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# Complementary Site-Selective Halogenation of Nitrogen-Containing (Hetero)Aromatics with Superacids

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**Abstract:** Site-selective functionalization of arenes that is complementary to classical aromatic substitution reactions remains a long-standing quest in organic synthesis. Exploiting the generation of halenium ion through oxidative process and the protonation of the nitrogen containing function in $HF/SbF_5$, the chlorination and iodination of classically inert $Csp^2$-H bonds of aromatic amines occurs. Furthermore, the superacid-promoted (poly)protonation of the molecules acts as a protection, favoring the late-stage selective halogenation of natural alkaloids and active pharmaceutical ingredients

The strategic role of organic synthesis is critical to the successful discovery and development of new drugs.[1] Consequently, synthetic methods able to afford new collections of bioactive diverse molecules are awaited.[2] In this context, reaching molecular sites that are not accessible by conventional methods would overcome the prominence of innate electrophilic aromatic halogenation.[3] The role of halogen-substituted arenes in drug discovery[4] has tremendously increased over the past years encouraging the development of new methods for their transformation (Figure 1A) [5] Accordingly, it is somehow puzzling that late-stage halogenation of elaborated nitrogen-containing aromatics remains challenging.[6] Sandmeyer reaction is a classic approach but it requires the pre-functionalization of the arenes.[7] $X_2$ and N-X reagents are also commonly used, but they can be too reactive, unselective or, conversely, unreactive requiring the presence of strong electron-donating groups or the use of an appropriate activator.[8] Metal-catalyzed halogenations are also well-established methods,[9] but need a pre-installed directing group to control the regioselectivity of the halogenation. As for electrophilic halogenation with N-X reagents, the halogenation with polyhalogen salts[10] also takes place at innate aromatic positions and oxidative halogenations[11] show the same limitation (Figure 1B).[12] Alternatively, the use of halogenase enzymes[13] is hold back due to selectivity difficulties and substrate-dependent specificity.[14] In superacid, Jacquesy reported the bromination of aniline in the presence of $Br_2$ (Figure 1C).[15] Despite a poor selectivity, the superacid-promoted electrophilic bromination of aniline led partially to the formation of the 3-bromoaniline. This suggests that the persistent protonation of the aniline in superacid[16] partially modified the selectivity of the electrophilic addition. Furthermore, the reaction needed only sub-*stoichiometric* amount of $Br_2$ suggesting that the in situ generated HBr must be oxidized in solution to generate the reactive bromenium ion, as already postulated by Sommer. [17] Here, we disclose the non-innate selective chlorination and iodination of aromatic amines (Figure 1D).

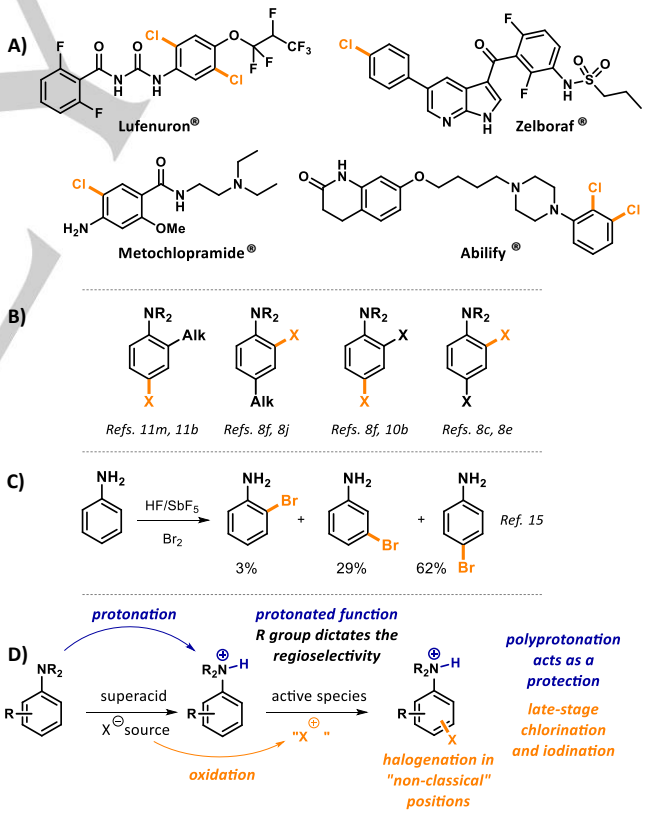


**Figure 1.** A) Halogenated active pharmaceutical ingredients; B) Recently reported electrophilic halogenation of aromatic amine derivatives on native reactive sites; C) Reported unselective bromination of aniline with $Br_2$ in superacid; D) This work.

