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Metal-Free Synthesis of Oxindoles via $(NH_4)_2S_2O_8$-Mediated Halocarbocyclization of Alkenes in Water

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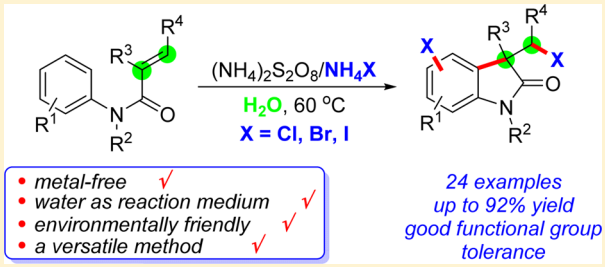
Supporting Information

ABSTRACT: A metal-free synthesis of oxindoles was achieved through the $(NH_4)_2S_2O_8$-mediated halocarbocyclization of alkenes. This protocol provides a practical and environmentally benign method for the construction of halo-containing oxindoles in water. The advantages of this reaction are its good functional group tolerance and mild reaction conditions. On the basis of experimental observations, a plausible reaction mechanism is proposed.

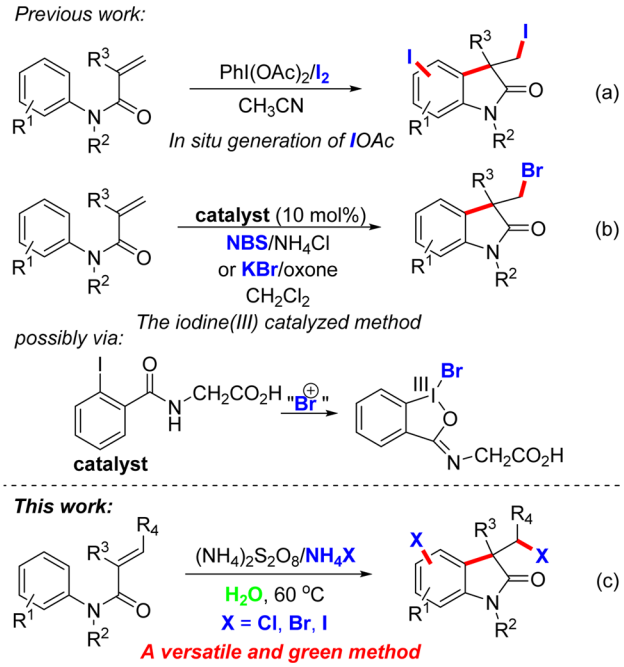


INTRODUCTION

Oxindole constitutes the central core of a wide variety of naturally occuring and pharmaceutical molecules[1] that exhibit potential biological activities (e.g., anti-inflammatory, anticancer, and *Plasmodium falciparum*-inhibitory activities).[2] Among the known strategies for obtaining an oxindole framework, transition-metal-catalyzed oxidative C−H functionalization/carbocyclization and direct oxidative C−H functionalization/cyclization of alkenes are the most popular methods,[3] particularly because these efficient approaches feature an easy availability of starting materials and excellent functional group compatibility. Additionally, visible-light-mediated radical C−H functionalization of alkenes provides a more direct and potentially more attractive strategy for the syntheses of oxindoles.[4] However, all of these approaches have some limitations, including low atom efficiency and the high cost of photocatalysts, which greatly restrict their application in synthesis chemistry. Therefore, a straightforward and highly efficient method is still required.

Recently, the introduction of heteroatomic groups was shown to induce the cyclization of alkenes, involving the simultaneous formation of C(sp^3)−X (X = O, N, P, S, halogen, etc.) and C(sp^2)−C(sp^3) bonds, thus arising as a highly attractive strategy for creating oxindoles.[5−10] For example, Zhu's group first documented a palladium-catalyzed carboheterofunctionalization of alkenes to form oxindoles and spirooxindoles.[5] The radical azidoarylation,[6] arylphosphorylation,[7] arylsulfonylation,[8] ayltrifluoromethylthiolation,[9] and aryltrifluoromethylation[10] of arylacrylamides have been reported subsequently by other groups. Despite these advances, examples of the halocarbocyclization of alkenes are quite rare.[11] In 2011, Zhu and coworkers realized the iodocarbocyclization of alkenes using $PhI(OAc)_2/I_2$ to afford 3,3′-disubstituted oxindoles (Scheme 1a).[11a] Gulder's group also realized bromocarbocyclization by treating *N*-arylacrylamides with NBS/NH_4Cl or KBr/oxone in the presence of a catalyst

Scheme 1. Halocarbocyclization of Alkenes



(Scheme 1b).[11b] To the best of our knowledge, however, there have been no reported examples concerning the chlorocarbocyclization of alkenes to access chloro oxindoles. In this regard, it is important to seek a practical and efficient method to broaden this area. Very recently, from economical and environmental points of view, establishing a green and sustainable approach to

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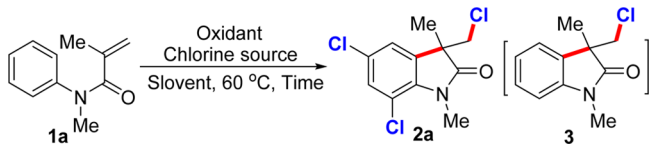
oxindole synthesis has attracted increasing attention.[12] In this context, many metal-free conditions have been successfully developed.[13] However, the use of water as the reaction medium for the C−H functionalization/cyclization of alkenes, especially without the addition of any organic cosolvents, is still a challenge.[8a,14] All of these pioneering studies encouraged us to explore a novel and environmentally friendly system for halocarbocyclization reactions to access halo-substituted oxindoles. Herein, we report the novel $(NH_4)_2S_2O_8$-mediated halocarbocyclization of alkenes using NH_4X (X = Cl, Br, I) as the halide source. It worth noting that this metal-free approach employs H_2O as a solvent and successfully provides a versatile method for obtaining a wide range of halogenated oxindoles (Scheme 1c).

