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Hexafluoroisopropanol-Promoted Haloamidation and Halolactonization of Unactivated Alkenes

Chenxiao Qi,[a] Guillaume Force,[a] Vincent Gandon*[a,b] and David Leboeuf*[c]

[a] C. Qi, Prof. Dr. V. Gandon
Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), CNRS UMR 8182
Université Paris-Saclay
91405 Orsay, France.
E-mail: vincent.gandon@universite-paris-saclay.fr
[b] Prof. Dr. V. Gandon
Laboratoire de Chimie Moléculaire (LCM), CNRS UMR 9168
Ecole Polytechnique, Institut Polytechnique de Paris
91128 Palaiseau, France
[c] Dr. D. Lebœuf
Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006
Université de Strasbourg
67000 Strasbourg, France
E-mail: dleboeuf@unistra.fr

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Abstract: Pyrrolidine and piperidine derivatives bearing halide functional groups are prevalent building blocks in drug discovery as halides can serve as an anchor for post-modifications. In principle, one of the simplest ways to build these frameworks is the haloamination of alkenes. While several progresses have been made in this field, notably the development of enantioselective versions, this reaction is still fraught with limitations in terms of reactivity. Besides, a major question remaining is to understand the mechanism at work. The formation of a haliranium intermediate is typically mentioned, but limited mechanistic evidence supports it. Herein, we report an efficient metal- and oxidant-free protocol to achieve the haloamidation of olefins, which is promoted by hexafluoroisopropanol, along with a DFT investigation of the mechanism. We anticipate that these findings should guide the future development of more complex transformations in the field of halofunctionalization.

Introduction

The intramolecular difunctionalization of unactivated alkenes, such as haloamidation reactions, is a powerful tool to build molecular complexity by both creating a new ring and installing halide functionalities, which are present in manifold bioactive molecules and can also serve for further derivatizations.[1] It therefore provides a rapid access to densely functionalized pyrrolidines and piperidines, which are by far the most represented 5- and 6-membered *N*-heterocycles in drug design (Scheme 1).[2] When it comes to intramolecular haloamidation reactions, sulfonamides have been primarily studied.[3] Yet, their deprotection to obtain the parent amine is not always straightforward, thereby limiting the utility of the transformation. On the other hand, the reactivity of more basic nitrogen functional groups such as carbamates, amides and ureas is less described, apart from few notable transition-metal- or organocatalyst-based methods.[4] One possible explanation might be that the strongly basic nitrogen functionalities compete with the alkene moiety for the electrophilic halide (*N*-halogenation *vs* *C*-halogenation). In consequence, it might preclude, or at least slow down, the reaction because the halide is no longer available. Another issue to take into account is the potential formation of an aziridinium given that the nitrogen functionality is more nucleophilic than a sulfonamide, which can not only lead to the formation of the 6-membered ring through a ring-expansion but also to other side products.[3f,4e-f] Although a large variety of transition metals, Lewis acids or organocatalysts (used with or without an oxidant) have been employed to trigger the transformation, methods exhibiting a wide functional group compatibility are scarce.[1] To overcome the current limitations tied to the haloamidation of unactivated alkenes, we envisioned a strategy that would allow to both activate the halide reagent, *N*-halosuccinimide (NXS) for instance, and prevent the deactivation of the halide source, while operating under mild reaction conditions to suppress the formation of piperidine derivatives. In this respect, we considered the use of hexafluoroisopropanol (HFIP) to be the solution best suited to fulfil these requirements. In the last decade, HFIP has garnered a growing attention owing to its remarkable intrinsic properties, including its ability to stabilize carbocationic species and to be a strong hydrogen bond donor, in addition to its low nucleophilicity.[5-6] One of the keys to the success of our approach would rely on the inherent capacities of HFIP, including its acidity and its H-bond donating ability, to effectively activate the *N*-halo succinimide reagent. In addition, we anticipated that, even if the halide is sequestered by the nitrogen functional group, especially the most basic ones, HFIP could favor its release, driving the process to turn over.[7] Moreover, its high dielectric constant and its low nucleophilicity would make it an ideal solvent to generate cations, which are commonly proposed intermediates in haloamidation processes. HFIP has already demonstrated its efficiency as a solvent in halofunctionalizations.[8] However, the reactivity described was limited to arene and oxygen nucleophiles, which are less nucleophilic than amines, hence less prone to quench the electrophile in a side reaction. In the study by the Gulder group,[8a] the mechanistic proposal was based on the putative formation of a haliranium intermediate, which was not supported by either experimental or computational studies.

