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Catalyst and Additive-Free Direct Amidation/ Halogenation of Tertiary Arylamines with *N*-haloimide/amides

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Abstract. An approach has been developed for the amidation (halogenation) of tertiary arylamines by electrophilic activation using *N*-haloimide/amides. Several control experiments have been performed, and the coupling reaction outcomes indicated that the *N*-haloimide/amide brings three major functions, including electrophilic activation, aromatic halogenation and nucleophilic nitrogen sources. This cascade reaction features simple manipulation, requires no additional catalyst, oxidant or additives, and is performed under mild conditions.

Keywords: catalyst-free; C-H activation; tertiary amines; amidation; *N*-haloimide

Nitrogen-containing organic structures with C–N bonds are some of the most abundant, versatile and important fundamental fragments in nature,[1] and they are widely presented in bioactive natural products,[2] synthetic drugs[3] and material sciences.[4] In addition, they can constitute the main backbone of biomolecules such as peptides and proteins.[5] Therefore, construction of C–N bonds has great synthetic importance in organic chemistry.[6]

Direct C–N bond formation through C–H activation represents an extremely attractive and efficient route because it is straightforward and more atom economical and environmentally friendly than traditional methods.[7] Over the past several years, significant progress has been made establishing a transition-metal catalyzed oxidative cross-coupling strategy for the activation of C(sp2)–H[8] and C(sp3)–H[9] bonds to construct C–N bonds. The development of environmentally benign methods[10] for C–N-bond construction is hugely significant,[11] and, more recently, metal-free approaches have received considerable attention for this reason.[12] *N*-haloimides can be generally used as a convenient source of both cationic halogens and halogen radicals. *N*-iodosuccinimide (NIS)–promoted methods have been successfully applied for cross-dehydrogenative coupling (CDC) or oxidative C–N cross-coupling reactions.[13] Recently, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)–activated *N*-bromosuccinimide (NBS) has been utilized in C–N bond formation.[14]

Amides are one of the most-important functional groups in life and are present in many biologically active compounds.[15] Selective functionalization of C−H bonds adjacent to a nitrogen atom in tertiary amines for the construction of amide containing compounds has been vastly studied, including extensive pioneering work with transition-metal-catalysts and iodine-based reagents. For example, Cu[16] and Fe[17] catalytic oxidative amidation has been performed for the direct C(sp3)-H amidation of tertiary amines (Scheme 1, a). Minakata and co-workers[18] have reported direct oxidative amidation of the C(sp3)–H bond of *N*,*N*-dimethylanilines with a phthalimidate-based hypervalent iodine (III) reagent (Scheme 1, b). Zheng and co-workers[19] have developed an NIS/succinimide condition for the 1,3-difunctionalization (imidation/iodination) of cyclopropylamines by an electrophilic ring opening pathway (Scheme 1, c). Du and co-workers[20] successfully developed an efficient intramolecular oxidative amidation method of *N*-aryl tetrahydroisoquinolines with the use of phenyliodine (III) diacetate (PIDA) and NaN_3 (Scheme 1, d). An electrochemical approach has also been developed by the Ley group.[21]

Although significant achievements have been made in this field, some limitations still exist such as the use of metal catalysts and excess external oxidants, tedious workup procedures and harsh reaction conditions. Therefore, the development of cheaper, milder and more environmentally friendly metal-free methods for the construction of C–N