The strategy relies on the continuous formation of the halenium ion by superacid oxidation of halide salts and on the modification

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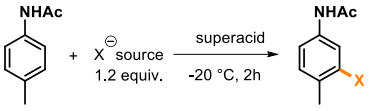
of the functional group directing effect by protonation in superacid. Moreover, the protection of the molecules by polyprotonation in superacid[18] is applied to selectively halogenate natural products and active pharmaceutical ingredients.

At the outset, 4-methylacetanilide **1a** was selected as a model substrate and submitted to superacid in the presence of halide ion sources. No reaction occurred with sodium chloride in neat HF or $CF_3SO_3H$ in the absence of oxidant (Table 1, entries 1-3). Addition of the strong oxidant oxone in $CF_3SO_3H$ led to the formation of a complex mixture of compounds, including the formation of polar hydroxylated products and of traces of 3-methylacetanilide after isomerization of the starting material (Table 1, entry 4).

**Table 1.** Halogenation of 4-methylacetanilide **1a** in the presence of halide ion source in superacid.




**1a** **2a$_X$**

| Entry | X⁻ source | Superacid | Conv[a] Yield (%)[b] |
|---|---|---|---|
| 1 | NaCl | $CF_3SO_3H$ | /[c] |
| 2[d] | NaCl | $CF_3SO_3H$ | /[c] |
| 3 | NaCl | HF | /[c] |
| 4 | NaCl | $CF_3SO_3H$[e] | /[f] |
| 5[g] | NaCl | HF/$SbF_5$ (7/1)[h] | 17 |
| 6[g] | NaCl | HF/$SbF_5$ (3/1)[h] | 48 |
| 7[g] | NaCl | HF/$SbF_5$ (2/1)[h] | 64 |
| 8 | NaCl | HF/$SbF_5$ (2/1)[h] | 100 (78) |
| 9 | $NH_4Cl$ | HF/$SbF_5$ (2/1)[h] | 100 (76) |
| 10 | NaBr | HF/$SbF_5$ (2/1)[h] | 87 (72)[i] |
| 11 | NaI | HF/$SbF_5$ (2/1)[h] | 90 (62) |
| 12 | NaF | HF/$SbF_5$ (2/1)[h] | /[j] |

[a] Conversion of **1a** determined by crude mixture NMR analysis; [b] Yield after purification by flash-chromatography; [c] No reaction; [d] Ambient temperature / 3 days; [e] Reaction conducted in the presence of 1.2 equiv. of oxone; [f] Complex mixture; [g] 15 min. reaction time; [h] HF/$SbF_5$ volumetric ratio / substrate concentration in this solution is 0.75 mol.L$^{-1}$; [i] Traces of a dibrominated product could be observed in the crude product. [j] No traces of fluorinated products by $^{19}F$ NMR analysis of the crude product.

Gratifyingly, the chlorinated product **2a$_{Cl}$** was generated in HF/$SbF_5$ solutions, and increasing $SbF_5$ amount favored the reaction to fully convert **1a** to **2a$_{Cl}$** (Table 1, entries 5-8). No significant impact of the counter cation was observed when performing the reaction in the presence of ammonium chloride (Table 1, entry 9). Under the same reaction conditions, the brominated and iodinated analogues **2a$_{Br}$** and **2a$_I$** were respectively obtained in 72% and 62% yield by performing the reaction in the presence of NaBr and NaI, the reaction with NaBr being less selective (Table 1, entries 10-11). As expected, no fluorinated product was generated from 1a in the presence of NaF (Table 1, entry 12).

