Halogenation

International Edition: DOI: 10.1002/anie.201607388
German Edition: DOI: 10.1002/ange.201607388

Highly *ortho*-Selective Chlorination of Anilines Using a Secondary Ammonium Salt Organocatalyst

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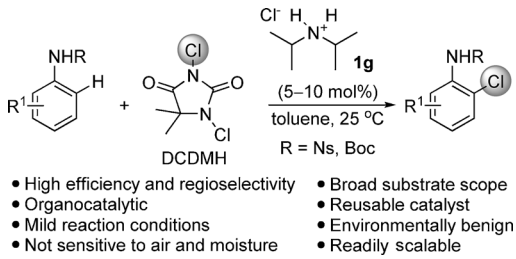
Abstract: *An organocatalytic, highly facile, efficient, and regioselective ortho-chlorination of anilines is described. A secondary ammonium chloride salt has been employed as the catalyst and the reaction can be conducted at room temperature without protection from air and moisture. In addition, the reaction is readily scalable and the catalyst can be recycled and reused. This catalytic protocol has been applied to the efficient synthesis of a highly potent c-Met kinase inhibitor. Mechanistic studies revealed that unique structural features of the secondary ammonium chloride salt are important for both the catalysis and regioselectivity of the electrophilic ortho-chlorination.*

Aromatic halogenation/C–H functionalization is one of the most important organic transformations. The resulting halogenated aromatic compounds are very useful and attractive building blocks. In addition, there are many well-developed methods for the derivatization of aryl halides.[1] Among the halogenated aromatic compounds, halogenated anilines are particularly attractive since aniline moieties frequently appear as pharmaceutical building blocks, constitutional components of novel functional materials, and cores of dyes and pigments.[2]

Electrophilic halogenation has been frequently employed in the preparation of halogenated anilines. However, a mixture of *ortho*- and *para*-halogenated anilines can be obtained, and halogenation at the less-hindered *para*-position is usually predominant.[3] The introduction of a substituent/blocking group at the *para*-position can lead to the halogenation at the second favorable position, the *ortho*-position of an aniline system.[4] However, highly selective *ortho*-halogenation of aniline in the absence of a blocking group at the *para*-position is a challenging task. Over the past decades, considerable effort has been devoted to the development of *ortho*-halogenation of anilines with the aim of high reaction efficiency and functional-group tolerance. Typically, electrophilic halogenations, halogenations of aryldiazoniums, and directed *ortho*-metalation are the main ways to access to halogenated aromatic compounds.[5] However, these methods suffered from low regioselectivity, tedious and harsh reaction procedures, and narrow substrate scope. The use of metals including Rh^{III}, Pd^{II}, Mg^{II}, and Cu^{II} in catalyzing the *ortho*-halogenation of anilines, along with either an N-acetyl or N-(2-pyridyl)sulfonyl directing group, has emerged in the recent years.[6] Thus, the development of a mild, selective, and effective catalytic protocol for the synthesis of *ortho*-halogenated anilines is still highly desired. Herein, we are pleased to report an organocatalytic and highly regioselective *ortho*-chlorination of N-Boc and N-Ns anilines under mild reaction conditions using a secondary ammonium chloride salt as the catalyst (Scheme 1). The reaction is not air and moisture sensitive and can be operated at room temperature. In addition, the N-Boc and N-Ns substituents can be easily removed and can enhance the flexibility in the derivation of the *ortho*-chlorinated aniline products. Moreover, the substrate scope is broad and the reaction is readily scalable.



Scheme 1. Organocatalytic *ortho*-selective halogenation of anilines.

Secondary ammonium salts can easily be prepared by the reaction between amines and acids, followed by recrystallization. The salts are air-stable, nontoxic, inexpensive, and easy to handle, and thus make them attractive organocatalysts for green and environmental benign chemical transformations. While secondary ammonium salts have been widely utilized as the organocatalysts in various transformations through the formation of iminium or aminal intermediates, their application to site-selective aromatic halogenation remains unknown.[7]

