Introducing N-X Anomeric Amides: Powerful Electrophilic Halogenation Reagents

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ABSTRACT: Electrophilic halogenation is a widely-used tool employed by medicinal chemists to either pre-functionalize molecules for further diversity or incorporate a halogen atom in drugs or drug-like compounds to solve metabolic problems or modulate off-target effects. Current methods to increase the power of halogenation rely either on the invention of new reagents or activating commercially available reagents with various additives such as Lewis/Brønsted acids, Lewis bases and hydrogen bonding activators. There is a high demand for new reagents that can halogenate otherwise unreactive compounds under mild conditions. Herein we report the invention a new class of powerful halogenating reagents based on anomeric amides, taking advantage of the energy stored in the pyramidalized nitrogen of N-X anomeric amides as a driving force. These robust halogenating methods are compatible with a variety of functional groups and heterocycles, as exemplified on over 50 compounds (including 13 gram-scale examples and 1 flow chemistry scale-up). Their high halogenating prowess is also demonstrated in other reactivity contexts. A DFT computational study supports the defining role of the anomeric amide motif.

Generally speaking, chlorine and bromine atoms are amongst the only functional groups that can be viewed as both facile precursors (gateways) to other functionality (through cross-coupling[1]) *and* potentially useful for their inclusion in a final drug substance[2-3]. Indeed, numerous FDA approved drugs contain these halogen atoms, and their introduction can often have a documented "magical" effect on desired properties[4]. For instance (Figure 1A), the potency of lead structures **1**[5]and **2**[6] could be improved by several orders of magnitude by the simple installation of chlorine and bromine atoms, respectively. Electrophilic aromatic halogenation[7] is arguably the earliest example of industrial practitioners embracing the now wildly popular strategies of "late-stage functionalization"[8-11] and C–H functionalization[12-13]. In fact, recent reviews point to electrophilic halogenation as being one of the reaction classes most prized by medicinal chemists[14-15]. Numerous elegant approaches relying on C–H activation[16-17] or indirect halogenation[18-21] via intermediate species have emerged to provide alternative tactics to access halogenated arenes. That said, there are numerous contexts for which the available reaction and reagent toolkit are insufficient to satisfy demand such as the halogenation of the simple triazole found in vericonazole (**3**, Figure 1A). Historical approaches to increase the power of electrophilic halogenation are summarized in Figure 1B and generally rely either on the invention of new reagents[22-24] or by activating known reagents with additives[25-30]. The majority of electrophilic halogenation reagents are based on stable N-X bonds wherein the flanking substituents on nitrogen include various electron withdrawing groups. Anomeric amides (Figure 1C), first introduced by Glover[31] and widely studied in the 1980's have historically been utilized as nitrenium ion precursors via nucleophilic attack *at nitrogen*[32-33]. In contrast, there have been no investigations we are aware of wherein these unusual species have been harnessed to activate a halogen atom. The premise of this study was that enhanced reactivity might result from the use of reagents based on an anomeric amide by virtue of a spring-loaded driving force to rehybridize following halogenation from a sp^3 to sp^2 nitrogen center. In this disclosure (Figure 1D), a new class of powerful electrophilic reagents based on anomeric amides is presented. Through extensive benchmarking with state-of-the-art protocols, it is shown that such reagents are extremely useful for achieving scalable (in batch and flow settings) and efficient arenes chlorination and bromination at both an early and late stage. Their halogenating power is not limited to arenes as advantages are observed with other reaction manifolds; a computational study supports the defining role of the anomeric amide motif.