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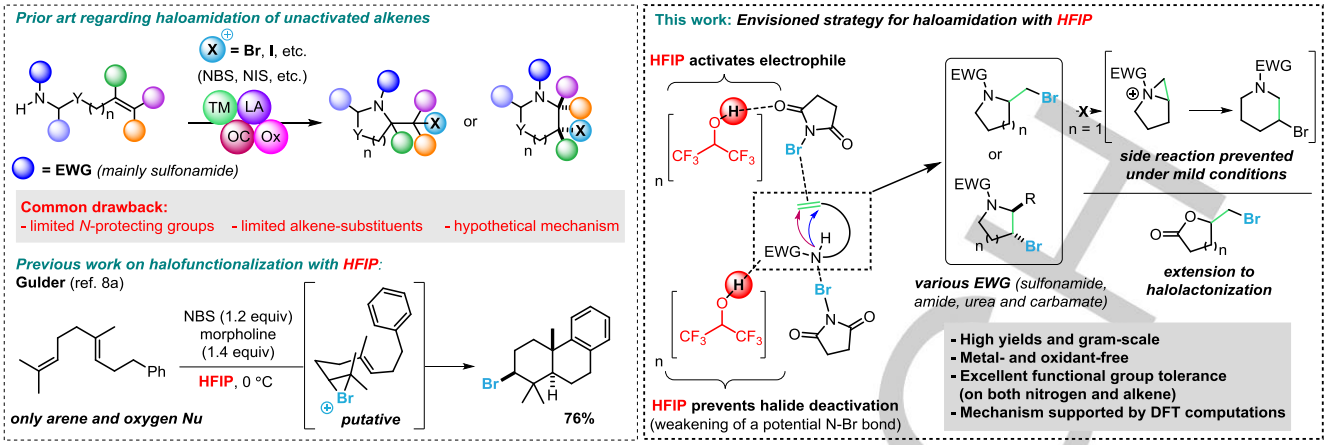


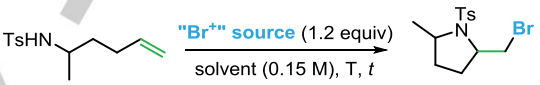
Scheme 1. Halofunctionalization of unactivated alkenes in the presence of HFIP

Herein, we report our findings on a broadly applicable and efficient metal- and oxidant-free haloamidation of unactivated alkenes promoted by HFIP as an additive rather than a solvent, which could also be extended to halolactonization with the same efficacy. Furthermore, an in-depth investigation of this reaction by DFT computations allowed us to better understand the mechanism of this transformation and shed light on the key role played by HFIP, discarding several mechanistic pathways postulated in precedent reports on haloamidation.

Results and Discussion

In our initial investigations, we studied the reactivity of *N*-tosyl aminoalkene **1a** to access bromo-pyrrolidine **2a** (Table 1). To optimize the efficacy and the selectivity of the haloamidation, we explored a variety of reaction conditions featuring HFIP as an activating agent and different bromine sources, starting with NBS. When HFIP was employed as a solvent, the reaction reached its full conversion in less than 5 min at rt, but the diastereoselectivity was moderate (Entry 1). The selectivity could be slightly improved by conducting the reaction at 0 °C (Entry 2). Because of the high cost of HFIP and its high corrosivity, we tested the possibility to use it as an additive. At the outset, we explored the reaction in a solvent mixture DCM/HFIP 5:1 (~10 equivalents of HFIP) (Entries 3-5). The best result was obtained at –40 °C, providing compound **2a** in 97% yield with a high diastereoselectivity (dr 6.5:1). Of note, the selectivity significantly decreased at –78 °C, which might be explained by the fact that the reaction mixture froze at this temperature. Operating at a lower concentration and screening other sources of bromine did not improve the selectivity (Entries 6-8). Other combinations of solvents were also tested (Entries 9-10) and, gratifyingly, performing the reaction in toluene led to the targeted product **2a** in 96% yield along with an excellent diastereoselectivity (dr 9:1).[9] On the other hand, replacing HFIP by another fluorinated alcohol such as trifluoroethanol (TFE) proved to be detrimental to both the reaction rate and the selectivity (Entry 11). Then, we evaluated the possibility to further decrease the amount of HFIP (~5 equivalents) (Entries 12-13); however, apart from slowing down the reaction, it did not have any impact on the selectivity or the yield of the transformation. To highlight the critical role of HFIP in this reaction, several control experiments were conducted (Entries 14-16). In the absence of HFIP, no reaction occurred. Switching from HFIP to *O*-methyl hexafluoroisopropanol (HFIPMe) to preclude any strong H-bonding with the substrates shut down completely the reactivity. Similarly, replacing HFIP by other alcohol solvents such as isopropanol and ethanol that did not possess the same H-bonding ability as HFIP did not mediate the reaction at –40 °C.[10] Finally, we demonstrated that the reaction could also be achieved on a

Table 1. Reaction optimization for the formation of pyrrolidine **2a**.



