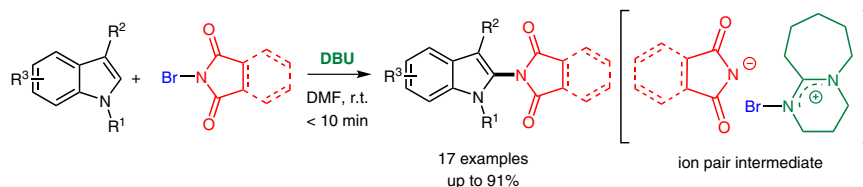


Rapid α -Amination of *N*-Substituted Indoles by Using DBU-Activated *N*-Haloimides as Nitrogen Sources

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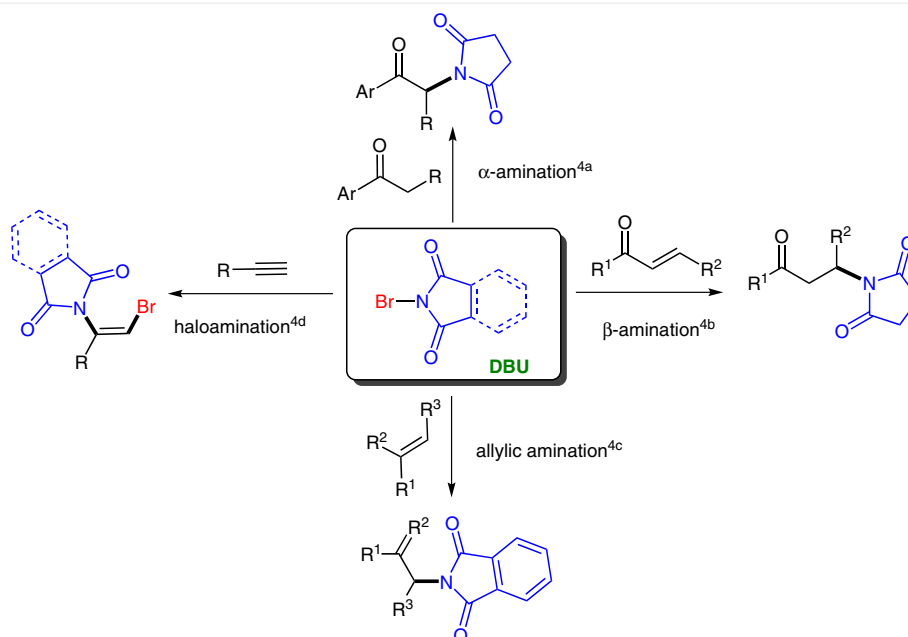
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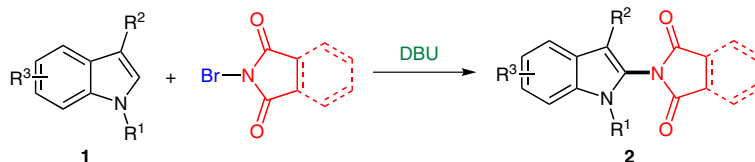
Abstract By using the *N*-haloimide/DBU protocol, the electrophilic imidation at C2-position of *N*-substituted indoles has been achieved in high efficiency. The dual activation of *N*-haloimide by DBU to simultaneously achieve a more electrophilic bromine and a more nucleophilic nitrogen atom, is demonstrated to be crucial in this transformation. The process involves tandem bromonium ion formation, electrophilic addition, and elimination of HBr. The protocol provides a novel, efficient, green, and complimentary access to α -imidated indoles under mild conditions, without the necessity of external nitrogen sources.