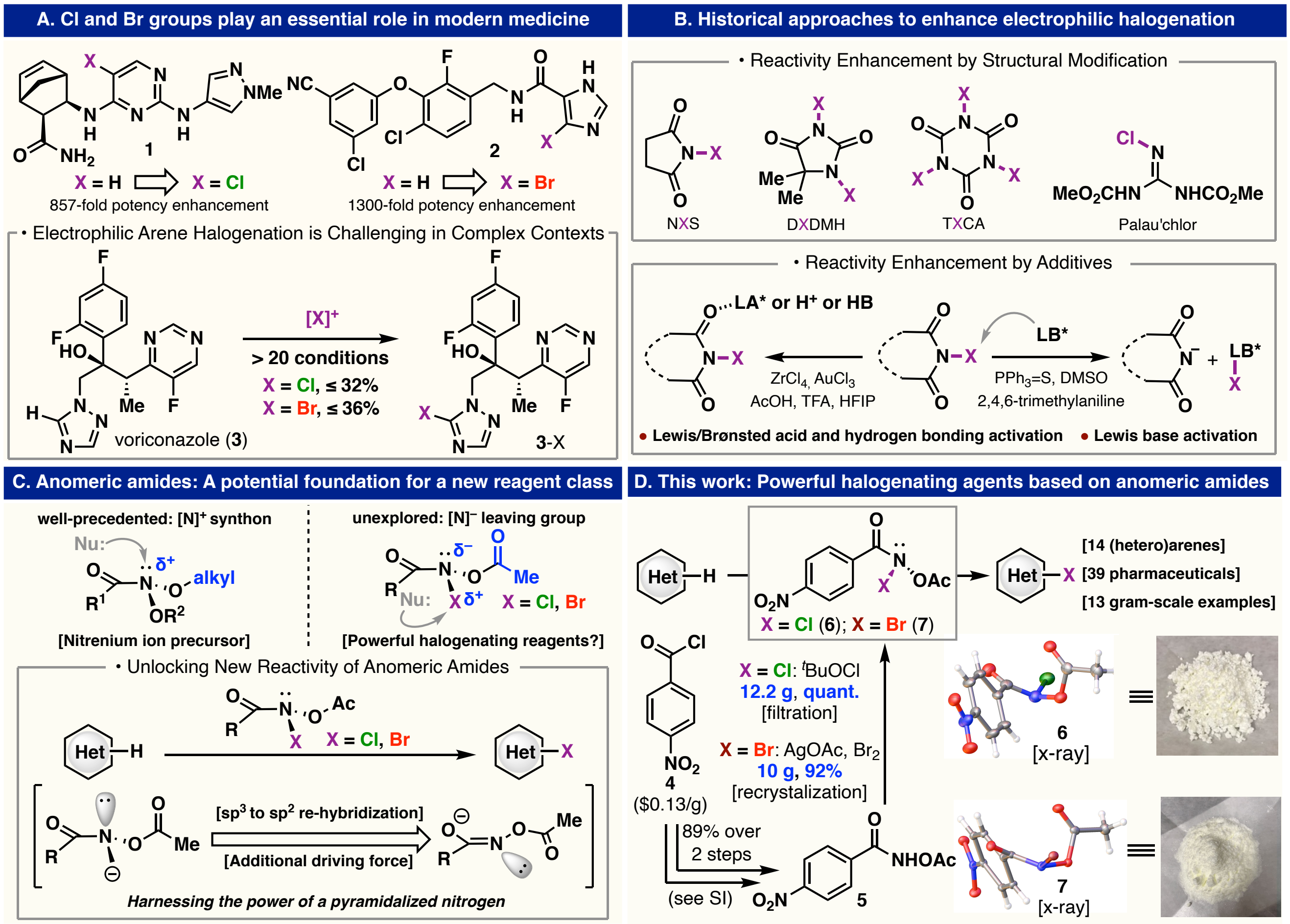


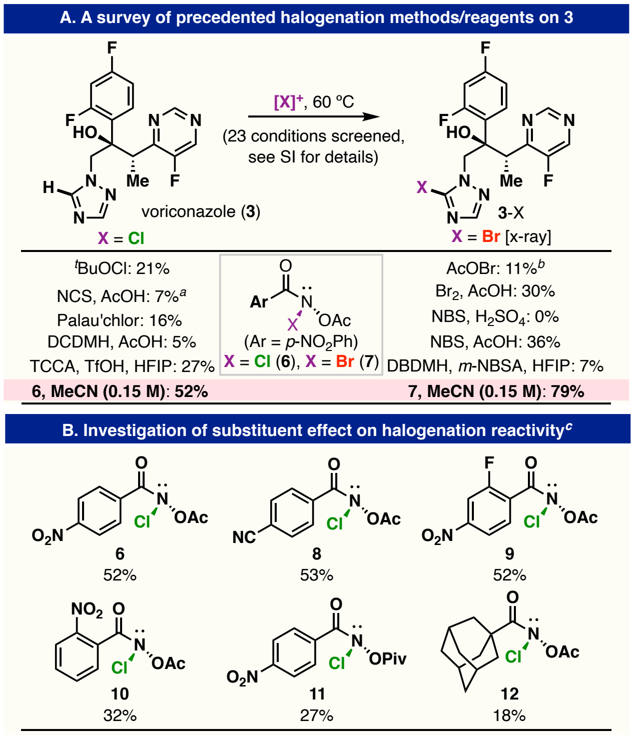
Figure 1. Electrophilic halogenation is a useful C-H functionalization tool, state-of-the-art and design of novel reagents based on anomeric amide. **A**, The medicinal importance of Cl and Br atoms in drug discovery arena; **B**, Selected halogenating reagents and commonly used Lewis/Brønsted, Lewis base and hydrogen bonding activation modes; **C**, Well-precedented usage of anomeric amide as nitrenium ion precursors and our design of it as powerful halogenating reagents; **D**, This work: practical synthesis of anomeric amide halogenating reagent **6** and **7** and their applications in (hetero)arenes chlorination and bromination.

Very little precedent exists for the synthesis of anomeric amide halogenating agents such as **6** and **7** (Figure 1D). Studies commenced from the known compound **5**, constructed using a modified procedure[34] that avoids chromatographic purification on decagram scale (see SI). In order to access chlorinating reagent **6**, ^{t}BuOCl was employed as it proceeded in quantitative yield and simplified subsequent purification (filtration). Related systems had been chlorinated before using TCCA[35] which was deliberately avoided for practical reasons. In the case of brominating reagent **7**, a AgOAc-mediated procedure using Br_2 was employed[36] followed by recrystallization. Although reagents **6** and **7** are bench-stable solids prepared through scalable and practical procedures, they were stored below 0°C to minimize gradual decomposition.