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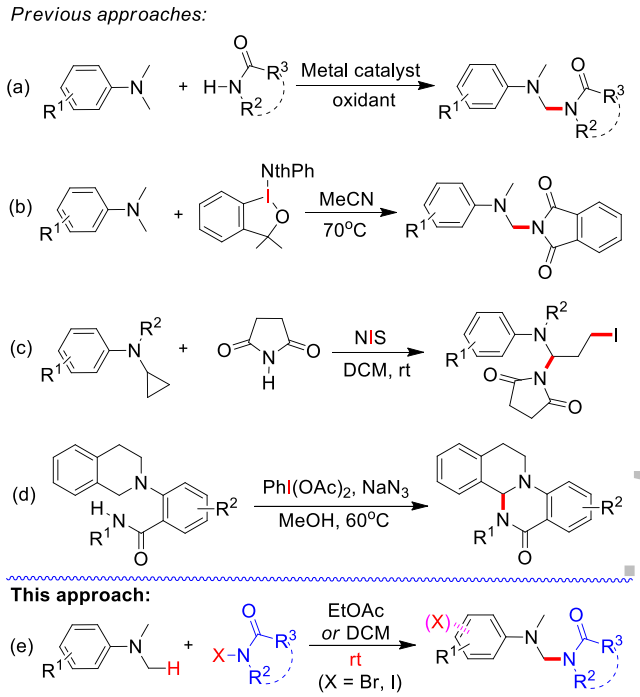
bonds through sp3 carbon-hydrogen bond activation is still a challenging task.

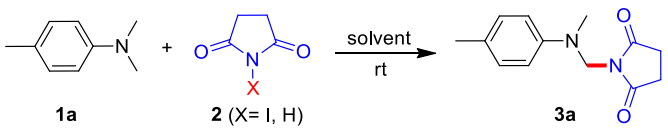
Based on our previous work on the oxidative functionalization of tertiary amines,[17b, 22] herein we report a simple catalyst and additive-free direct amidation (halogenation) of tertiary arylamines through electrophilic activation with *N*-haloimide/amide under ambient conditions without using external oxidants (Scheme 1, e).

Initial studies focused on investigating the coupling reaction of *N*,*N*-dimethyl-*p*-toluidin **1a** and NIS in methanol at room temperature under air. The expected coupling product **3a** was isolated in 65% yield after 3 h with 1.5 equiv of NIS (Table 1, entry 1), and the reaction led to I_2 generation, which was confirmed by an iodine-starch test.[23] Subsequently, we examined this transformation with different solvents (Table 1, entries 2–9) and the best result was obtained in ethyl acetate (EtOAc), in which **3a** was isolated with 71% yield (Table 1, entry 8). Hence, EtOAc was chosen as the best solvent for this transformation. Then, as the NIS loading was increased from 1.5 equiv to 1.8 equiv, the yield also increased from 71% to 75% (Table 1, entry 10).



Scheme 1. Direct amidation of a tertiary amine through activation of the C–H bond adjacent to a nitrogen

Table 1. Optimization of the reaction conditions[a]



Entry	**2** (equiv)	Solvent	Additive	Time/h	Yield (%)[b]
1	NIS (1.5)	CH_3OH	-	3	65
2	NIS (1.5)	CH_3CN	-	3	64
3	NIS (1.5)	THF	-	12	30
4	NIS (1.5)	Acetone	-	6	52
5	NIS (1.5)	DCM	-	6	50
6	NIS (1.5)	DCE	-	6	66
7	NIS (1.5)	$CHCl_3$	-	6	65
8	NIS (1.5)	EtOAc	-	6	71
9	NIS (1.5)	CCl_4	-	6	64
10	NIS (1.8)	EtOAc	-	1.5	75
11	NIS (1.8)	EtOAc	$NaHCO_3$	6	75
12	NIS (1.8)	EtOAc	Na_2CO_3	6	73
13	NIS (1.8)	EtOAc	NaOH	6	65
14	NIS (1.8)	EtOAc	KOH	**6**	55
15	NIS (1.8)	EtOAc	Cs_2CO_3	6	57
16	NIS (1.8)	EtOAc	2,6-Lutidine	6	72
17	NIS (1.8)	EtOAc	DBU	6	34
18	**NIS (2.0)**	**EtOAc**	**-**	**1.5**	**81**
19	NIS (2.2)	EtOAc	-	1.5	81
20[c]	NIS (2.0)	EtOAc	-	1.5	80
21[d]	NIS (2.0)	EtOAc	-	1.5	78
22	NHS (2.0)	EtOAc	-	12	NR[e]

[a] Reaction conditions: **1a** (0.4 mmol) with additive (0.4 mmol) in solvent (2.0 mL) under air atmosphere at room temperature in a 5-mL vial.
[b] Isolated yield.
[c] Under an argon atmosphere.
[d] The reaction was carried out in darkness.
[e] No reaction.