RESULTS AND DISCUSSION

We initiated our studies by screening for the optimal conditions for the chlorocarbocyclization of *N*-arylacrylamide **1a**. It was found that when the reaction was carried out in the presence of $(NH_4)_2S_2O_8$ (3.0 equiv) and NH_4Cl (3.0 equiv) in H_2O at 60 °C for 24 h, cyclized product **3** was produced in 40% yield (Table 1, entry 1). In the absence of $(NH_4)_2S_2O_8$, no reaction occurred, highlighting the importance of the oxidant (Table 1, entry 2). Changing the solvent to H_2O−CH_3CN or H_2O−DCE afforded only a trace amount of **3** (Table 1, entries 3 and 4). It is worth noting that in this case aromatic C5- and C7-chloro-substituted oxindole **2a** was also obtained in 10% yield (Table 1, entry 3). No further improvement was seen at higher temperature (80 °C, Table 1, entry 5), whereas increasing the amount of $(NH_4)_2S_2O_8$ increased the yield of **2a** (Table 1, entries 6 and 7). Encouraged by these results, we expected to obtain **2a** as a single product in a controllable manner. Unfortunately, a combination of $K_2S_2O_8$ with KCl in H_2O furnished only **3** in 37% yield (Table 1, entry 8). Even after the addition of phase-transfer catalysts such as 18-crown-6 (10 mol %) and TBACl (10 mol %), no amount of desired product **2a** was observed (Table 1, entry 9). To our delight, **2a** was produced as a single product in 65% yield after prolonging the reaction time to 48 h (Table 1, entry 10). It is worth noting that the reaction resulted in the production of **2a** in nearly the same yield under an air or N_2 atmosphere, thereby excluding the influence of air on this conversion (Table 1, entry 10 vs entry 11). We found that neither increasing the amount of NH_4Cl nor using KCl as a chlorine source improved the reaction efficiency drastically; in fact, a trace amount of **3** was detected in these reactions (Table 1, entries 12 and 13). Subsequently, other oxidants, such as O_2 (balloon) and $PhI(OAc)_2$, were tested, but they were found to be less efficient than $(NH_4)_2S_2O_8$ (Table 1, entries 14 and 15). In addition, we investigated the solubility of starting material *N*-arylacrylamide **1a** and product **2a** in water. It was shown that in the $(NH_4)_2S_2O_8/NH_4Cl/H_2O$ reaction system, 1.0 mL of solvent is capable of hosting a large amount of **2a** (up to 0.32 mmol; for details, see Table S1); the reason was not very clear at this stage because very complicated concerted mechanisms might be involved during the solvation process.

With the optimized conditions in hand, we next set out to explore the substrate scope and the limitations of the chlorocarbocyclization reaction (Table 2). The effect of various substitution patterns on the *N*-aryl moiety was first investigated. Unsurprisingly, the substrates with chloro substituents at the para and ortho positions of the *N*-aryl moiety resulted in moderate to good yields of product **2a**. Other halo substitutions such as F, Br, and I groups on the *N*-aryl moiety were also tolerated, providing the corresponding oxindoles in 43−69% yields (products **2b**−**2d**). Gratifyingly, strong electron-withdrawing substituents, such as a CN group, on the *N*-aryl moiety resulted in a moderate yield of product **2e**, whereas electron-donating groups, such as a methyl group, were also tolerated on the aryl ring (product **2f**). To our delight, the amide at which the *N*-methyl substituent is replaced by an ethyl group was also viable for the reaction. As expected,

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant (equiv)	chlorine source (equiv)	solvent	time (h)	yield (%)[b] 2a	yield (%)[b] 3
1	$(NH_4)_2S_2O_8$ (3.0)	NH_4Cl (3.0)	H_2O	24	0	40
2		NH_4Cl (3.0)	H_2O	24	0	0
3[c]	$(NH_4)_2S_2O_8$ (3.0)	NH_4Cl (3.0)	H_2O−CH_3CN	24	10	trace
4[d]	$(NH_4)_2S_2O_8$ (3.0)	NH_4Cl (3.0)	H_2O−DCE	24	trace	trace
5[e]	$(NH_4)_2S_2O_8$ (3.0)	NH_4Cl (3.0)	H_2O	24	12	trace
6	$(NH_4)_2S_2O_8$ (5.0)	NH_4Cl (3.0)	H_2O	24	23	0
7	$(NH_4)_2S_2O_8$ (6.0)	NH_4Cl (3.0)	H_2O	24	30	0
8	$K_2S_2O_8$ (3.0)	KCl (3.0)	H_2O	24	0	37
9[f,g]	$K_2S_2O_8$ (6.0)	KCl (3.0)	H_2O	24	0	19
10	$(NH_4)_2S_2O_8$ (6.0)	NH_4Cl (3.0)	H_2O	48	65	0
11[h]	$(NH_4)_2S_2O_8$ (6.0)	NH_4Cl (3.0)	H_2O	48	64	0
12	$(NH_4)_2S_2O_8$ (6.0)	NH_4Cl (4.0)	H_2O	48	68	trace
13	$(NH_4)_2S_2O_8$ (6.0)	KCl (3.0)	H_2O	48	61	trace
14	O_2 (balloon)	NH_4Cl (3.0)	H_2O	48	0	0
15	$PhI(OAc)_2$ (3.0)	NH_4Cl (3.0)	H_2O	48	41	25

[a]Reaction conditions: **1a** (0.2 mmol), solvent (1.0 mL), 60 °C. [b]Yield of isolated product. [c]H_2O−CH_3CN (v−v, 1:1). [d]H_2O−DCE (v−v, 1:1). [e]Temperature = 80 °C. [f]18-crown-6 = 10 mol %. [g]TBACl = 10 mol %. [h]Under a N_2 atmosphere.

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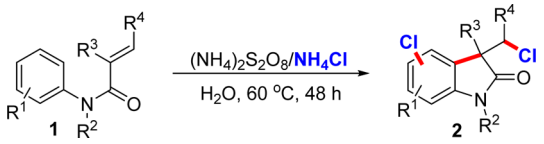
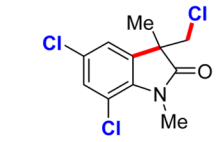
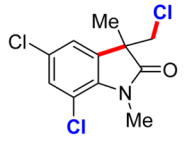
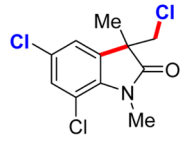
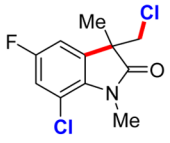
Table 2. Scope of the Chlorocarbocyclization Reaction[a,b]

