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Halogenation

Selective Halogenation Using an Aniline Catalyst

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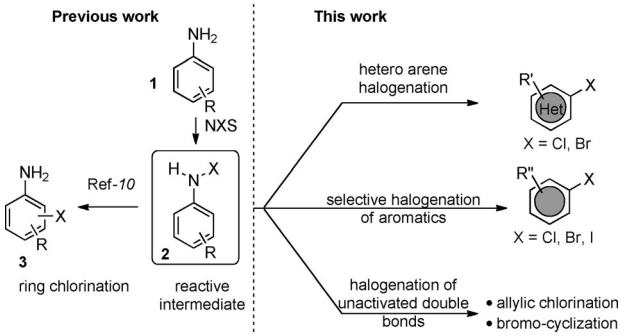
Abstract: Electrophilic halogenation is used to produce a wide variety of halogenated compounds. Previously reported methods have been developed mainly using a reagent-based approach. Unfortunately, a suitable "catalytic" process for halogen transfer reactions has yet to be achieved. In this study, arylamines have been found to generate an *N*-halo arylamine intermediate, which acts as a highly reactive but selective catalytic electrophilic halogen source. A wide variety of heteroaromatic and aromatic compounds are halogenated using commercially available *N*-halosuccinimides, for example, NCS, NBS, and NIS, with good to excellent yields and with very high selectivity. In the case of unactivated double bonds, allylic chlorides are obtained under chlorination conditions, whereas bromocyclization occurs for polyolefin. The reactivity of the catalyst can be tuned by varying the electronic properties of the arene moiety of catalyst.

The carbon-halogen (C–X) bond forming process is one of the most fundamental reactions in organic synthesis, and the applications of halogenated compounds in pharmaceuticals, agrochemicals, and the material sciences are of crucial importance.[1] They are indeed extensively used as precursors for the synthesis of organometallic reagents.[2] Since the discovery of cross-coupling reactions, aromatic halides are necessary parts for the synthesis of complex molecules.[3] Therefore, the development of efficient and more selective catalytic methods to easily access this class of compounds is essential.[4]

Classical electrophilic halogenation is still the method of choice.[5] However, regioselectivity is not always satisfactory in usual halogenation of aromatic and heteroaromatic compounds with multiple reaction centers.[4] Among various halogenating reagents, *N*-halosuccinimides (NXS; X = Cl, Br, I) have turned out to be practically useful reagents in terms of their easy and safe handling. Due to their low reactivity, several methods have been developed to activate NXS by using Lewis or Brønsted acids, which slightly increase the rate of reactions.[6] Recently, nucleophiles are also being used in halogen transfer reactions.[7] Alternatively, electrophilic halogenation of arenes using expensive metal catalysts (Pd, Rh, etc.) and *N*-haloimide as the halogenating reagent has been studied over the last decade.[8] Very recently, a guanidine-based chlorinating reagent, chloro-bis(methoxycarbonyl) guanidine (CBMG), was developed by the Baran group,[9] which showed increased reactivity together with selectivity compared to classical reagents, whilst similar brominating and iodinating reagents are not readily available.

Aromatic amines **1** are known to form amino halides even at low temperature, and the intermediately formed compounds **2** are known to rearrange into the ring halogenated products **3** at ambient temperature (Scheme 1).[10] Although this reaction



Scheme 1. *N*-halo arylamine, an active electrophilic halogen source.

was known to proceed intramolecularly, the resulting halogenated aniline should be less reactive than starting aniline and thus the intermolecular reaction may be faster than the intramolecular process. We envisioned that, in the presence of a nucleophilic substrate, the consequential *N*-haloaniline **2** might then transfer the halogen atom intermolecularly to regenerate the aniline. In principle, the reaction could be feasible in "catalytic aniline" with stoichiometric NXS.

With this hypothesis in hand, the initial experiment was performed with *N*-pivaloylindole as the nucleophilic substrate using aniline as a catalyst with an equimolar amount of NCS in dry DCM at room temperature. After 24 h, the chlorination product was obtained in 15% yield (Table 1, entry 2). Although the *N*-chloro amine was previously identified from *N*-methylaniline,[10b] the reaction did not proceed. Similarly, *N*-phenylaniline failed to deliver any chlorination product. Fortunately, the more nucleophilic aliphatic amine (benzylamine) was used as a catalyst. To our delight the reaction was successful and 75% of the chlorination product was obtained after 18 h (Table 1, entry 5). Furthermore, 2,6-dimethylaniline, which cannot undergo an intramolecular 1,2-chlorine transfer reac-

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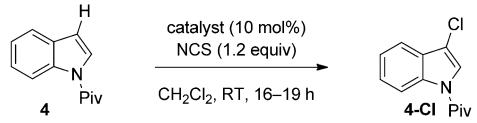
Table 1. Screening of different amines.



