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Pd-Catalyzed C–H Halogenation of Indolines and Tetrahydroquinolines with Removable Directing Group

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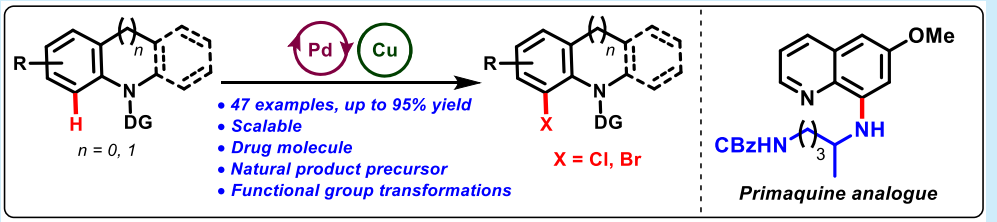
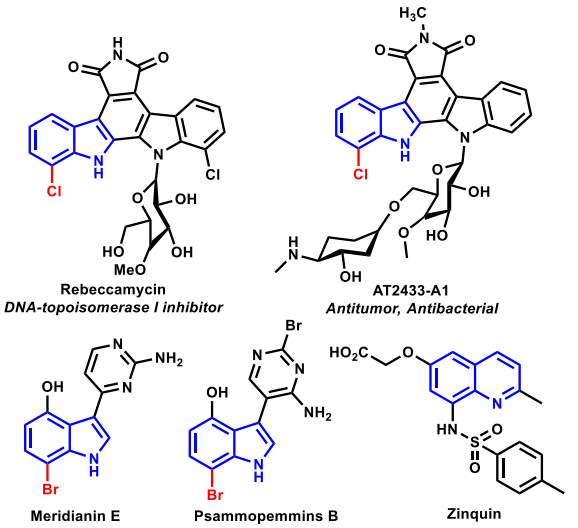


ABSTRACT: Pd-catalyzed directing-group-assisted regioselective halogenations to C7 of indolines and C8 of tetrahydroquinolines were achieved in good to excellent yields. The practicality and utility of the developed method have been illustrated by various functional group transformations such as arylation, alkenylation, cyanation, and silylation utilizing the installed synthetic handle. The concise synthesis of primaquine, an antimalarial drug, and formal syntheses of two bioactive natural products, hippadine and pratosine, have also been demonstrated.

Indole and quinoline derivatives share a major portion of the heterocyclic cores present in the biological system and pharmaceuticals, polymers, and materials.[1] In particular, C7-substituted indoles and C8-substituted quinolines display diverse bioactivities that include hMGMAT2 inhibition and antiproliferative, antiperoxidative, and antimalarial properties (Scheme 1).[2] Consequently, there has been a significant growth in the past decade to introduce valuable functional groups at these positions of these privileged molecules by means of a step-economical C–H activation strategy. This, in turn, leads to the development of new methods for the formation of C–C and C–X (X = N, O, halogen, etc.) bonds.[3−7] Unarguably, halogen functionality is considered to be the most synthetically valuable functional group that not only is convertible to various other functionalities but also is an important functionality in medicinal chemistry for molecular interaction.[2f,8] Thus the development of a general yet practical and efficient method for the halogenation of these scaffolds would be of immense importance.

Scheme 1. C7 Halogenated Bioactive indole and C8-Substituted Quinoline Derivatives



Since Fahey's seminal discovery of the Pd-catalyzed *ortho*-C–H chlorination of azobenzene in 1970,[8a] several protocols for the C(sp^2)–H and C(sp^3)–H halogenation to numerous scaffolds have been reported by various research groups using ruthenium,[9] rhodium,[10] palladium,[11] manganese,[12] nickel,[13] cobalt,[14] and copper catalysts.[15] In particular, Pd catalysis plays a dominant role in the halogenation to arenes,[11a−f] anilines,[11g,h] benzoic acids,[11i] phenols,[11j] and benzaldehydes.[11k] In 2015, Jiang et al. reported a copper-mediated protocol for the C2 chlorination of indoles exploiting the preferred five-membered cyclometalation and intrinsic reactivity of the C(2)=N bond (Scheme 2).[15b] Preferential