The scope and functional group tolerance of this transformation was next evaluated (Figure 2). The bromination which seemed rather prone to favor polyhalogenation was not further evaluated. Acetanilide **1b** yielded products **2b$_X$** in good yields using an excess of NaX. Gratifyingly, 4-halogeno acetanilides **1c-1e** were selectively chlorinated and iodinated in position 3. While standard electrophilic aromatic halogenation of 4-halogen- or 4-alkyl-substituted aniline derivatives furnish their 2-halogenated analogue (Figure 1B), the 3-position is attained by the superacid-promoted strategy. Noteworthy, 4-bromoacetanilide **1e** led to chlorinated and iodinated products that are classically difficult to be obtained by standard procedures. Trifluoromethylated acetanilide **1f** was efficiently converted to products **2f$_{Cl}$** and **2f$_I$**. To expand the reaction scope beyond, 3-substituted acetanilides (**1g-1k**) were also submitted to the halogenation protocol. Halogenation occurred in position 4 from 3-methyl-acetanilide **1g** in good yields. Surprisingly, while the chlorination of 3-fluoro **1h** and 3-chloroacetanilide **1i** occurred predominantly in position 6, the iodination of the same substrate **1i** led to the formation of the 4-iodinated product **2i$_I$**, a position also chlorinated after reaction of brominated substrate **1j**. A difference of behaviour between chlorination and iodination was also observed from 3-trifluoromethylated acetanilide **1k**. The iodination occurred in position 5 from this substrate when chlorination occurred in position 4, this regioselectivity coming probably from steric hindrance effect of the $CF_3$ group. To our delight, as expected, the halogenation of 2-alkyl and 2-halogeno-substituted acetanilides occurred regioselectively at the non-native position 5 of the aromatic ring (**2l$_X$-2o$_X$**), when classically encountered halogenation from these substrates occurs in position 4 (Figure 1B). From the trifluoromethylated substrate **1p**, the halogenation occurs in position 4. The nitro-substituted acetanilide **1q** was less reactive and deprotected chlorinated amine **3** was obtained in poor yield after 48 hours reaction. The iodinated tertiary amide **2r$_I$** and the non-protected aniline **5** could also be directly synthesized from **1r** and 4-methylaniline **4**. The formation of the iodinated product **2s$_I$** from the protected diamine **1s** and of the 4-chloro-4-iodobenzene **7** from chlorobenzene **6** confirmed the extended scope of the method. The selectivity of the method over competing α-halogenation of carbonyl function[19] was also proved by the formation of product **9** from oxindole **8**. To summarize, this scope and limitation study revealed that in superacid solutions, in which neutral acetamide function must be in equilibrium with its protonated form, halogen atom(s) and alkyl group(s) orientate the electrophilic addition (halogenation in position 3 for substrates bearing alkyl or halogens in position 4 / halogenation in position 5 for substrates bearing alkyl or halogens in position 2). When no substituent is present, or from acetanilide bearing a strong electronwithdrawing group (in 2- and 4-trifluoromethyl acetanilides), the amide seems to orientate the reaction. When acetanilide is substituted in position 3 with halogen or trifluoromethyl groups, the regioselectivity is strongly dependent on the nature of the inserted halogen and on the electronic (and steric) repulsion between the inserted atom and the ones already located on the ring.

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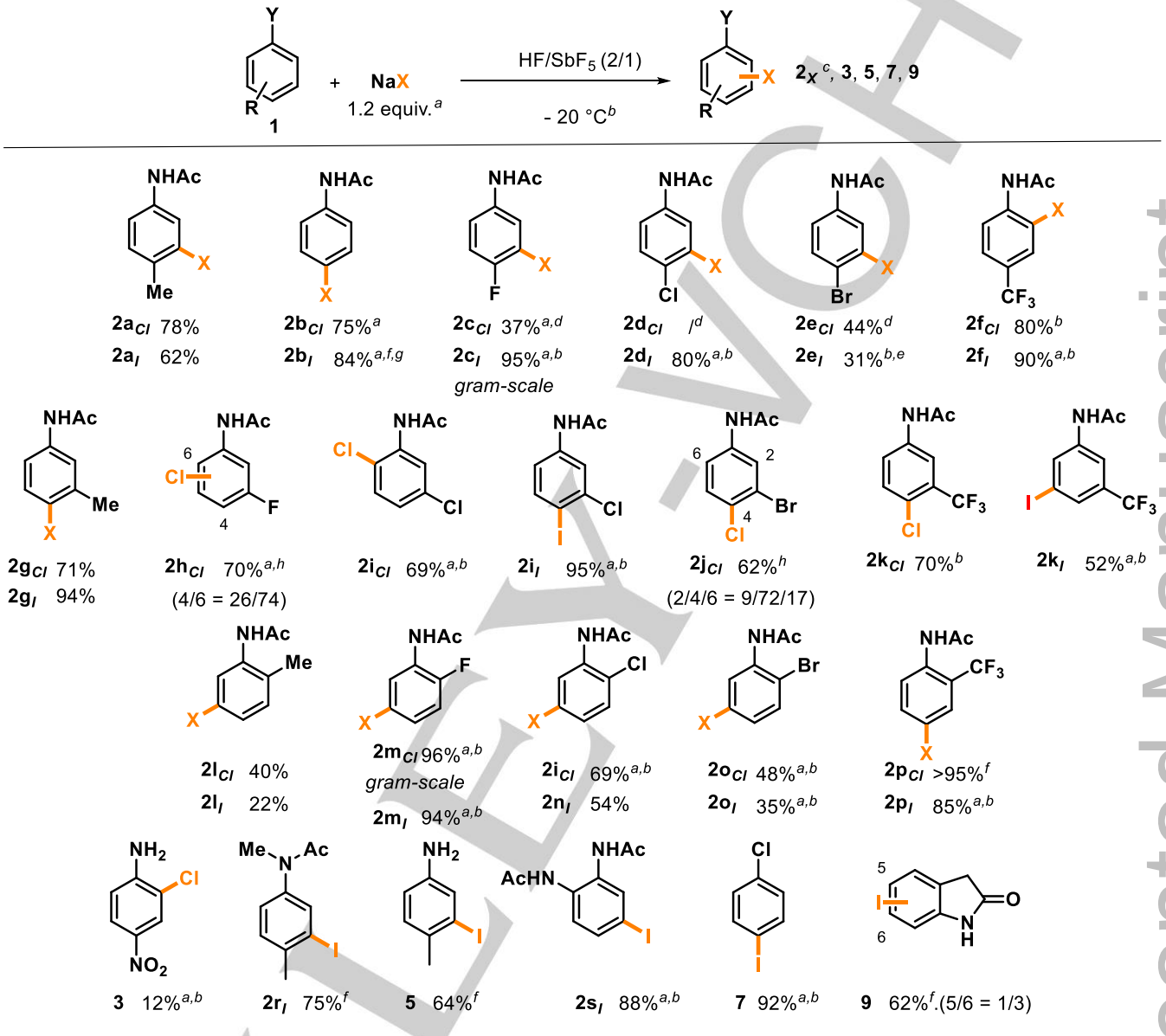
**Figure 2.** Chlorination and iodination of aromatics in superacid.