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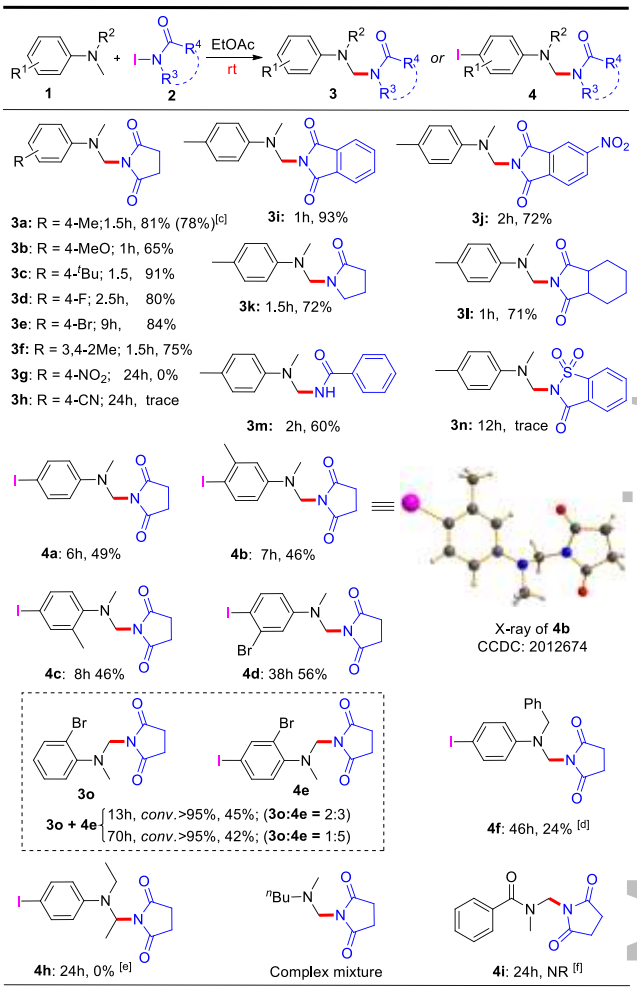
Because bases may promote the deprotonation of methyl hydrogen,[24] various inorganic and organic bases were tested (Table 1, entries 11–17). However, no obvious improvement to the reaction outcome was found, and moderate-to-good yields were achieved in most bases. Surprisingly, the addition of DBU resulted in a dramatic decrease in the yield of **3a** to 34% (Table 1, entry 17). Probably, NIS was reacted with DBU and hampered the transformation.[25] When the NIS loading was gradually increased to 2.0 equiv, the yield reached 81% (Table 1, entry 18). However, with more NIS, the yield was no longer improved (Table 1, entry 19). Furthermore, the reaction also proceeded smoothly with 80% yield under an argon atmosphere (Table 1, entry 20). It should be noted that when the reaction was conducted in darkness, **3a** was isolated with 78% yield (Table 1, entry 21). The reaction of **1a** and succinimide (NHS) does not occur under same conditions (Table 1, entry 22). Therefore, the best reaction was performed using 2 equiv NIS at room temperature in EtOAc.