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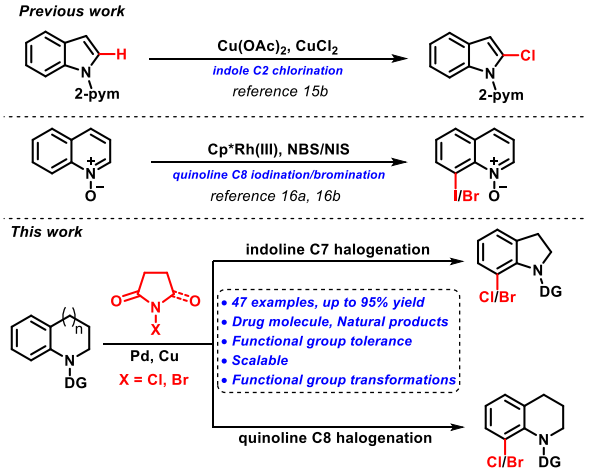
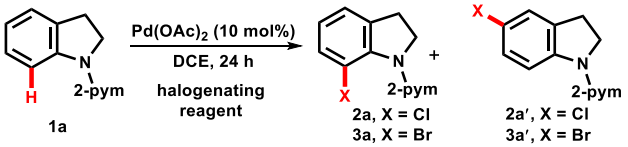
Scheme 2. Reports on Indole and Quinoline Halogenation



electrophilic iodination at the C3 position of carbazole has also been reported.[15i] On the contrary, although numerous protocols have been developed to functionalize the C7 of indole/indoline via arylation,[3] alkylation,[4] acylation,[5] chalcogenation,[6] and amination,[7] to the best of our knowledge, no report has been demonstrated for the C7−H halogenation to indole scaffold. Besides this, there has not been a general protocol that could efficiently functionalize the C7−H and C8−H bonds of indole and quinoline, respectively. In regard to the quinoline halogenation, only Chang et al. in 2014 reported C8−H iodination to quinoline *N*-oxides using Rh(III) catalysts (Scheme 2).[16a] Unfortunately, despite using a highly electrophilic and expensive $[RhCp^*Cl_2]_2$ catalyst along with silver salt, the developed condition did not facilitate chlorination and bromination. Following Chang's strategy, very recently, Sharma et al. disclosed a method for the C8−H bromination to quinoline *N*-oxides.[16b] In a continuation of our work on indole[17] and quinoline functionalization,[18] we wondered whether a halogenation protocol could be established that would be applicable to both of these privileged scaffolds. Herein we report the palladium-catalyzed C−H halogenation of indolines and quinolines at the C7 and C8 positions, respectively, using a removable directing group strategy. Notably, the developed method is very general for both of these privileged scaffolds. The method has been applied to the formal synthesis of two natural products and a drug molecule.

We employed *N*-pyrimidyl indoline (**1a**) as a model substrate to evaluate the possibility of developing a method for the C7-selective halogenation and thus tested various electrophilic chlorinating reagents, metal catalysts, solvents, and additives (Table 1). However, a recent study described that an electrophilic halogenating reagent could be useful for the C5−H halogenation of indoline.[11d,g,19] Thus our initial aim was to minimize the formation of electrophilic aromatic substitution (S_EAr) products. Therefore, we aimed to identify a halogenating reagent that would be the least reactive for the electrophilic aromatic substitution (S_EAr) reaction to indoline. First, the reactivities of *N*-chlorophthalimide (**A**), *N*-Chlorosaccharin (**B**), *N*-chlorosuccinimide (**C**), and *N*-chloropyrrolidinone (**D**) were tested at room temperature in both the