At the initial stage of investigation, the halogenation of the nosyl aniline **2a** was examined at room temperature using toluene and 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as the solvent and halogenation source, respectively (Table 1). In the absence of catalyst, no reaction was observed after 14 hours (entry 1). On the other hand, 75% yield of the *ortho*-chlorinated product $\mathbf{3a_{Cl}}$ was obtained when using 10 mol% of the dimethylammonium chloride salt **1a** as the catalyst (entry 2).[8] Next, a series of cyclic and acyclic secondary ammonium chloride salt catalysts (**1**) were subjected to the study. To our delight, it was realized that the bulky diisopropylammonium salt catalyst **1g** gave the desired product $\mathbf{3a_{Cl}}$ exclusively in 94% yield (entries 3–8).[8] More importantly, no *para*-chloroaniline product was detected. While the reaction

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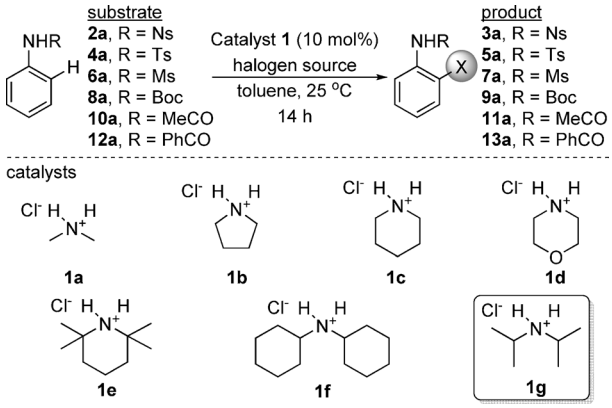
Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201607388.

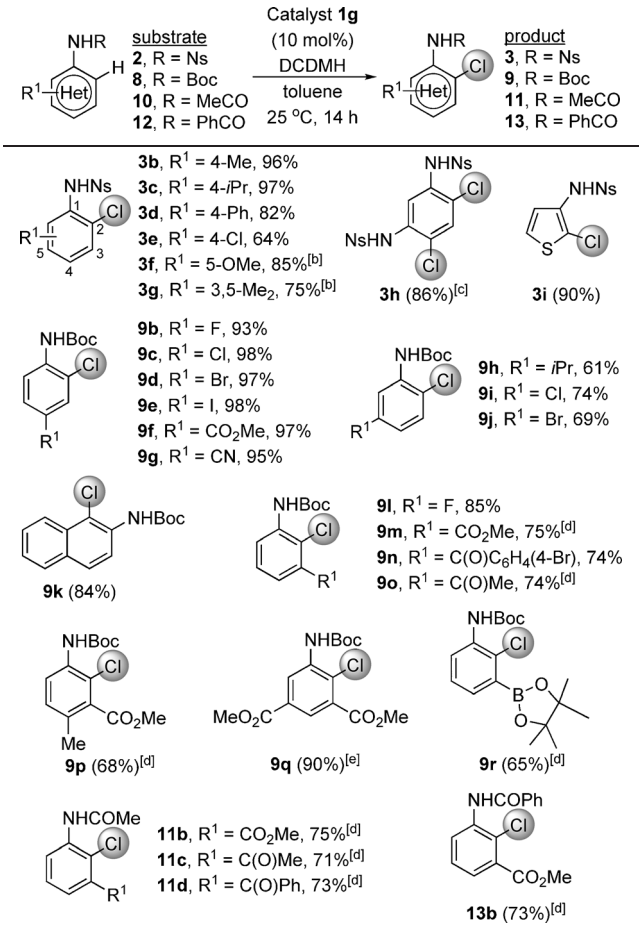
Table 1: Optimization of the reaction conditions.[a]



Entry	Halogen source	Substrate, R	Catalyst	Yield [%][b]
1	DCDMH	**2a**, Ns	–	n.r.
2	DCDMH	**2a**, Ns	**1a**	75
3	DCDMH	**2a**, Ns	**1b**	87
4	DCDMH	**2a**, Ns	**1c**	90
5	DCDMH	**2a**, Ns	**1d**	26
6	DCDMH	**2a**, Ns	**1e**	91
7	DCDMH	**2a**, Ns	**1f**	90
8	DCDMH	**2a**, Ns	**1g**	94
9	NCS	**2a**, Ns	**1g**	trace
10	NBS	**2a**, Ns	**1g**	61
11	DCDMH	**4a**, Ts	**1g**	90
12	DCDMH	**6a**, Ms	**1g**	68
13	DCDMH	**8a**, Boc	**1g**	82
14	DCDMH	**10a**, MeCO	**1g**	60
15	DCDMH	**12a**, PhCO	**1g**	71

[a] Reactions were carried out with aniline substrate (0.1 mmol), catalyst **1** (0.01 mmol), and halogen source (0.095 mmol) in toluene (2 mL) in the absence of light at 25 °C. [b] Yield of the isolated product based on the substrate. Boc = *tert*-butoxycarbonyl, DCDMH = 1,3-dichloro-5,5-dimethylhydantoin, Ms = methanesulfonyl, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide, Ns = 4-nitrobenzenesulfonyl, Ts = 4-toluenesulfonyl.

