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FULL PAPER

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Halogen Bonding of *N*-Halosuccinimides with Amines and Effects of *Brønsted* Acids in Quinuclidine-Catalyzed Halocyclizations

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Dedicated to Professor *E. Peter Kündig* on the occasion of his 75th birthday in recognition of his outstanding contributions to catalysis

An arguable expectation in halogen chemistry is that an amine will react oxidatively with an *N*-halosuccinimide (NXS) to form an *N*-halogenated species bearing a covalent N–X bond. While likely for NCS under most conditions, we find this expectation simply not true for NIS and largely inaccurate for NBS. Herein, we disclose evidence through systematic NMR and X-ray studies that non-covalent halogen bonded amine complexes of NIS predominate over covalent *N*-halogenated species, even with primary and secondary amines. For example, during the catalytic electrophilic halocyclization of *gem*-disubstituted alkenes by cinchona-like amines, the quinuclidine complexes of NIS and NBS display lower reactivity than their parent *N*-halosuccinamides and require the presence of an appropriate *Brønsted* acid. Specifically, a *Brønsted* acid and quinuclidine jointly catalyze the halo-cycloetherification of γ-alkenyl alcohols with NIS or NBS, while only quinuclidine acts as a catalyst in the halolactonization of γ-alkenoic acids. Although our evidence confirms a transient *N*-halogenated quaternary ammonium salt as the halonium species, it is important to note that NIS predominantly forms 'off-cycle' halogen bonded amine complexes in solution.

Keywords: halocyclization, halogen bonding, halogens, amine catalyst, reaction mechanisms, iodine complex.

Introduction

Halogen bonding is a non-covalent, attractive interaction that occurs between a halogen atom (a *Lewis* acid) and a *Lewis* base.[1–8] Until relatively recently, the majority of applications of halogen bonding are concerned with the solid state, for example, in crystal engineering,[9–11] self-assembly,[12,13] and organic semiconductors.[14,15] The investigation of halogen bonding in the solution-phase has lagged behind considerably, although recent applications,[16–18] fundamental studies[19] and receptor anion transport have been reported in the last decade.[20,21] The utility and importance of halogen bonding is now growing in recognition in the organic synthesis communities, whereby halogen bonded complexes have been used as reagents[22] and the *Lewis* acidic nature of electrophilic halogen reagents has been used to activate reactions or even initiate catalytic events.[23–30] Indeed, we became intrigued by the halogen bonding nature of the electrophilic reagents NIS and NBS that are commonly used in catalytic halo-functionalizations, specifically their mechanistic role and reactivity in the halo-cyclization of γ-olefinic alcohols and acids in the presence of amine catalysts (*Scheme 1*).[31–42] For instance, according to literature reports, NIS and NBS

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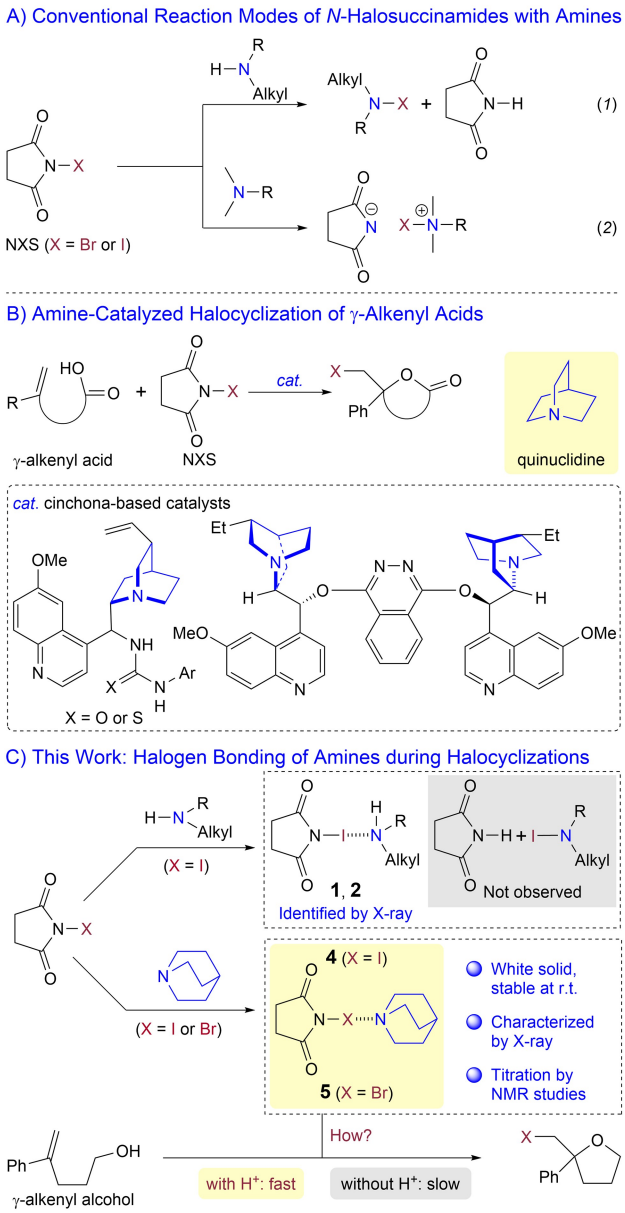


