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Optically active *N*-alkyl aziridines *via* stereospecific reductive cyclization of α-mesylated acetamides†

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An efficient method for the synthesis of optically active *N*-alkyl aziridines has been realized for the first time by stereospecific reductive cyclization of optically active α-mesylated acetamides. A series of optically active *N*-alkyl aziridines are prepared in moderate to good yields and excellent ees. The employment of $(9\text{-BBN})_2$ as the reagent is crucial for the success of the transformation.

Optically active aziridine moieties exist in a number of biologically important alkaloids[1] and therapeutic agents such as mitomycin A,[2a,b] madurastatin A1,[2e] ficellomycin,[2f] and azicemicin B[2c,d] (Fig. 1). They also belong to key structural motifs in agrochemicals and dyes.[2] Structurally, the ring strain possessed by aziridine makes them highly reactive species. For example, they can undergo ring-opening reactions in the presence of nucleophiles,[3] and they can also be employed for cycloaddition reactions.[4] Optically active aziridines have become highly valuable building blocks for the synthesis of nitrogen-containing compounds.

The synthesis of optically active aziridines has thus gained significant interest. Common methods for the stereoselective synthesis of aziridines include Wenker cyclization or Mitsunobu reaction of optically active amino alcohols,[5] reaction of imines with carbene compounds (aza-Darzens reaction)[6] or sulfur ylides (Corey–Chaykovsky aziridination),[7] or reaction of alkenes with nitrenes *in situ* generated from various nitrene precursors in the presence of a catalyst.[8] However, most of these methods applied well to the synthesis of aziridines with *N*-acyl or -sulphonyl functionalities in order to achieve a good yield. So far, only a few methods are available for the synthesis of optically active *N*-alkyl aziridines. Lindsley and coworkers[9] described a three-step protocol for the synthesis of terminal *N*-alkyl aziridines (Fig. 2a). An enantioselective aziridination was reported by Buchwald and coworkers from allylic hydroxylamine ester through a CuH-catalyzed regioselective intramolecular hydroamination[10] (Fig. 2b). Nevertheless, a facile and straightforward synthetic methods for optically active *N*-alkyl aziridines from readily accessible starting material remains highly desirable. We have recently reported a stereospecific nucleophilic substitution of optically active α-aryl-α-mesylated acetamides with arylboronic acids as nuclephiles.[11] The readily availability of optically active α-aryl-α-mesylated acetamides from mandelic acid derivatives or by asymmetric hydrogenation[12] makes them attractive feedstocks for preparing other valuable optically active intermediates. Herein we report a facile preparation of optically active *N*-alkyl aziridines by stereospecific reductive cyclization of α-mesylated acetamides using $(9\text{-BBN})_2$ as a reducing reagent (Fig. 2c).

Optically active (*R*)-2-(benzylamino)-2-oxo-1-phenylethyl methanesulfonate (**1a**) was chosen as the model substrate for study of reductive cyclization (Table 1). The reaction was

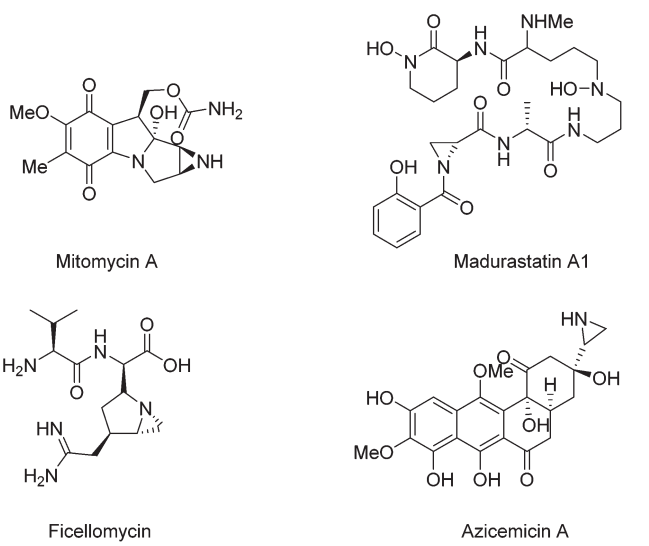

Fig. 1 Therapeutic agents containing optically active aziridine moieties.