[a] 3.5 equiv. of NaX was used in the indicated cases; [b] Activation at room temperature was needed in some indicated cases; [c] Yield obtained after purification by flash chromatography; [d] Products from polyhalogenation were concomitantly generated; [e] Undetermined side products formation; [f] Conversion determined by $^1$H NMR analysis of the crude product; [g] Generated in a 92/8 ratio with its 2-iodoisomer; [h] yield of the major isomer obtained after purification.

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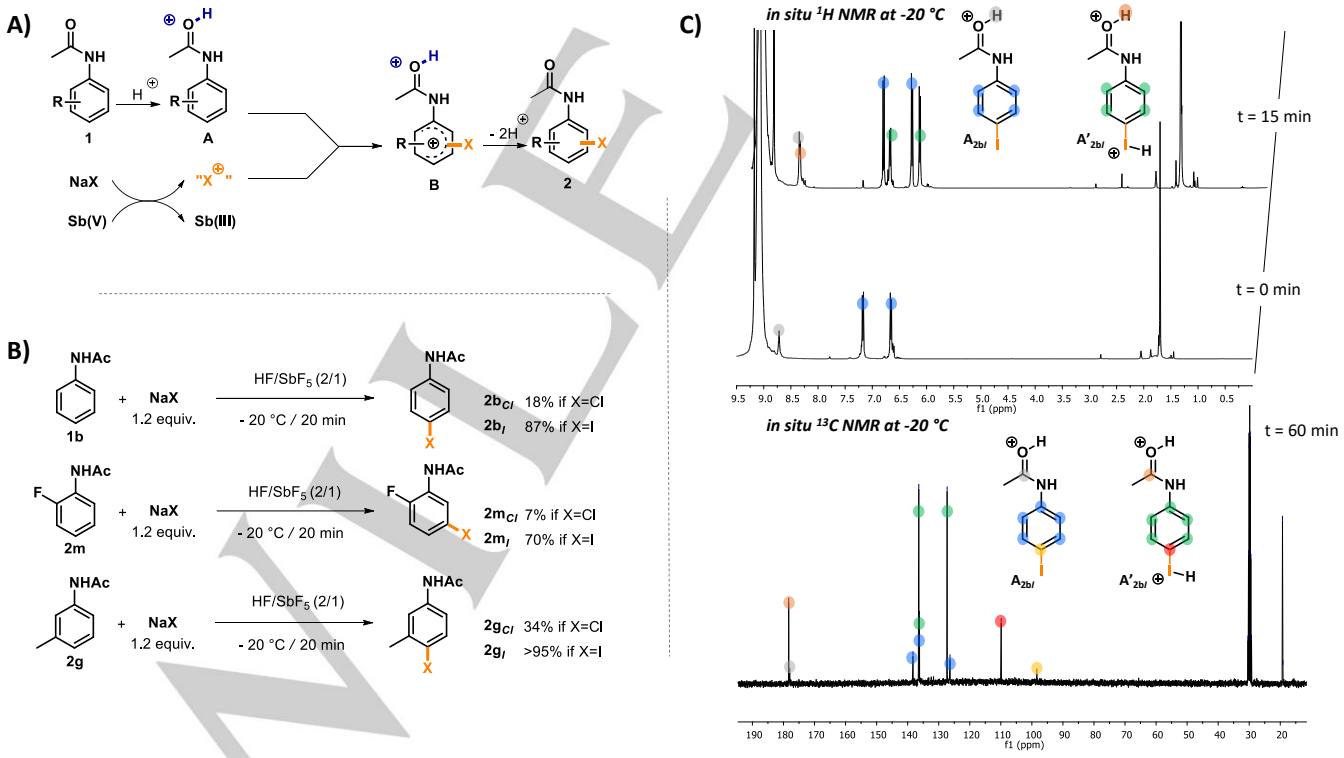
The following mechanism can be proposed to account for the halogenation reaction (Figure 3A). Ions **A** are obtained after acetanilides protonation.[20] A beneficial effect of $SbF_5$ amount on reaction efficiency was demonstrated (Table 1, entries 3-6). This can be directly correlated to the fact that when the concentration of $SbF_5$ in HF is higher than 20 mol%, increasing amounts of non-associated $SbF_5$ appears.[21] Moreover, it is important to note that the chlorination of the substrates often requires longer reaction time and excess of NaCl compared to the iodination process. This difference of behavior was confirmed by comparing the reactivity of some selected acetanilides in the presence of NaX after a short reaction time (Figure 3B). While slow chlorination occurs, the iodination was quickly performed from the same substrates. These results follow a general trend in accordance with the redox properties of halogens and halide ions. Thus, as previously demonstrated,[22] $SbF_5$ act as an oxidant in $HF/SbF_5$ solutions and oxidise chloride and iodide ions to generate elemental halogen in solution.[23] This was confirmed by evidencing the formation of $SbI_3$ and $I_2$ by X-ray diffraction analysis of the crude powder collected after reaction of NaI in $HF/SbF_5$ (see SI). The generated halenium ion can then react with ion A to generate the intermediate **B**, precursor of products **2**. To further understand the absence of polyiodination, monoiodinated product $\mathbf{2b_I}$ behaviour in superacid solutions was evaluated by in situ low-temperature NMR spectroscopy (see SI). The ion $\mathbf{A_{2b_I}}$ resulting from the O-protonation of the amide function was first generated (Figure 3C). A diprotonated species $\mathbf{A'_{2b_I}}$ was also detected after few minutes and gradually increased in solution over time. It must result from a subsequent protonation of the iodine atom, evidenced by the deshielding of the C4 carbon atom at 109.9 ppm (+ 11.5 ppm compared to ion $\mathbf{A_{2b_I}}$).[24] This result accounts for the protonation of the inserted halogen, protecting the substrate from any undesired further halogenation. Under these highly acidic conditions, the formation of the thermodynamically most stable product could have been hypothesized to explain the regioselectivity of the process.[25] The thermodynamically directed isomerization of products can only be explained by intramolecular isomerization within an arenium ion intermediate. However, as shown for the halogenation of non-substituted acetanilide **1b**, chlorination and iodination leads only to the para product $\mathbf{2b_X}$, and even after prolonged reaction time, no product halogenated in meta position could be detected in the crude (also confirmed by low-temperature NMR (Figure 3C). It suggests the absence of thermodynamically directed isomerization of the iodinated product after reaction in the reaction conditions.[26]

