermediates.[11] In this context, a range of nitrogen- and oxygen-containing directing groups such as phenols,[12a] heterocycles (e.g., benzo[*h*]quinoline, pyrazole, pyridine, quinoline),[12b] imines,[12c] amides,[12d] carboxylic acids,[12e] esters,[12f] and ketones[12g] have been used for C−H functionalization. However, C−H activation using 7-azaindole as the directing group has not been reported yet in all the aforementioned cases.

Isocyanides have proven to be uniquely versatile building blocks in organic synthesis due to their structural and reactive properties and have been widely applied in the synthesis of heterocycles.[13] As their sustainable contribution, isocyanides were recognized as an efficient cyanated reagent for the preparation of (hetero)aryl nitriles.[14] For example, Zhu[14a] and we[14b] have reported a palladium-catalyzed oxidative C−H cyanation reaction independently using easily available *tert*-butyl isocyanide as the novel cyanide source. As a complementary method to our previously palladium-catalyzed cyanation reaction,[14b] a rhodium-catalyzed regioselective C−H bond cyanation of arenes was developed to achieve (hetero)aryl and cycloalkenyl nitriles successfully in the presence of *tert*-butyl isocyanide (Scheme 1).[14c] However, attempting to expand this rhodium catalysis protocol to *N*-phenyl-7-azaindole (**1a**) failed. To our surprise, an *ortho* aryl C−H bond chlorination reaction had taken place instead and afforded the corresponding chlorinated product **2a** in 53% isolated yield (Table 1, entry 1), without observation of any desired cyanated product or isomeric product **2a**′ which was chlorinated at the more favored electron-rich C3 position of the azole ring.[15] To continue our research interests on the isocyanide chemistry[14b,c,16] and assembling heterocycles through C−H bond functionalization,[17] herein we report an unexpected rhodium-catalyzed regioselective C−H chlorination of 7-azaindoles (Scheme 1). To our knowledge, this approach represents the first example of Rh-catalyzed intermolecular C−H chlorination using 1,2-

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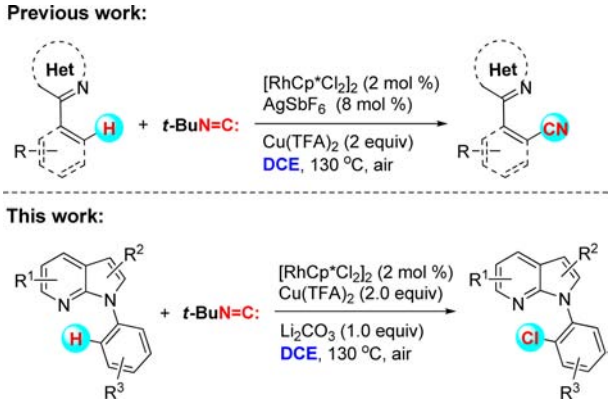
Scheme 1. Rh-Catalyzed Regioseletive C−H Functionalization of Heteroarenes



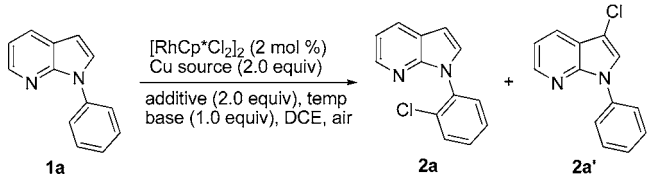
dichloroethane (DCE) as a chlorinating agent[18] and 7-azaindole as the new directing group for C−H activation.