With abundant quantities of **6** and **7** in hand, their halogenating potential was explored on the antifungal agent voriconazole (**3**), a substrate identified as being particularly difficult to halogenate under a variety of conditions (Table 1A). Indeed, 23 different chlorinating and brominating reagents/conditions were explored. A small selection of the most potent of these combinations are depicted with the highest yields ranging from 27-36%. In these optimal known conditions, the yields were determined by NMR; many of these reactions produced a number of other impurities aside from recovered starting material. In contrast, reagents **6** and **7** cleanly provided the desired chlorinated (**3-Cl**, 52% isolated) and brominated (**3-Br**, 79% isolated) products respectively, along with recovered starting material without the use of exotic solvents or acidic additives. The optimal conditions (generally 0.1 to 0.15M in MeCN at room temperature-60°C, 1-40 h) were arrived upon after extensive screening (see SI for solvent effect). Notably, unlike many other halogenating agents and conditions, the reaction workup is extremely simple involving only solvent removal followed by purification with no aqueous wash needed. A number of other anomeric amide derivatives were also explored (Table 1B) by varying the N- and O-substituents however no improvement was observed. Increasing the steric hindrance around either atom substantially decreased reactivity. Finally, considering that the starting material (4-nitrobenzoyl chloride) for preparing **6** is less expensive than 4-cyanobenzoly chloride for making **8**, **6** was chosen as the optimal chlorinating reagent.