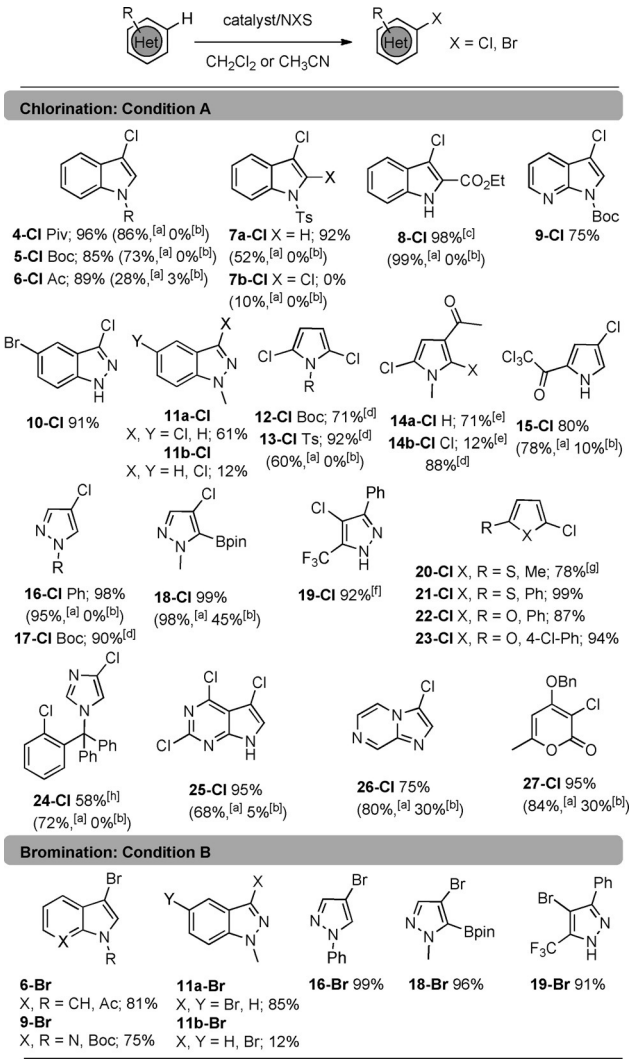
Entry	Catalyst	Yield [%][a]
1	none	0
2	aniline	15
3	*N*-Me-aniline	0
4	*N*-Ph-aniline	0
5	benzylamine	75
6	2,6-di-Me-aniline	95
7	2,4,6-tri-Me-aniline	96[b]
8	2,6-di-*i*Pr-aniline	93

[a] Determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [b] Yield of isolated product. Piv = pivaloyl, NCS = *N*-chlorosuccinimide

tion, was employed as a catalyst and the chlorination product was obtained in 95% yield (Table 1, entry 6). 2,4,6-Trimethylaniline delivered the chlorination product in a slightly better yield (96%) after 16 h (Table 1, entry 7). Increased steric bulkiness was also tolerated, and catalytic 2,6-diisopropylaniline turned out to be slightly less efficient, with a 93% yield in 20 h (Table 1, entry 8).