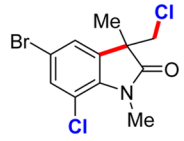


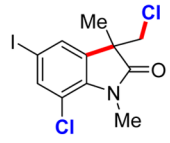

2a, 65%

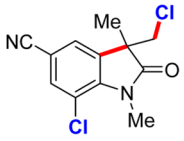

R^1 = *p*-Cl, **2a**, 60%

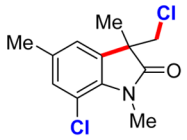

R^1 = *o*-Cl, **2a**, 54%

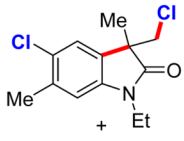

2b, 48%

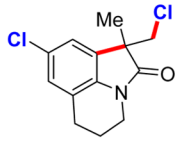

2c, 69%

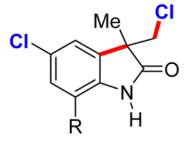

2d, 43%

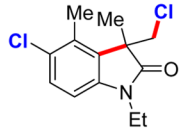

2e, 52%

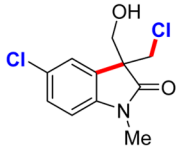

2f, 55%[c]

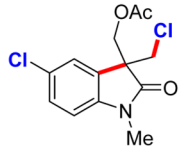


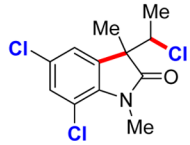

2h, 67%


R = H or Cl, **2i**, 0%


2g+2g', 79% (1:2.3)


2j, 73%


2k, 36%


2l, 61%
>20:1 d.r.[d]

[a]Reaction conditions: **1** (0.2 mmol), $(NH_4)_2S_2O_8$ (1.2 mmol), NH_4Cl (0.6 mmol), and H_2O (1.0 mL) at 60 °C for 48 h. [b]Yield of isolated product. [c]Reaction time = 24 h. [d]Determined by ^1H NMR.

substrates bearing *m*-methyl substituents afforded mixtures of two regioselective products (**2g**/**2g**′ in a ratio of 1:2.3). In addition, a tetrahydroquinoline derivative was also viable as a substrate to furnish tricyclic oxindole **2h** in good yield, whereas an *N*-hydrogen atom-substituted amide resulted in no conversion (product **2i**). Next, the substituent effect at the R^3 position was investigated; a CH_2OH substituent was well tolerated in this reaction (product **2j**). Notably, 2-(methyl(phenyl)carbamoyl)allyl acetate was also a suitable substrate, albeit with a relatively low conversion and yield (product **2k**). It was noted that substrates bearing a methyl group at the terminal alkene provided product **2l** as a mixture of diastereoisomers (61%, >20:1 d.r.).

Encouraged by these good results, we next set out to expand the application of such a reaction system to bromo- and iodocarbocyclization reactions. Much to our surprise, after optimization of the reaction conditions, the reaction of *N*-arylacrylamide **1a** gave desired oxindoles **2m** and **2r** in good to high yields by using $(NH_4)_2S_2O_8$ (2.5 equiv) and NH_4X (X = Br, I; 2.5 equiv) in H_2O (1.0 mL) at 60 °C (Table 3). The effect of substituent groups on the *N*-aryl moiety was subsequently examined. Screening showed that both electron-withdrawing and -donating substituents, such as Cl, I, MeO, and Me groups, were well tolerated under the optimal conditions. For instance, substrates bearing Cl and I groups at the para position of the *N*-aryl moiety provided corresponding bromo and iodo oxindoles in moderate to good yields. It is worth noting that the bromocarbocyclization of para-substituted substrates furnished aromatic ring bromo-substituted oxindoles (products **2n**−**2p**). As for iodocarbocyclization, additional iodination of the phenyl ring was not observed (products **2r**−**2t**). Notably, a *meta*-methyl-substituted substrate gave a mixture of two regioselective products **2q**/**2q**′ and **2u**/**2u**′ in ratios of 1.1:1 and 2:1, respectively. We were delighted to discover that pure **2q** and **2u** could be isolated by recrystallization from ethyl acetate/petroleum ether in 29 and 45% yields, respectively. The fact that a *meta*-methyl-substituted substrate furnished phenyl ring iodo-substituted oxindoles is worth noting. In comparison, the *para*-methoxy-substituted substrate failed to give a phenyl ring-iodinated product, presumably because of the directing effect of the substituted amino group that caused other positions on the aromatic ring to be less reactive than the C5 position as well as the weak eletrophilicity of the I^+ species.

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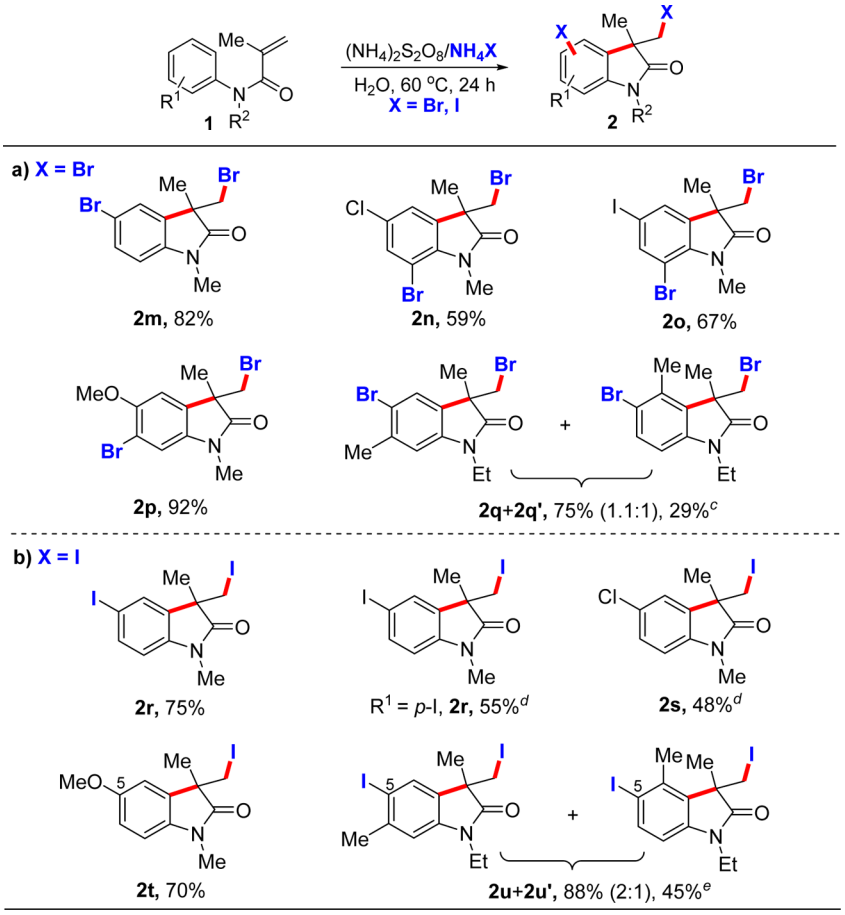
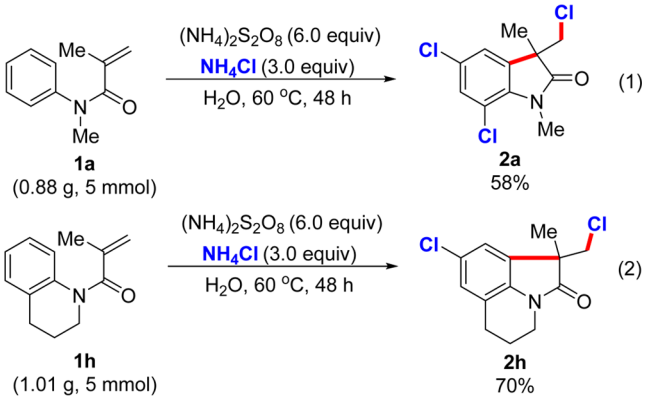
Table 3. Scope of the Bromo- and Iodocarbocyclization[a,b]