1a **2a**

Entry	Br^+ source	Solvent	T [°C]	*t* [h]	Conversion [%] (yield, *trans*/*cis*)
1	NBS	HFIP	20	0.05	100 (2.7:1)
2	NBS	HFIP	0	0.2	100 (3.3:1)
3	NBS	DCM/HFIP (5:1)	0	0.2	100 (4.9:1)
4	NBS	DCM/HFIP (5:1)	–40	1	100 (97%, 6.5:1)
5	NBS	DCM/HFIP (5:1)	–78	6	100 (4.4:1)
6	NBS	DCM/HFIP (10:1)[a]	–40	1	100 (6.3:1)
7	BDMS	DCM/HFIP (5:1)	–40	1	100 (5.3:1)
8	DBDMH	DCM/HFIP (5:1)	–40	1	100 (4.4:1)
9	NBS	$MeNO_2$/HFIP (5:1)	–40	4	100 (6.2:1)
10	NBS	Toluene/HFIP (5:1)	–40	3	100 (96%, 9:1)
11	NBS	Toluene/TFE (5:1)	–40	16	100 (5.6:1)
12	NBS	DCM/HFIP (10:1)	–40	2	100 (6.4:1)
13	NBS	Toluene/HFIP (10:1)	–40	8	100 (95%, 9:1)
14	NBS	DCM	–40	1	<5
15	NBS	Toluene	–40	3	<5
16	NBS	Toluene/HFIPMe (5:1)	–40	3	<5
17	NBS	Toluene/*i*PrOH (5:1)	–40	3	<5
18	NBS	Toluene/EtOH (5:1)	–40	3	<5

[a] 0.075 M. NBS = *N*-bromosuccinimide. BDMS = bromodimethylsulfonium bromide. DBDMH = 1,3-dibromo-5,5-dimethylhydantoin.

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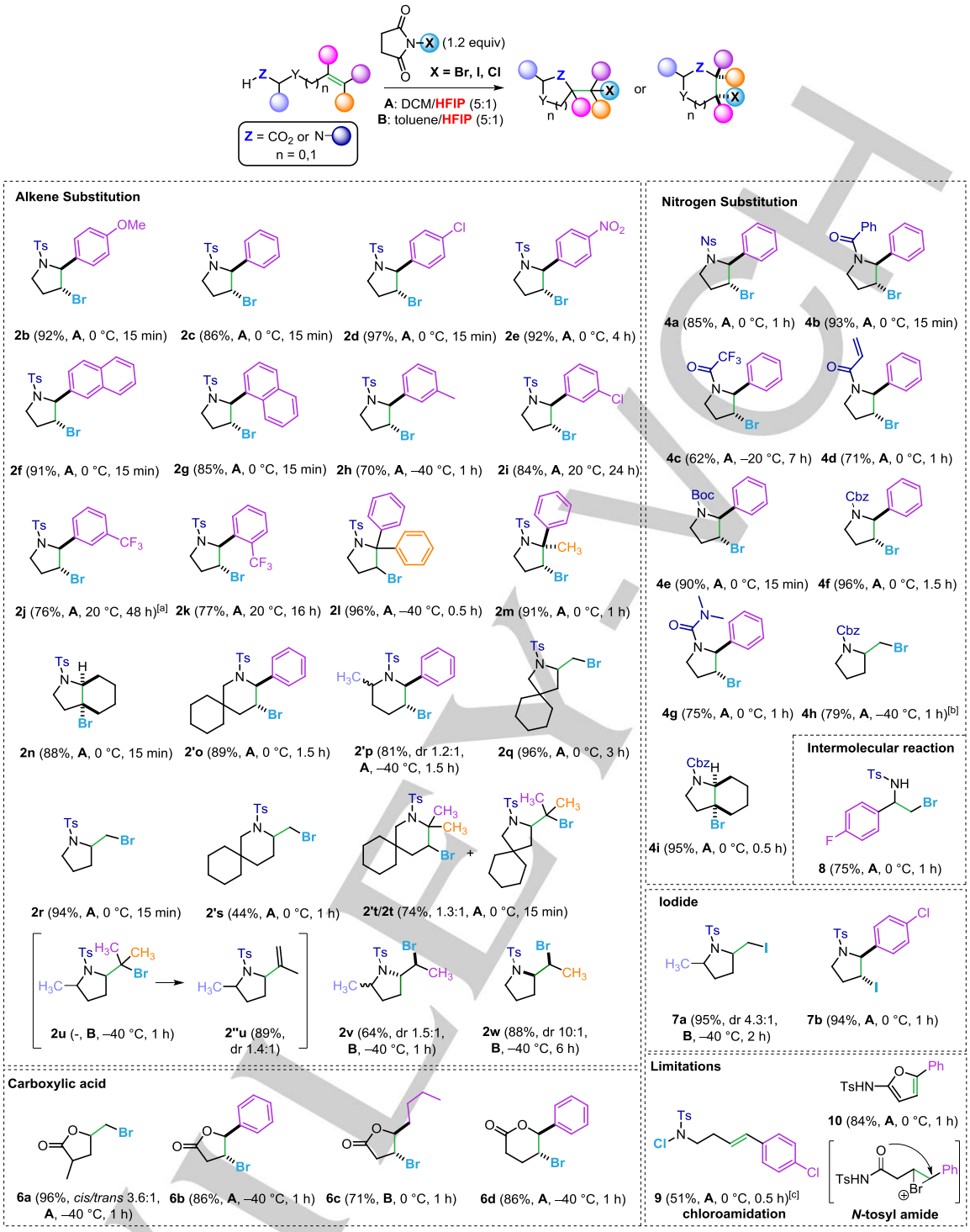