With the optimal conditions in hand, we next evaluated the synthetic scope of the coupling reaction. As depicted on Table 2, NIS and *para*-substituted *N*,*N*-dimethylaniline derivatives were first applied in this transformation. A wide range of electron-donating and halide substituents were well tolerated and furnished the corresponding desired products in good to high yields (**3a**–**3e**). Moreover, *N*,*N*-dimethylanilines bearing both *para*- and *meta*-dimethyl groups were also used as reaction partners, yielding corresponding coupling products **3f** in 75% yield. Unfortunately, when strongly electron-withdrawing groups such as nitro and cyano were present, no product was observed (**3g** and **3h**). The decrease in the electron density on the nitrogen of aniline may attenuate their reactivity toward NIS. Then, various *N*-iodoimide/amides, including *N*-iodo-4-nitrophthalimide (INPT), *N*-iodophthalimide (IPT), *N*-iodohexahydrophthalimide, *N*-iodobutyrolactam and *N*-iodobenzamide, were also subjected to the coupling reaction and proved to be reliable reaction partners with tertiary aryl amines, delivering good to excellent yields (**3i**-**3m**). The highest yield (93%) was generated using IPT (**3i**). Unfortunately, this methodology did not work with *N*-iodosaccharin (NISac) (**3n**). Next, we investigated the reactivity of *ortho*-, *meta*- and unsubstituted anilines and, interestingly, found that when the *para* position of the benzene ring is vacant, both *para* iodination and *N*-methyl amidation reactions occurred on the same molecule, giving corresponding products **4a**-**4e** with moderate yields. In contrast, *ortho*-iodination analogs were not observed. This result can be attributed to the fact that the bulky iodine atom at the *ortho* position may cause steric hindrance in the molecule. The structure of compound **4b** was confirmed by X-ray

Table 2. The amidation of tertiary arylamines with *N*-iodoimides[a,b]



[a] Reactions were conducted using 1 (0.4 mmol) and 2 (0.8 mmol) in EtOAc (2.0 mL) under air atmosphere at room temperature.
[b] Isolated yield.
[c] Gram scale reaction in 5h.
[d] *N*-benzyl-4-iodo-*N*-methylaniline was isolated in 34% yield.
[e] *N*,*N*-diethyl-4-iodoaniline and *N*-ethyl-4-iodoaniline were obtained in 42% and 18% yield, respectevily.
[f] No reaction.

crystallographic analysis.[26] Notably, 2-bromo-*N*,*N*-dimethylaniline was used as a reaction partner. After 13 h of reaction, a mixture of **3o**/**4e** (nearly 2:3 ratio) was obtained with 45% total yield. When the reaction time was extended to 70 h, the **3o**/**4e** ratio changed to 1:5 (the products ratio was determined by ^{1}H NMR), which means that **3o** may gradually convert to **4e**. Furthermore, the reactions were also attempted with other anilines such as *N*-methyl-*N*-benzylaniline and *N*,*N*-diethylaniline, and it was found that substitution on the nitrogen had a significant impact on the reaction. With *N*-methyl-*N*-benzylaniline, only 24% yield of desired **4f** and 34 % of the *para*-iodinated aniline by-product were isolated after a prolonged reaction time (46 h). However, with *N*,*N*-

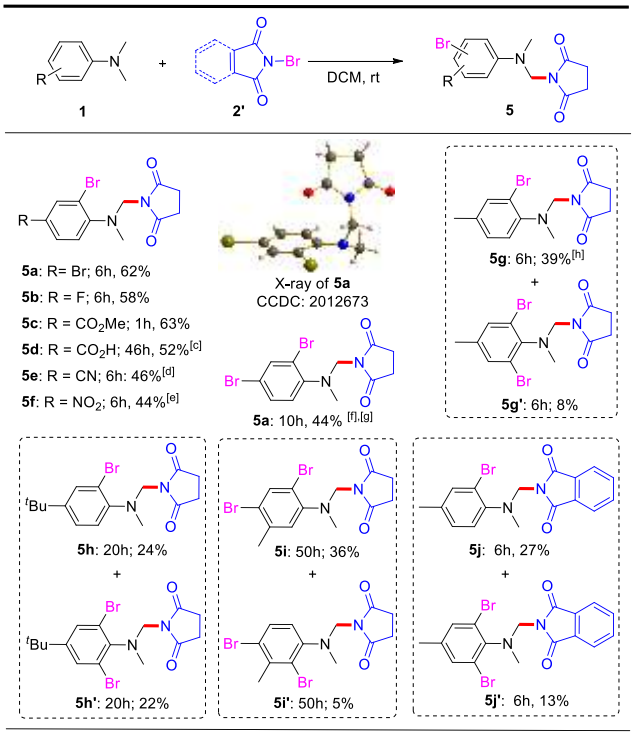
diethylaniline the corresponding amidated product could not be obtained under the optimized conditions. It is noteworthy that, these reactions are accompanied by a certain amount of iodinated aniline by-products. And then, *N*,*N*-dimethylalkylamine and *N*,*N*-dimethylamide were also applied to examine the reactivity. Anfortunatly, when *N*,*N*-dimethylbutylamine was used, the reaction turned a complex mixture, and the reaction did not occurr with *N*,*N*-dimethlybenzamide under standard conditions.