Scheme 1. Modes of halogen bonding in relation to amine-catalyzed halocyclizations: A) Conventional halogenative modes. B) Rapid halocyclization of γ-alkenoic acids. C) Role of halogen bonded amine complexes.

are one of the most common reagents used to oxidize N–H bonds to N–X bonds.[43] Indeed, it is reported that primary and secondary amines are readily oxidized by NIS to give *N*-iodo amines,[44] while secondary amines are readily oxidized by NBS to generate *N*-bromo amines (*Scheme 1,A, equation 1*).[45] Also, tertiary amines are reported to react readily with NIS or NBS to form *N*-halo-ammonium salts (*Scheme 1,A, equation 2*).[47] In only two examples, as far as we could find, were halogen bonded complexes reported between amines and NIS/NBS, DABCO·2NBS and hexamethylenetetramine·NIS/NBS,[48] and the importance of halogen bonding in amine-catalyzed halofunctionalizations appears to be underappreciated (*Scheme 1,B, vide infra*).

Concerns in this area arose during our development of an efficient oxidative amidation of primary nitroalkanes by the reaction of amines and NIS under O_2, as well as our cyanoalkane oxidative studies.[49–54] During our mechanistic interrogations, we observed and isolated a previously unknown 1:1 adduct **1** between allylamine and NIS instead of the *N*-iodoamine, which is the generally expected species according to traditional reaction modes (*Scheme 1,C*). Having identified **1** as a stable halogen-bonded complex of the primary amine, which is arguably uncommon according to literature precedence,[55–57] we began to systematically investigate the reaction of amines with NIS and NBS in more detail. Herein, we not only summarize our findings of the fundamental structure and reactivity of halogen-bonded complexes between amines and NBS/NIS, but also provide additional insights into the mechanistic role of NBS/NIS-amine complexes and *Brønsted* acids in the quinuclidine-catalyzed halocyclization of γ-olefinic alcohols and acids (*Scheme 1,B*).