Table 2: Substrate scope of the organocatalytic *ortho*-chlorination of anilines.[a]



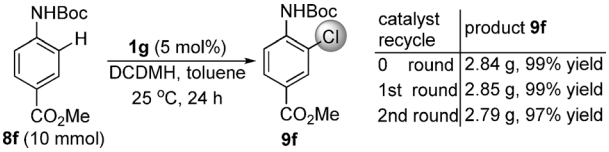
[a] Reactions were carried out with aniline substrate (0.1 mmol), catalyst **1g** (10 mol%, 0.01 mmol), and DCDMH (0.095 mmol) in toluene (2 mL) in the absence of light at 25 °C. The yields are those of isolated products based on the substrates. [b] Reactions were carried out at −20 °C. [c] 0.19 mmol of DCDMH was used. [d] A minor portion of isomer was observed. For details, see in the Supporting Information. [e] CH_2Cl_2 was used as the solvent.

was sluggish when using *N*-chlorosuccinimide (NCS), 61% of the *ortho*-brominated product $\mathbf{3a_{Br}}$ could be obtained when employing *N*-bromosuccinimide (NBS) as the halogen source (entries 9 and 10). A brief survey of the reaction media revealed the superior performance of toluene as the solvent in the secondary ammonium salt catalyzed electrophilic *ortho*-chlorination of aniline.[9] With the optimized reaction conditions in hand, we examined the compatibility of different N-substituents. It was realized that the reaction still could proceed smoothly when replacing the Ns group with Ts and Ms. A range of carbonyl substituents including Boc, acetyl, and benzoyl could also be tolerated (entries 11–15). Prompted by these results, other substrates with N-Ns and N-Boc substituents were investigated since Ns and Boc groups can easily be removed under mild reaction conditions, and this advantage is of great importance for late-stage manipulation and derivatization.

We next explored the generality of this organocatalytic reaction (Table 2). In general, the chlorination proceeded smoothly with excellent *ortho* selectivity. In addition, different functional groups were well-tolerated. For the N-Ns aniline substrates **2**, substituents such as methyl, isopropyl, phenyl, and chloride at the *para*-position were compatible with the reaction, thus providing the desired products **3b–e** in good to excellent yields. For the *meta*-substituted substrates **2f** (methoxy) and **2g** (3,5-dimethyl), the corresponding *ortho*-chlorinated products **3f** and **3g** were also obtained smoothly. Interestingly, double *ortho*-chlorination of **2h** proceeded readily to give **3h**. Again, the reaction was found to be highly *ortho* selective. The substrate **2i**, which has a thiophene core, could also be converted into **3i** in 90% yield. The reactions worked equally smoothly when employing the N-Boc substrates **8**. Under the optimized reaction conditions, the *para*-substituted substrates **8b–g** were successfully chlorinated at the *ortho*-position of the aniline to give **9b–g** in excellent yields. For the *meta*-substituted N-Boc-anilines, *ortho*-chlorination at C6 occurred readily when subjecting substrates **8h** and **8i** to the catalytic protocol. **9k** could be furnished smoothly when using the naphthyl substrate **8k**.

Surprisingly, the *ortho*-chlorination happened selectively at the bulkier C2 position when changing the *meta*-substitutions to fluorine, ester, ketone, and boronic ester (i.e., substrates **8l–r**), thus giving the corresponding chlorinated products **9l–r** in good yields upon isolation.[10] The amide substrates **10b–d** and **12b**, which have either ester or ketone substituents at the *meta*-position, also gave rise to the C2 chlorinated products **11b–d** and **13b**. The structures of **3f** and **13b** were confirmed unambiguously by X-ray crystallographic studies.[11] It is important to note that these compounds are expensive and valuable building blocks for many bioactive compounds.[12] They are difficult to achieve by using conventional synthetic methods, but can easily be prepared using this mild and efficient secondary ammonium salt catalytic protocol.[13]