[a]Reaction conditions: **1** (0.2 mmol), $(NH_4)_2S_2O_8$ (0.5 mmol), NH_4X (X = Br, I) (0.5 mmol) and H_2O (1.0 mL) at 60 °C for 24 h. [b]Yield of isolated product. [c]Yield of **2q** after recrystallization. [d]Reaction time = 48 h. [e]Yield of **2u** after recrystallization.

To demonstrate the viability of this procedure, we carried out the chlorocarbocyclization of two substrates on a large scale. The reaction of 0.88 g (5 mmol) of *N*-arylacrylamide **1a** in the presence of 6.0 equiv of $(NH_4)_2S_2O_8$ and 3.0 equiv of NH_4Cl in water gave **2a** (0.81 g) in 58% isolated yield (eq 1). Additionally, the reaction of tetrahydroquinoline derivative **1h** according to the same procedure successfully yielded desired tricyclic oxindole **2h** (0.95 g) in 70% yield (eq 2).



To gain insight into the reaction mechanism, we next gathered some additional information. First, under dark conditions or in the presence of radical scavengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the transformation retains its reactivity (Scheme 2a,b).[15] These results suggest that a radical mechanism for this chlorocarbocyclization is unlikely. Second, when monochloro product **3** was reacted under the standard reaction conditions, **2a** was isolated in high yield (Scheme 2c). The data indicated that the cyclization of **1a** is probably the first step in this transformation. Third, the change in the color of the reaction mixture indicates the formation of molecular halogen during the reaction (Figure S1).[16] In this transformation, a chlorinating agent was a key issue in investigating whether HClO or Cl_2 was the activated chloride species, and verification experiments were performed. The treatment of **1a** in 3.0 equiv of HOCl at room temperature in the dark smoothly provided **2a** in 51% yield, but when the same reaction was carried out at 60 °C, 30% of product **2a** was also obtained. The combination of Cl_2 and H_2O markedly increased the yield of **2a**, whereas interestingly, the replacement of water with 1,2-dichloroethane under otherwise identical reaction conditions gave poor reactivity (7%, Scheme 2d). These results indicated that HOCl is presumably the real chlorinating agent in our reaction system. Finally, we envisioned that hydroxychlorination or dichlorination of an olefin may occur when the cyclization sites are blocked by other substituents. To prove this hypothesis, we synthesized a 2,6-disubstituted substrate (**4**) and subjected it to the standard reaction conditions, obtaining a mixture of dichlorinated and hydroxychlorinated products (**5** and **6**, respectively) in 45% yield (Scheme 2e). This is powerful proof that the reaction proceed via an electrophilic mechanism.

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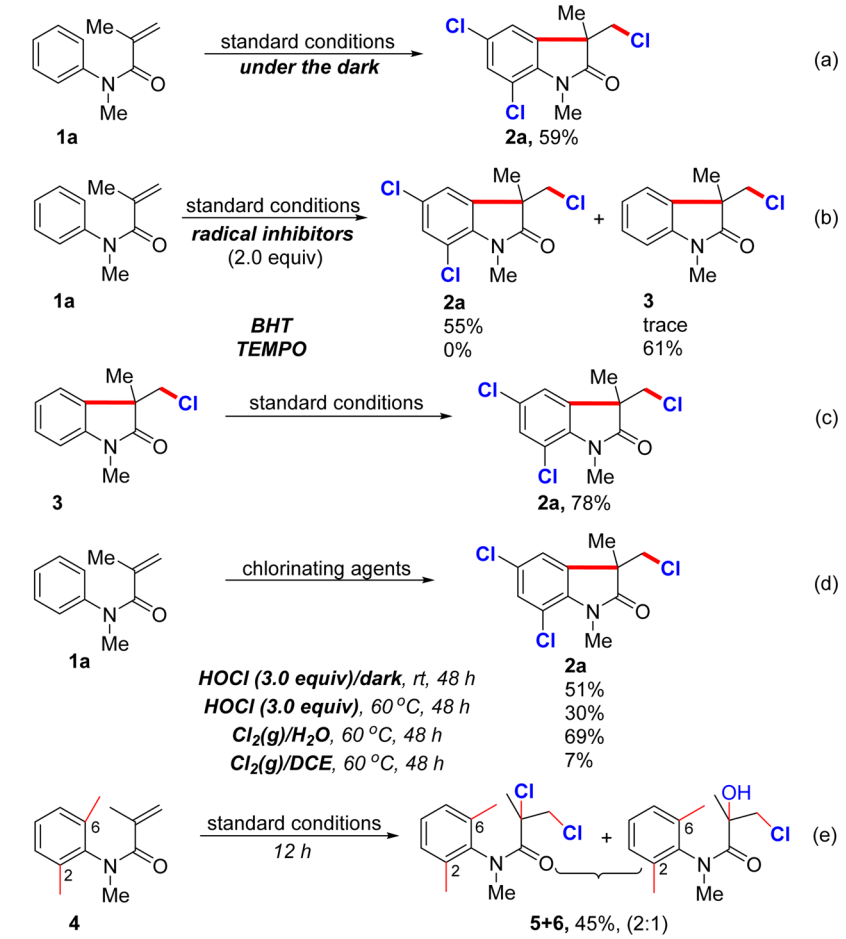
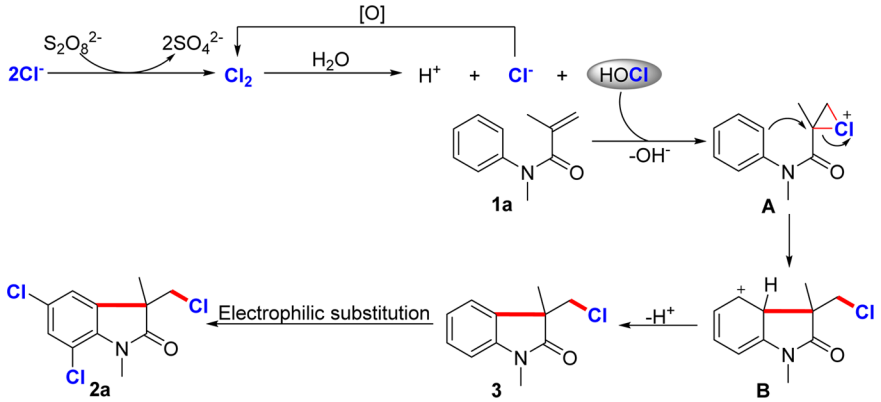
Scheme 2. Control Experiments



