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Diastereoselective synthesis of functionalized pyrrolidines through *N*-bromosuccinimide-induced aziridine ring expansion cascade of cinnamylaziridine†

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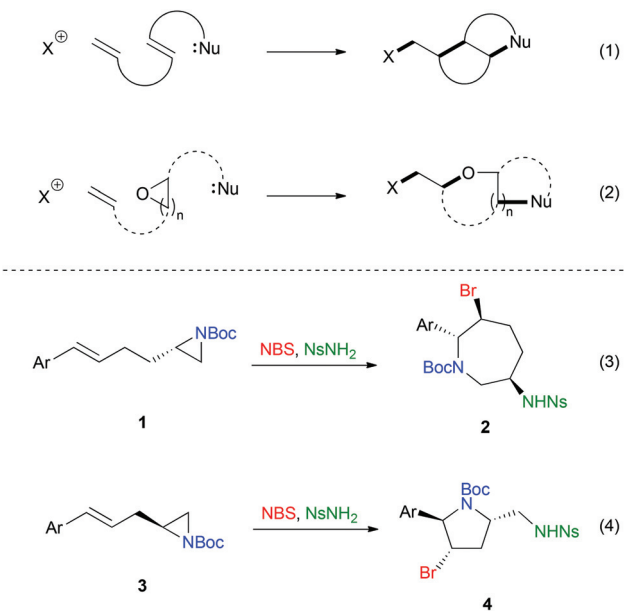
An efficient aziridine ring expansion cascade of cinnamylaziridine has been developed. *N*-Bromosuccinimide was used as the promoter. The resulting functionalized pyrrolidines are the fundamental units of many useful molecules.

Inefficient chemical synthesis does cause problems in pharmaceutical industry and obstructs the development of life-saving drugs.[1] The negative impact of inefficient synthetic processes on the environment has also become an important concern in recent years.[2] Electrophilic halogen-induced cascade reactions, which are considered as efficient and environmentally benign processes since multiple bonds can be formed (sometimes multiple stereocentres can also be obtained) in a single chemical operation,[3,4] have been developed in recent years.[5] For instance, transformations such as polyene cyclization (Scheme 1, eqn (1))[6] and domino cyclization/cyclic ether ring expansion (Scheme 1, eqn (2)) have been documented.[7] These reactions have proven to be highly valuable as a number of applications have been demonstrated. In contrast, the utilization of aziridine in such kind of cascade is less studied.[8] Recently, we have reported a novel bromonium ion-initiated asymmetric aminocyclization–aziridine ring expansion cascade to afford substituted azepanes **2**, which could be further transformed to other functional molecules (Scheme 1, eqn (3)).[9] We reasoned that the same reaction protocol can be applied to the homolog cinnamylaziridine **3**. Herein, we are pleased to report the diastereoselective synthesis of pyrrolidine **4**,[10] which contains three stereocenters through the electrophilic aminocyclization–ring expansion cascade using *N*-bromosuccinimide (NBS) as the halogen source (Scheme 1, eqn (4)).

It is noteworthy that functionalized pyrrolidines have been widely applied in various areas such as medicinal chemistry,[11]



Scheme 1 NBS-induced aminocyclization–aziridine ring expansion cascade.

organocatalysts,[12] and chiral metal complexations.[13] Some examples are shown in Fig. 1.

3 was readily achievable by metathesis of L-aspartic acid-derived ethenylaziridine **6** and substituted styrene using Grubbs 2nd generation catalyst (Scheme 2).[14]

Initially, **3a** was subjected to the investigation using *p*-nosyl amide as the nucleophilic partner. In this kind of cyclization cascade, two possible products, pyrrolidine and piperidine, can be obtained through path a and path b, respectively (*vide infra*, Scheme 3). Ethyl acetate, which was found to be a superior solvent medium for the cascade reaction of **1** in our previous study,[9a] gave poor selectivity of **4a** : **5a** (1.1 : 1.0) despite the high overall reaction yield (Table 1, entry 1). The selectivity was slightly improved when reducing the reaction temperature to −20 °C (entry 3). After screening some common organic solvents, it was found that relatively