Furthermore, the reaction was found to be readily scalable. For instance, 10 mmol of the aniline **8f** was subjected to the reaction and 2.84 grams (99% yield) of the desired *ortho*-chlorinated product **9f** was obtained (Scheme 2). The

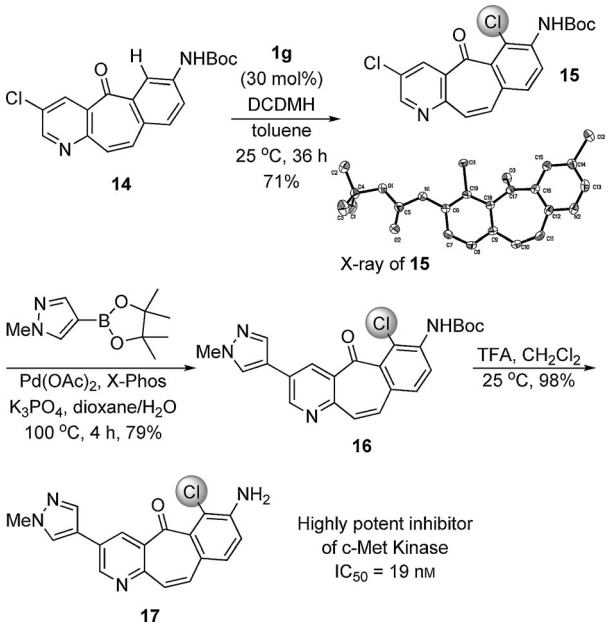


Scheme 2. Reaction scale-up and catalyst recycling.

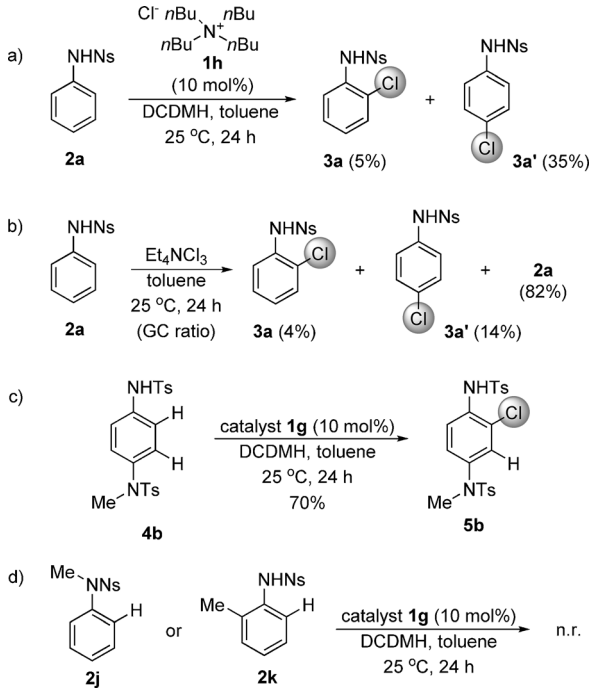
secondary ammonium salt catalyst **1g** could be recovered by aqueous extraction followed by evaporation of the water. The recycled catalyst **1g** was found to be equally effective (both reaction conversion and selectivity) in the catalytic chlorination. The chlorination/catalyst recycling process was repeated twice and no deterioration of the catalytic performance was observed. The catalyst loading could be reduced to 5 mol% although a longer reaction time was required. These practical and environmentally benign features are keys of sustainable development which are of great importance to the modern manufacturing sectors.[14]

This newly developed methodology can be applied to the preparation of valuable biologically relevant advanced intermediates. For example, the compound **17** (Scheme 3) is a highly potent inhibitor of c-Met Kinase for cancer treatment (c-Met $IC_{50} = 19$ nM), but the existing synthesis methods are not efficient.[15] By using **1g** as the catalyst, **14** was chlorinated regioselectively to give **15** in 71% yield (with 10% recovery of starting material) and the structure of **15** was confirmed unambiguously by an X-ray crystallographic study.[11] A relatively higher catalyst loading was required to achieve a reasonable reaction rate attributable to the electron-deficient nature of the substrate. Subsequent coupling of **15** with the the pyrazole-boronic ester furnished **16**. The Boc group in **16** could be unmasked using TFA to give **17**.