Key words indoles, amination, *N*-haloimides, DBU

2-Amino-substituted indoles and pyrroles are one class of biologically active compounds and occupy an important position in pharmaceuticals and natural products.¹ In this context, direct C–N bond functionalization of indole derivatives has attracted considerable interest. However, it is particularly challenging due to the poor control of both the chemo- and regioselectivities. Two types of representative methods can be summarized toward α -C–H amination of *N*-substituted indoles. One is the metal-catalyzed (e.g., copper and/or palladium, rhodium) oxidative C–H bond amination, independently reported by Li,^{2a} Liang,^{2b} and Zhou^{2c} groups. The other is halogen-mediated (e.g., molecular io-



Scheme 1 Imidation via *N*-haloimide/DBU protocol developed in our group



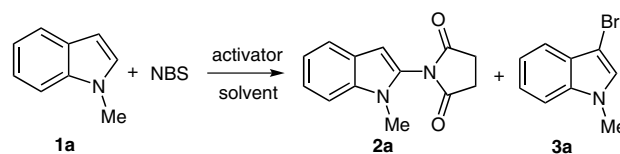
Scheme 2 α -C–H imidation of indole derivatives by using *N*-haloimides as self-immolating amination reagents

dine and NIS) amination, developed by Liang,^{3a,b} Wang and Ji,^{3c} Huang,^{3d} and Nagarajan.^{3e} In consideration of the significance of 2-aminated indoles, it is still required to develop new and effective approaches for the chemo- and regioselective construction of C–N bonds of *N*-substituted indoles, especially that under mild and environmentally benign conditions, and in an atom economic fashion.

In our research on halogen-mediated organic transformation,⁴ we disclosed that DBU-activated *N*-bromosuccinimide (NBS) or *N*-bromophthalimide (NBP) via halogen-bond interaction can be utilized as an efficient amination reagent^{4a–c} and haloamination reagent (Scheme 1).^{4d} In our continued work, we became interested in the exploration of halo- and/or amination of arenes and heteroarenes by using the *N*-haloimide/DBU combination. Herein, we would like to report the most recent result of direct β -C–H imidation of indole derivatives enabled by DBU-activated *N*-haloimides as both electrophilic and nucleophilic reagents (Scheme 2). The *N*-haloimide/DBU combination is anticipated to provide a convenient and economic protocol toward α -C–H imidation of indoles. Compared to the methods previously reported,^{2,3} the *N*-haloimide/DBU protocol has the distinct feature without the necessity of external nitrogen sources. Hence, *N*-haloimide functions as a self-immolating imidation reagent.⁵

Initially, the model reaction of *N*-methylindole (**1a**) with NBS was examined under a variety of conditions (Table 1). As expected, in the solvents like toluene, CH₂Cl₂, THF, and dioxane, the α -imidated indole **2a** could be obtained in moderate yields (Table 1, entries 1–4). DCE and MeCN gave improved yields (Table 1, entries 5 and 6). Among all the solvents tested, DMF proved to be the most efficient. In this case, the mixture of **1a** with NBS (2.2 equiv), DBU (2.2 equiv) rapidly afforded compound **2a** in 79% yield within three minutes (Table 1, entry 7). Except DBU, other types of activators were also investigated. DBN and MTBD gave relatively lower efficiency compared to DBU (Table 1, entries 8 and 9). However, tertiary amines including Et₃N and DABCO appear to be completely inert (Table 1, entries 10 and 11). Surprisingly, NIS and NCS showed quite different reactivity to NBS (Table 1, entries 12 and 13). The reaction of **1a** with NCS (2.2 equiv), DBU (2.2 equiv) gave no reaction, with the substrate **1a** intact (Table 1, entry 12). When NIS was used, the target molecule was not detected, with unidentified product generated (Table 1, entry 13). By contrast, in the absence of DBU, the reaction gave a complex mixture, without **2a** observed (Table 1, entry 14).⁶