With optimized reagents and conditions in hand for halogenation, a broad screen of both building blocks and pharmaceutically relevant substances was pursued as illustrated in Table 2. In nearly all cases, a dramatic increase in yield was observed for chlorination and bromination relative to either literature results or comparison to in-house results using Palau'chlor or NBS. Thus, heterocycles such as 1,2,4-triazoles (**13**, **14**, **33**), pyridine (**15**, **22**), pyrazoles (**16**, **26**), indazole (**17**), thiazole (**18**, **24**), quinoline (**27**-**28**, **42**), pyrimidine (**29**-**31**), thiophene (**36**), imidazole (**43**), others (**19**, **25**) as well as multisubstituted phenyl rings (**20**, **35**, **40**, **46**) can all be cleanly halogenated.

Table 1. Demonstration of the electrophilic halogenation reactivity of anomeric amides (6 - 12). A, Comparison of **6** and **7** with known halogenating reagents/conditions; **B,** Investigation of substituent effect on halogenation reactivity arrived on optimal reagent **6**.



[a]110 °C instead of 60 °C; [b]room temperature; [c]using **3** as the model substrate.

Generally, the position-selectivity for halogenation was in accord with what one would normally predict[37], although 13 out of the 41 examples favored different sites (see SI for predicted halogenation sites). In some cases, such as **20**, **44**, and **46**, the halogenation regioselectivity using **6**/**7** can be dramatically improved relative to known protocols. Anomeric amide halogenating reagents also exhibit exquisite chemoselectivity relative to the state-of-the-art. For instance, attempted chlorination of celecoxib (**26**) using Palau'chlor furnished only sulfonamide N-chlorination rather than the desired chloropyrazole product which was exclusively observed using reagent **6** (93% yield on gram-scale). When the simple indazole building block **17** was exposed to Palau'chlor (1.2 equiv, rt, 24 h), ca. 50% conversion to the N-Cl adduct was observed. Subsequent heating at 70 °C for 20 h delivered 47% of **17**-Cl, 24% recovered **17**, and 27% of dichlorinated **17** (NMR yield). In contrast, using reagent **6** (1.2 equiv, rt, 24 h), a 91% isolated yield of the desired product **17**-Cl was observed. In the case of pesticide **42**, reagent **7** delivered **42**-Br in 47% isolated yield whereas treatment with NBS/AcOH led to 6% desired product (NMR yield) along with a variety of unidentified products. Similarly, the tertiary-alcohol containing antifungal agent **33** could be brominated in 58% isolated yield. In contrast, exposure to NBS (in DMF or AcOH) led to 10-14% of **33**-Br (NMR yield) along with extensive decomposition (20-65% of **33** could be recovered). When thiazole **18** was exposed to excess Palau'chlor (5.0 equiv, 70 °C, 7 days), 14% **18**-Cl along with 70% **18** was observed, while using reagent **6** (1.6 equiv, 50 °C, 40 h) delivered 44% **18**-Cl as well as 50% recovered starting material **18**.

The ability to cleanly halogenate at the end of a synthetic route could have benefits in a medicinal chemistry program. For example, structures **27**[38], **30**[39], and **34**[40] have only been previously prepared through early-stage chlorine introduction. Anomeric amide reagents can give those in a drug discovery program optionality enabling chlorination of end-stage products. In the specific case of rivaroxaban (**34**), reagent **6** is uniquely successful for this late-stage chlorination relative to Palau'chlor.