**Figure 3** A) Postulated superacid-promoted halogenation reaction mechanism; B) Comparison of the reactivity of selected acetanilides toward chlorination and iodination after 20 minutes of reaction at -20 °C; C) $^{1}H$ and $^{13}C$ NMR spectrum of the superacid $HF/SbF_5$ solution of compound $\mathbf{2b_I}$ at -20 °C.



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The generality of the proposed superacid-promoted halogenation method for more complex nitrogen containing derivatives, such as those that might be encountered in pharmaceutical or agrochemical research, needed to be assessed. Generating analogues of bioactive natural products and/or active pharmaceutical ingredients through direct functionalization of unactivated bonds is now considered as a standard method in the medicinal chemist's toolbox.[27] Thus, we first investigated the late stage halogenation of lidocaïne **11a** and anticancer agent dasatinib **11b** (Figure 4).

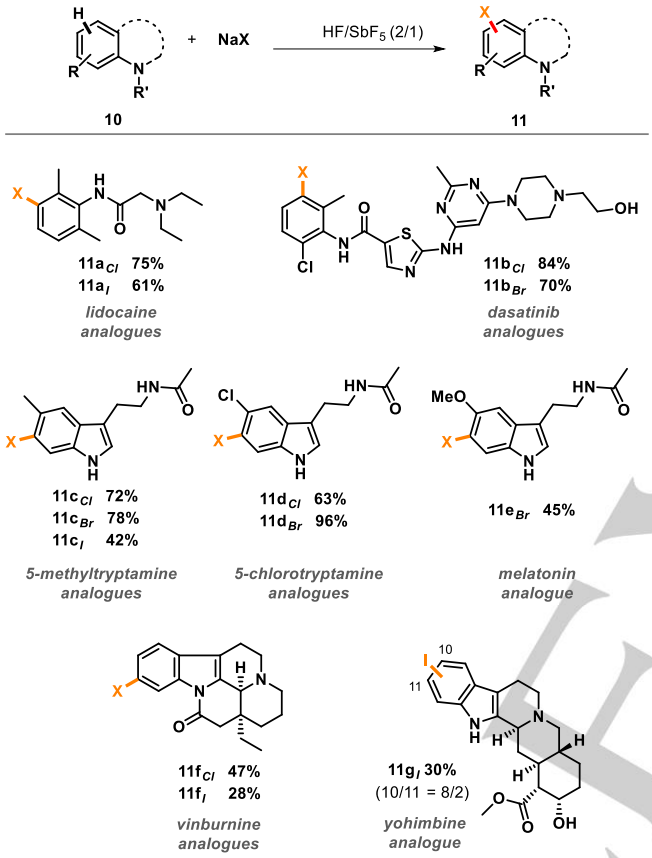


**Figure 4.** Direct halogenation of bioactive pharmaceutical ingredients and natural products.

With success, their halogenated analogues could be regioselectively generated in good yields. To test the feasibility of the halogenation methodology to create new structural space around a complex but structurally distinct class of biologically active compounds, we next screened indole alkaloids. 5-Methyl, 5-chloro-N-acetyltryptamine and melatonin **10c-e** were efficiently and selectively halogenated in position 6 in one step. The unusual selectivity for an electrophilic substitution on indole derivatives can be attributed to the formation of an iminium ion after protonation of the carbon atom of the pyrrole ring β to the nitrogen atom in superacid. The substituent located in position 5 and the alkyl ring orientate the electrophilic substitution. The complexity of vinburnine **10f** is apparent from its dense array of functionalities and the presence of chiral centres. Exploiting the halogenation method, its chlorinated and iodinated analogues **11f$_{Cl}$** and **11f$_{I}$** were directly generated. In this case, traces of the 6-halogenated isomers could be detected in the reaction crude. One step further in complexity, and consequently rising up the challenge for clean and direct functionalization, the halogenation of the *Pausinystalia Yohimbe* alkaloid **10g** was tested. The iodination was shown to be effective and led to the formation of 10- and 11-iodoyohimbine. The former **11g$_{I}$** predominating as the major isomer could be cleanly separated from its minor regioisomer. To our delight, these data demonstrate that the method provides rapid and efficient access to analogues of indole-containing pharmaceutically interesting compounds that could not be generated by conventional methods or at the expense of troublesome multi-step synthetic sequence.