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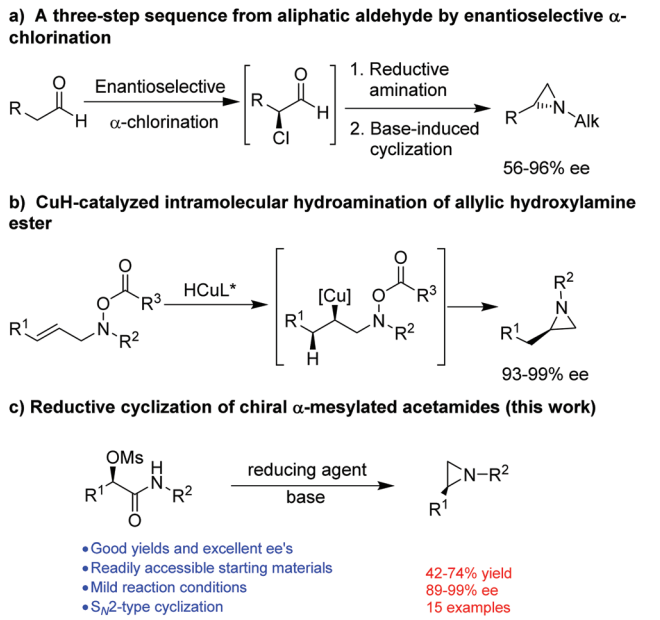
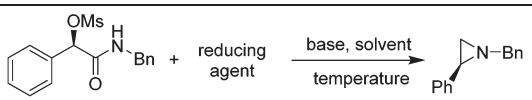


Fig. 2 The construction of aziridines.

Table 1 Reductive cyclization of (*R*)-2-(benzylamino)-2-oxo-1-phenylethyl methanesulfonate (**1a**)



1a **2a** **3a**

Entries[a]	Base	Solvent	Reducing agent	Yield[b] (%)	ee[c] (%)
1	K_2CO_3	Toluene	$(9\text{-BBN})_2$	25	97
2	K_2CO_3	Toluene	BH_3·THF	0	ND
3	K_2CO_3	Toluene	$LiAlH_4$	0	ND
4	K_2CO_3	Toluene	DABAL-H	Trace	ND
5	K_3PO_4	Toluene	$(9\text{-BBN})_2$	62	97
6	TEA	Toluene	$(9\text{-BBN})_2$	14	97
7	KO*t*Bu	Toluene	$(9\text{-BBN})_2$	0	ND
8	DABCO	Toluene	$(9\text{-BBN})_2$	0	ND
9	CsF	Toluene	$(9\text{-BBN})_2$	7	98
10	KOH	Toluene	$(9\text{-BBN})_2$	0	ND
11	Cs_2CO_3	Toluene	$(9\text{-BBN})_2$	40	93
12	None	Toluene	$(9\text{-BBN})_2$	0	ND
13	K_3PO_4	DCE	$(9\text{-BBN})_2$	27	91
14	K_3PO_4	Dioxane	$(9\text{-BBN})_2$	0	ND
15	K_3PO_4	THF	$(9\text{-BBN})_2$	0	ND
16	K_3PO_4	DMF	$(9\text{-BBN})_2$	0	ND
17	K_3PO_4	Cyclohexane	$(9\text{-BBN})_2$	22	94
18	K_3PO_4	CH_3CN	$(9\text{-BBN})_2$	0	ND
19	K_3PO_4	Mesitylene	$(9\text{-BBN})_2$	20	97

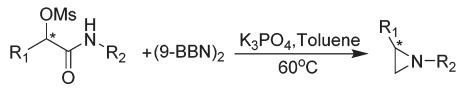
[a] Unless otherwise specified, all reactions were performed at 60 °C for 8 h in the selected solvent (5 mL) with **1a** (0.5 mmol), **2a** (1 mmol), base (2 equiv.). [b] Isolated yields. [c] Determined by chiral HPLC on a chiralcel column.

initially carried out in toluene with $(9\text{-BBN})_2$ as the reducing reagent and K_2CO_3 as the base. A decent yield (25%) of **3a** with an excellent ee (97%) was achieved at 60 °C for 8 h (entry 1). However, no **3a** was formed with other reducing reagents including BH_3, $LiAlH_4$, and DIBAL-H (entries 2–4). We thus employed $(9\text{-BBN})_2$ as the reducing reagent for the rest of study. When K_3PO_4 was used as the base, the yield of **3a** increased to 62% without loss of ee (97%, entry 5). Further screening of the base including inorganic and organic bases did not further improve the yield (entries 6–11). It is noteworthy that no product of **3a** was achieved in the absence of base (entry 12). We further investigated the effect of the solvents. Polar solvents such as dioxane, THF, DMF or CH_3CN did not yield any product (entries 14–16 and 18). Nonpolar or less polar solvent such as DCE, cyclohexane, or mesitylene provided the desired product, albeit with lower yields (entries 13, 17 and 19). The absolute configuration of **3a** was determined as *S* by comparing the optical rotation with reported data,[13] indicating that **1a** was cyclized reductively to form **3a** through an S_N2-type process.