Scheme 3. Possible Mechanism



On the basis of these results as well as related reports,[17] a plausible mechanism is proposed in Scheme 3. Initially, the oxidation of the chlorine ion with persulfate ion generates molecular chlorine in situ, which is further transformed in water into HOCl and HCl. The reduced chlorine ion is reoxidized again by a persulfate ion to form molecular chlorine that becomes involved in the next reaction cycle. Subsequent electrophilic addition of HOCl in the form of a chlorinium ion (Cl^+) at the double bond in **1a** affords a three-membered cyclic chlorinum cation intermediate (**A**).[17a] Intramolecular nucleophilic attack of intermediate **A** with an aryl ring gives rise to cyclization intermediate **B**, followed by proton loss (H^+) to afford intermediate **3**. Finally, electrophilic substitutions on the phenyl ring in intermediate **3** by a chlorinium ion (Cl^+) take place to furnish desired product **2a**.[17b,c] However, in our reaction system, the possibility of a related electrophilic mechanism via dichlorine monoxide (Cl_2O)[17c] cannot be completely ruled out at present.

CONCLUSIONS

We have successfully developed a new and metal-free synthesis method for the oxidative halocarbocyclization of alkenes. This transformation provides a versatile and green method for the construction of halogenated oxindoles. Most importantly, the use of NH_4X (X = Cl, Br, I) as the halide source, $(NH_4)_2S_2O_8$

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as a versatile oxidant, and H_2O as the solvent makes this new transformation sustainable and practical. Ongoing studies are focused on applying this reaction to more complex molecules as well as gaining detailed insights into the reaction mechanism.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents used were obtained commercially and used without further purification unless otherwise indicated. Column chromatography was carried out on silica gel. All products were characterized by ^{1}H NMR and ^{13}C NMR and further characterized by HRMS. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$, and ^{13}C NMR spectra were recorded on a 100 MHz spectrometer in $CDCl_3$ using TMS as the internal standard. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quintet), and m (multiplet), and coupling constants (J) are reported in hertz. HRMS was measured on an electrospray ionization (ESI) apparatus using time-of-flight (ToF) mass spectrometry. IR spectra were obtained via a neat film on a NaCl plate. Melting points were determined using a XT-4 apparatus and are uncorrected.

Preparation of *N*-Arylacrylamides. *N*-Arylacrylamide substrates **1** and **4** were prepared according to the literature.[10b,11b,18]

Preparation of HClO. HClO was prepared according to known procedures[17a,19] and stored in the dark at about 0 °C before use.

Typical Experimental Procedure for the Chlorocarbocyclization of Alkenes. To a 25 mL Schlenk tube were added $(NH_4)_2S_2O_8$ (6.0 equiv), NH_4Cl (3.0 equiv), *N*-arylacrylamide **1** (0.2 mmol), and H_2O (1.0 mL). Then the tube was stirred at 60 °C for the indicated time until complete consumption of the starting material (as detected by TLC). After the reaction was finished, the reaction mixture was cooled to room temperature, and ethyl acetate (EtOAc, 20 mL) and water (10 mL) were added. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuum. The desired product was obtained after purification by flash column chromatography (petroleum ether/ethyl acetate) or preparative TLC on silica (petroleum ether/ethyl acetate or petroleum ether/DCM).

Typical Experimental Procedure for Bromo- and Iodocarbocyclization of Alkenes. To a 25 mL Schlenk tube were added *N*-arylacrylamide **1** (0.2 mmol), $(NH_4)_2S_2O_8$ (2.5 equiv), NH_4X (X = Br, I) (2.5 equiv), and H_2O (1.0 mL). Then the tube was stirred at 60 °C for the indicated time until complete consumption of the starting material (as detected by TLC). After the reaction was finished, ethyl acetate (EtOAc, 20 mL) was added, the reaction mixture was washed with sat. $Na_2S_2O_3$ and brine, and the organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (silica gel, petroleum ether/ethyl acetate) to afford the corresponding products.

Experimental Procedure for Preliminary Mechanistic Studies with Cl_2. To a 15 mL tube were added *N*-arylacrylamide **1a** (0.2 mmol) and H_2O (1.0 mL). Then the reaction tube was charged with chlorine gas (approximately 0.67 mmol/15 mL) and stirred at 60 °C for 48 h. After the reaction, the mixture was cooled to room temperature, and saturated aqueous NaCl (15 mL) and EtOAc (30 mL) were added. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash column chromatography (petroleum ether/ethyl acetate, 10:1) to afford desired compound **2a** (38.4 mg, 69%).

*3-(Chloromethyl)-1,3-dimethylindolin-2-one (**3**).* The product was isolated via the general procedure as a light-yellow solid in 40% yield (16.8 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 41−42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 6.9 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 3.82−3.75 (m, 2H), 3.24 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 143.5, 131.4, 128.6, 123.1, 122.8, 108.2, 49.6, 48.9, 26.4, 21.2; IR (neat film, cm^{-1}) 2919, 1700, 1652, 1540, 1515, 1456, 672; HRMS m/z (ESI) calcd for $C_{11}H_{12}NOCl^+$ [M$^+$], 209.060 2; found, 209.060 2.