To conclude, exploiting the unique chemical properties of superacid, namely its oxidative properties and its capability to polyprotonate compounds, a site-selective non-innate halogenation of nitrogen-containing compounds has been developed. Given tremendous momentum in the field of late stage CH functionalization, this method proved its efficiency for the direct halogenation of (poly)functionalized natural alkaloids and active pharmaceutical ingredients, thereby offering a distinct approach to control site-selectivity. This strategy can now be considered as a new development in the field of chemical and pharmaceutical industries. By protecting the molecules by protonation, it opens perspectives to directly modify bioactive compounds at any stage of a synthetic plan.

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**Keywords:** Late-stage • halogenation • diversity • reaction mechanism • active pharmaceutical ingredients

[1] a) National Research Council (US). Health and Medicine: Challenges for the Chemical Sciences in the 21st Century. Washington (DC): National Academies Press (US); **2004**. 2, New Methods in Synthesis and Development for Pharmaceuticals; b) D. P. Rotella, *ACS Chem. Neurosci*. **2016**, *7*, 1315-1316; c) K. D. Warner, C. E. Hajdin, K. M. Weeks, *Nat. Rev. Drug. Discov.* **2018**, *17*, 547-558.

[2] a) C. Lipinski, A. Hopkins, *Nature* **2004**, *432*, 855-861; b) V. Abet, A. Mariani, F. R. Truscott, S. Britton, R. Rodriguez, *Bioorg. Med. Chem.* **2014**, *22*, 4474-4489; c) J. L. Reymond, *Acc. Chem. Res.* **2015**, *48*, 722-730. d) S. L. Schreiber, *Science* **2000**, *287*, 1964-1969.

[3] R. C. Larock, L. Zhang, *Aromatic halogenation in* Larock, R. C. Ed. Comprehensive organic transformations 3rd Ed. (Wiley 2018).

[4] a) R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger, F. M. Boeckler, *J. Med. Chem.* **2013**, *56*, 1363-1388; b) G. W. Gribble, Naturally occurring organohalogen compounds: A comprehensive Update (Springer, Vienna 2010); c) L. Wang, X. Zhou, M. Fredimoses, S. Liao, Y. Liu, *RSC Adv.* **2014**, *4*, 57350-57376.

[5] a) For a recently developed ortho functionalization of halogenoarene and their exploitation, see: J. Wang, R. Li, Z. Dong, P. Liu, G. Dong, *Nat. Chem.* **2018**, *10*, 866-872; b) For a monograph, see: Metal-Catalyzed Cross-Coupling Reactions", Eds A. de Meijere and F. Diederich, Wiley-

VCH, Weinheim, 2004, vols 1 and 2; c) For a recent example of photoredox transformation, see: B. Michelet, C. Deldaele, S. Kajouj, C. Moucheron, G. Evano, *Org. Lett.* **2017**, *19*, 3576-3579.

[6] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257-10274; b) Y. Sasson, *Aromatic halo*genation in S. Patai, Z. Rappoport. Ed. *Supplement D2; The Chemistry of Halides, Pseudo-Halides and Azides.* (Wiley and Sons 1995).

