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# *N*-Bromosuccinimide-Induced Aminocyclization–Aziridine Ring-Expansion Cascade: An Asymmetric and Highly Stereoselective Approach toward the Synthesis of Azepane

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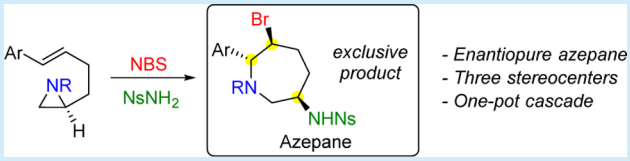
Supporting Information

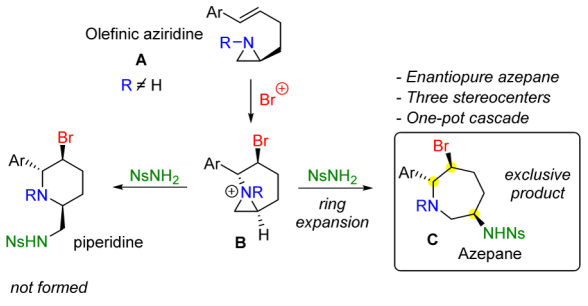
**ABSTRACT:** A novel *N*-bromosuccinimide induced aminocyclization–aziridine ring expansion cascade is reported. Substituted azepanes were isolated exclusively in good yields. The azepane products could be transformed into a number of functional molecules including piperidines, a bicyclic amine, and a bridgehead amide.




Albeit a fundamental organic reaction, electrophilic activation of a carbon–carbon double bond by a halonium ion[1] has been revived in recent years mainly in two areas: (1) catalytic and asymmetric halogenation[2] and (2) halogen-induced cascade and multicomponent reactions, and their synthetic applications.[3,4] In particular, bromonium ion induced cyclic ether ring-expansion cascade reactions received much attention due to their facile construction of the scaffolds of many natural products.[3] Recently, our group reported the *N*-bromosuccinimide (NBS)-induced multicomponent reactions which involve cyclic ether ring-opening cascades. By using epoxide as the nucleophilic partner, the multicomponent reactions proceeded smoothly, and the methodology has been successfully applied in the synthesis of bioactive morpholines.[4]

As a chemical analogue of epoxide, aziridine displays similar reactivities.[5] Because of the highly strained ring system of aziridine, the lone pair of aziridine's nitrogen can hardly resonate with the neighboring conjugated group, which results in a certain degree of nucleophilicity of aziridine's nitrogen (e.g., aziridine **A**; R ≠ H).[5] We reasoned that the olefinic aziridine **A** should be able to react with a brominating source to give the aziridinium ion intermediate **B**. Subsequently, **B** could be attacked by a nucleophile at the tertiary carbon to give the product **C** (Scheme 1). Although using aziridine in electrophilic cascade is seldom,[6] herein we are pleased to report a novel and highly stereoselective bromoaminocyclization of olefinic aziridine cascade which resulted in the formation of enantiopure substituted azepanes, and *no piperidine was detected*; ring-opening of activated aziridines by nucleophiles at the less substituted carbons are commonly observed which will result in the formation of piperidines in this case.[5,6]

**Scheme 1. NBS-Induced Cascade Reaction**




Functionalized azepanes are useful in various areas such as biomedical chemistry.[7] It is important to note that direct cyclization (e.g., halocyclization) of olefinic amine/amide to give azepane is not trivial as such kind of reaction suffers from high entropy and enthalpy barrier.[8] In addition, enantioselective approach toward substituted azepane remains under-exploited.[9] This methodology can be considered as a detour of the direct seven-membered ring halocyclization in the asymmetric synthesis of azepanes.[10]

To verify our hypothesis, enantiopure olefinic aziridine **1a** (R = Boc), which could be readily synthesized from L-glutamic acid, was subjected to the investigation.[11] NBS and $NsNH_2$ were used as the halogenating agent and the nucleophilic partner, respectively. To our delight, upon halogen source initiation, the cyclized product azepane **2a** was obtained in 54% yield when using dichloromethane as the solvent. A quick survey on some common organic solvents revealed that the reaction worked best in ethyl acetate, and **2a** (R = Boc, X = Br) was obtained in 82% yield (Table 1, entry 1).[11]

After subsequent optimization of the reaction temperature, it was found that the reaction worked better at −30 °C which resulted in 88% yield of the desired product (Table 1, entries 1–3). The yield was slightly improved to 90% when freshly recrystallized NBS was applied (entry 4). The reaction concentration could be increased to 0.1 M (entry 5) with slightly improved yield, while lowering the concentration (0.025 M, entry 6) had a significant detrimental effect. The optimized conditions were then applied to a large-scale reaction