Table 1. Optimizing Conditions[a]



entries	catalyst	solvent	chlorinating source	temp (°C)	yield [**2a**/**2a′**] (%)
1		DCE	A	rt	14/69
2	$Pd(OAc)_2$	DCE	A	rt	traces
3		DCE	B	rt	11/66
4	$Pd(OAc)_2$	DCE	B	rt	26/63
5		DCE	C	rt	traces
6	$Pd(OAc)_2$	DCE	C	rt	traces
7		DCE	D	rt	traces
8	$Pd(OAc)_2$	DCE	D	rt	traces
9	$Pd(OAc)_2$	DCE	C	45	traces
10		DCE	C	70	12/62
11	$Pd(OAc)_2$	DCE	C	70	30/18
12		DCE	C	90	11/76
13	$Pd(OAc)_2$	DCE	C	90	57/18
14[b]	**$Pd(OAc)_2$**	**DCE**	**C**	**90**	**91/05**
15[b]	$Pd(OAc)_2$	DCE	D	90	88/10
16[b]	$Pd(OAc)_2$	ACN	C	90	39/00
17[b]	$Pd(OAc)_2$	DMF	C	90	18/00
18[b]	$Pd(OAc)_2$	DMA	C	90	72/00
19[b]	$Pd(OAc)_2$	DCE	C	rt	17/05
20[b]	$Pd(TFA)_2$	DCE	C	90	89/08
21[b]	$Pd(OTs)_2(MeCN)_2$	DCE	C	90	80/18

[a]Reaction conditions: 0.25 mmol of **1**, 1.2 equiv of chlorinating source, 2 mL of solvent, NMR yield using 1,3,5-trimethoxybenzene as internal standard. [b]1.0 equiv of CuO.

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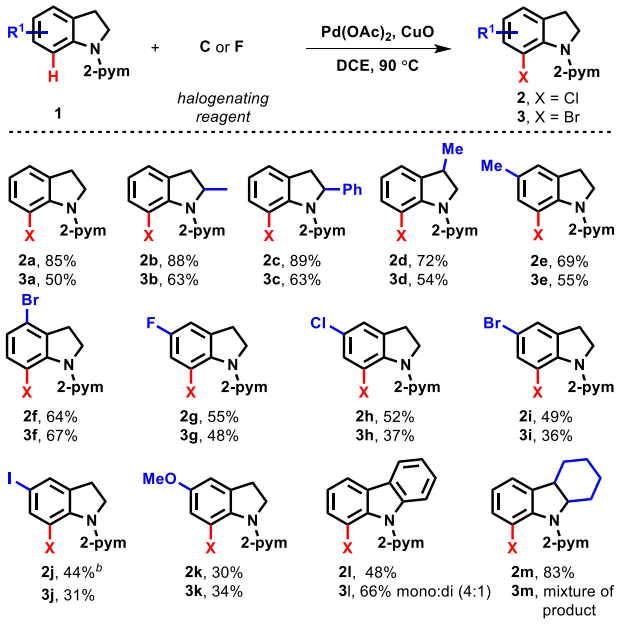
absence and the presence of the palladium catalyst (entries 1–8). **C** and **D** were found to be the least reactive and therefore considered to be suitable for further examination (entries 7 and 8). Unfortunately, the formation of undesired product **2a′** (62%) was predominant at higher temperature (70 °C, entry 10). Intriguingly, although the addition of $Pd(OAc)_2$ reduced the overall yields, the ratio of the products was improved in favor of the desired product **2a** (1.6:1, entry 11). The ratio (3.2:1) and overall yields were further improved by raising the temperature to 90 °C (entry 13). However, the formation of 18% of **2a′** via the S_EAr reaction could not be stopped. Gratifyingly, the addition of 1.0 equiv of CuO almost completely inhibited the formation of **2a′**, and **2a** was obtained in 91% yield (entry 14). Under this condition, **D** also furnished **2a** in 88% yield (entry 15). However, the inexpensive **C** was considered for further studies. Solvent screening studies did not help to improve the yield of the desired product (entries 16–18). Although the reason is unclear to us, it is notable that the addition of copper salt as an additive completely inhibited the formation of **2a′**. Inspired by the outcome with CuO, we wondered whether the reaction could be executed at room temperature. Unfortunately, a very low yield of **2a** was obtained (entry 19). Considering the strong aggregating properties of $Pd(OAc)_2$ in a weakly polar solvent, we also tested other Pd salts such as $Pd(TFA)_2$ and $Pd(OTs)_2(MeCN)_2$, which are known to offer more accessible active sites. Unfortunately, none of them showed better efficacy than $Pd(OAc)_2$ (entries 20 and 21).