[7] V. Snieckus, *Chem. Rev.* **1990**, *90*, 879-933.

[8] a) Y. Nishii, M. Ikeda, Y. Hayashi, S. Kawauchi, M. Miura, *J. Am. Chem. Soc.* **2020**, *142*, 1621-1629; b) C. Cooze, R. Dada, R. J. Lundgren, Angew. Chem. **2019**, *131*, 12374-12379; *Angew. Chem. Int. Ed.,* **2019**, *58*, 12246-12251; c) C-Y; Zhou, J. Li, S. Peddibhotla, D. Romo, *Org. Lett.* **2010**, *12*, 2104-2107; d) K. Verma, T. Zang, T. M. Penning, P. C. Trippier, *J. Med. Chem.* **2019**, *62*, 3590-3616; e) T. Mahajan, L. Kumar, K. Dwivedi, D. D. Agarwal, *Int. Eng. Chem. Res.* **2012**, *51*, 3881-3886; f) D. T. Racys, C. E. Warrilow, S. L. Pimlott, A. Sutherland, *Org. Lett.* **2015**, *17*, 4782-4785; g) F. Mo, J. M. Yan, F. Li, Y. Zang, J. Wang, *Angew. Chem. Int. Ed.* **2010**, *49*, 2028-2032; h) S. Kathiravan, I. A. Nicholls, *Chem. Eur. J.* **2017**, *23*, 7031-7036; i) R. A. Rodriguez, C. -M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 6908-6911; j) Z. Lu, Q. Li, M. Tang, P. Jiang, H. Zheng, X. Yang, *Chem. Commun.* **2015**, *51*, 14852-14855; For superacid promoted halogenation with N-X reagents, see: k) G. K; S. Prakash, T. Matthew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul, G. A. Olah, *J. Am. Chem. Soc.* **2004**, *126*, 15770-15776; l) G. A. Olah, W. Wang, G. Sandford, G. K. S. Prakash, *J. Org. Chem.* **1993**, *58*, 3194-3195.

[9] F. Lied, T. Para, F. Glorius, *Israel. J. Chem.* **2017**, *57*, 945-952; b) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003-8104; c) W. Hao, Y. Liu, *Belstein J. Org. Chem.* **2015**, *11*, 2132-2144.

[10] a) I. T. Alt, C. Guttroff, B. Plietker, *Angew. Chem.* **2017**, *129*, 10718-10722; *Angew. Chem. Int. Ed.* **2017**, *56*, 10582-10586; b) A. Deshrmukh, B. Gore, H. V. Thulasiram, V. P. Swamy, *RSC Adv.* **2015**, 5, 88311-88315; c) B. Hu, W. H. Miller, K. D. Neumann, E. J. Linstad, S. G. DiMagno, *Chem. Eur. J.* **2015**, *21*, 6394-6398.

[11] a) L. Zhang, J. Zhang, J. Ma, D.-J. Cheng, B. Tan, *J. Am. Chem. Soc.,* **2017**, *139*, 1714-1717; b) N. Narender, K. S. K. Reddy, K. V. V. K. Mohan, S. J. Kulkarni, *Tetrahedron Lett.* **2017**, *48*, 6124-6128; c) A. Podgorsek, M. Zupan, J. Iskra, *Angew. Chem. Int. Ed.* **2009**, *48*, 8424-8450; d) L. Zhang, X. Hu, *Chem. Sci.* **2017**, *8*, 7009-7013; e) D. Petzold, B. Köning, *Adv. Synth. Catal.* **2018**, *360*, 626-630; f) M. Gurry, M. Sweeney, P. McArdle, F. Aldabbagh, *Org. Lett.* **2015**, *17*, 2856-2859; g) A. K. Mohanakrishnan, C. Prakash, N. Ramesh, *Tetrahedron* **2006**, *62*, 3242-3247; h) H. Kajita, A. Togni, *Chemistry Select* **2017**, *2*, 1117-1121; i) L. Gu, T. Lu, M. Zhang, L. Tou, Y. Zhang, *Adv. Synt. Catal.* **2013**, *355*, 1077-1082; j) B. S. Moon, H. Y. Choi, H. Y. Koh, D. Y. Chi, *Bull. Korean Chem. Soc.* **2011**, *32*, 472-476; k) T. Mahajan, L. Kumar, K. Dwivedi, D. D. Agarwal, *Synth. Commun.* **2012**, *42*, 3655-3663; l) S. Kajigaeshi, Y. Shinmasu, S. Fujisaki, T. Kakinami, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 941-943; m) E. M. Gayakwad, K. P. Patel, G. S. Shankarling, *New J. Chem.* **2019**, *43*, 6001-6009.