Table 1 Optimization of the Reaction Conditions^a



Entry	Activator (equiv)	NXS	Solvent ^b	Time (min)	Yield of 2a (%) ^c	Yield of 3a (%) ^c
1	DBU (2.2)	NBS	toluene	10	43	42
2	DBU (2.2)	NBS	THF	10	48	35
3	DBU (2.2)	NBS	CH ₂ Cl ₂	5	61	31
4	DBU (2.2)	NBS	dioxane	10	64	18
5	DBU (2.2)	NBS	MeCN	5	73	17
6	DBU (2.2)	NBS	DCE	5	78	16
7	DBU (2.2)	NBS	DMF	3	79	15
8	DBN (2.2)	NBS	DMF	5	63	21
9	MTBD ^d (2.2)	NBS	DMF	5	65	26
10	Et ₃ N (2.2)	NBS	DMF	60	n.r.	0
11	DABCO (2.2)	NBS	DMF	30	0	0
12	DBU (2.2)	NCS	DMF	60	n.r.	–
13	DBU (2.2)	NIS	DMF	60	n.d.	–
14	–	NBS	DMF	70	complex	–

^a Reactions were carried out with **1a** (1.0 mmol), NBS (2.2 equiv), and activator (2.2 equiv) in solvent (2.0 mL) at r.t.

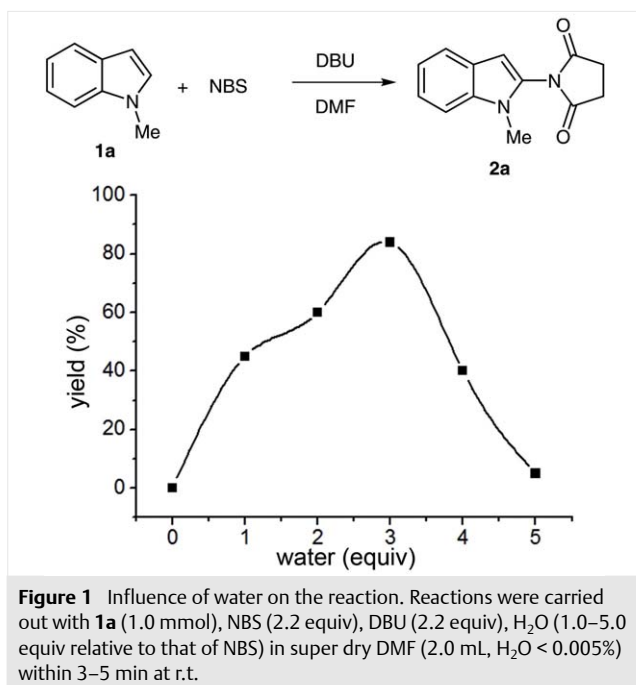
^b Solvent was directly used as received.

^c Isolated yield; n.r. = no reaction, n.d. = not determined.

^d MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.

In our previous study on the β -imidation of chalcones with NBS/DBU combination, we found that trace amount of water is crucial for the reaction to proceed.^{4b} Herein, the influence of water on the α -imidation reaction of indole derivatives was investigated in details (Figure 1). Different amount of water was introduced to the reaction system of **1a** with NBS (2.2 equiv) and DBU (2.2 equiv) in super dry

DMF (2.0 mL). As a result, the yields changed dramatically, depending on the feed ratio of water to NBS. Without any water, the reaction did not occur at all. Approximately 3.0 equivalents of water relative to NBS amount led to the formation of **2a** in the highest yield (84%).⁷ When the water amount reaches up to 5.0 equivalents relative to that of NBS, only trace amount of target product was detected.⁸