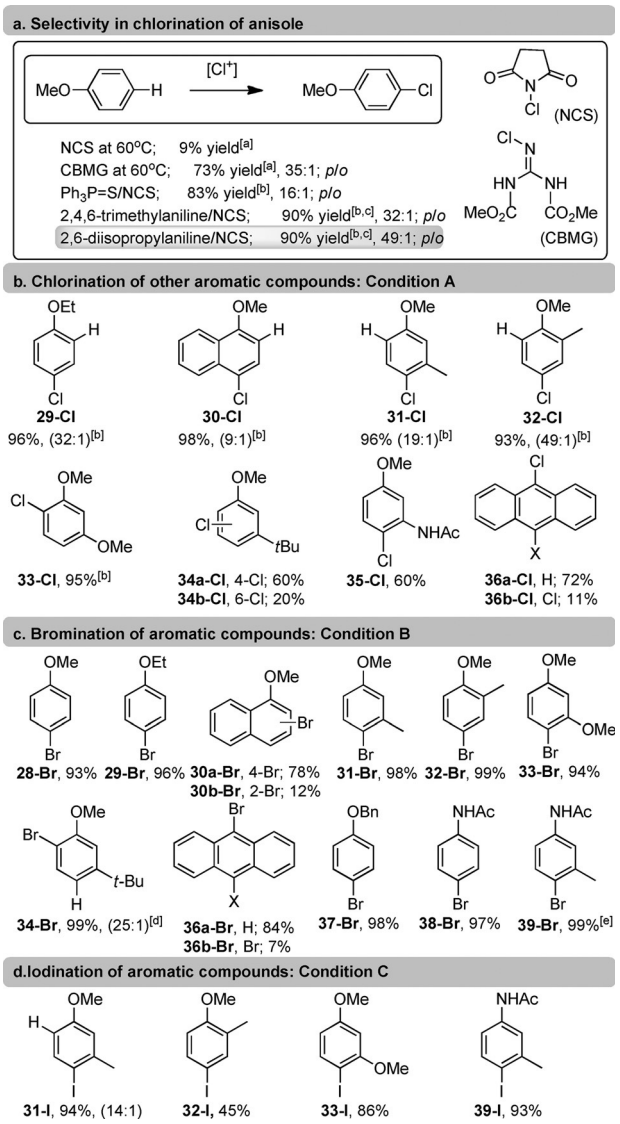
With this newly developed method, the scope of the chlorination of heteroaromatic compounds was investigated (Scheme 2). A wide variety of heteroaromatic compounds are compatible under optimized conditions. Several indoles (**4**–**9**), indazoles (**10**, **11**), pyrroles (**12**–**15**), pyrazoles (**16**–**19**), thiophenes (**20**, **21**), furans (**22**, **23**), and other important nitrogen- and oxygen-containing heterocycles (**24**–**27**) were chlorinated with good to excellent yields. In the case of indoles (**4**–**9**), the reaction works with complete C-3 selectivity and no halogenation at any other possible positions (C-2, C-5 and C-7) was observed. Compounds **12**–**14**, where the mixture of mono and bis chlorination products was obtained by using 1.2 equiv of NCS, were treated with 2.2 equiv of NCS to render bis chlorination as a single product. For less reactive substrates, a necessary excess of NCS was used for *N*-Boc pyrazole **17** (2.2 equiv NCS) and 5-trifluoromethyl 3-phenyl pyrazole **19** (2.0 equiv NCS). It is known that heteroaromatic compounds are difficult to brominate because of the ambident nucleophilicity associated with heteroatoms. However, several heteroaromatic compounds (**6**, **9**, **11**, **16**, **18**, and **19**) were reacted with *N*-bromosuccinimide (NBS) (1.1 equiv) in the presence of 2,4,6-trimethylaniline (2.0 mol%), the required monobromination products were obtained with excellent yields and selectivity. In the case of *N*-methylindazole (**11**), the bromination occured at the C3-position (**11 a-Br**, 85%), together with a minor amount of 5-bromo compound (**11 b-Br**, 12%).

We next tested our method for simple aromatics, because the regioselective halogenation of aromatic compounds has been a long-standing problem. Prior to the recently developed CBMG, experiments often resulted in rather unsatisfactory selectivity for the chlorination of anisole at higher temperature, except in the presence of the Brønsted acids.[9] To our delight,



Scheme 2. Halogenation of heteroaromatic compounds. All the reactions were performed in 0.5 mmol scale and yields of isolated products are given. Condition A: 2,4,6-trimethylaniline (10 mol%), NCS (1.2 equiv), CH_2Cl_2 or CH_3CN (0.25 M) at RT for 15–24 h. Condition B: 2,4,6-trimethylaniline (2.0 mol%), NBS (1.1 equiv), CH_2Cl_2 (0.25 M) at −40 to 0 °C for 6–24 h. [a] Yield using only CBMG. [b] Yield using only NCS. [c] 5 mol% catalyst. [d] 2.2 equiv NCS. [e] 2,6-dimethylaniline as catalyst. [f] 2.0 equiv NCS. [g] NMR yield with CH_2Br_2 internal standard. [h] 40 h reaction time.