Scheme 2. Scope and limitations of the halofunctionalization of unactivated alkenes. [a] HFIP (20 equiv). [b] HFIP (5 equiv). [c] in the presence of DCDMH (1.2 equiv).

larger scale (5 mmol) to afford 1.57 g of **2a** (95% yield, dr 9:1).

Then, we explored the scope of the transformation with a wide range of *N*-protected aminoalkenes (Scheme 2). Depending on the substrate, either DCM or toluene was employed in association with HFIP as a solvent mixture. First, we evaluated the impact of the substituents at the terminal position of the alkene. The transformation worked smoothly with arenes bearing electron-donating and, more importantly, -withdrawing groups at the *para*-position to furnish the targeted products **2b**-**2e** in high yields (86-97%). Even a highly deactivated substrate such as **1e** which incorporates a far less nucleophilic *para*-nitrostyrene moiety, proved to be compatible with the optimized conditions, albeit at a slower reaction rate (4 h *vs* 15 min). The reaction was also extended to polycyclic aromatic hydrocarbons such as naphthyl to yield the corresponding products **2f** and **2g** in high yields (91% and 85%, respectively). The transformation is also tolerant to the presence of electron-donating and -withdrawing groups at the *meta*-position. However, in the case of an electron-donating group (**1h**), the reaction had to be conducted at a lower