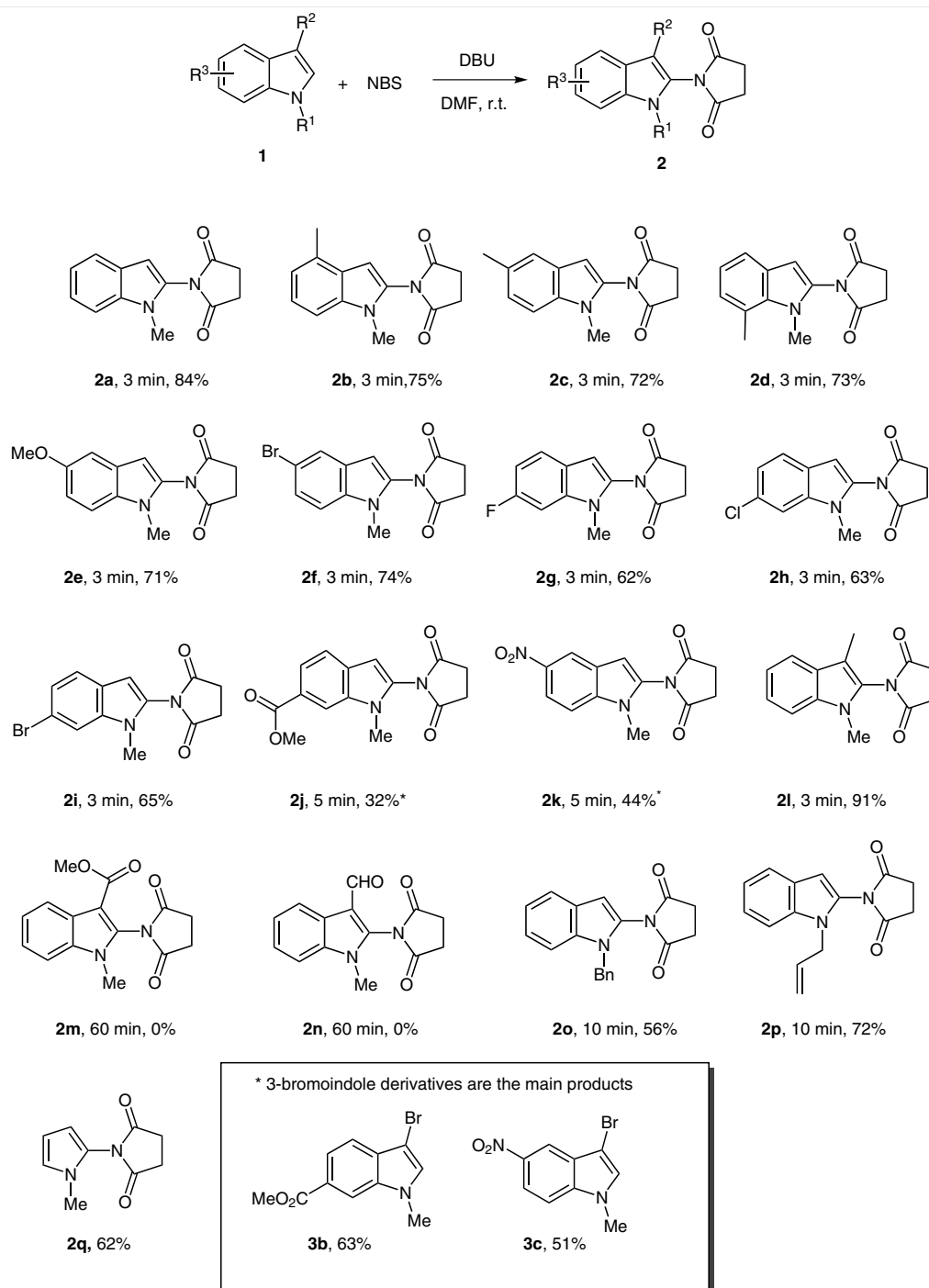


In the following work, NBS (2.2 equiv), DBU (2.2 equiv) in super dry DMF (2.0 mL), along with the addition of H₂O (120 μ L, 6.6 equiv) was selected as the optimized conditions. We explored the scope of the method. A variety of *N*-protected indole derivatives were then subjected to the reaction sequence (Scheme 3). *N*-Methylindole substrates containing either electron-donating methyl, methoxy, or weak electron-withdrawing groups like halogens (F, Cl, and Br) on the phenyl ring of the indole skeleton, afforded the corresponding imidated products **2b–i** in moderate yields (62–75%).^{9,10} As for strong electron-withdrawing groups like methoxycarbonyl and nitro on the phenyl ring of *N*-methylindoles, the yields were fairly low. The corresponding 3-bromo-*N*-methylindole derivatives **3b** and **3c** were ob-

tained in 63% and 51% yields.¹¹ In the case of a methyl group located at the 3-position of *N*-methylindole, compound **2l** was obtained in 91% yield. However, the electron-withdrawing methoxycarbonyl group at the same position gave no reaction. From above one can see that electron-rich groups on the indole ring displayed higher reactivity than electron-withdrawing groups in this reaction. *N*-Benzyl and *N*-allylindoles afforded products **2o** and **2p** in respective 56% and 72% yields. The allyl functional group exhibits a good tolerance. *N*-Methylpyrrole was also efficient to afford the target product **2q** in 62% yield. All the reactions proceeded rapidly and completed within ten minutes to furnish products **2a–q**.