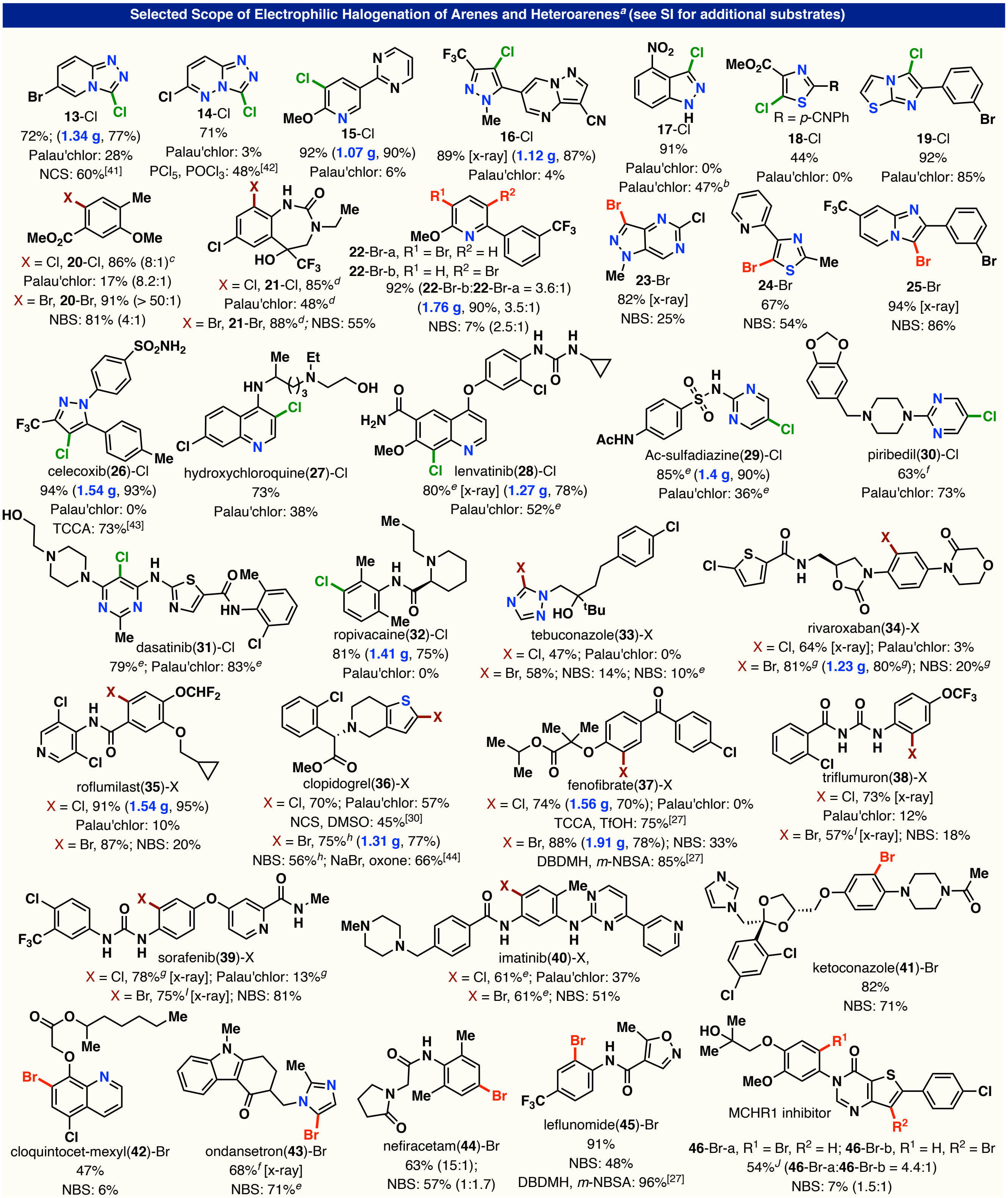
Halogenation using **6**/**7** can be easily performed on gram-scale in batch, with 13 such examples shown in Table 2. Sulfonamides, amides, amines, tertiary alcohols, α-CF_3-alcohols, 1,2-aminoalcohols, acetals, and cyclopropanes are all compatible functional groups. The current limitations of this method are not surprising with alkene, alkyne and sulfoxide-containing substrates being incompatible. Arenes which are too electron-deficient are recalcitrant to halogenation (see SI for examples of this).