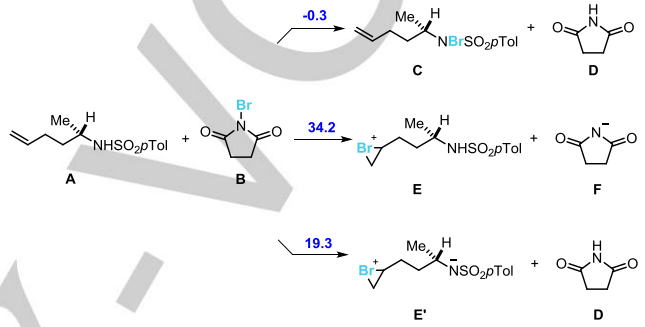
10.1002/anie.202010846

temperature (–40 °C) to obtain **2h** in a good yield (70%). The reason is that, at 0 °C, we observed a partial bromination of the arene ring, resulting in the formation of **2h** in 56% yield. On the other hand, in the presence of electron-withdrawing groups (**1i** and **1j**), the reaction had to be executed at rt to reach its completion, delivering **2i** and **2j** in 84% and 76% yields, respectively. Of note, in the case of the trifluoromethyl group (**1j**), 20 equivalents of HFIP were required for activating the electrophile. Lastly, substrate with an *ortho*-substituent (**1k**) underwent the haloamidation to form **2k** in 77% yield. Importantly, the reaction was expanded to sterically hindered 1,1-disubstituted alkenes such as **1l** and **1m** to give pyrrolidines **2l** and **2m** in excellent yields (96% and 91%). Bicyclic structures such as **2n** were also accessed in 88% yield. Using this method enabled the preparation of piperidines, notably spirocyclic compounds (**2'o**, **2'p** and **2's**), in up to 89%yield, starting from substrates bearing either a terminal alkene or a styrene moiety. In turn, with a 1,1-dimethyl substitution on the alkene (**1t**), a mixture of piperidine **1't** and **1t** was obtained. In the case of **1u**, while the haloamidation worked without problem, the resulting product was not stable and compound **2''u** was obtained in 89% following the elimination of bromide. With respect to this protocol, the control of 2 stereocenters was not an issue, but the control of 3 ones was more problematic and the overall selectivity was moderate (**2v**). It is important to stress out that the reaction was not limited to alkenes with a (*Z*)-configuration as alkenes with a (*E*)-configuration such as **1w** could also be subjected to the optimized conditions to afford pyrrolidine **2w** in 88% yield with an excellent control of the diastereoselectivity (dr 10:1). In that case, the formation of the minor diastereoisomer might result from a *syn*-addition to the alkene.

Then, we focused on the compatibility of the reaction with a large range of protecting groups on the nitrogen (**1a**-**1i**). This protocol offers a remarkable scope regarding nitrogen functional groups, from sulfonamide to amides, carbamates and even ureas with yields ranging from 62% to 96%. Nonetheless, in the case of substrate **1g**, which is more prone to generate an aziridinium species, we had to slightly modified the reaction conditions by using 5 equivalents of HFIP at –40 °C, which yielded **4g** as a sole product in 79% yield. In addition, our standard reaction conditions could also be applied to unsaturated carboxylic acids to provide bromo-lactones **5a**-**5d** in high yields (up to 96%).

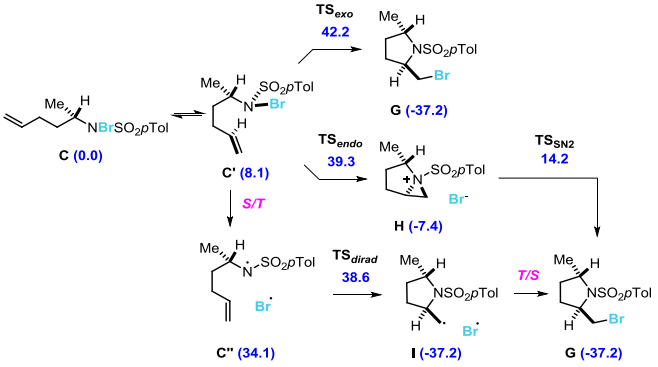
Encouraged by these results, we considered the iodoamidation process, using *N*-iodosuccinimide as an iodide source, and the intermolecular bromoamidation of *p*-fluorostyrene. In each case (**7a**-**7b** and **8**), the haloamidation reaction was accomplished in high to excellent yields (75%-95%). Regarding the limitations of this method, we failed to execute the chloroamidation reaction. In the presence of *N*-chlorosuccinimide, no reaction occurred, and, by replacing it by 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), we only observed the chlorination of the sulfonamide. Both chloride sources appeared to be not sufficiently electrophilic to trigger the targeted reaction. Additionally, in the case of a *N*-tosyl amide functional group, the carbonyl ended up being more nucleophilic than the sulfonamide and a subsequent elimination of bromide led to furan **10** in 84% yield.[11]

While the transformation displayed a wide scope under our standard protocol, the critical point was to determine the mechanism of the haloamidation, which has been less studied than that of halolactonization.[12] Several mechanisms have been postulated but they are not based on experimental or computational evidences. In our case, DFT computations were performed at the OPBE/6-31G(d,p) level of theory to gain insight into the reaction mechanism.[13] A full discussion is presented in the Supporting Information (SI) and only the main conclusions are outlined here. The model substrate **A** (corresponding to **1a** above) was used in this study, as shown in Scheme 3. At first, we envisioned that its reaction with NBS **B** might lead to the bromination of the nitrogen atom as in **C**, or to that of the alkene moiety to give either bromonium **E** or **E'**. Those are commonly proposed intermediates for the haloamidation of alkenes. The computed free energy is slightly negative for the former (-0.3 kcal/mol) and very high for the others (34.2 and 19.3 kcal/mol respectively).



Scheme 3. Free energies (ΔG_{233}, kcal/mol) of various bromine exchange reactions between *N*-tosylaminoalkene **A** and NBS **B**.