At the outset of this investigation, we commenced our study by conducting this chlorination reaction in the absence of $AgSbF_6$, and a comparable yield was obtained after reacting for 18 h at 130 °C (Table 1, entry 2). The use of $Cu(OAc)_2$ or $Cu(acac)_2$ instead of $Cu(TFA)_2$ gave worse results with a longer reaction time (entries 3−4), while a C3-chlorinated product **2a′** was produced predominately in the presence of $Cu(OTf)_2$ or $CuCl_2$ (entries 5−6). The addition of bases could improve the reaction, and the use of Li_2CO_3 turned out to be the best choice (entries 7−10). Lowering the reaction temperature simply resulted in decreased yields with poor conversions even prolonging the reaction time (entries 11−12), and diminished yields were obtained by decreasing the amount of Li_2CO_3 and *t*-BuNC (entries 13−14). Further investigations revealed that in the absence of $[RhCp^*Cl_2]_2$ (entry 15) or *t*-BuNC (entry 16), or when reaction was conducted under a nitrogen atmosphere (entry 17), the reaction became sluggish and furnished **2a** in lower yields. No reaction could be observed in the absence of $Cu(TFA)_2$, which indicated that the copper source was crucial for this reaction (entry 18).

With the establishment of the optimal conditions, the scope and limitation of this chlorination reaction were next investigated, as shown in Scheme 2. Substrates bearing an electron-donating or electron-withdrawing group reacted smoothly to afford the desired products in moderate to good yields, in which the functional groups such as alkyl (**2b**, **2l**), alkoxyl (**2c**, **2m**), phenyl (**2k**), halides (F, Cl, Br, I) (**2d**−**2g**), ester (**2h**), acyl (**2i**), and nitro (**2j**) were all tolerated, regardless of their electronic properties. The substrate with a strong electron-withdrawing nitro group resulted in a slightly complicated reaction, and the corresponding product **2j** was isolated in 32% yield. For *meta*-substituted substrates, the *ortho* monochlorinated reaction selectively occurred at the less sterically hindered position (**2l**−**2m**).

Encouraged by the success of a direct C−H chlorination reaction of azaindoles, to further explore the generality and scope of this practical approach, a variety of substituted 7-azaindoles were investigated (Scheme 3). This chlorination reaction worked well with many functionalized azaindoles bearing substitutions at the C2−5 positions with different electronic properties and gave desired products in moderate to

Table 1. Optimization of Reaction Conditions[a]



entry	Cu source	additive	base	temp (°C)	time (h)	yield (%)[b] 2a	2a′
1	$Cu(TFA)_2$	*t*-BuNC/$AgSbF_6$	–	130	20	53	–
2	$Cu(TFA)_2$	*t*-BuNC	–	130	18	58	–
3	$Cu(OAc)_2$	*t*-BuNC	–	130	48	31	–
4	$Cu(acac)_2$	*t*-BuNC	–	130	48	N.R.	–
5	$Cu(OTf)_2$	*t*-BuNC	–	130	48	–	32
6	$CuCl_2$	*t*-BuNC	–	130	13	–	72
7	$Cu(TFA)_2$	*t*-BuNC	$NaHCO_3$	130	50	61	–
8	$Cu(TFA)_2$	*t*-BuNC	Na_2CO_3	130	35	73	–
9	**$Cu(TFA)_2$**	***t*-BuNC**	**Li_2CO_3**	**130**	**26**	**76**	–
10	$Cu(TFA)_2$	*t*-BuNC	pyridine	130	41	74	–
11	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	120	47	61	–
12	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	100	55	30	–
13	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	130	40	66[c]	–
14	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	130	37	55[d]	–
15	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	130	54	52[e]	–
16	$Cu(TFA)_2$	–	Li_2CO_3	130	31	45	–
17	$Cu(TFA)_2$	*t*-BuNC	Li_2CO_3	130	55	27[f]	–
18	–	*t*-BuNC	Li_2CO_3	130	52	N.R.	–

[a]Reaction conditions: **1a** (0.2 mmol), $Rh[Cp^*Cl_2]_2$ (2.0 mol %), Cu source (2.0 equiv), additive (2.0 equiv), base (1.0 equiv), 130 °C, air, DCE (1.0 mL). $Cu(TFA)_2$ = Cupric trifluoroacetate. DCE = 1,2-Dichloroethane, N.R. = No Reaction. [b]Isolated yield. [c]Li_2CO_3 (0.5 equiv) was used. [d]*t*-BuNC (1.0 equiv) was used. [e]Without $Rh[Cp^*Cl_2]_2$. [f]Under N_2.