To obtain a clearer picture on the mechanism and probe the sole origin of the catalytic activity of the secondary ammonium salt **1**, a series of control experiments were conducted (Scheme 4). First, the tetra-*n*-butyl ammonium chloride salt **1h**, which has no NH proton, was examined. It was found that the *ortho*-selectivity was very poor when



Scheme 3. Synthesis of the highly potent c-Met kinase inhibitor **17**. TFA = trifluoroacetic acid.

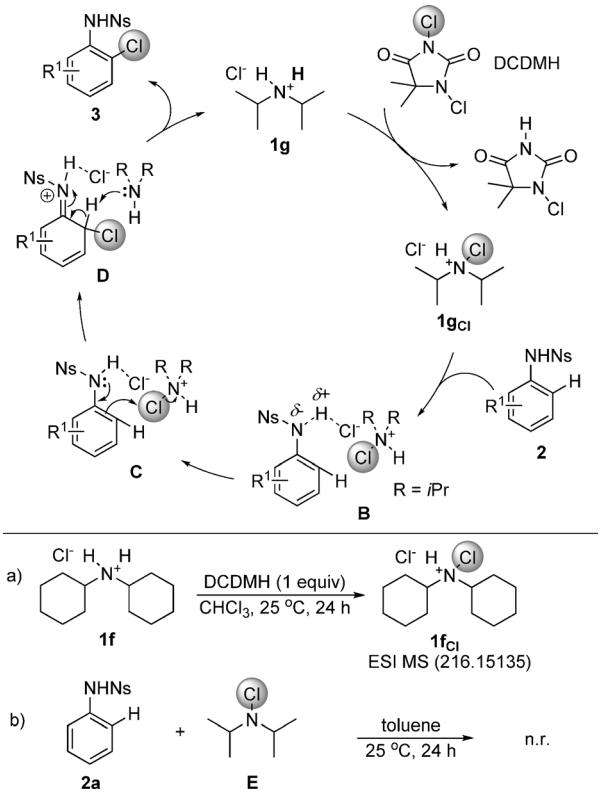


Scheme 4. Control experiments and mechanistic studies.

employing 10 mol% of **1h** (Scheme 4a). Next, the Mioskowski reagent[16] was used as the chlorinating agent in the halogenation of **2a** and poor regioselectivity was observed (Scheme 4b). The substrate **4b**, which contains a NHTs and NMeTs group at the 1- and 4-positions, respectively, was also examined. Although NMeTs is a stronger electron-donating group as compared to NHTs, the chlorination exhibited a strong preference for the *ortho*-position of the NHTs moiety to give the product **5b** (Scheme 4c). It was also found that

both the N-methyl nosylaniline **2j** and 2-methyl-substituted aniline **2k** returned a sluggish reaction under the optimized reaction conditions, thus suggesting that the NH hydrogen bonding and the steric factor might play crucial roles in the catalysis (Scheme 4d).

A proposed catalytic cycle is proposed based on the results from the mechanistic studies (Scheme 5). We believe that DCDMH could undergo halogen exchange with **1g** to



Scheme 5. Proposed catalytic cycle.

give the species $\mathbf{1g_{Cl}}$, which was evidenced by the detection of species $\mathbf{1f_{Cl}}$ using ESI high-resolution mass spectrometry (Scheme 5a; see Table 1, entries 7 and 8, the performance of catalysts **1f** and **1g** are comparable). An ^{1}H NMR experiment on a mixture of **1g** and DCDMH also revealed the existence of $\mathbf{1g_{Cl}}$.[9] In the ^{1}H NMR experiment, it was realized that some of $\mathbf{1g_{Cl}}$ decomposed to give the species **E** (probably through the elimination of a molecule of HCl), thus leading us to suspect that **E** might act as the active chlorinating agent. However, this possibility was ruled out since no reaction was observed when reacting **E** (prepared according to the literature method)[17] with **2a** (Scheme 5b). The chloride anion in $\mathbf{1g_{Cl}}$ might then hydrogen bond to the weakly acidic hydrogen in **2**, and it could bring the electrophilic Cl in close proximity to the *ortho*-position of **2** through Coulombic interactions (i.e., intermediate **B**).[18] The poor regioselectivity when using **1h** could be rationalized since there is no N-H in **1h** and the formation of **B** becomes impossible (Scheme 4a).[19] The chloride anion in **B** could then deprotonate the NsNH in **2** to give the basic NsN nitrogen center, which could trigger the electrophilic aromatic chlorination reaction through the proposed mechanistic pathway **B**→**C**→**D**, and give the product **3** together with the regeneration of **1g**. Although the reaction between **1** and DCDMH might generate molecular chlorine,[20] the poor performance of the Mioskowski reagent in the reaction (Scheme 4b) suggests that molecular chlorine might not play a crucial role in the *ortho*-chlorination of **2**. The regioselectivity in the electrophilic chlorination of **4b** and the low reactivity of substrate **2j** could be explained by the lack of N–H in the substrates (Scheme 4c,d). We believe that the mechanistic pathway **B**→**C** might be energetically less favorable with the bulkier 2-methyl-substituted substrate **2k** and hence inhibit the formation of the desired product.[21]