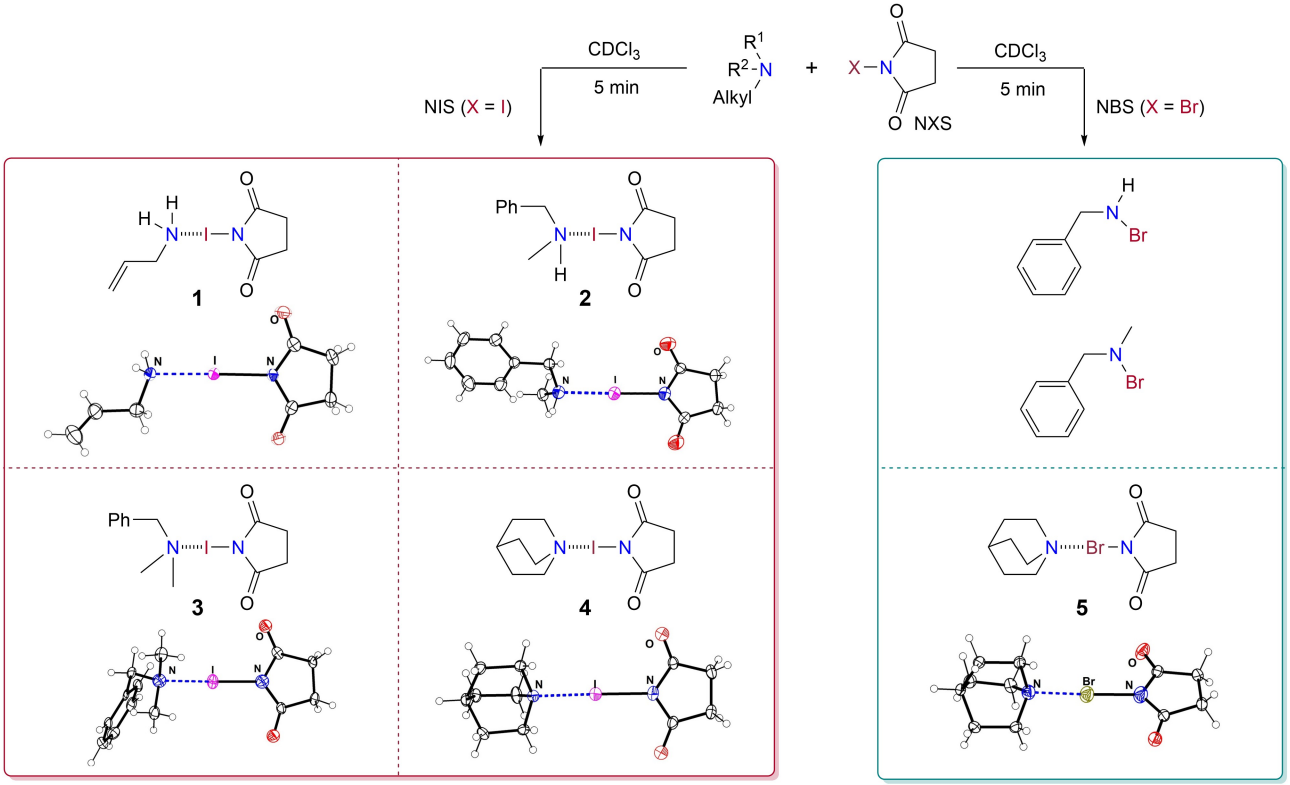
Results and Discussion

Reactivity of NIS and NBS with Amines

First, we investigated the reaction of amines with NIS (*Scheme 2,A*). Different primary, secondary, and tertiary amines, such as allylamine, *N*-methylbenzylamine, *N,N*-dimethylbenzylamine, and quinuclidine (1 equiv.), were mixed with NIS (1 equiv.) in $CDCl_3$ and monitored by ^{1}H-NMR spectroscopy. Immediately after mixing, the methylene signals of NIS were shifted upfield compared with free NIS, and the proton signals alpha to the nitrogen of the amine were shifted downfield compared with the free amine (see *Figures S1–S4* in *Supporting Information* for spectroscopic details).

In all cases, the pure halogen bonded complex could be readily isolated as a solid by evaporating the solvent and washing with dry Et_2O. The thermal stability of complexes **1**–**4** both in solid and solution form depended highly upon the type of amine. For example, the allylamine NIS complex **1** and the *N*-methylbenzylamine·NIS complex **2** darkened slowly and decomposed to a complex mixture at r.t. within one day. The *N,N*-dimethylbenzylamine-NIS complex **3**

A) Reactivity of NIS and NBS with Amines and X-Ray Stuctures of Halogen Bonded Amine Complexes **1–5**



B) XRD Bond Lengths and Bond Angles of Halogen Bonded Amine Complexes **1–5**

	1	2	3	4	5
Bond length of N---X [Å]	2.369	2.399	2.433	2.370	2.211
Bond length of X–N [Å]	2.190	2.165	2.170	2.185	2.030
Angle [deg] N---X–N [°]	178.54	178.81	175.20	178.80	178.28

Scheme 2. Bonding modes of *N*-halosuccinimides with primary, secondary, and tertiary amines: A) Reactivity of NBS and NIS with various amines and X-ray structures of isolated NXS-amine complexes **1**–**5**. B) Selected halogen bond information for complexes **1**–**5** from XRD data.

decomposed rapidly at r.t. within ten minutes.[46,47] However, all complexes can be stored at −30 °C for more than three months. The quinuclidine·NIS complex **4** was found to be very stable and can be stored at r.t. for more than three months without any decomposition.

Next, the reaction of amines with NBS was investigated in $CDCl_3$ (*Scheme 2,A*). Primary benzylamine and secondary *N*-methylbenzylamine were readily oxidized to their *N*-bromo amines and released succinimide even at low temperature, as evidenced by ^{1}H-NMR spectroscopy (see *Supporting Information* for details).[45] However, when NBS was mixed with equimolar amounts of quinuclidine, the NBS and quinuclidine signals shifted upfield and downfield, respectively. Similar to the NIS-quinuclidine complex **4**, this indicated that *Lewis* basic quinuclidine donates electron density to the *Lewis* acidic NBS. The bromine bonded complex **5** was obtained only when quinuclidine was employed as the tertiary amine. Pure solid **5** was generated after evaporation of the solvent and washing with Et_2O, and this complex was stable at room temperature for more than three months without any decomposition. The studies summarized in *Scheme 2,A* indicate that NIS reacts with primary, secondary, and tertiary amines to form halogen bonded complexes. On the other hand, NBS reacts with primary and secondary amines to afford oxidized products with N–Br bonds, while it reacts with quinuclidine to generate a halogen-bonded complex.