*5,7-Dichloro-3-(chloromethyl)-1,3-dimethylindolin-2-one (**2a**).* The product was isolated via the general procedure as a light-yellow solid in 65% yield (36.2 mg); flash chromatography (petroleum ether/ethyl acetate, 8:1); mp 58−59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 3.79 (d, J = 10.9 Hz, 1H), 3.70 (d, J = 10.9 Hz, 1H), 3.58 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 138.2, 135.1, 130.4, 128.2, 122.2, 116.1, 49.8, 48.3, 29.7, 21.4; IR (neat film, cm^{-1}): 2918, 1697, 1648, 1541, 1514, 1459, 669; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOCl_3^+$ [M$^+$], 276.983 2; found, 276.982 2.

*7-Chloro-3-(chloromethyl)-5-fluoro-1,3-dimethylindolin-2-one (**2b**).* The product was isolated via the general procedure as a white solid in 48% yield (25.2 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02−6.97 (m, 2H), 3.79 (d, J = 11.0 Hz, 1H), 3.70 (d, J = 10.9 Hz, 1H), 3.58 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 159.6, 157.2, 135.7, 135.3, 135.2, 117.6, 117.3, 115.8, 115.7, 110.3, 110.0, 50.0, 48.5, 29.7, 21.4; IR (neat film, cm^{-1}) 2922, 1699, 1652, 1539, 1514, 1456, 1336, 676; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOCl_2F^+$ [M$^+$], 261.011 9; found, 261.011 8.

*5-Bromo-7-chloro-3-(chloromethyl)-1,3-dimethylindolin-2-one (**2c**).* The product was isolated via the general procedure as a light-yellow oil in 69% yield (44 mg); preparative TLC (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.29 (s, 1H), 3.74 (dd, J = 38.5, 10.9 Hz, 2H), 3.57 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 138.8, 135.6, 133.2, 125.0, 124.7, 115.2, 49.7, 48.4, 29.7, 21.5; IR (neat film, cm^{-1}) 2920, 1706, 1649, 1536, 1509, 1456, 756, 673; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOCl_2Br^+$ [M$^+$], 320.931 8; found, 320.931 7.

*7-Chloro-3-(chloromethyl)-5-iodo-1,3-dimethylindolin-2-one (**2d**).* The product was isolated via the general procedure as a light-yellow oil in 43% yield (31.8 mg); preparative TLC (petroleum ether/DCM = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 1.6 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 3.79 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 10.8 Hz, 1H), 3.58 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 143.2, 138.9, 138.6, 130.4, 116.7, 93.8, 49.5, 48.4, 29.7, 21.5; IR (neat film, cm^{-1}) 2922, 1704, 1645, 1538, 1512, 1457, 755, 672; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOCl_2I^+$ [M$^+$], 368.918 4; found, 368.918 2.

*7-Chloro-3-(chloromethyl)-1,3-dimethyl-2-oxoindoline-5-carbonitrile (**2e**).* The product was isolated via the general procedure as a white solid in 52% yield (28 mg); preparative TLC (petroleum ether/ethyl acetate, 5:1); mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.44 (s, 1H), 3.81 (d, J = 10.9 Hz, 1H), 3.72 (d, J = 11.0 Hz, 1H), 3.63 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 143.7, 135.40, 134.8, 124.7, 117.6, 116.2, 106.9, 49.4, 48.0, 29.8, 21.3; IR (neat film, cm^{-1}) 2921, 2225, 1704, 1651, 1542, 1515, 1462, 673; HRMS m/z (ESI) calcd for $C_{12}H_{10}N_2OCl_2^+$ [M$^+$], 268.015 3; found, 268.016 5.

*3-(Chloromethyl)-1,3,5-trimethylindolin-2-one (**2f**).* The product was isolated via the general procedure as a yellow oil in 55% yield (28.4 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 7.6 Hz, 2H), 3.79 (d, J = 10.8 Hz, 1H), 3.55 (d, J = 10.8 Hz, 1H), 3.29 (s, 3H), 2.39 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 140.6, 138.5, 130.0, 129.8, 128.2, 66.5, 51.8, 41.8, 27.6, 21.1; IR (neat film, cm^{-1}) 2918, 1699, 1649, 1539, 1513, 1456, 672; HRMS m/z (ESI) calcd for $C_{12}H_{13}NOCl_2^+$ [M$^+$], 257.037 4; found, 257.036 9.

*5-Chloro-3-(chloromethyl)-1-ethyl-3,6-dimethylindolin-2-one and 5-Chloro-3-(chloromethyl)-1-ethyl-3,4-dimethylindolin-2-one (**2g** + **2g′**).* The product was isolated via the general procedure as a yellow oil in 79% yield (43 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.3 Hz, 1H), 7.27 (s, 0.43H), 6.75 (s, 0.45H), 6.68 (d, J = 8.3 Hz, 1.02H), 4.01−3.91 (m, 2.21H), 3.89−3.75 (m, 2.18H), 3.75−3.62 (m, 2.15H), 2.40 (d, J = 4.9 Hz, 4.77H), 1.47 (s, 3H), 1.40 (s, 1.59H), 1.27−1.22 (m, 5.78H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 177.1, 141.7, 141.2, 136.4, 132.8, 130.5, 129.8, 129.1, 129.0, 127.8, 124.1, 110.8, 107.0, 51.3, 49.6, 48.7, 46.7, 34.9, 21.2, 20.7, 20.1, 15.4, 14.2, 12.6, 12.5; IR (neat film, cm^{-1}) 2925, 1701, 1632, 1545, 1521, 1509, 1455, 681; HRMS m/z (ESI) calcd for $C_{13}H_{15}NOCl_2^+$ [M$^+$], 271.053 1; found, 271.053 3.

*8-Chloro-1-(chloromethyl)-1-methyl-5,6-dihydro-1H-pyrrolo-[3,2,1-ij]quinolin-2(4H)-one (**2h**).* The product was isolated via the general procedure as a yellow oil in 67% yield (36.2 mg); flash

chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.07 (s, 1H), 3.78−3.67 (m, 4H), 2.77 (t, J = 5.7 Hz, 2H), 2.00 (t, J = 5.8 Hz, 2H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 137.8, 131.3, 127.6, 127.5, 121.7, 121.6, 51.1, 48.6, 38.9, 24.4, 21.0, 20.8; IR (neat film, cm^{-1}) 1700, 1652, 1539, 1514, 1455, 671; HRMS m/z (ESI) calcd for $C_{13}H_{13}NOCl_2^+$ [M$^+$], 269.036 8; found, 269.036 9.