Based on those results, we evaluated the feasibility of the cyclization from the N-Br product **C** (Scheme 4). The direct formation of the final product **G** could be computed by reacting the nitrogen with the internal alkene carbon of **C'**, which is a pre-organized isomer of **C**, resulting in a formal insertion of the C=C bond into the N-Br bond. While being markedly exergonic by 37.2 kcal/mol, this process requires to overcome a high activation barrier of 42.2 kcal/mol and can thus be ruled out. Addition of the terminal alkene carbon to give ammonium **H** also faces an unsurmountable barrier of 39.3 kcal/mol. Then, a radical pathway was studied. Intermediate **C'** was re-optimized in the triplet state to give the diradical species **C''**. Although its cyclization could be modeled through **TS$_{diRad}$**, **C''** already lies too high on the energy surface to make this approach viable (34.1 kcal/mol).[14] We also re-investigated the cyclization under either neutral, ionic or radical pathways, but could not model the formation of the final product **G** (see the SI).



Scheme 4. Computed neutral and diradical pathways towards the final product **G** from *N*-tosylaminoalkene **C** (ΔG_{233}, kcal/mol; S: singlet; T: triplet).

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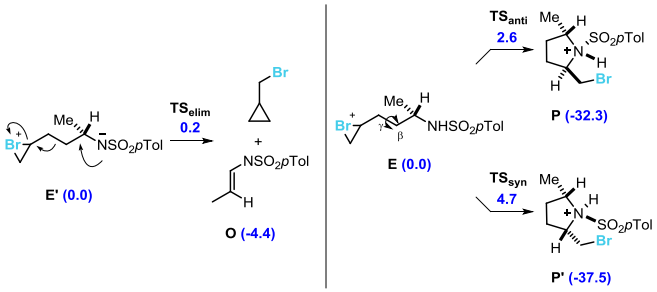
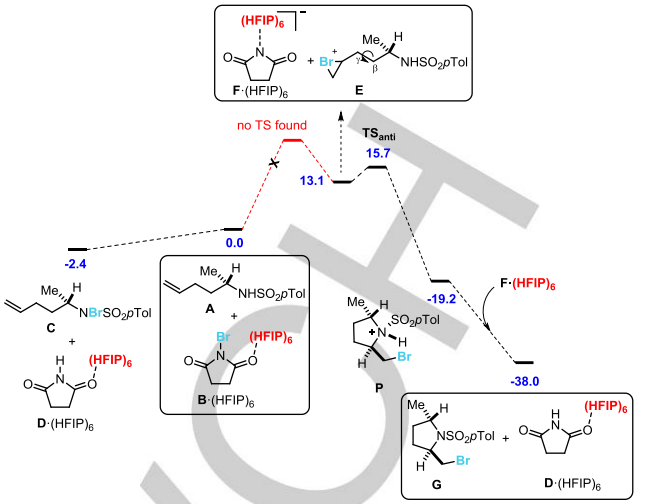
On this basis, we suppose that, even if it is formed during the reaction, the N-Br species **C** may not be a viable intermediate towards **G**.[15,16] We thus hypothesized that the bromination of the alkene moiety of **A** could be productive via either **E** or **E'**. We found that if bromonium **E'** forms, it readily eliminates through a very low-lying transition state (Scheme 5). As for **E**, we found that its cyclization into the diastereomeric ammoniums **P** or **P'** is a straightforward process that is only based on the conformational change of the alkyl chain. A simple rotation around the C_β-$C\gamma$ bond is enough to trigger the cyclization.



Scheme 5. Computed evolution of bromoniums **E** and **E'** (ΔG_{233}, kcal/mol).

With **E** as best candidate, it remained to explain how it could be formed efficiently. As shown in Scheme 3, the formation of **E** from **A** and **B** is endergonic by as much as 34.2 kcal/mol, but the possible role of HFIP was only considered through the SMD solvent model, not as explicit molecules. We added incrementally H-bonded HFIP molecules to see their effect on the alkene bromination step. One HFIP significantly lowered the free energy to 25.8 kcal/mol, and, with up to six H-bonded HFIP molecules, the free energy of this step was dramatically reduced to 13.1 kcal/mol (Scheme 6). Thus, this co-solvent provides a powerful stabilization of the succinimidate. At this point, the following free energy profile involving a 6-unit HFIP cluster was proposed. Of course, more HFIP molecules could be involved, but it already provides a reasonable picture. Compound **A** reacts with NBS H-bonded to a $(HFIP)_6$ cluster to give bromonium **E** and the corresponding succinimidate **F**·$(HFIP)_6$ lying at 13.1 kcal/mol on the free energy surface. A simple rotation around the C_β-C_γ bond triggers the cyclization to ammonium **P**. This step requires only 2.6 kcal/mol of free energy of activation and is exergonic by 29.0 kcal/mol (placing **P** at -15.9 kcal/mol). $\mathbf{TS_{anti}}$ is 2.1 kcal/mol lower in energy than $\mathbf{TS_{syn}}$, which is consistent with the experimentally observed diastereoselectivity (see Table 1). A proton exchange between **P** and the succinimidate **F**·$(HFIP)_6$ to give the final product **G** and succinimide is exergonic by 19.3 kcal/mol. The bromination of the nitrogen atom of **A** to give **C** is exergonic by 2.4 kcal/mol when using H-bonded NBS. It is thus logical to isolate such products when the cyclization cannot take place. However, this process is easily reversible, and the bromine can be shifted to the C=C bond.