The scope of the reaction was further investigated by exploring other types of *N*-haloimides as potential self-immolating nitrogen sources (Scheme 4). The reaction of **1a** with *N*-bromophthalimide (2.2 equiv), DBU (2.2 equiv) gave the imidated product **4** in 73% yield. 2-(1-Methyl-1*H*-indol-2-yl)benzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide (**5**) was successfully prepared in 55% yield by the reaction of **1a** with *N*-bromosaccharin at room temperature. In this case, 1.1 equivalents of *N*-bromosaccharin, along with 1.1 equivalents of DBU is enough to drive the reaction to completion.¹² One can see from above (Table 1, Scheme 3, and Scheme 4) that different *N*-haloimides (e.g., NBS, NIS, NCS, NBP, NCP, *N*-bromosaccharin, etc.) exhibit different reactivity in the explored reaction.

On the basis of all the results described above, along with previous work by Liang,^{3b} Huang,^{3d} and us,⁴ a plausible mechanism for the α -imidation of *N*-substituted indoles was proposed, as depicted in Scheme 5.¹³ Firstly, a tight ion-pair intermediate **I** is supposed to generate from the 1:1 adduct of NBS and DBU.^{14–17} The DFT structure of intermediate **I** was shown in Figure 2. Secondly, reaction between indole substrate **1a** and reactive intermediate **I** furnishes DBU-stabilized bromonium ion **II**,^{18,10a} which will further transform into an open-formed carbocation **III** and its resonance structure, iminium ion **IV**.¹⁹ Thirdly, nucleophilic attack of **IV** by the succinimide anion leads to the formation of α -imino- β -brominated indoline **V**. Finally, DBU-mediated elimination of HBr delivers α -imidated indole **2a**. Noteworthy that proton elimination in **IV** is ascribed to the reason for the observation of the 3-bromoindole derivatives **3**.



Scheme 3 Scope of indole derivatives. Reactions were carried out with **1** (1.0 mmol), NBS (2.2 equiv), and DBU (2.2 equiv) in super dry DMF (2.0 mL, with 120 μL H_2O added). Isolated yields are reported.

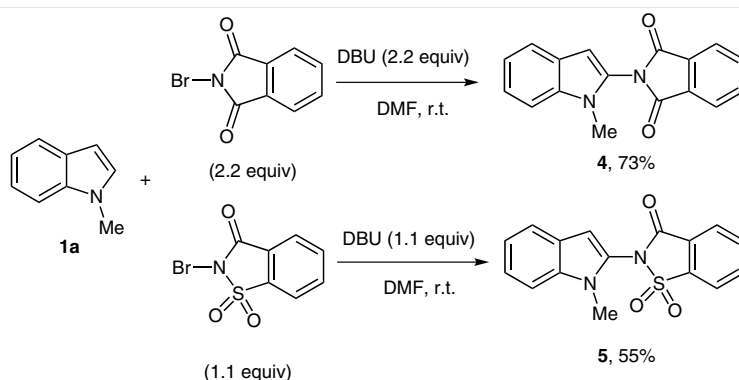
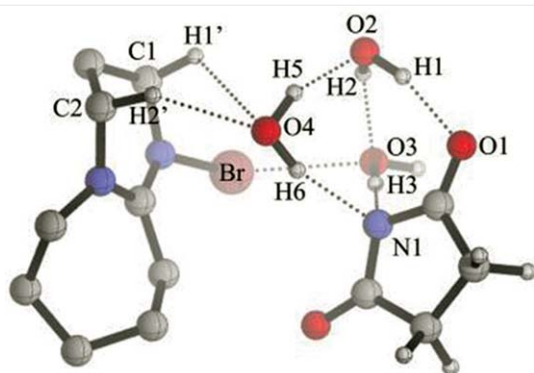
Scheme 4 Scope exploration of *N*-haloimides