After the use of *N*-iodoimides/amides in this reaction was examined, we turned our attention to using other commercially available *N*-haloimides. The reaction of 4-bromo-*N*,*N*-dimethylaniline and NBS was optimized. DCM was identified as the best solvent (for details, see ESI S2) and the *ortho*-brominated amidation product **5a** was isolated. The structure of **5a** was further determined by X-ray crystallographic analysis.[26] Thus, the reactions were conducted with 2 equiv. of *N*-bromoimides at room temperature (Table 3). The *N*,*N*-dimethylanilines bearing electron withdrawing groups (Br, F, CO_2Me, CO_2H, CN and NO_2,) gave monobrominated amidation products (**5a–5f**) with 44–63% yields, together with corresponding brominated aniline by-products. In contrast, the anilines with electron donating substituents afforded monobrominated and dibrominated products (**5g/5g'–5j/5j'**) with lower yields under the established conditions. Unsubstituted aniline was tested in the presence of 3.0 equiv NBS and the dibrominated product **5a** was obtained (44% yield). With a *N*,*N*-dimethyl-*m*-toluidine, the bromination occurred at both the *para* and *ortho* positions of the aniline, affording a 7:1 mixture of **5i** and **5i'** with 41% yield (the product ratio was determined by ^{1}H NMR). When *N*-bromophthalimide (NBP) was used, the reaction proceeded smoothly and delivered the desired products (**5j** and **5j'**) with 40% yield. Unfortunately, only traces of the coupling product could be detected when the same reaction was conducted with *N*-chlorosuccinimide (NCS).

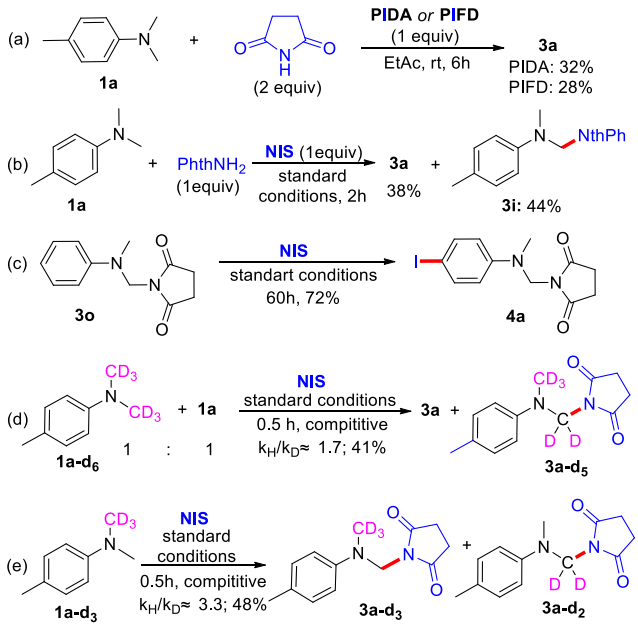
To probe the reaction pathway, in situ NMR monitoring experiments were initially performed. From a crude ^{1}H NMR spectrum of the reaction mixture of **1a** and NIS (1.2 equiv) in $CDCl_3$, chemical shifts associated with coupling product **3a** and succinimide were observed, as well as another component related to **1a.** Interestingly, the chemical shifts related to **1a** shifted to low field, which could be attributed to the adjacent electropositive nitrogen atom in the $ArN^+(Me)_2$-I complex.[27] Next, a HRMS experiment of the reaction mixture was investigated and to our delight, the signal at m/z 262.0094 (calcd for $C_9H_{13}IN^+$, 262.0087) was detected. (for details, see ESI S6). In addition, the reaction occurred in darkness under standard conditions with the same efficiency. Since homolysis of N–I bonds generally requires light or heat, the dark condition suggests that the reaction did not involve homolysis of NIS (N–I bond). Furthermore, upon the addition of radical inhibitor 2,2,6,6-tetramethylpiperidinyloxy (TEMPO, 1.0 equiv) under standard conditions, no negative influence on the reaction was observed and, interestingly, mono- and bis-amidated products were generated (for details, see ESI S10). These results suggesting that the reaction proceeds via an ionic pathway.