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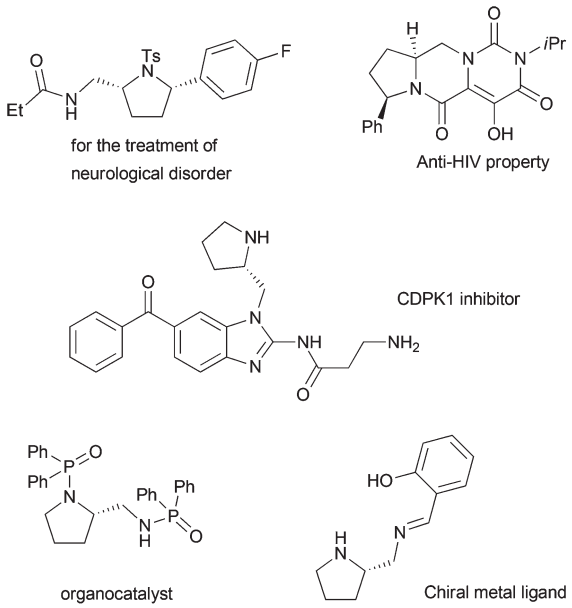
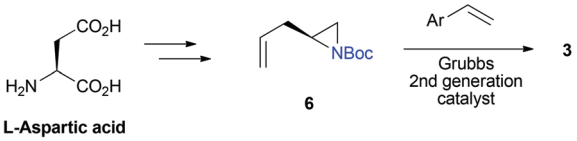
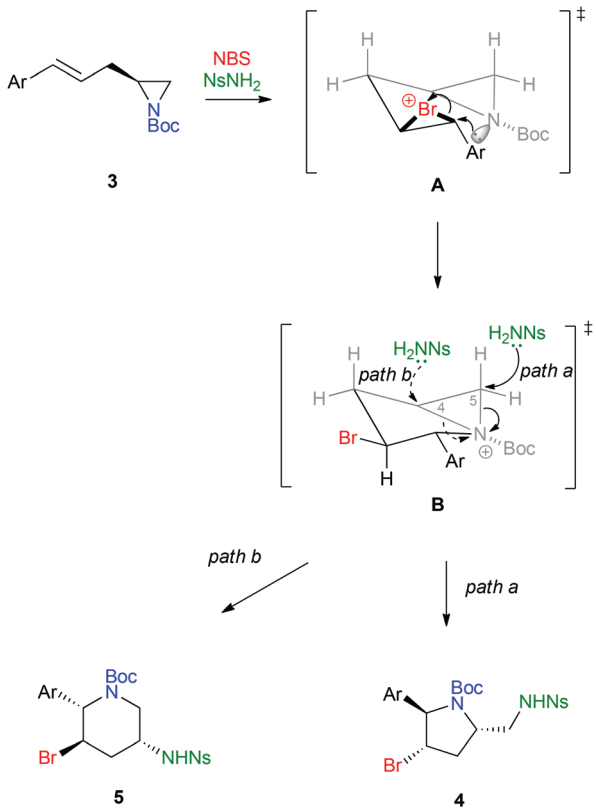


Fig. 1 Examples of pyrrolidine-containing functional molecules.



Scheme 2 The synthesis of **3**.

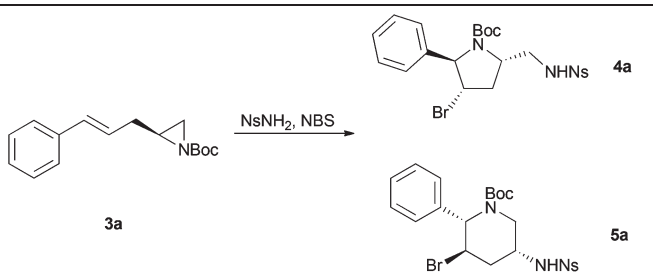


Scheme 3 Proposed mechanism.

non-polar solvents such as diethyl ether and toluene gave a sluggish reaction while polar solvents generally gave much better conversion (entries 4–12). Finally, the optimal solvent and temperature were found to be acetonitrile and −20 °C, respectively, which gave the selectivity of **4a** : **5a** up to 3.2 : 1.0 (entry 7). Other halogenation sources, including *N*-chlorosuccinimide (NCS) and *N*-iodosuccinimide (NIS), were also examined under the optimal conditions and the reactions were found to be sluggish (entries 13 and 14). The structure of pyrrolidine **4a** was determined by 2D-NMR analysis while piperidine **5a** was confirmed by an X-ray crystallographic study on its tosylated derivative (CCDC 970435).[15]

Having identified the optimal conditions, we then explored the scope of the reaction and the results are listed in Table 2. In all cases, good yields of aziridine ring expansion products were obtained. No aromatic bromination was observed even for the electron-rich substituted systems (Table 2, entries 1–4). Compared with other substrates, *ortho*-CH_3 phenyl system gave slightly lower reaction yield (72%), presumably due to the steric repulsion. Similar to our previous discovery,[9a] it appears that the electronic effect has no significant effect on the yield of the reaction. Generally, substrates with electron-rich substituents gave better regioselectivity, while substrates with relatively electron-poor substituents returned lower selectivity. The best selectivity (**4e** : **5e** = 4 : 1) was obtained with the *tert*-butyl