Preliminary explorations also point to the enhanced reactivity of anomeric amide reagents in settings other than electrophilic aromatic substitution (Figure 2A). For instance, in the α-bromination of (hetero)aromatic methyl ketones (**47**-**49**), superior selectivity for mono-bromination is observed across the board. Similarly, the acidic methylene group of cyclic N-sulfonylimine **50** could be efficiently brominated with a superior yield (83%) compared with known procedure (24%) using Py-HBr_3[45]. An improved yield was also observed in allylic bromination of (*R*)-carvone (**51**) relative to standard conditions[46-47]. Finally, enol acetate **52** (prasugrel) could be chlorinated in nearly quantitative yield.

The most glaring concern a practitioner would have in considering the use of anomeric amides such as **6** and **7** is safety on scale. This potential issue was studied extensively (see SI for experimental data). Since differential scanning calorimetry (DSC) showed both compounds **6** and **7** had decomposition energies above the Yoshida correlation for predicting shock sensitivity and explosive propagation, internal explosivity testing was carried out using modified accelerating rate calorimetry type equipment equipped with a fast rate data card and pressure transducer. The tests recorded pressure rise rates below the instrument's calibrated threshold, hence were thought to be negative for potential explosivity[48]. UN Dangerous Goods Test 3a (ii) BAM Fall Hammer impact testing of **6** and **7** at 60J resulted in decomposition, producing a change in both materials' color and an odor without flame or explosion. The decomposition observed may be due to the impact test generating enough heat to reach each material's low thermal onset at 79 °C and 84 °C, respectively, to catalyze their exothermic decomposition. During the many gram-scale batch runs using **6** and **7** (*vide supra)* no hazardous events were observed. However, in order to preemptively address potential concerns on scale, reagent **6** was tested on even larger scale using a flow setup (Figure 2B). Thus, chlorination of celecoxib analogue (**53**) was pursued in flow at 20 gram-scale. A separate substrate specific optimization was pursued in order to increase the reaction rate and subsequent potential throughput of the reaction. The reaction rate was sensitive to both temperature and solvent composition where the conditions shown in Figure 2B were found to provide >95% conversion in 25 minutes. From these optimized conditions a flow experiment was designed wherein 20 grams of **53** was converted to the desired product over 130 minutes in flow with 82% isolated yield. Observations from the lab-scale demonstration in flow determined that the reaction could be further scaled with minimal consideration.

Finally, the initial hypothesis that halogenating agents based upon an anomeric amide backbone would exhibit superior reactivity was evaluated computationally (Figure 3). Although anomeric amide chlorinating reagent **6** and Palau'chlor have the same N-Cl bond length (both 1.73 Å, longer than 1.66 Å for TCCA[49] and 1.69 Å for NCS[50]), the conversion of **14** to **14**-Cl is calculated to be more energetically favorable by a factor of 10^2.7 (ΔΔG = –3.75 kcal/mol) using **6** (Figure 3A), which is in accord with experimental findings. To gain deeper insight into this higher reactivity, DFT calculations of the N-Cl bond breaking energy (from the ground state to the corresponding anion and Cl^+) for both reagents was performed. Calculations indicate that this bond breaking event is significantly uphill for both reagents, but reagent **6** requires 25 kcal/mol less energy for bond breaking than Palau'chlor, which means **6** has a more active N-Cl bond (Figure 3B). In the case of reagent **6**, when

Table 2. Substrate scope of (hetero)arenes electrophilic halogenation.



[a]Conditions: for chlorination: reagent **6** or Palau'chlor (1.2 – 2.4 equiv), CH_3CN (0.1 – 0.15 M), rt – 60 °C, 1 – 40 h; for bromination: reagent **7** (1.2 – 2.4 equiv), CH_3CN (0.1 – 0.15 M), rt – 60 °C, 1 – 40 h; or NBS (1.2 – 2.4 equiv), AcOH (0.1 – 0.15 M), rt – 60 °C, 1 – 40 h; for reagents 6 and 7, yields refer to isolated yields; for Palau'chlor and NBS, yields refer to ^1H NMR yield using CH_2Br_2 as internal standard; note: for substrates with a poor solubility in CH_3CN, DMF was used instead; [b]rt for 24 h then 70 °C for 20 h; [c]48 h; [d]CH_3CN/DMF (4:1, v/v) as solvent; [e]DMF as solvent; [f]$CHCl_3$ as solvent; [g]0.05 M; [h]CH_3NO_2 as solvent; [I]AcOH as solvent; [J]CH_3CN/DMF (2:1, v/v) as solvent.