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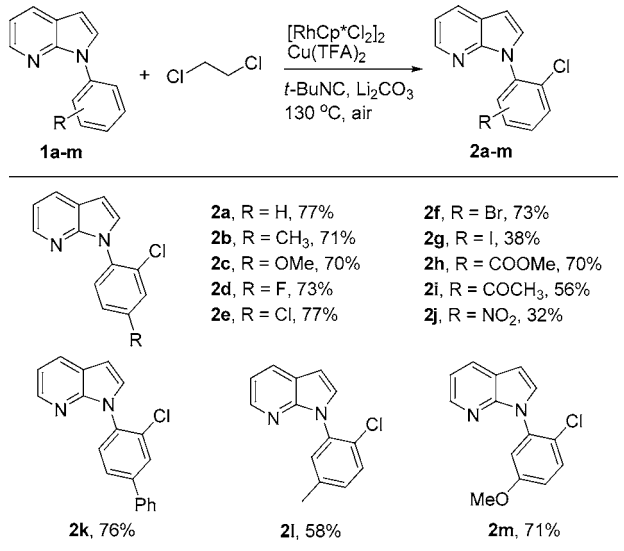
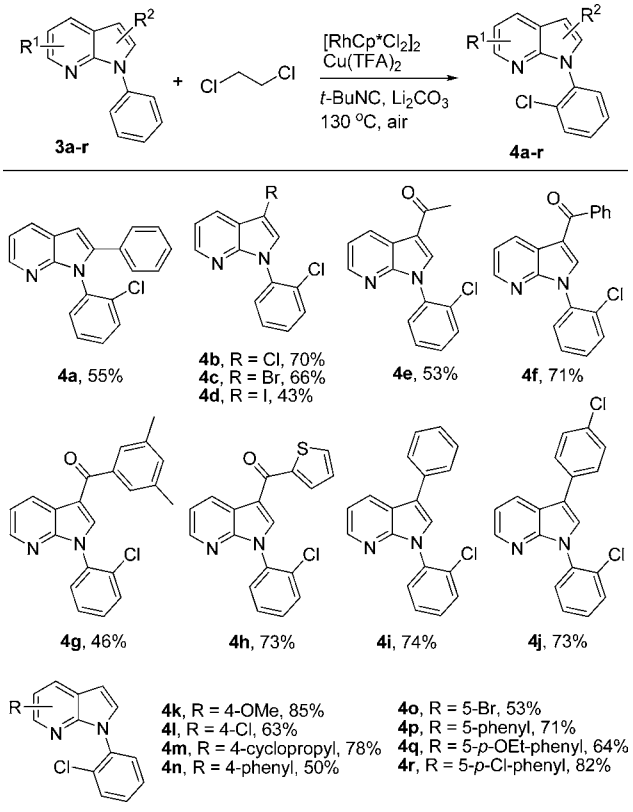
Scheme 2. Scope of Azaindoles Varying with *N*-Aryl Ring[a,b]



[a]Reaction conditions: **1** (0.3 mmol), $Rh[Cp^*Cl_2]_2$ (2.0 mol %), $Cu(TFA)_2$ (2.0 equiv), *t*-BuNC (2.0 equiv), Li_2CO_3 (1.0 equiv), DCE (1.5 mL), 130 °C, air, 23−53 h. [b] Isolated yield.

Scheme 3. Scope of Azaindoles Varying with Azaindole Ring[a,b]

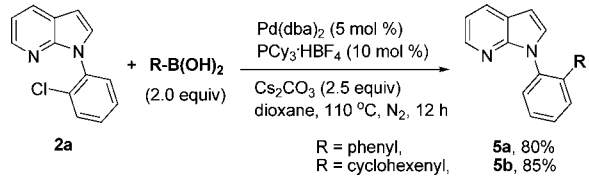


[a]Reaction conditions: **3** (0.3 mmol), $Rh[Cp^*Cl_2]_2$ (2.0 mol %), $Cu(TFA)_2$ (2.0 equiv), *t*-BuNC (2.0 equiv), Li_2CO_3 (1.0 equiv), DCE (1.5 mL), 130 °C, air, 22−49 h. [b] Isolated yield.