To further clarify the details of this reaction, several control experiments were conducted (Scheme 2). First, the reaction of **1a** and NHS was performed in the presence of hypervalent iodine (III) reagents such as PIDA or phenyl iodine (III) bis-trifluoroacetate (PIFA) and the desired **3a** was delivered with 32% and 28% yield, respectively (Scheme 2, a). This result attributes that an ionic

Table 3. The amidation of tertiary aromatic amines with *N*-bromoimides[a,b]



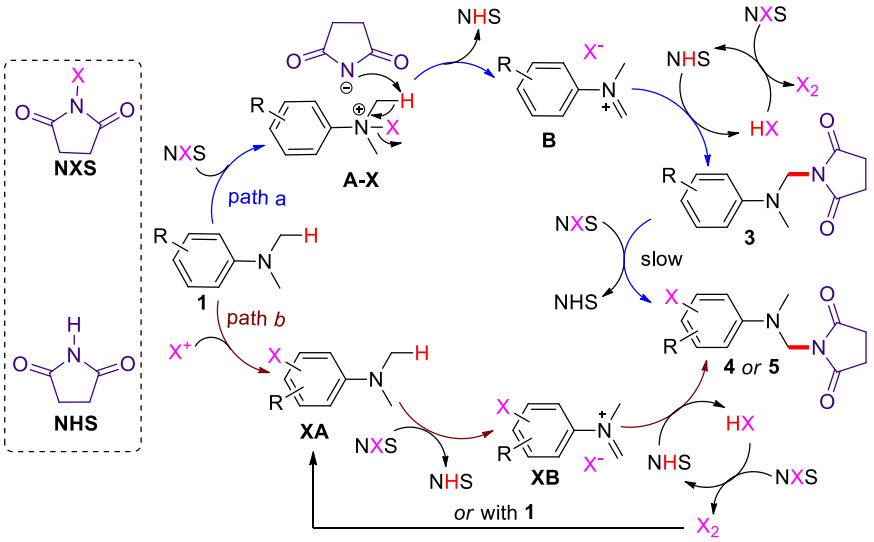
[a] Reactions were conducted using **1** (0.4 mmol) and **2'** (0.8 mmol) in DCM (2.0 mL) under air atmosphere at room temperature.
[b] Isolated yield.
[c] 3-Bromo-4-(dimethylamino)benzoic acid was isolated in 28% yield yield.
[d] 3-Bromo-4-(dimethylamino)benzonitrile was isolated in 34% yield.
[e] 2-Bromo-*N*,*N*-dimethyl-4-nitroaniline was isolated in 33% yieid
[f] 3.0 Equiv of NBS was used.
[g] 2,4-Dibromo-*N*,*N*-dimethylaniline was isolated in 15% yield.
[h] 2-Bromo-*N*,*N*,4-trimethylaniline was isolated in 12% yield.