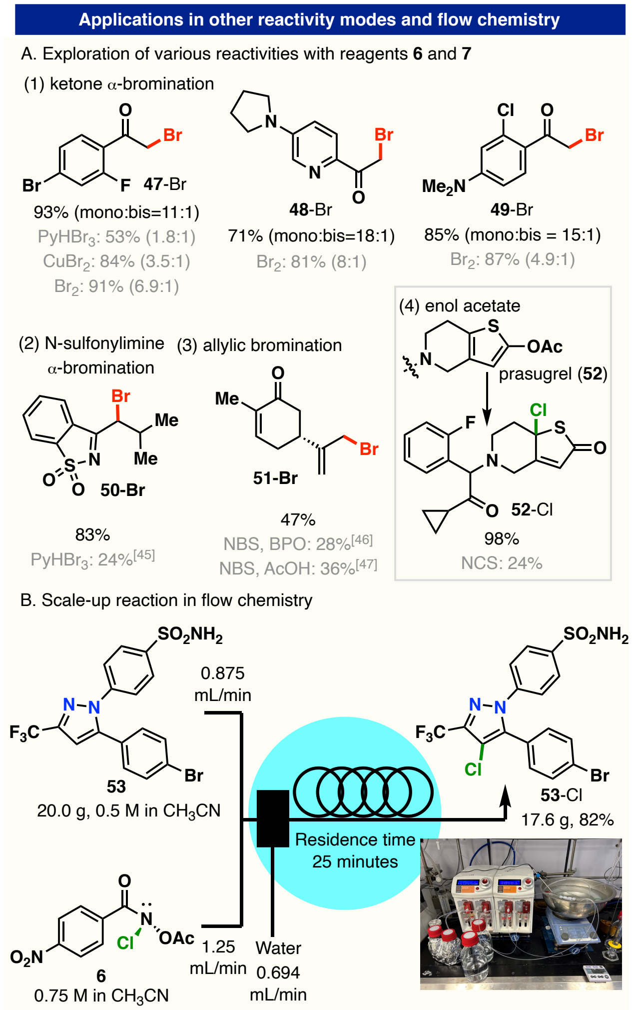


Figure 2. Application of anomeric amide halogenating reagents 6 and 7. **A**, Explorations of reactivities other than (hetero)arene electrophilic halogenation; **B**, Large-scale reaction enabled by continuous flow technology.

the Cl atom has departed from the N atom, rehybridization at N from sp^3 to sp^2 occurs and the C-N bond shortens from 1.44 Å (1.42 Å according to X-ray structure) to 1.33 Å., indicating a large energy release during this process. Attempts to determine the ΔΔG if the conjugate anion were to maintain sp^3 character failed as it immediately "fell" into the sp^2 sink. Thus, the driving force is too exothermic for it to remain sp^3-hybridized. Since the nitrogen of an anomeric amide such as **6** is well-known to adopt a pyramidal configuration, the process of nitrogen inversion was also calculated and the energy barrier was found to be 3.5 kcal/mol (Figure 3C), which is similar to that of the ΔG between Palau'chlor and the new reagent (Figure 3A, 3.75 kcal/mol). Given these results, the additional driving force of **6** (compared to Palau'chlor) is attributed to the additional energy released as a result of conjugation between the N-lone pair and the carbonyl group, a structural feature that is absent in Palau'chlor (or any other known halogenation agent for that matter). In addition, kinetic studies using **15** and roflumilast **35** as model substrates were performed, demonstrating that the chlorination reaction has first-order dependences of both substrate and reagent **6** (see SI for details).