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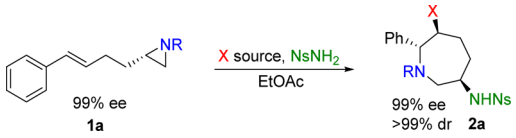
**Table 1. Reaction Optimization**[a]




| entry | R | X source | temp (°C) | time (h) | yield[b] (%) |
|---|---|---|---|---|---|
| 1 | Boc | NBS | −20 | 10 | 82 |
| 2 | Boc | NBS | −30 | 48 | 88 |
| 3 | Boc | NBS | −40 | 72 | 86 |
| 4[c] | Boc | NBS | −30 | 48 | 90 |
| 5[c,d] | Boc | NBS | −30 | 48 | 91 |
| 6[c,e] | Boc | NBS | −30 | 48 | 79 |
| 7[c,f] | Boc | NBS | −30 | 48 | 88 |
| 8 | Boc | NCS | −30 | 48 | <5 |
| 9 | Boc | NIS | −30 | 48 | 11 |
| 10 | Boc | NBP | −30 | 48 | 89 |
| 11 | Boc | DBDMH | −30 | 48 | 86 |
| 12 | Ts | NBS | −30 | 48 | 31 |
| 13 | Cbz | NBS | −30 | 48 | 82 |

[a]Reactions were carried out with compound **1a** (0.2 mmol), halogen source (0.3 mmol), and $NsNH_2$ (0.3 mmol) in anhydrous EtOAc (4 mL). [b]Isolated yield. [c]Recrystallized NBS was used. [d]2 mL of EtOAc (0.1 M) was used. [e]8 mL of EtOAc (0.025 M) was used. [f]1.0 g scale, 0.1 M.

(entry 7); azepane **2a** was obtained in 88% yield starting from 1.0 g of **1a**. Other halogen sources were also investigated. *N*-Chlorosuccinimide (NCS) (entry 8) and *N*-iodosuccinimide (NIS) (entry 9) were not as effective as NBS in mediating the reaction, while some other commonly used brominating agents such as *N*-bromophthalimide (NBP) (entry 10) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (entry 11) gave comparable yields. Finally, the effect of the *N*-protecting group was examined. Cbz-activated aziridine (entry 13) gave considerably higher yield than that of the Ts group (entry 12). It is noteworthy that the reaction is highly chemo-, enantio-, and stereoselective in which *out of eight possible stereoisomers (with three stereogeneric centers), **2a** was furnished exclusively and no piperidine product was detected.*[12] The absolute configuration of **2a** was established unambiguously by an X-ray crystallographic study of its analogue **2a-Bn** (Figure 1).[11,13]

Having identified the optimal system, we then explored the scope of the reaction as listed in Table 2. In all cases, good yields of azepanes were obtained with each product isolated as a

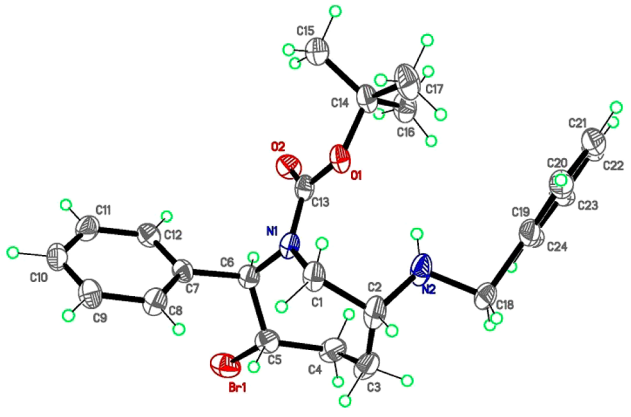
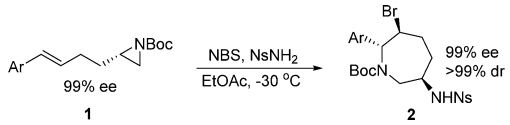



**Figure 1.** X-ray structure of **2a-Bn** (R = Boc; X = Br).

**Table 2. Scope of the Reaction**[a]




| entry | substrate | Ar | product | yield (%) |
|---|---|---|---|---|
| 1 | **1b** | 2-Me-$C_6H_4$ | **2b** | 70 |
| 2 | **1c** | 3-Me-$C_6H_4$ | **2c** | 80 |
| 3 | **1d** | 4-Br-$C_6H_4$ | **2d** | 82 |
| 4 | **1e** | 4-Cl-$C_6H_4$ | **2e** | 83 |
| 5 | **1f** | 3-F-$C_6H_4$ | **2f** | 71 |
| 6 | **1g** | 3-*t*BuOC(O)-$C_6H_4$ | **2g** | 82 |
| 7[b] | **1h** | 4-CHO-$C_6H_4$ | **2h** | 81 |
| 8 | **1i** | 4-Ph-$C_6H_4$ | **2i** | 92 |
| 9 | **1j** | 2-naphthyl | **2j** | 87 |
| 10 | **1k** | 3-thienyl | **2k** | 73 |