when anisole **28** was reacted with NCS in the presence of catalytic 2,4,6-trimethylaniline in DCM as the solvent at room temperature, the mono chlorination product was obtained in 90% yield with a 32:1; *para*/*ortho* selectivity (Scheme 3). By increasing steric bulkiness of the catalyst, the use of 2,6-diisopropylaniline delivered the product with 49:1 *para*/*ortho* selectivity. This encouraged us to expand our study to other challenging substrates to determine whether or not they also produce similar selectivities under chlorination conditions. Aromatic compounds (**28**–**36**) (1.0 equiv) were reacted with NCS (1.2 equiv) in the presence of 2,4,6-trimethylaniline (10 mol%), and monochlorination products were obtained with very good yields and with very high *para*-selectivity. In the case of **34**, due to its high steric bulkiness, *ortho*-chlorination was ob-



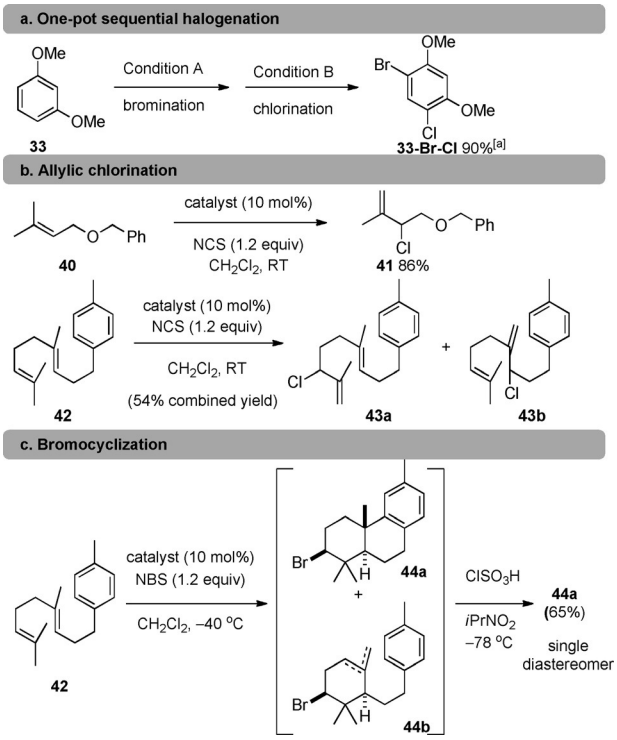
Scheme 3. Regioselective halogenation (Cl, Br, I) of aromatic compounds. Condition A: reactions were performed in 0.5 mmol scale, using 2,4,6-trimethylaniline (10 mol%), NCS (1.2 equiv), CH_2Cl_2 (0.25 M), RT, 5–24 h. Selectivity was determined by gas chromatography. Condition B: reactions were performed in 1.0 mmol scale, using 2,4,6-trimethylaniline (1.0 mol%), NBS (1.1 equiv), CH_2Cl_2 (0.25 M), −40 °C, 2–9 h. Condition C: reactions were performed in 0.25 mmol scale, using 2,4,6-trifluoroaniline (10 mol%), NIS (1.1 equiv), CH_2Cl_2 (0.25 M), RT for 24 h. Yield of the isolated products are given unless otherwise specified. [a] GC yield. [b] NMR yield using CH_2Br_2 as internal standard. [c] Yield of the major isomer. [d] 0.5 mmol scale. [e] 1.0 equiv NBS.

served in a substantial amount (**34b-Cl**, 20%) together with a major *para* product (**34a-Cl**, 60%).

The generality of this selective halogenation method was verified by performing other halogenation reactions. Gratifyingly, anisole, which does not react with sole NBS at room temperature, was efficiently brominated in the presence of 2,4,6-trimethylaniline (1.0 mol%) as a catalyst at −40 °C. The 4-Br-anisole was obtained in 93% yield. In order to examine the scope of this selective bromination reaction, different aromatic compounds (**29**–**34**, **36**–**39**) were reacted under optimized reaction conditions. Monobromination products were obtained in excellent yields and with very high *para*-selectivity. The presence of a bulky *tert*-butyl substituent switched the selectivity, and 3-*tert*-butyl anisole (**34**) was brominated in a 99% yield with a product distribution of 25:1 (C-6/C-4 position).

Surprisingly, 2,4,6-trimethylaniline turned out to be a much less active catalyst for iodination reactions. After screening several amines, electron-deficient 2,4,6-trifluoroaniline was identified as an effective catalyst in combination with *N*-iodosuccinimide (NIS) as the iodinating reagent and mono-iodination products **31-I**, **33-I**, and **39-I** were obtained in good to excellent yields, whereas **32-I** was obtained in a slightly lower yield of 45% (poor conversion 50%) and with very high *para* selectivity. This may be due to the higher reactivity of the *N*-iodo species. When 1,3-dimethoxybenzene (**33**) was treated with NBS and sequential treatment with NCS in the same pot delivered the bromo-chloro-substituted compound **33-Br-Cl** in 90% yield (Scheme 4). This sequential halogenation may be advantageous for a catalyst system.