Anomeric amides have been known and extensively studied for over 40 years. This work points to a new use for halogenated variants (Cl and Br) of such structures that can take advantage of embedded hybridization/strain that is restored/released when those halogen atoms depart. The resulting reagents demonstrate high reactivity, regio-, and chemoselectivity in challenging electrophilic aromatic halogenations when even the most powerful conditions currently known are low yielding or unfeasible. The safety profile of these structures was studied and numerous gram-scale batch reactions and a decagram flow reaction in mock process setting were demonstrated. Preliminary findings suggest these reagents can have utility in other halogenation reactions as well. Computational studies support the initial hypothesis and may serve as a foundation for the development of other versatile reagents and uses of anomeric amide scaffolds in synthesis.

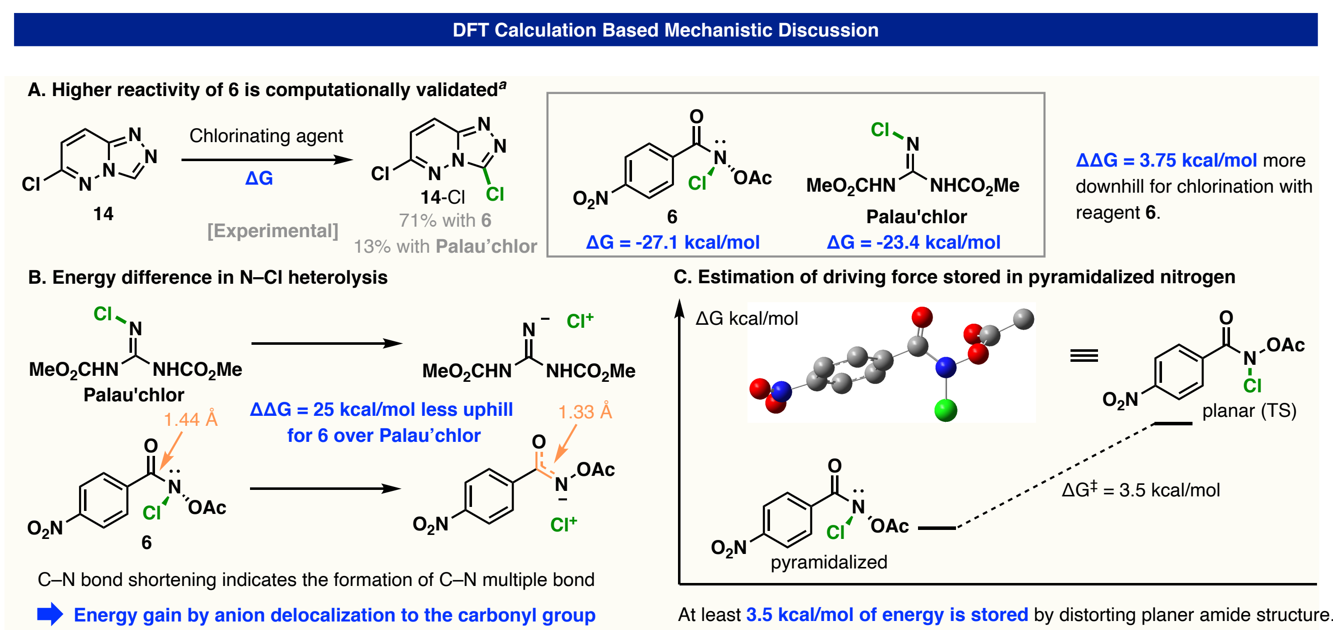


Figure 3. DFT based mechanistic study. **A**, Higher reactivity of **6** than Palau'chlor is consistent with a more downhill ΔG; **B**, Calculated N-Cl disassociation energy indicates a weaker N-Cl bond in reagent **6**, C-N bond shortening is observed during this process; **C**, Calculated energy for N-inversion in reagent **6**. [a]Calculation was performed with B3LYP/6-311G++(d,p) level of theory with solvation (PCM, CH_3CN).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no conflict of interest.

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