good yields. 1,2-Diphenyl-7-azaindole with high steric hindrance was found to be a suitable substrate and afforded **4a** in good yield. Substituents including alkoxyl (**4k**), aryl (**4i**−**4j**, **4n**, **4p**−**4r**), cycloalkyl (**4m**), acyl (**4e**−**4h**), and halide (**4b**−**4d**, **4l**, **4o**) groups were all compatible in the reaction. Furthermore, azaindoles having a bromo or iodo substitution at the C3 or C5 position (**4c**−**4d** and **4o**) could also undertake this reaction smoothly with a halide atom remaining, which provided potential application for further transformation. The identity of **4j** was determined by spectral analysis and further confirmed by X-ray crystallographic analysis.[19]

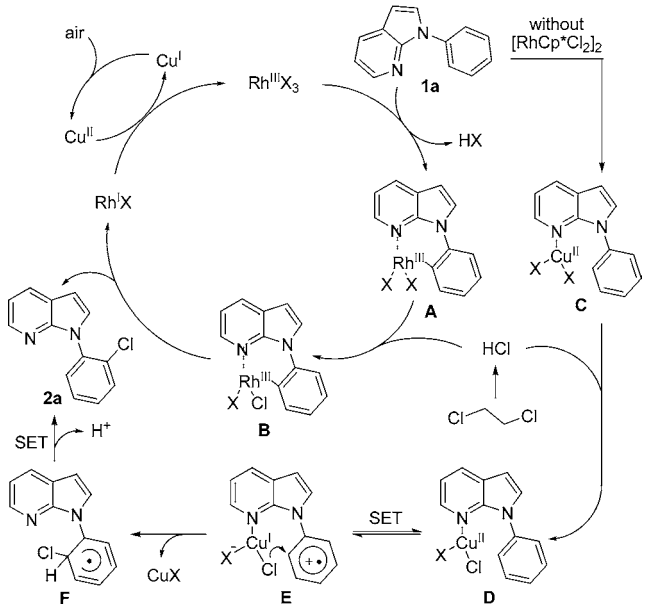
The produced *ortho*-chlorinated *N*-aryl azaindoles represent a class of potential antagonists of corticotropin-releasing hormone-1 receptor (CRH_1-R)[20] and provide a useful template for further analogue synthesis (Scheme 4). For example, *ortho*-functionalized *N*-aryl azaindoles **5a**−**5b** could be generated in high yields from aryl or vinyl boronic acids using a well-documented Suzuki reaction.

Scheme 4. Application of Chlorinated Product



Although a detailed reaction pathway remains to be clarified, a tentative mechanism for this rhodium-catalyzed C−H chlorination reaction is depicted in Scheme 5. One experiment

Scheme 5. Proposed Mechanism for Synthesis of 2a



was performed to provide support for the proposed mechanism, involving the addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) to effectively quench the reaction. This reaction may involve the formation of a C−Rh bond in the first step to afford intermediate **A**, which presumably reacts with hydrogen chloride generated in situ from 1,2-dichloroethane[18,21] to afford rhodium complex **B**. The formed intermediate **B** followed by reductive elimination to give the final product **2a**, and the rhodium catalyst could be regenerated by the oxidation of Cu(II) and atmospheric oxygen. For the case without using a rhodium catalyst (Table 1, entry 15), the reaction will go through copper complexes **C** and **D** followed

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by a single electron transfer (SET) from the aryl ring to the coordinated Cu(II), leading to the cation-radical intermediate **E**, which will convert to intermediate **F** and further afford the product **2a**.[21]

In conclusion, we have developed a rhodium-catalyzed regioselective C−H chlorination reaction using easily available 1,2-dichloroethane (DCE) as a "Cl" source and 7-azaindole as the directing group. This protocol provides an efficient access to chlorinated 7-azaindoles with operational simplicity, good functional group tolerance, and a wide substrate scope. Further insight into the mechanism, reaction scope, and synthetic applications for bioactive compounds are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds, X-ray structure of compound **4j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: xubin@shu.edu.cn.
*E-mail: bxliu@shu.edu.cn.

Notes

The authors declare no competing financial interest.

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