At this point, what was missing was a transition state connecting **A** and **B**·$(HFIP)_n$ to **E** and **F**·$(HFIP)_n$. Despite all our efforts, we did not find a transition state forming a bromonium intermediate. In fact, it has been demonstrated that olefins are often incompetent to capture an electrophile such as Cl^+, and that the assistance of a nucleophile to activate the alkene can be required.[12b] The proximity of a nucleophile compensates the loss of electron density during the attack and favors the formation of the C-Cl bond. In our case, we tried to use the oxygen atoms of the SO_2



Scheme 6. Incomplete bromonium pathway (ΔG_{233}, kcal/mol) of the bromocyclization of *N*-tosylaminoalkene **A** in the presence of a 6-unit HFIP cluster.

moiety, but it did not promote the bromination. We then used the nitrogen atom and, gratifyingly, we could locate a transition state connecting **A** and **B** to ammonium **P** and succinimidate **F** (n = 0) (Scheme 7). Of note, the ammonium intermediate has 3 stereogenic centers (2 C and 1 N) and thus 4 diastereomers are expected. Only the most energetically favorable option is shown here. The complete sequence involves first the formation of an adduct between **A** and **B**, in which the alkene provides electron density to the bromine σ-hole.[17] This weak non-covalent interaction has a maximum electron density between the alkene and the bromine of ρ_{max} = 0.0135 e.Å^3, which does not provide sufficient energy to compensate the entropic factor, hence the endergonicity of 5.5 kcal/mol for the formation of adduct [**A**·**B**]. Conformer [**A**·**B**]', preorganized for cyclization, is less stable by a few kcal/mol. The non-covalent interaction between NBS and the alkene involves more electron density, a value of ρ_{max} = 0.0233 e.Å^3 being obtained. The bromonium transfer is achieved though $[\mathbf{TS_{cyclization}}]^0$, which also involves the concomitant formation of the C-N bond. The free energy of activation is of 20.9 kcal/mol and the formation of ammonium **P** is endergonic by 0.9 kcal/mol. Proton exchange between **P** and succinimidate **F** liberates 38.4 kcal/mol of free energy, generating the final products **G** and **D** (at -37.5 kcal/mol on the potential energy surface). We then introduced explicit HFIP molecules in the system (from n =1 to 6, see the SI), which considerably lowered the free energy of activation with an optimum of 3. In the case of a 3-unit HFIP cluster H-bonded to a NBS carbonyl, the free energy of the cyclization transition state $[\mathbf{TS_{cyclization}}]^3$ dropped to 14.2 kcal/mol, while this step became appreciably exergonic (-14.9 kcal/mol).[18] Of note, replacing HFIP by TFE resulted in a higher cyclization barrier of 19.3 kcal/mol. This is in line with the experimental results, which revealed that TFE is a fine additive for the reaction, albeit at slower rate than the one in HFIP (Table 1, entry 11). Thus, the lower p*Ka* of TFE makes it less effective than HFIP for the ionization of the N-Br bond.

In agreement with the work of Berkessel,[19] and our own findings on the alkoxylate walk in H-bonded alcohol clusters,[20] it seems probable that the acidity of HFIP increases after forming a H-bonding network, so that the cluster can accommodate the negative charge of succinimidate **D**. Thus, the role of HFIP in this