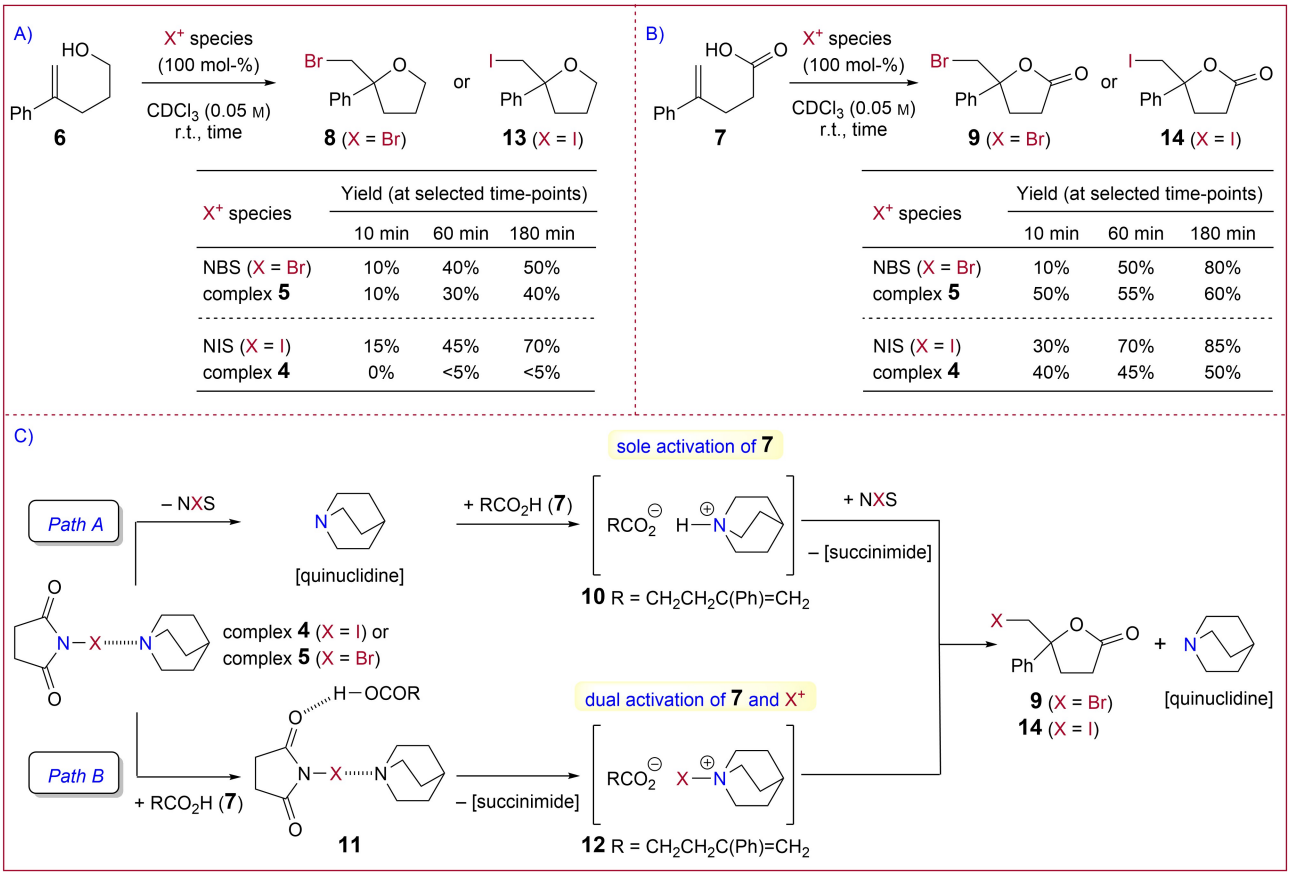
To provide fundamental data on halogen bonding characters, the amine complexes **1**–**5** of NBS/NIS were

subjected to X-ray structural analysis (see *Scheme 2,B*). All angles of N–I–N of the complexes **1**–**4** are near to 180°, having essentially linear geometry, ranging from 175.2° to 178.8°. The corresponding N---I distances of the NIS·amine complexes between the *Lewis* basic amine and NIS vary from 2.369 to 2.433 Å, longer than the N–I bond (1.96 Å) of NIS.[58] In addition, the N–I bond of NIS varies from 2.165–2.190 Å, which are longer than the N–I bond (1.96 Å) of NIS.[59] In the case of the NBS-quinuclidine complex **5**, the angle of N–Br–N is essentially linear at 178.3° and the N---Br bond is 2.21 Å, which is much shorter than the *van der Waals* radii of the involved atoms (3.40 Å).[60] These linear bond angles and short bond lengths are clear features of amine halogen bonding.[48,55–57]