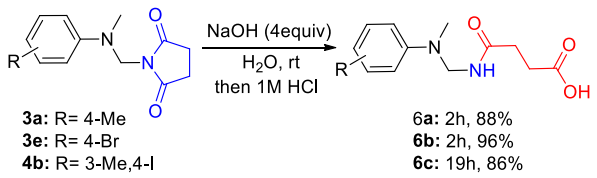
Scheme 2. Control experiments and KIE studies.

pathway might be involved in the reaction. [20, 28] Next, the reaction of **1a** and phtalimide ($PhthNH_2$) was treated in the presence of 1 equiv NIS under standard conditions, wherein a mixture of **3a** and **3i** was obtained in 38% and 44% yield, respectively (Scheme 2, b). This indicates that imides are released during the reaction[29] and react with the active iminium cation[30] to form the final product. Another control experiment was conducted with amidative *N,N*-dimethylaniline **3o** and NIS under standard conditions and the *para*-iodination product **4a** was isolated in 72% yield after 60 h, which suggests that slow halogenation can occur after the amidation process (Scheme 2, c). After that the kinetic isotope effect (KIE)[31] experiments were conducted by deuterium-labeling (for details, see ESI S8) and they showed that the intramolecular and intermolecular KIE (K_H/K_D) were 1.7 and 3.3 respectively (Scheme 2, d and e). These results suggest that the cleavage of the C(sp3)−H bond may actively participate in the reaction, but it is not the rate determining step.

Combined with the experimental results and the related literature, a plausible mechanism for this coupling reaction is proposed in Scheme 3. According to the reaction order, there are two possible pathways that can be suggested. In path a, NXS initially provides a cationic halogen to tertiary aryl amine to form *N*-haloaminium complex **A-X** through ionic interactions. Since the reaction conditions are base free, the succinimide ion might abstract a proton from the methyl group to give the *N*-aryl iminium intermediate **B**. In these cases, succinimide (NHS) would be liberated as a by-product. Subsequently, **B** would be prone to reacting with nucleophilic NHS to generate product **3** and eliminate HX. The HX can be further converted to halogen molecules in the presence of NXS, rereleasing NHS.[32] This may explain the excess amount of NXS required for this transformation. In path b, the initial step begins with an electrophilic halogenation reaction of an aromatic ring with NXS (X^+) [24, 33] or molecular halogen (X_2)[34] to form *para-/ortho*-halogenated aniline **XA**, which is followed by a similar reaction as pathway (a) to sequentially form the iminium ion **XB**. Then, nucleophilic substitution with NHS occurs to generate halogenative amidation products **4 or 5**. In addition, if the substrate structure is appropriate, **3** can be gradually changed to **4 or 5** with the use of NXS.



Scheme 3. Tentative mechanistic pathway



Scheme 4. Further elaboration of compounds **3** and **4**

At last, to illustrate the synthetic utilities of this method, we investigated further transformations of amidated anilines (Scheme 4), because amido acids are a useful functional group that have been reported to exhibit broad spectrum of biological and pharmaceutical activities.[35] After treatment of **3a, 3e** or **4b** with NaOH in water at room temperature, the succinimide ring smoothly opened and afforded the corresponding amido acid derivatives (**6a–6c**) with high yield.

In conclusion, a simple, novel and efficient one-pot amidation (halogenation) of *N*,*N*-dimethyl anilines has been developed using *N*-haloimide/ amides by the electrophilic activation strategy. This protocol proceeds under mild conditions without the need for any catalysts or external oxidants and tolerates a wide range of substrates bearing broad functional groups. Further development and the catalytic application of *N*-haloimide in other reactions are currently underway in our laboratory.

Experimental Section

General procedure for the amidation of tertiary arylamines

In a 5-mL screw cap vial with a stir bar, tertiary arylamines **1** (0.4 mmol) was dissolved in ethyl acetate or DCM (2.0 mL) and the *N*-haloimide/amides (0.8 mmol) was added under air atmosphere and stirred at room temperature for the indicated reaction time. The reaction mixture washed with cold saturated sodium thiosulfate, and then extracted with ethyl acetate or DCM (3 x 10 mL). The combined organic layer was dried over sodium carbonate. Organic solvents were removed under reduced pressure and the crude reaction mixture was purified by column chromatography on a silica gel column (ethyl acetate /petroleum ether /triethylamine) to afford the desired product.

Acknowledgements

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Catalyst and Additive-Free Direct Amidation/ Halogenation of Tertiary Arylamines with *N*-haloimide/amides

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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