Figure 2 DFT structure of ion-pair intermediate I

In conclusion, we have developed a highly efficient, convenient, environmentally friendly, and metal-free methodology for direct C2-amination of indoles with *N*-haloimide (activated by DBU) as both electrophilic and nucleophilic reagent at ambient temperature. The reaction exhibited broad scope for indole derivatives and *N*-haloimides. Without the necessity of external nitrogen sources, a variety of imidation products can be prepared rapidly in moderate to excellent yields. Further research on the utilization of the *N*-haloimide/DBU protocol in organic transformations is ongoing in our laboratory.

Acknowledgment

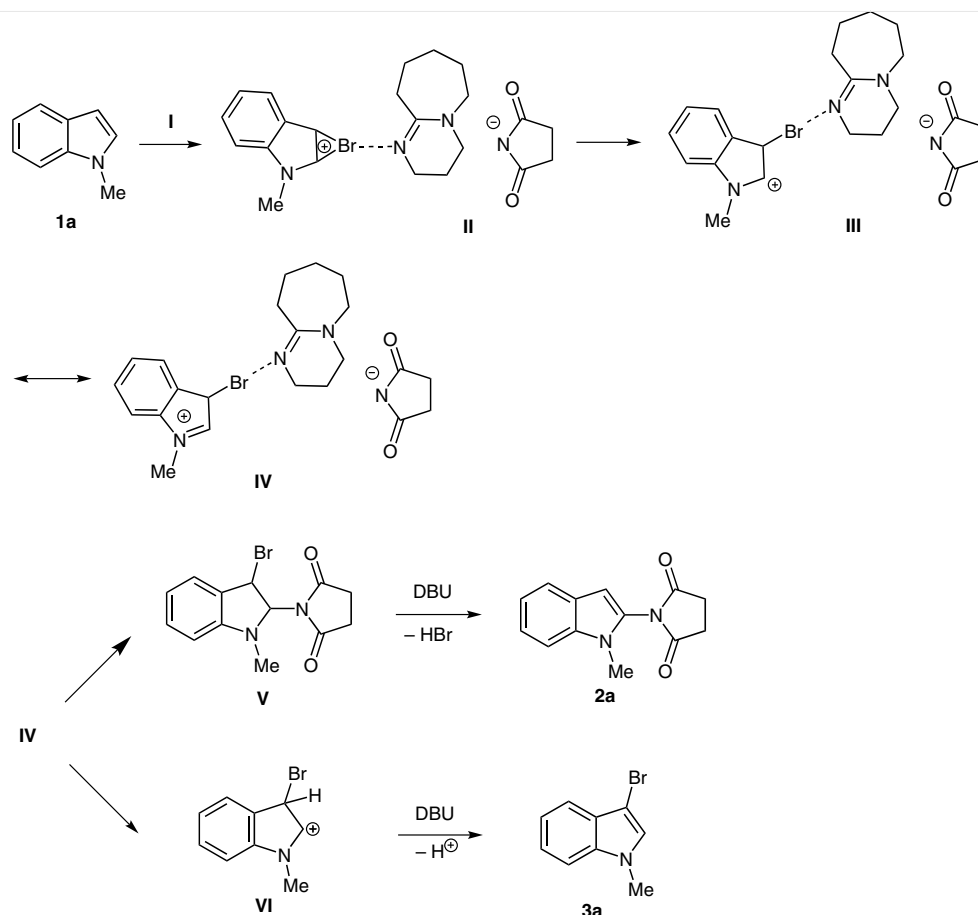
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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0034-1379488>.