*5-Chloro-3-(chloromethyl)-3-(hydroxymethyl)-1-methylindolin-2-one (**2j**).* The product was isolated via the general procedure as a yellow oil in 73% yield (38 mg); flash chromatography (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.33 (m, 2H), 6.83 (d, J = 8.3 Hz, 1H), 4.01−3.81 (m, 4H), 3.23 (s, 3H), 2.08 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 142.6, 129.3, 129.1, 128.5, 124.5, 109.4, 64.7, 55.2, 44.9, 26.5; IR (neat film, cm^{-1}) 3625, 2924, 1699, 1652, 1539, 1513, 1457, 1150, 1061, 677; HRMS m/z (ESI) calcd for $C_{11}H_{11}NO_2Cl_2^+$ [M$^+$], 259.016 7; found, 259.016 5.

*(5-Chloro-3-(chloromethyl)-1-methyl-2-oxoindolin-3-yl)methyl Acetate (**2k**).* The product was isolated via the general procedure as a yellow oil in 36% yield (21.7 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.34 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 4.54 (d, J = 11.2 Hz, 1H), 4.24 (d, J = 11.2 Hz, 1H), 3.92 (d, J = 11.1 Hz, 1H), 3.82 (d, J = 11.1 Hz, 1H), 3.24 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 170.1, 142.6, 129.3, 128.8, 128.3, 124.7, 109.3, 65.0, 53.4, 45.0, 26.6, 20.6; IR (neat film, cm^{-1}) 2928, 1702, 1651, 1608, 1540, 1511, 1139, 1049, 675; HRMS m/z (ESI) calcd for $C_{13}H_{13}NO_3Cl_2^+$ [M$^+$], 301.027 2; found, 301.027 5.

*5,7-Dichloro-3-(1-chloroethyl)-1,3-dimethylindolin-2-one (**2l**).* The product was isolated via the general procedure as a yellow oil in 61% yield (35.6 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.27 (d, J = 5.3 Hz, 1H), 4.36 (q, J = 6.2 Hz, 1H), 3.56 (s, 3H), 1.51 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 138.1, 134,5, 130.3, 128.3, 123.5, 115.9, 62.1, 53.1, 29.7, 22.9, 20.4; IR (neat film, cm^{-1}) 2922, 1693, 1649, 1558, 1540, 1506, 1456, 681; HRMS m/z (ESI) calcd for $C_{12}H_{12}NOCl_3^+$ [M$^+$], 290.997 0; found, 290.997 9.

*5-Bromo-3-(bromomethyl)-1,3-dimethylindolin-2-one (**2m**).*[11b] The product was isolated via the general procedure as a light-brown solid in 82% yield (54.6 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.42 (m, 2H), 6.75 (d, J = 8.1 Hz, 1H), 3.62 (dd, J = 32.9, 10.0 Hz, 2H), 3.22 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 142.4, 133.7,131.5, 126.2, 115.4, 109.7, 49.3, 36.4, 26.4, 22.1; IR (neat film, cm^{-1}) 2923, 1713, 1652, 1539, 1514, 1456, 672, 623; HRMS m/z (ESI) calcd for $C_{11}H_{11}NOBr_2^+$ [M$^+$], 330.920 7; found, 330.921 0.

*7-Bromo-3-(bromomethyl)-5-chloro-1,3-dimethylindolin-2-one (**2n**).* The product was isolated via the general procedure as a light-yellow solid in 59% yield (43.3 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 98−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.19 (s, 1H), 3.67 (d, J = 10.2 Hz, 1H), 3.59 (s, 3H), 3.53 (d, J = 10.2 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 139.6, 135.9, 133.5, 128.5, 122.5, 102.7, 49.2, 36.2, 30.0, 22.5; IR (neat film, cm^{-1}) 2926, 1701, 1655, 1539, 1514, 1456, 672, 619; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOClBr_2^+$ [M$^+$], 364.882 2; found, 364.881 2.

*7-Bromo-3-(bromomethyl)-5-iodo-1,3-dimethylindolin-2-one (**2o**).* The product was isolated via the general procedure as a yellow solid in 67% yield (61.5 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.31 (s, 1H), 3.67 (d, J = 10.1 Hz, 1H), 3.59 (s, 3H), 3.53 (d, J = 10.1 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 140.1, 136.6, 136.2, 125.2, 115.6, 103.1, 49.2, 36.2, 30.0, 22.5; IR (neat film, cm^{-1}) 2923, 1698, 1651, 1538, 1515 1455, 673, 613, 517; HRMS m/z (ESI) calcd for $C_{11}H_{10}NOBr_2I^+$ [M$^+$], 456.816 9; found, 456.817 1.

*6-Bromo-3-(bromomethyl)-5-methoxy-1,3-dimethylindolin-2-one (**2p**).*[11b] The product was isolated via the general procedure as a brown solid in 92% yield (66.8 mg); flash chromatography (petroleum ether/ethyl acetate, 5:1); mp 66−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 1H), 6.95 (s, 1H), 3.90 (s, 3H), 3.62 (q, J = 10.1 Hz, 2H), 3.19 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 152.2, 137.4, 131.8, 113.2, 111.2, 108.4, 57.0, 49.6, 36.8, 26.5, 22.1; IR (neat film, cm^{-1}) 2940, 1708, 1661, 1557, 1508, 1423, 1129, 675, 617; HRMS m/z (ESI) calcd for $C_{12}H_{13}NO_2Br_2^+$ [M$^+$], 360.931 2; found, 360.931 1.

*5-Bromo-3-(bromomethyl)-1-ethyl-3,6-dimethylindolin-2-one and 5-Bromo-3-(bromomethyl)-1-ethyl-3,4-dimethylindolin-2-one (**2q** + **2q′**).* The product was isolated via the general procedure as a yellow oil in 75% yield (54.2 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.3 Hz, 0.88H), 7.42 (s, 0.94H), 6.77 (s, 1H), 6.63 (d, J = 8.3 Hz, 0.81H), 3.90−3.76 (m, 4H), 3.73−3.60 (m, 3H), 3.56 (d, J = 10.0 Hz, 1H), 2.42 (d, J = 8.6 Hz, 6H), 1.52 (s, 3H), 1.44 (s, 3H), 1.27−1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 177.0, 142.2, 141.9, 138.2, 134.3, 132.3, 131.2, 130.4, 126.9, 117.5, 110.8, 107.6, 50.9, 49.0, 36.8, 34.9, 34.5, 29.7, 23.6, 22.2, 20.9, 18.3, 12.6, 12.5; HRMS m/z (ESI) calcd for $C_{13}H_{15}NOBr_2^+$ [M$^+$], 358.951 0; found, 358.951 5.