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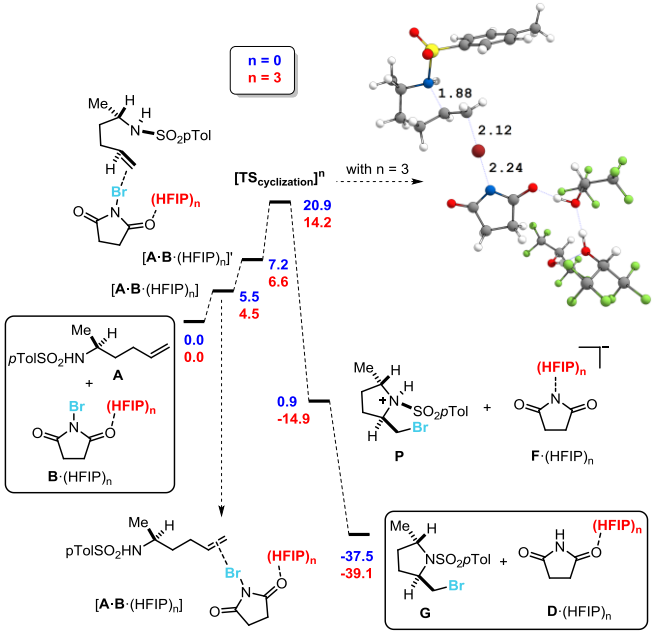

Scheme 7. Free energy profile (ΔG_{233}, kcal/mol) of the bromo-cyclization of *N*-tosylaminoalkene **A** without HFIP or in the presence of a 3-unit HFIP cluster.

reaction is to facilitate the ionization of the N-Br bond of NBS, notably by stabilizing the resulting succinimidate, and trigger a cationic cyclization. What is true for NBS might also be true for the *N*-bromination of substrates, whose formation may quench the *C*-bromination process. Of course, in solution, more HFIP molecules can be involved but our computations reveal, at least qualitatively, a positive effect of the formation of a H-bonded NBS rather than a free NBS in triggering a nucleophile-assisted alkene bromination.

Conclusion

In summary, we have developed a broadly applicable haloamidation of unactivated alkenes to provide a convenient route to pyrrolidine and piperidine derivatives, as well as γ-lactones. This transformation was efficiently and rapidly promoted by HFIP as an additive under mild conditions and exhibits a remarkable functional group tolerance, whether at the nitrogen or alkene moiety. A key feature of this study is also our in-depth investigations of the mechanism, including the role played by HFIP, which was carried-out by means of DFT computations. In contrast with previous reports, which suggested either the formation of a haliranium or a *N*-bromoamide intermediate, our investigations lean towards an activation of the alkene assisted by a nitrogen nucleophile in order to trigger the cyclization, which is in agreement with previous reports on halolactonization. Further applications of this approach are underway in our laboratory, including its extension to chlorofunctionalizations.

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Keywords: halofunctionalization • hexafluoroisopropanol • DFT computations • unactivated alkenes • heterocycles

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[10] We also attempted the reaction in the presence of a catalytic amount of a Lewis acid ($Ca(NTf_2)_2$/nBu_4NPF_6) or a Brønsted acid (TfOH) (5 mol%), without HFIP. While the reaction worked smoothly (full conversion in less than one hour), the dr remained inferior (<5.5:1)

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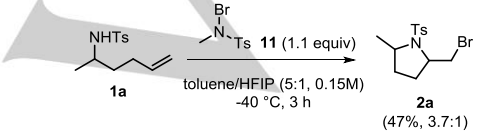
[14] We cannot however exclude that UV irradiation or traces of a transition metal could generate traces of radical **C''** from **C** and trigger a radical chain mechanism through **I**.

[15] We are aware that intramolecular haloamidations starting from *N*-halo precursors are feasible, see inter alia: a) I. A. Schulte-Wulwer, J. Helaja, R. Göttlich, Synthesis **2003**, 1886-1890; b) reference 1f and the references cited therein.

[16] We cannot exclude that **C** instead of NBS might function as the brominating agent on a second molecule of **A**. To test this hypothesis, we performed the reaction in the presence of **11**. While the target product was still generated, it was obtained in a lower yield and a modest selectivity.



1a **2a** (47%, 3.7:1)

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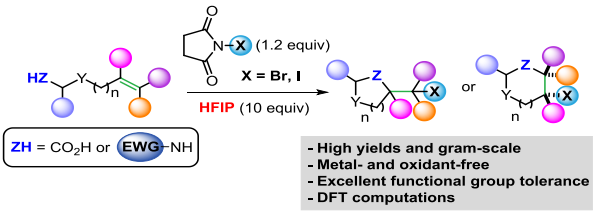

Less but better: The use of hexafluoroisopropanol as an additive enables the halofunctionalization of unactivated alkenes with a remarkable functional group tolerance under mild reaction conditions. DFT computations were carried out to shed light on the mechanism of haloamidation featuring as a key step an alkene activation assisted by a nitrogen nucleophile.

Institute and/or researcher Twitter usernames: @djpleboeuf and @vincent_gandon