NIS/ NBS-Quinuclidine Complex **4**/**5** *in Halocyclization*

At this juncture, we decided to study the reactivity of the NIS/NBS-quinuclidine complexes **4**/**5** with a view to providing mechanistic insights into modified cinchona alkaloids being widely adopted as quinuclidine-based catalysts in the enantioselective iodo- and bromocyclizations of olefins.[61–67] The results are summarized in *Scheme 3,A* and *3,B*. While the *N*-halosuccinimides (NXS) are more reactive and provide greater reaction conversions than their halogen-bonded counterparts **4** or **5**, we can collectively make the following two main observations: *1*) the NIS- or NBS-quinuclidine complex **4** or **5** reacts with the acid substrate **7** much faster than the alcohol substrate **6**, and *2*) the reaction of the acid substrate **7** with complex **4** or **5** never exceeds 70%, leaving unreacted reactants and reagents (see *Scheme 4,A* and *4,B* and *Supporting Information* for full reaction profiles).

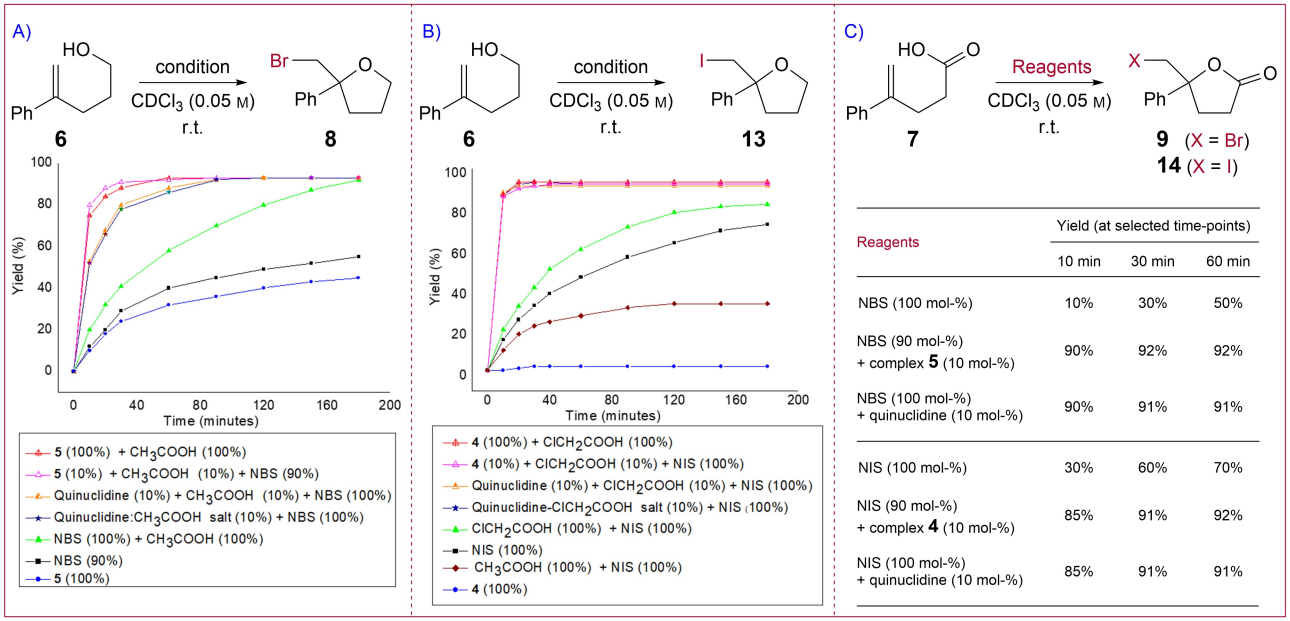
Two possible reaction pathways were considered to explain these observations (*Scheme 3,C*). In one case (*Path A*), the complex **5** reversibly releases the free quinuclidine ligand from NXS, which we confirmed by titration experiments (see *Supporting Information* for details). The generated quinuclidine then serves as a base and reacts with the acid substrate **7** to form an



A) X+ species	Yield (at selected time-points)		
	10 min	60 min	180 min
NBS (X = Br)	10%	40%	50%
complex **5**	10%	30%	40%
NIS (X = I)	15%	45%	70%
complex **4**	0%	<5%	<5%

B) X+ species	Yield (at selected time-points)		
	10 min	60 min	180 min
NBS (X = Br)	10%	50%	80%
complex **5**	50%	55%	60%
NIS (X = I)	30%	70%	85%
complex **4**	40%	45%	50%

Scheme 3. Alkene Reactivity of NIS/NBS versus NIS-quinuclidine/NBS-quinuclidine complex **4** or **5**: A) Study with alcohol **6** (see *Figures S6,A*, *S7* and *S8* for full reaction profiles). B) Study with acid **7** (see *Figures S6,B*, *S9* and *S10* for full reaction profiles). C) Proposed halogenation of γ-alkenyl acid **7** through sole (*Path A*) or dual (*Path B*) activation modes.