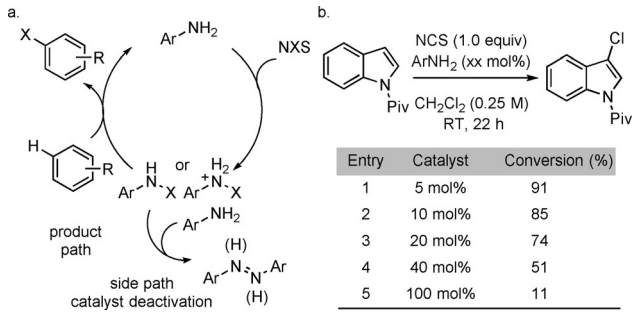
Finally, we tested the efficiency of our halogenation method for simple double bonds. When compound **40** was reacted under chlorination conditions, the corresponding allylic chloride **41** was obtained in 86% yield. No succinimide addition product was observed. Polyene compound **42** was also reacted under identical conditions (1.2 equiv of NCS), and a mixture of allylic chlorination products **43a** and **43b** was obtained in 54% yield. However, the same polyene compound **42** was treated under bromination conditions, and the bromocycli-



Scheme 4. One-pot sequential halogenation and halogenation of unactivated double bonds. Condition A: 2,4,6-trimethylaniline (1.0 mol%), NBS (1.0 equiv), CH_2Cl_2 (0.25 M), −40 °C for 4 h. Condition B: 2,4,6-trimethylaniline (10 mol%), NCS (1.2 equiv), RT for 12 h. [a] Isolated together with 2% dichloro and 3% dibromo compound. Catalyst = 2,4,6-trimethylaniline.

zation product **44a** was formed together with the partially cyclized product **44b**. Further treatment with chlorosulfonic acid promotes the cyclization to the single product **44a** in 65% yield.

To elucidate the mechanism of this reaction, the following experiments were performed. It was assumed that the reaction consists of two steps: first, arylamine is halogenated to give intermediate *N*-haloarylamine, which then transfers the halogen to an aromatic/olefinic system (Scheme 5). In a model reaction,



Entry	Catalyst	Conversion (%)
1	5 mol%	91
2	10 mol%	85
3	20 mol%	74
4	40 mol%	51
5	100 mol%	11

Scheme 5. a) Proposed catalytic cycle. b) Effect of catalyst concentration

2,4,6-trimethylaniline (1.0 equiv) was exposed to NCS (1.2 equiv) at 20 °C in a short time, then the reaction was frozen at −80 °C and analyzed by NMR spectroscopy (see the Supporting Information). This experiment showed a dramatic shift of the NH_2 signal (1.2 ppm) and the integration value for the NH_2 signal decreased (close to 1). This is a clear indication of the formation of the intermediate *N*-chloro species.[11] Low catalyst concentration is necessary in order to achieve high conversion as the catalyst is deactivated under high concentration to form catalytically inactive species (Scheme 5 and the Supporting Information). The second step in the halogen transfer from this intermediate to the olefin can occur either by a classical ionic pathway or a radical pathway. However, under identical reaction conditions for the heteroarene chlorination, **4** was reacted in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxyl radical (TEMPO) (20 mol%), a well-known radical quencher, and a 96% chlorination product **4-Cl** was obtained with a 24 h reaction time. Additionally, high diastereoselectivity was also observed during the bromocyclization reaction. These observations support the ionic pathway hypothesis, while the radical pathway can most likely be excluded.

In summary, an efficient catalytic halogenation method has been developed by using arylamine as a catalyst and NXS as a halogenating reagent. This protocol offers practical halogenation (Cl, Br, I) for a wide variety of heteroaromatic and aromatic compounds, with multiple reaction centers with very high yields and selectivity. Bromocyclization occurred under bromination conditions. One-pot sequential bromination and chlorination enable the synthesis of multi-halogenated arene. This method has high potential towards the development of new arylamine-derived catalysts for selective halogenation.

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Keywords: aniline catalyst · aromatic compounds · halocyclization · heteroaromatic compounds · halogenation

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[11] *N*-Haloarylammonium salt can also be a potent intermediate for halogen transfer reactions.

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