*5-Bromo-3-(bromomethyl)-1-ethyl-3,6-dimethylindolin-2-one (**2q**).* Light-yellow solid (20.9 mg, 29%); mp 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 6.77 (s, 1H), 3.83 (td, J = 7.2 Hz, 6.8 Hz, 6.4 Hz 1H), 3.72−3.63 (m, 2H), 3.56 (d, J = 10.0 Hz, 1H), 2.44 (s, 3H), 1.45 (s, 3H), 1.26 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 141.9, 138.2, 131.2, 126.9, 117.5, 110.8, 49.0, 36.8, 34.9, 23.6, 22.2, 12.6; IR (neat film, cm^{-1}) 2933, 1704, 1664, 1539, 1514, 1459, 1253, 1138, 680, 629; HRMS m/z (ESI) calcd for $C_{13}H_{15}NOBr_2^+$ [M$^+$], 358.951 0; found, 358.951 5.

*5-Iodo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2r**).*[11a] The product was isolated via the general procedure as a white solid in 75% yield (64 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.1 Hz, 1H), 7.54 (s, 1H), 6.66 (d, J = 8.1 Hz, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.37 (d, J = 9.8 Hz, 1H), 3.21 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 143.0, 137.5, 135.0, 131.5, 110.4, 85.2, 48.7, 26.4, 23.0, 9.9; IR (neat film, cm^{-1}) 2925, 1706, 1648, 1539, 1516, 1459, 673, 529; HRMS m/z (ESI) calcd for $C_{11}H_{11}NOI_2^+$ [M$^+$], 426.893 0; found, 426.893 2.

*5-Chloro-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2s**).* The product was isolated via the general procedure as a white solid in 48% yield (32.2 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.3 Hz, 1H), 7.25 (d, J = 4.9 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 3.51 (d, J = 9.8 Hz, 1H), 3.38 (d, J = 9.8 Hz, 1H), 3.23 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 141.8, 134.3, 128.6, 128.2, 123.3, 109.3, 48.9, 26.5, 23.0, 9.9; IR (neat film, cm^{-1}) 2919, 1703, 1649, 1541, 1510, 1425, 668, 536; HRMS m/z (ESI) calcd for $C_{11}H_{11}NOClI^+$ [M$^+$], 334.956 1; found, 334.956 8.

*3-(Iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one (**2t**).*[11a] The product was isolated via the general procedure as a light-yellow solid in 70% yield (46.3 mg); flash chromatography (petroleum ether/ethyl acetate, 5:1); mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.4, 2.5 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.45 (dd, J = 43.7, 9.8 Hz, 2H), 3.22 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 156.0, 136.6, 133.9, 112.5, 110.3, 108.5, 55.8, 49.0, 26.4, 23.0, 10.8; IR (neat film, cm^{-1}) 2932, 1701, 1662, 1559, 1511, 1426, 1125, 676, 541; HRMS m/z (ESI) calcd for $C_{12}H_{14}NO_2I^+$ [M$^+$], 331.006 9; found, 331.007 1.

*1-Ethyl-5-iodo-3-(iodomethyl)-3,6-dimethylindolin-2-one and 1-Ethyl-5-iodo-3-(iodomethyl)-3,4-dimethylindolin-2-one (**2u** + **2u′**).* The product was isolated via the general procedure as a yellow oil in 88% yield (80 mg); flash chromatography (petroleum ether/ethyl acetate, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 0.49H), 7.61 (s, 1H), 6.79 (s, 1.06H), 6.50 (d, J = 8.2 Hz, 0.5H), 3.90−3.76 (m, 1.72H), 3.69−3.54 (m, 2.79H), 3.48 (d, J = 9.8 Hz, 1.1H), 3.34 (d, J = 9.8 Hz, 1.07H), 2.45 (s, 3.42H), 2.40 (s, 1.65H), 1.55 (s, 1.67H), 1.46 (s, 3.34H), 1.27−1.22 (m, 5.87H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 171.1, 142.9, 142.8, 141.7, 139.0, 137.3, 132.8, 132.4, 131.1, 110.0, 108.3, 94.6, 91.7, 50.5, 48.2, 35.0, 34.9, 28.8, 23.6, 23.0, 21.2, 12.7, 12.6, 10.3, 8.1; HRMS m/z (ESI) calcd for $C_{13}H_{15}NOI_2^+$ [M$^+$], 454.924 1; found, 454.923 8.

*1-Ethyl-5-iodo-3-(iodomethyl)-3,6-dimethylindolin-2-one (**2u**).* Yellow solid (40.88 mg, 45%); mp 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 6.80 (s, 1H), 3.88−3.79 (m, 1H), 3.73−3.61

(m, 1H), 3.50 (d, J = 9.8 Hz, 1H), 3.35 (d, J = 9.8 Hz, 1H), 2.47 (s, 3H), 1.48 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 142.8, 141.7, 132.8, 132.4, 110.0, 91.6, 48.2, 34.9, 28.8, 23.0, 12.7, 10.2; IR (neat film, cm^{-1}) 2929, 1699, 1658, 1539, 1515, 1455, 1261, 1127, 674, 543; HRMS m/z (ESI) calcd for $C_{13}H_{15}NOI_2^+$ [M^+], 454.924 1; found, 454.923 8.

*2,3-Dichloro-N-(2,6-dimethylphenyl)-N,2-dimethylpropanamide and 3-Chloro-N-(2,6-dimethylphenyl)-2-hydroxy-N,2-dimethylpropanamide (**5** + **6**).* Yellow oil (23.8 mg, 45%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.07 (m, 4.59H), 4.37 (d, J = 10.2 Hz, 0.96H), 4.19 (d, J = 11.7 Hz, 0.54H), 3.99 (d, J = 11.7 Hz, 0.53H), 3.63 (d, J = 10.2 Hz, 1H), 3.51 (s, 1.58H), 3.21 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H), 2.21 (s, 1.64H), 2.17 (s, 1.57H), 2.03 (s, 1.68H), 1.77 (bs, 0.59), 1.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 166.9, 142.0, 141.3, 136.3, 135.9, 134.6, 134.3, 128.9, 128.8, 128.7, 128.6, 128.5, 127.7, 67.6, 66.7, 53.7, 52.1, 38.8, 38.3, 26.3, 26.1, 18.3, 18.1, 17.4, 17.2; LRMS m/z calcd for $C_{13}H_{17}Cl_2NO$ [M + H], 273; found, 273; LRMS m/z calcd for $C_{13}H_{18}ClNO_2$ [M + H], 255; found, 255.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all products, solubility experiment data, and halogen formation pictures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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