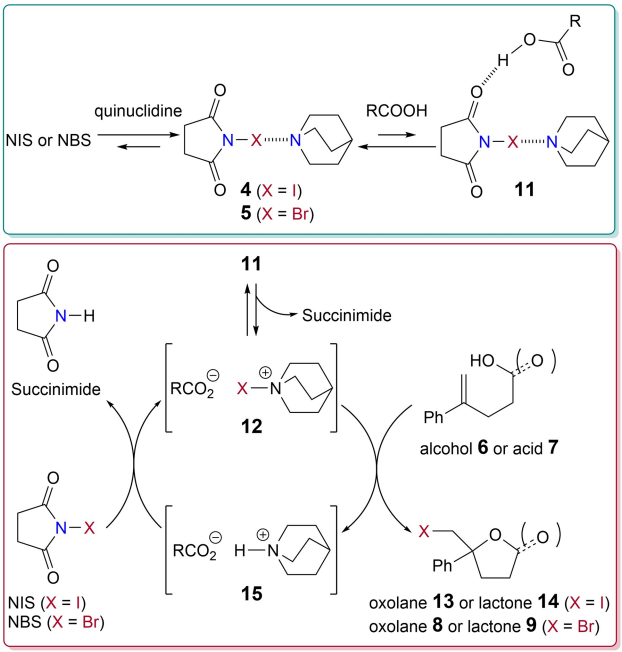
Reagents	Yield (at selected time-points)		
	10 min	30 min	60 min
NBS (100 mol-%)	10%	30%	50%
NBS (90 mol-%) + complex **5** (10 mol-%)	90%	92%	92%
NBS (100 mol-%) + quinuclidine (10 mol-%)	90%	91%	91%
NIS (100 mol-%)	30%	60%	70%
NIS (90 mol-%) + complex **4** (10 mol-%)	85%	91%	92%
NIS (100 mol-%) + quinuclidine (10 mol-%)	85%	91%	91%

Scheme 4. Effect of catalytic combinations of quinuclidine and sources of acid on halocyclization: A) Bromoetherification of **6** under various reaction conditions with NBS-based systems to oxolane **8**. B) Iodoetherification of **6** under various reaction conditions with NIS-based systems to oxolane **13**. C) NBS·quinuclidine complex **5** catalyzes bromolactonization to **9** (see *Figure S9* for full reaction profiles) and NIS·quinuclidine complex **4** catalyzes iodolactonization to **14** (see *Figure S10* for full reaction profiles).

ammonium salt **10**. Here the carboxylate part of **10** is more nucleophilic than its acid counterpart and thereby can cyclize with free NBS and afford **9**. This process finally releases succinimide as a byproduct and free quinuclidine for another cycle (if used catalytically). In the other case (*Path B*, *Scheme 3,C*), the unsaturated acid **7** can reversibly hydrogen bond with the NBS-quinuclidine complex **5**. This would form a protonated intermediate like **11**, which can facilitate its dissociation into a reactive *N*-bromo-ammonium carboxylate salt **12** and release succinimide. Here, not only is the *N*-bromo-ammonium part of **12** more electrophilic than either **5** or NBS, but also the nucleophilic component is activated as its carboxylate anion. Subsequent intra- or intermolecular electrophilic bromination and carboxylate cyclization would afford the lactone **9**, again releasing free quinuclidine for another cycle (if used catalytically). To support *Path A* (*Scheme 3,C*) as a possibility, the soluble potassium carboxylate salt of alkene **7** was prepared in $CDCl_3$ by treating **7** with potassium carbonate and 18-crown-6 before adding NBS. This salt would thus mimic the ammonium carboxylate salt **10**. In this case, the salt of **7** remained largely unreacted after 12 hours. This indicated *Path A* to be unlikely at the stage of converting salt **10** to **9** with free, non-coordinated NBS species.