[a]Reactions were carried out with olefinic aziridine **1** (0.1 mmol), recrystallized NBS (0.15 mmol), and $NsNH_2$ (0.15 mmol) in anhydrous EtOAc (1 mL). The yields were isolated yields. [b]The corresponding dimethyl acetal protected aldehyde was used as the starting material.

single diastereoisomer. No bromination on the aromatic ring or at the benzylic position was observed even for electron-rich substituted systems (Table 2, entries 1, 2, 8, and 9). Compared with other substrates, *o*-$CH_3$-substituted substrate **1b** gave 70% yield, presumably due to the steric repulsion between the bulky Boc group and the *ortho* substitution. The electronic effect appears to be less dominating in this type of reaction. Halogen-substituted substrates **1d**−**f** (entries 3−5) and ester substrate **1g** (entry 6) also performed well. Additionally, the hetero-aromatic substrate **1k** was well tolerated to give 73% yield of the desired product (entry 10).

Substituted azepane is the pharmacophore of many interesting bioactive molecules.[7] In addition, **2** is a versatile synthetic precursor of many functional molecules. For instance, the Boc group in azepane **2a** could be removed under an acidic environment to yield the corresponding deprotected amine, which could be then transformed into azabicyclo[3.1.0]hexane derivative **3** simultaneously (Scheme 2).[14] Subsequent reaction with acetic acid gave rise to the piperidine derivative **4**. The stereochemistry was determined by an X-ray crystallographic study on the tosylate derivative **5**.[11]

Other than acetic acid, **3** could react with *p*-fluorothiophenol and trimethylsilyl azide to furnish the thioether **6** and the azide derivative **9**, respectively (Scheme 3). For thioether **6**, subsequent cyclization reaction by connecting the two nitrogen atoms gave rise to bicyclic systems **7** and **8**; these skeletons consist of a rigid tertiary amine moiety which resembles the cinchona alkaloid scaffold. The antipodes of **7** and **8** can readily be prepared from *ent*-**1**, which can result in an enantiomeric pair of privileged catalyst skeletons' mimics.[15] In addition, **8** contains a bridgehead amide which potentially possesses unusual physical and chemical properties.[16]

On the other hand, azide **9** could be converted into 1,2-diamine **10** by the Staudinger reduction. Treatment of **10** with triphosgene under basic conditions furnished urea **11**. These amine systems consist of modifiable handles which can potentially be utilized as metal ligands[17] and organocatalyst building blocks.[18]

Toward a better understanding of the mechanism, we examined the stability of aziridine in the presence of the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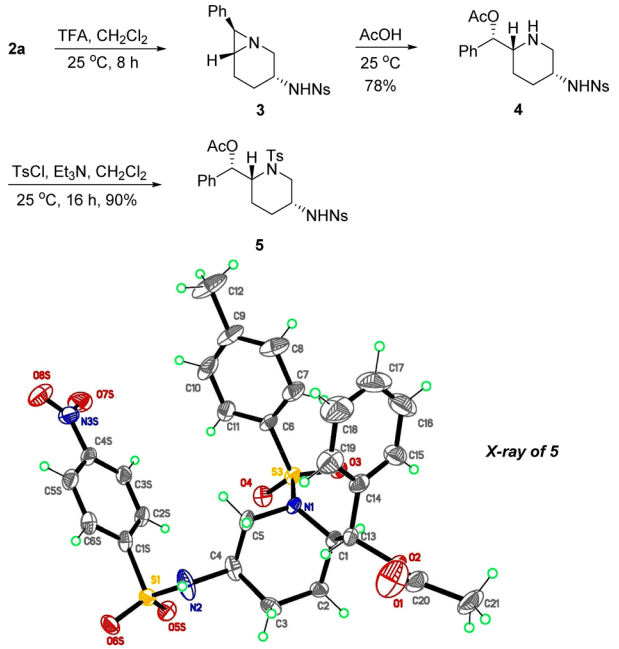
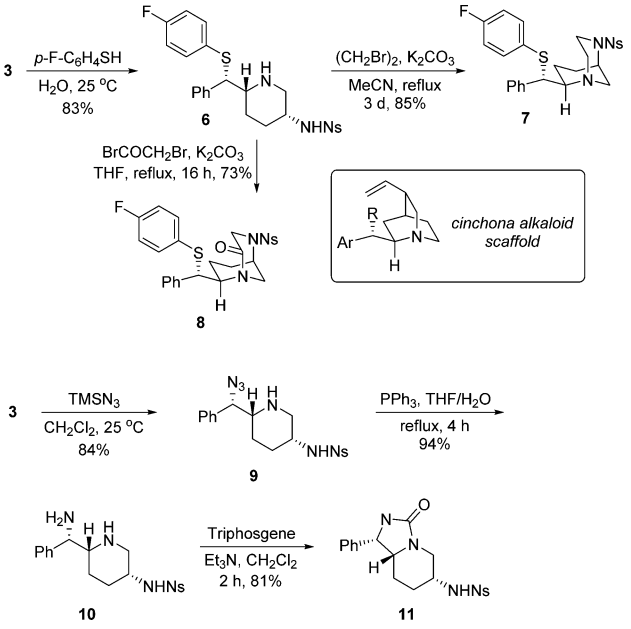
**Scheme 2. Synthesis of Piperidine 4**