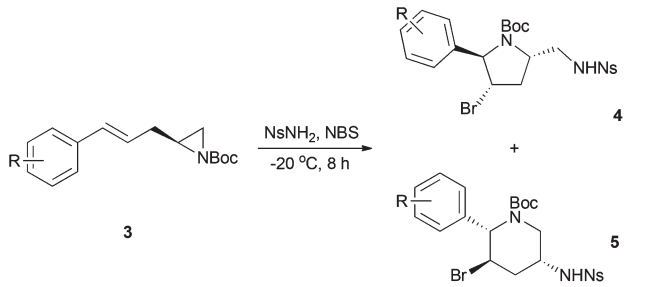
Table 1 Reaction optimization



Entry[a]	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	**4a** : **5a**[c]
1	EtOAc	25	1	82	1.1 : 1.0
2	EtOAc	0	2	81	1.3 : 1.0
3	EtOAc	−20	8	82	1.7 : 1.0
4	THF	−20	8	79	1.3 : 1.0
5	Acetone	−20	8	80	2.0 : 1.0
6	$MeNO_3$	−20	8	73	3.1 : 1.0
7	*MeCN*	*−20*	*8*	*82*	*3.2 : 1.0*
8	MeCN	−40	16	81	3.2 : 1.0
9	CH_2Cl_2	−20	16	76	2.0 : 1.0
10	$CHCl_3$	−20	16	70	1.5 : 1.0
11	Et_2O	25	24	Trace	—
12	Toluene	25	24	Trace	—
13[d]	MeCN	−20	24	Trace	—
14[e]	MeCN	−20	24	Trace	—

[a] Reactions were conducted using aziridine **3a** (0.1 mmol), NBS (0.15 mmol), and $NsNH_2$ (0.15 mmol) in solvent (1 mL). [b] Isolated yield of the mixture **4a** and **5a**. [c] The ratios were determined by ^1H NMR analysis of the product mixture. [d] NCS was used. [e] NIS was used.

Table 2 NBS-induced aminocyclization–aziridine ring expansion cascade of **3**



Entry[a]	Substrate	R	Yield[b] (%)	**4** : **5**[c]
1	**3b**	4-OCH_3	80	2.1 : 1.0
2	**3c**	4-CH_3	82	3.0 : 1.0
3	**3d**	2-CH_3	72	3.8 : 1.0
4	**3e**	4-*t*-Bu	80	4.0 : 1.0
5	**3f**	4-F	85	3.5 : 1.0
6	**3g**	3-F	82	2.7 : 1.0
7	**3h**	3-Cl	84	2.6 : 1.0
8	**3i**	4-Br	83	3.0 : 1.0
9	**3j**	4-$COOCH_3$	74	2.3 : 1.0
10[d]	**3k**	3-NO_2	67	1.1 : 1.0

[a] Reactions were conducted using aziridine **3** (0.1 mmol), NBS (0.15 mmol), and $NsNH_2$ (0.15 mmol) in MeCN (1 mL) at −20 °C for 8 h. [b] Isolated yield of the mixture **4** and **5**. [c] Ratios were determined by ^{1}H NMR analysis of the product mixture. [d] The reaction time was 16 h.

phenyl substrate **3e** (entry 4). It is noteworthy that only one diastereomer for both **4** and **5** was observed.

For the mechanism of this type of cascade, we believe that the cyclization might involve intermediate **A** through the bromination of **3** by the NBS/$NsNH_2$ protocol (Scheme 3).[9] Subsequently, the aziridine in **A** could react with the bromonium ion to give the aziridinium ion intermediate **B**.[16] At this stage, $NsNH_2$ could attack at either C-5 (path a) or C-4 (path b) position to give pyrrolidine **4** or piperidine **5**, respectively. The preference on the formation of pyrrolidine **4** could be attributed to the substitution taken place at the less hindered C-5 position. The excellent diastereoselectivity in the formation of the cyclic amine products also suggests that the nucleophilic attacks in **A** and **B** occur in a S_N2 manner.

Conclusions

In conclusion, we have developed an efficient bromonium ion-induced aziridine ring expansion cascade to afford functionalized pyrrolidines containing three stereocenters. These compounds are potential building blocks in various areas, and their possible synthetic applications are currently being studied.

Acknowledgements

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