[12] For a rare example of non-innate halogenation, see: X. Xiong, Y. -Y. Yeung, *Angew. Chem.* **2016**, *128*, 16335-16339; *Angew. Chem. Int. Ed.* **55**, 16101-16105.

[13] C. Schnepel, N. Sewald, *Chem. Eur. J.* **2017**, *23*, 12064-12086.

[14] a) V. Weichold, D. Milbredt, K. -H. van Pée, *Angew. Chem.* **2016**, *128*, 6482-6498; *Angew. Chem. Int. Ed.* **2016**, *55*, 6374-6389; b) J. Latham, E. Brandenburger, S. A. Sheperd, B. K. R. Menon, J. Mickfield, *Chem. Rev.* **2018**, *118*, 232-269; For a recent marine viral halogenase for iodination, see: D. S. Gkotsi, H. Ludewig, S. V. Sharma, J. A. Connolly, J. Dhaliwal, Y. Wang, W. P. Unsworth, R. J. K. Taylor, M. M. W. McLachlan, S. Shanahan, J. H. Naismith, R. J. M. Goss, *Nat. Chem.* **2019**, *11*, 1091-1097.

[15] C. Berrier, J.-C. Jacquesy, A. Renoux, *Bull. Soc. Chim. Fr.* **1990**, *127*, 93-97.

[16] S. R. Hartshorn, J. H. Ridd, *J. Chem. Soc. B* **1968**, 1068-1074.

[17] a) G. Cherry, J.-C. Culman, J. Sommer, *Tetrahedron Lett.* **1990**, *31*, 2007-2010; b) S. Delavarenne, S. Simon, M. Fauconet, J. Sommer, *J. Am. Chem. Soc.* **1989**, *111*, 383-384; c) J. Sommer, J. Bukala, M. Hachoumy, R. Jost, *J. Am. Chem. Soc.* **1997**, *119*, 3274-3279.

[18] a) G. A. Olah, G. K. S. Prakash, A. Molnar, J. Sommer, *Eds.* Superacids (2nd ed), Wiley Intersciences: New-York, **2009**; b) For a recent example, see: L. J. C. Bonazaba Milandou, H. Carreyre, S. Alazet, G. Greco, A. Martin-Mingot, C. Nkounkou Loumpangou, J. -M. Ouamba, F. Bouazza, T. Billard, S. Thibaudeau, *Angew. Chem.* **2017**, *129*, 175-178; *Angew. Chem. Int. Ed.* **2017**, *56*, 169-172.

[19] L. Zhang, X. Hu, X. *Chem. Sci.* **2017**, *8*, 7009-7013.

[20] D. A. Klumpp, Y. Zhang, A. Gomez, A. McElrea, *Org. Lett.* **2004**, *6*, 1789-1792.

[21] The presence of an initially small but increasing amount of uncomplexed $SbF_5$ has been observed for concentrations above 20 mol% $SbF_5$ in HF solutions, see: J. -C. Culmann, M. Fauconet, R. Jost, J. Sommer, *New J. Chem.* **1999**, *23*, 863-867.

[22] Sb(V) is a strong oxidant in the superacid media HF/$SbF_5$ (Sb(V)/Sb(III), $E_{1/2}$ = + 1.9 V vs Ag/AgCl), see : G. Brilmyer, R. Jasinski, *J. Electrochem. Soc.* **1982***, 129,* 1950-1954.

[23] The formation of antimony pentafluoride adducts of chlorine monofluoride or iodine monofluoride cannot be discarded, these adducts readily decomposing to yield disproportionation interhalogen products, see: M. Gambardella, S. Kongpricha, J. J. Pitts, A. W. Jache, *Can. J. Chem.* **1989**, *67*, 1828-1831.

[24] G. A. Olah, Y. Yamada, R. J. Spear, *J. Am. Chem. Soc.,* 1975, **97**, 680-681.

[25] For the superacid-promoted bromination of aniline in the presence of $Br_2$, isomerisation was suggested to occur at ambient temperature, see ref 15.

[26] As for superacid-promoted acetylation and, contrary to superacid-promoted alkylation, no isomerization occurs in our conditions, suggesting that the halogenation process is not subject to thermodynamically directed isomerization, see: G. A. Olah, O. Farook, S. Morteza, F. Farnia, J. A. Olah, *J. Am. Chem. Soc.* **1988**, *110*, 2560-2565.

[27] T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546-576.

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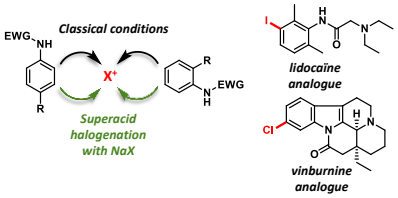


Complementary site-selective halogenation of nitrogen containing arenes has been developed in superacid HF/$SbF_5$ in the presence of halide salts. By protecting the molecules by protonation, this method can also be applied to the late-stage selective halogenation of natural alkaloids and active pharmaceutical ingredients