In summary, we have developed the first organocatalytic highly *ortho*-selective halogenation of anilines using the secondary ammonium salt **1g** under mild reaction conditions. The catalyst could be easily prepared, recovered, and reused, thus providing an excellent platform for the green and scalable preparation of *ortho*-chloroanilines.

Acknowledgments

We thank The Chinese University of Hong Kong (Project code 4053157) for financial support.

Keywords: arenes · halogenation · organocatalysis · regioselectivity · synthetic methods

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[8] The cut-off time was set at 14 h in order to have a parallel comparison. However, the less bulky catalyst **1a** could promote the reaction faster, but with a lower regioselectivity, as compared to that of the bulkier catalyst **1g**. For detail, see Scheme S1 in the Supporting Information.

[9] The details appear in the Supporting Information.

[10] We speculated that the substitutions at C1 and C3 of the substrates might coordinate to the electrophilic Cl, potentially through a mechanism similar to the *ortho*-lithiation of 1,3-disubstituted aryl compounds (D. W. Slocum, C. A. Jennings, *J. Org. Chem.* **1976**, *41*, 3653), and direct the chlorination at the more hindered C2. However, a more detailed study is underway to elucidate this result.

[11] CCDC 1496929 (**3f**), 1496930 (**13b**) and 1496931 (**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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[18] An ^{1}H NMR experiment on a mixture of $\mathbf{1g_{Cl}}$ (in situ generated from **1g** and DCDMH in $CDCl_3$) and **8q** was performed and an appreciable up-field shift of the aromatic signal was observed, and could be attributed to the hydrogen-bond interaction. The detail appears in Figure S3 in the Supporting Information.

[19] We have also examined a tertiary ammonium chloride salt. The reaction was relatively sluggish but the *ortho*-selectivity was found to be comparable to that of the secondary ammonium salt. However, the tertiary ammonium chloride salt is hydroscopic and hard to handle. For details, see Scheme S2 in the Supporting Information.

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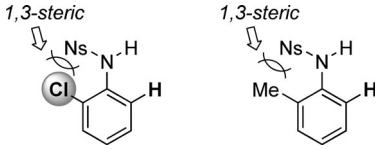
[21] The formation of the intermediate **C** with substrate **2k** might be inhibited because of the 1,3-*syn* steric stress between the Ns and the *ortho*-methyl group. Indeed, this 1,3-*syn* steric stress appears to be important to avoid over chlorination of the substrate. For detail, see Scheme S3 in the Supporting Information.



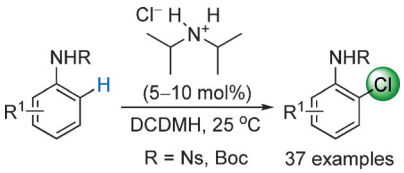
Manuscript received: July 30, 2016
Revised: October 11, 2016
Final Article published: ■■ ■■, ■■■■

Communications

Halogenation

X. Xiong, Y.-Y. Yeung* ——— ■■■■–■■■■

Highly *ortho*-Selective Chlorination of Anilines Using a Secondary Ammonium Salt Organocatalyst



Worth its salt: An efficient regioselective *ortho*-chlorination of anilines is described. A secondary ammonium chloride salt is employed as the organocatalyst and the reaction can be conducted at room temperature without protection from air and moisture. This catalytic protocol has broad substrate scope, is scalable, and was applied to the efficient synthesis of a potent c-Met kinase inhibitor. DCDMH = 1,3-dichloro-5,5-dimethylhydantoin.