Having optimized the reaction conditions in hand for the C7–H chlorination, we wondered whether similar conditions could be applied for the selective bromination to **1a**. Unfortunately, *N*-bromosuccinimide (**E**) could not be successfully used for the desired transformation (data not shown; see the Supporting Information for further details). Gratifyingly, 10 mol % of $Pd(OAc)_2$ in the presence of 1.0 equiv of *N*-bromopyrrolidinone (**F**) and 2.0 equiv of CuO furnished the desired product **3a** in 50% isolated yield.

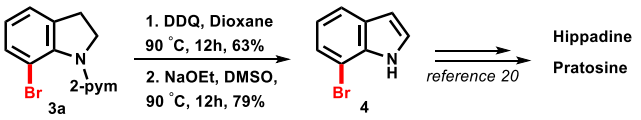
We next examined the scope and limitation of the developed chlorination and bromination reactions with respect to the indoline derivatives (Scheme 3). In general, chlorination was found to be more efficient than the bromination reaction. As shown in Scheme 3, indolines bearing alkyl and aryl substituents furnished the chlorinated products (**2a–e**) in good to excellent yields (69–89%). The corresponding brominated products (**3a–e**) were also obtained, albeit in lower yields (50–63%). It is noteworthy to mention that indolines bearing halogen substituents also furnished the desired C7 chlorinated (**2f–j**) and brominated (**3f–j**) products in moderate to good yields (31–67%). This proves that the developed methods are very mild and these synthetic handles could be used for further derivatizations. The electronically rich substrate **1k** furnished a low yield along with the formation of the oxidized products. The use of other Pd catalysts was also unsuccessful at increasing the yield. Whereas carbazole derivative **1l** favored the formation of the monohalogenated prduct **2l** in 48% yield, the corresponding bromination furnished a 66% halogenated product in a mixture of mono- and dibrominated derivatives (4:1). However, hexahydrocarbazole derivative **1m** provided **2m** in 83% yield. Notably, a two-step conversion of **3a** provided 7-bromoindole (**4**), which is the precursor for the synthesis of natural products hippadine and pratosine (Scheme 4).[20]

Scheme 3. Scope of Indolines[a]



[a]Reaction conditions: **1a–m** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), **C** (1.2 equiv, for chlorination), **F** (1.0 equiv, for bromination), CuO (1.0 equiv), 2 mL of DCE, 90 °C, isolated yields. [b]$Pd(TFA)_2$ (10 mol %) was used.

Scheme 4. Synthetic Application



To prove the generality, we next sought to test our protocol to functionalize the C8–H of quinoline (Scheme 5). In this regard, 1,2,3,4-tetrahydroquinoline was chosen as the model substrate for selective halogenation at the C8 position. To our delight, various tetrahydroquinolines bearing substituents at the C2, C3, and C6 positions were very well tolerated by both the chlorination and bromination methods, and the corresponding products were obtained in very good to excellent yields (56–86%). Under the optimized conditions, tetrahydroquinolines bearing methyl (**5b–d**), methoxy substituents (**5e**), were halogenated in excellent yields (up to 95%). In addition, halogen-substituted quinolines (**5f–h**) were also successfully functionalized at the C8 position using the developed method. Notably, despite using a Pd catalyst, Ar–Br and Ar–I bonds were unaffected by the optimized reaction conditions. Considering that the biaryl ring plays an important role in the pharmaceuticals,[21] **5i** was halogenated to furnish **6i** and **7i** as the corresponding chloro and bromo derivatives, respectively, in good yields. The pharmaceutically useful sulfonamide functionality was also tolerated with substrate **5j**, and the halogenated products were obtained in respectable yields. Finally, substrate **5k** bearing a morpholine functionality, a pharmacokinetically important scaffold, has also been shown to tolerate the protocol for the developed halogenation reaction. Gratifyingly, the reaction was also tolerated in the larger scale set up, and 2.36 mmol of **5a** furnished the desired bromo derivative (**7a**) in 75% yield.