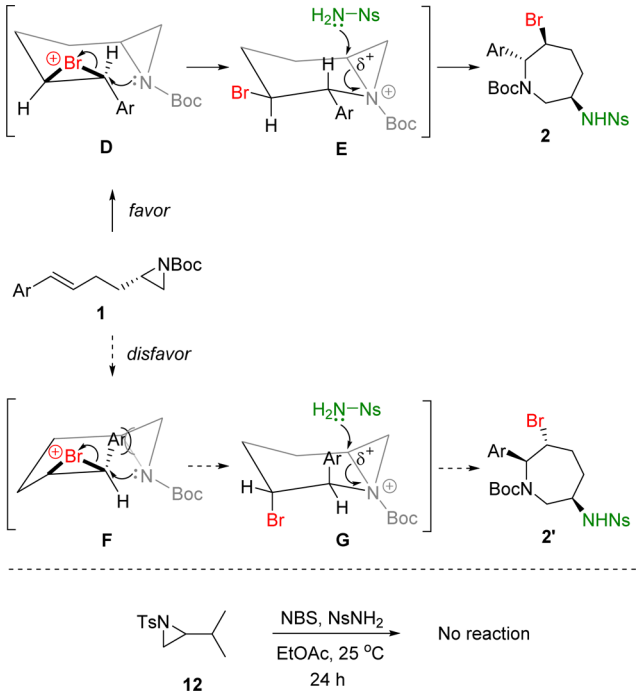

**Scheme 3. Synthetic Application of 3**




halogenating agent (Scheme 4). No reaction was observed when aziridine **12** was mixed with NBS and $NsNH_2$ in ethyl acetate at 25 °C for 24 h. This suggests that the aziridine ring was not preopened before the aminocyclization step.

Based on this result and our previous experience on electrophilic halogenation reactions, we believe that NBS might be activated by $NsNH_2$.[4,19] Electrophilic addition of activated NBS to the olefin in substrate **1** would give bromonium ion intermediate **D**. Acting as a nucleophile, the aziridine could then react with bromonium ion to gave aziridinium ion intermediate **E**. Finally, $NsNH_2$ would open the ring to afford the desired azepane compound **2**. The excellent stereoselectivity in the formation of **2** also suggests that the nucleophilic attacks in **D** and **E** were in $S_N2$ manner.

**Scheme 4. Proposed Mechanism of the Cyclization**




On the other hand, bromination of the olefin at the opposite side as **D** to give **2′** through intermediates **F** and **G** might be disfavored due to the steric stress in the pseudo-six-membered boat transition state **F**. However, the sole origins of chemo- and stereoselectiviy remain unclear and are subject to further investigation.

In conclusion, a novel NBS-induced aminocyclization–aziridine ring expansion reaction was developed. This methodology could be applied in the preparation of functionalized piperidines and rigid amine systems. Further application to other substrates is underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data for all new compounds, and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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(11) Details appear in the Supporting Information.

(12) In many cases, nucleophilic attack of aziridines at the less substituted carbons occurred even in the presence of Lewis acids. For detail, see ref 5.

(13) The structure of azepanes **2** was also determined on the basis of the HMBC experiment of **2a**. For details, see the Supporting Information.

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(19) We also attempted to perform the cyclization of **1a** in the absence of either NBS or $NsNH_2$, which yielded no reaction. This further supports that NBS might be activated by $NsNH_2$. For details, see the Supporting Information.




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