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- For a recent nice example of using *N*-succinimidylperester as a self-immolating imidation reagent, see: Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279.
- As one reviewer suggested, the reaction with Na_2CO_3 and Cs_2CO_3 as the base was explored. As a result, Na_2CO_3 gave no reaction, and Cs_2CO_3 afforded product **2a** in 61% yield.
- Reaction performed under N_2 protection gave similar yield to that in the open air, indicating that molecular oxygen has no effect on the reaction, contrary to our previous observation in ref. 4b.
- The experimental result is well consistent with the theoretical calculation result shown in the mechanism part.
- Preparation of 2a; Typical Procedure**
To a solution of NBS (2.2 mmol, 0.3916 g) and DBU (2.2 mmol, 0.3344 g) in super dry DMF (2.0 mL, with the addition of 120 μL H_2O), *N*-methylindole **1a** (1.0 mmol, 0.1312 g) was added. The reaction mixture was stirred at r.t. for 3 min. After the starting material **1a** was consumed as indicated by TLC, the reaction mixture was poured into H_2O and then extracted with CH_2Cl_2 (3×10 mL). The combined organic phase was washed with H_2O (3×10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel; PE-EtOAc, 8:1) to give **2a**



Scheme 5 Plausible mechanism

(0.1917 g, 84%) as a white solid.

1-(1-Methyl-1H-indol-2-yl)pyrrolidine-2,5-dione (2a)

Mp 171–173 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.01 (s, 4 H), 3.55 (s, 3 H), 6.50 (s, 1 H), 7.13–7.16 (m, 1 H), 7.28 (d, *J* = 7.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃) δ = 28.4, 29.3, 99.9, 109.6, 120.1, 121.2, 122.6, 125.9, 126.2, 135.9, 175.8. ESI-HRMS: *m/z* calcd for C₁₃H₁₂N₂O₂ [M + H]⁺: 229.0977; found: 229.0988.

- (10) In most cases, 3-bromoindole derivatives **3** could be observed. It seems that the electron-donating group on the indole ring is favorable for the formation of α-aminated product, and the electron-withdrawing group on the indole ring affords 3-bromoindoles as the main products.
- (11) 3-Haloindole derivatives are important building blocks in the functionalization of indoles at the 3-position.
- (12) In the presence of NBS (2.2 equiv) and DBU (2.2 equiv), a bromoimidation product was obtained in 92% yield.
- (13) To a solution of NBS (2.2 equiv), DBU (2.2 equiv) in DMF (2.0 mL), and H₂O (120 μL), TEMPO (2.2 equiv) was added. Then substrate **1a** (1.0 mmol) was added under stirring. No reaction was observed within an hour. This result may help to exclude a possible radical mechanism.
- (14) (a) For evidence for the formation of the ion-pair intermediate, see refs. 9–11. For a recent review of NBS activation by Lewis base, see: Denmark, S. E.; Kuester, W. E.; Burk, M. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10938. (b) Selected papers – for NBS/Ph₃P, see: Sakakura, A.; Ukai, A.; Ishihara, K. *Nature (London, U.K.)* **2007**, *445*, 900. (c) For Et₂SBr·SbCl₅Br, see: Snyder, S. A.; Treitler, D. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899. (d) For bromocollidinium ion, see: Cui, X.-L.; Brown, R. S. *J. Org. Chem.* **2000**, *65*, 5653.
- (15) The theoretical calculation result supports the proposed ion-pair intermediate in which three molecules of water are required. The role of the water is supposed to distribute the negative charge on the succinimide anion, thus stabilizing the ion pair formed.
- (16) The ion-pair intermediate is also supported by measuring the ion conductivities of NBS/DBU vs. NBS in DMF. The ion conductivity for the former is two orders of magnitude higher than the latter.
- (17) As a reviewer suggested, DBU (0.25 mmol) and NBS (0.25 mmol) were dissolved in CDCl₃, and the ¹H NMR spectrum was measured. Compared with the NMR data of free NBS and DBU, the chemical shifts of the NBS/DBU mixture change to some

extent (the protons on DBU move downfield and protons on NBS move toward upfield) indicating intermolecular interaction exists between NBS and DBU.

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