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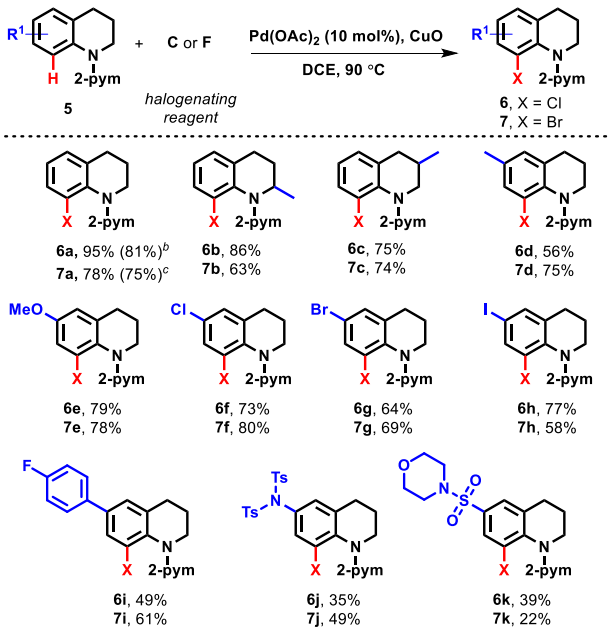
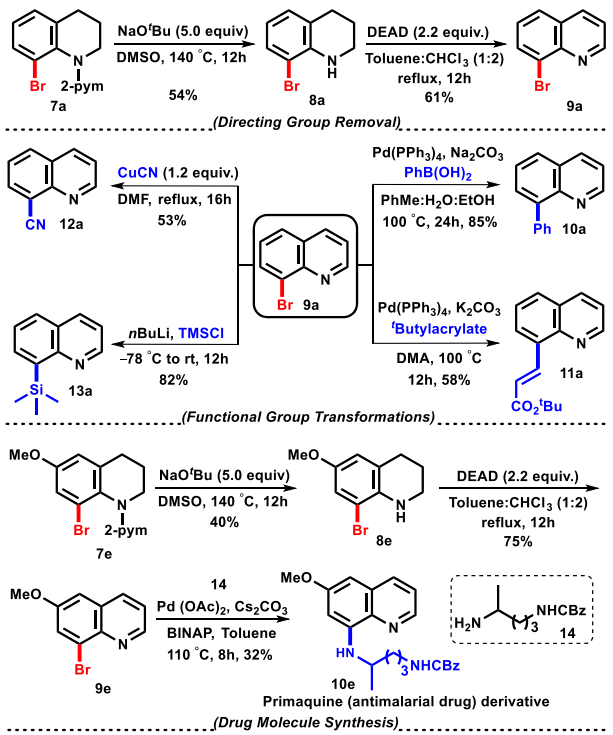
Scheme 5. Scope of Quinolines[a]



[a]Reaction conditions: **5a–k** (0.25 mmol), $Pd(OAc)_2$ (10 mol %), **C** (1.2 equiv, for chlorination), **F** (1.0 equiv, for bromination), CuO (1.0 equiv), 2 mL of DCE, 90 °C, isolated yields. [b]1.18 mmol of **5a**. [c]2.36 mmol of **5a**.

A broad variety of follow-up chemistry using the newly installed synthetic handle is shown in Scheme 6. First, the removal of the directing group (54%) followed by the oxidation led to the formation of 8-bromoquinoline (**9a**) in 61% yield. To exploit further, the bromo functionality of **9a** was converted to aryl (**10a**), alkenyl (**11a**), cyano (**12a**), and silyl (**13a**) functionalities in good to very good yields. Finally, the synthetic usefulness of the developed protocol was demonstrated by synthesizing an antimalarial drug, primaquine, from **7e** in three steps.

Scheme 6. Synthetic Application



In summary, a general strategy for the ortho-halogenation of indolines and tetrahydroquinolines has been demonstrated by a palladium–copper-catalyzed reaction using a removable directing group. The protocol is applicable to chlorination and bromination, and substrates bearing electron-donating as well as electron-withdrawing groups were well tolerated. As a proof of principle, the method was applied to synthesize many useful synthetic scaffolds, including the syntheses of primaquine and the precursor of hippadine and pratosine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01963.

Full experimental details, characterization data for new compounds, and copies of NMR (PDF)

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Notes

The authors declare no competing financial interest.

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