The *Path B* model is similar to *Denmark*'s *Lewis* base/*Lewis* acid co-catalyzed halocyclizations and *Lewis* base/*Brønsted* acid co-enhanced seleno- and thiocycloetherifications.[69–72] In other words, the *Brønsted* acid would activate the halogen-bonded NXS-quinuclidine complex **4**/**5** to form a more reactive 'X^+' species (**12** in this case) through hydrogen bonding and facilitate proton transfer to eventually eject succinimide as a byproduct. If this *Path B* (*Scheme 3,C*) is to be supported experimentally, *Brønsted* acids would not only accelerate halolactonizations but also accelerate haloetherifications through *N*-halo quinuclidinium salts like **12**. These experiments are summarized in *Scheme 4*.

In the event, a carboxylic acid was indeed found to dramatically accelerate the halogenative cyclization reaction of the relatively neutral unsaturated alcohol **6** with either NBS or NIS, which neared completion within 20 minutes (*cf. Scheme 4,A* and *4,B*). Experiments using stoichiometric and sub-stoichiometric amounts of NXS-quinuclidine complexes **4** or **5**, and the addition of an acetic acid to the alcohol substrate **6** also support *Path B* (*Scheme 3,C*). In short, we can reason that: *1*) the NXS-quinuclidine complex **4**/**5** is not the actual halogenating species which, under the reaction conditions, generates a less reactive system than its parent NXS. *2*) The reactivity of the NBS



Scheme 5. Proposed catalytic cycle of quinuclidine-catalyzed halocyclizations from the 'off-cycle' halogen bonded amine complexes **4** or **5** in the presence of a suitably strong *Brønsted* acid that can set up equilibria between species **11**, **12** and **15**.

complex **5** is greatly enhanced by CH_3COOH ($pK_a = 4.8$), while the reactivity of the NIS complex **4** requires a stronger acid $ClCH_2COOH$ ($pK_a = 2.9$ in water). *3*) The reactivity of NXS is only slightly enhanced by a *Brønsted* acid in the absence of an amine component. *4*) The order of the addition of NXS, quinuclidine, and the *Brønsted* acid is not important for a fast, complete reaction result. *5*) Quinuclidine and MeCOOH can both function effectively in catalytic quantities.

These results indicate that a suitably strong acid is needed to match the halogen bonding strength of the NBS or NIS amine complex, which further supports the observation that the NIS complex **4** is less reactive (more stable) than the NBS complex **5**. It was also observed that the NIS complex **4** also works in catalytic amounts with chloroacetic acid, and that quinuclidine itself works in a catalytic fashion with chloroacetic acid, both giving superior yields and reaction rates (see *Scheme 4,B*). Furthermore, the NBS·quinuclidine complex **5** and NIS·quinuclidine complex **4** are clearly less reactive than NBS and NIS used in the absence of quinuclidine. A combination of NBS or NIS with a suitable *Brønsted* acid increases the reaction rate moderately and, although reactions go to completion, the reactions are greatly accelerated by a combination of these three components: quinuclidine, *Brønsted* acid, and NBS/NIS. A catalytic amount of complex **4** or **5** in combination with a catalytic amount of acid also serves as an efficient system for the halocyclization of the δ-unsaturated alcohol **6** with NBS or NIS, whether the complex **4** and **5** is pre-formed or formed *in situ*.

Next, halolactonization of the unsaturated acid **7** was studied with catalytic quantities of either the NBS·quinuclidine complex **5** or the NIS·quinuclidine complex **4** (*Scheme 4,C*). From previous experiments (*Scheme 3,B*), the reaction of the alkene-acid **7** was found to be initially fast in the stoichiometric presence of the NBS·quinuclidine complex **5** (100 mol-%), but the reaction never surpassed a yield of 70%. This outcome can be reasoned to occur because of increasing concentrations of the free amine quenching sources of free protons from **7**. Indeed, the addition of MeCOOH rapidly completed such reaction cases (yields $< 90\%$). In comparison, the table entries of *Scheme 4,C* show that halolactonizations essentially complete within ten minutes without the addition of extra acid, only when catalytic amounts of the NXS·quinuclidine complex **4**/**5** (10 mol-%) or quinuclidine (10 mol-%) were used. Clearly, compound **7** serves as its own source of needed protons to activate the halogen bonded amine complexes **4**/**5** to a more reactive 'X^+' species, which again supports *Path B* of *Scheme 3,C*.

Through these collective studies of the reactivity of the NBS·quinuclidine complex **5** and NIS·quinuclidine complex **4**, including supporting control studies detailed in *Figures S11–S17* in the *Supporting Information*, we propose the following catalytic cycle for halocyclizations (*Scheme 5*). As evidenced by NMR titration studies (see *Supporting Information*), there exists an equilibrium between the NXS complex **4**/**5** with NXS (X=I or Br) and quinuclidine. The rate of exchange of the NIS·quinuclidine complex **4** (X=I) was found to be slower than the NBS·quinuclidine complex **5** (X=Br). Importantly, the NXS complexes **4**/**5** are not the reactive halogenating species. However, these species become protonated with MeCOOH or $ClCH_2COOH$ to afford a reactive halogenating species (*e.g.* **12** through **11**) with the expulsion of succinimide. As these reactions are under equilibrium, as evidenced by the order of addition of reagents being independent to the reaction outcome, the reaction progress proceeds efficiently if quinuclidine, NXS and acid are all present. The reactive species **12** would then react with the unsaturated alcohol **6** (or unsaturated carboxylic acid **7**) to afford the halogenated oxacycles **8**/**13** (or the halogenated lactone **9**/**14**) and generate the protonated quinuclidinium salt **15**. Salt **15** can then react

with NBS or NIS to re-generate the active halogenating species (*e.g.* **12**) and release succinimide.

Conclusions

In summary, while the reaction of primary and secondary amines with NIS are often understood to generate N–I bonded compounds by analogy to the reactivity of chlorinating agents like NCS, we have shown that primary, secondary and tertiary amines all react with NIS to predominantly afford halogen bonded amine complexes **1**–**4**. In addition, tertiary amines such as quinuclidine react with NBS to form the halogen bonded complex **5**. Their structural features and thermal stabilities were then revealed by X-ray crystallographic analysis. As expected, the NBS-quinuclidine complex **5** and NIS-quinuclidine complex **4** were found to be less reactive as brominating and iodinating reagents than NBS and NIS. However, the addition of *Brønsted* acid to **5** and **4** was found to generate a highly reactive halogenating system (*e.g.* by virtue of the reactivity of **12**, *Scheme 3*). The presence of a suitable *Brønsted* acid was found to be key to defining a fast reaction rate and percentage-of-completion for the halocyclization reactions under the equilibrium conditions reported herein. Thus, the NBS-quinuclidine complex **5** and NIS-quinuclidine complex **4** are precursors to a reactive halogenating species. Reactive, transient species such as **12** can also be generated by mixing NBS or NIS, quinuclidine and acid in catalytic amounts. In haloetherification reactions of γ-olefinic alcohols, for example, both quinuclidine and a *Brønsted* acid are effective in catalytic amounts, while only catalytic quinuclidine is required in the halolactonization of γ-olefinic carboxylic acids because of a stoichiometric supply of protons in the starting material.

We believe the systematic evidence and specific findings described herein not only provides new mechanistic guidance in understanding haloaddition and halocyclization reactions of alkenes and alkynes, especially those catalyzed by quinuclidine-bearing cinchona alkaloids as illustrated by the groups of *Yeung*, *Tang*, *Henneke*, *Denmark*, *Ishihara*, *Yamamoto* and others,[33–42,61–78] but also provides fundamental knowledge in expanding halogen bond-based reactions in synthesis, particularly concerning iodine-based reagents and amine catalysis. Wider implications of the current work to chalcogen- and pnictogen-based *Lewis* acids, which similarly feature sigma-hole acceptor capabilities, is an intriguing proposition and represents a growing field of applications in catalysis, anion-transport and may even be considered a less 'unorthodox' approach to the design of new reactions and methods in the future.[79–84]

Experimental Section

Full experimental procedures and XRD data with analyses are provided in the *Supporting Information.*

Solution-Phase NMR Studies

See *Figures S1–S5* for the preparation compounds and characterization of **1**–**5**, *Figures S6–S10* for full details of kinetic plots, *Figures S11–S16* for detailed NMR mechanistic studies in $CDCl_3$ solution.

Solid-Phase XRD Studies

Calculation of X-ray structural parameters, normalized contact distances, calculated second order perturbation energies of the donor (lone pair of amine nitrogen) and acceptor (halogen atom of *N*-halosuccinimide) and stabilization energies of intermolecular interactions of all complexes are also provided in *Tables S1–S3.* The data for the X-ray crystallographic structures of **1**, **2**, **3**, **4**, **5** are available free of charge from the *Cambridge Crystallographic Data Center* under accession numbers CCDC 1031277, 1495217, 1495215, 1495214, 1495216, respectively.

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Author Contribution Statement

Y. H. and *M. L.* directed the project. *M. L.* and *J. L.* wrote the manuscript. *Y. H.*, *M. L.* and *J. L.* conceived the research strategies for the project. *J. L.* conducted all experiments, isolated all products, and prepared the supplemental material. *E. K.* analyzed all the X-ray structure and collected the data. All authors discussed the results and commented on the manuscript.

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