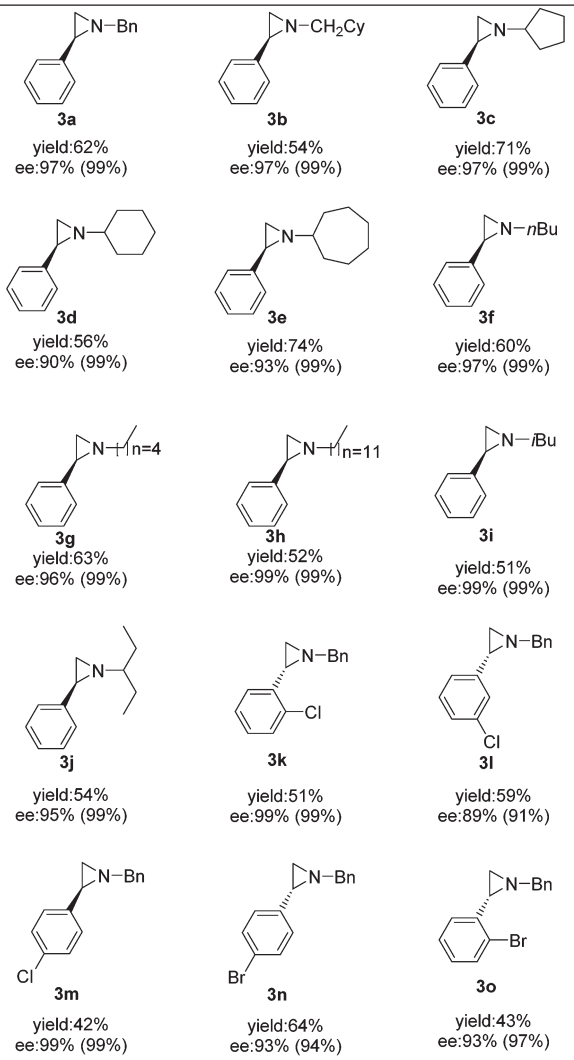
We then looked into the substrate scope of this reaction. As depicted in Table 2, a series of optically active aziridines were formed in excellent enantioselectivities and moderate to good yields from optically active α-substituted-phenyl-α-mesylated acetamides with $(9\text{-BBN})_2$ as the reducing reagent with a minimum loss of enantiomeric purity. Various optically active *N*-alkyl aziridines including *N*-cyclic alkyl (**3c–e**), *N*-noncyclic primary alkyl (**3f–h**) and *N*-noncyclic secondary aziridines (**1i–g**) were prepared in moderate to good yields and excellent ee's. Surprisingly, no desired aziridine product was formed when an *N*-aryl substrate was employed. Halogen-substituted benzylic mesylates (**1k–o**) at various positions were all applicable. However, mesylates with electron-donating substituents at aryl groups were generally too unstable to prepare. It should be noted that *ortho*-halo substituted benzylic mesylates such as **1k**, **1o** were also suitable for the transformation, providing the optically active aziridines **3k** and **3o** in excellent enantioselectivities and moderate yields.

To shed light on the mechanism of this transformation, the following experiments were implemented (Scheme 1). Firstly, a deuterium-labeling experiment with **1c′** as the substrate proved no deprotonation occurring at the benzylic position (eqn (1)). Secondary, no deuterium was included in **3c** with C_6D_6 as solvent, indicating that the hydrogen in the product is derived from $(9\text{-BBN})_2$ rather than solvent (eqn (2)). Thirdly, only a trace amount of the target product **3c** was isolated when the $(9\text{-BBN})_2$ was reduced to 0.5 equiv., indicating that multiple equivalents of 9-BBN were needed for a complete transformation of **1c** to the target product **3c** (eqn (3)). Fourthly, no target product **3a** was formed without base in the reaction, and only a large amount of **1a** was recovered (eqn (4)), demonstrating that the base had played a crucial role in the reduction of amide. We believe that the addition of base not only enhanced the reducing ability of 9-BBN, but also promoted the formation of the aziridine ring. To understand why no aziridine was formed when DIBAL-H was used as the reducing reagent, we isolated a secondary amine as a major product from the reaction (eqn (5)), indicating that DIBAL-H was too active as the reducing agent for the transformation. When an

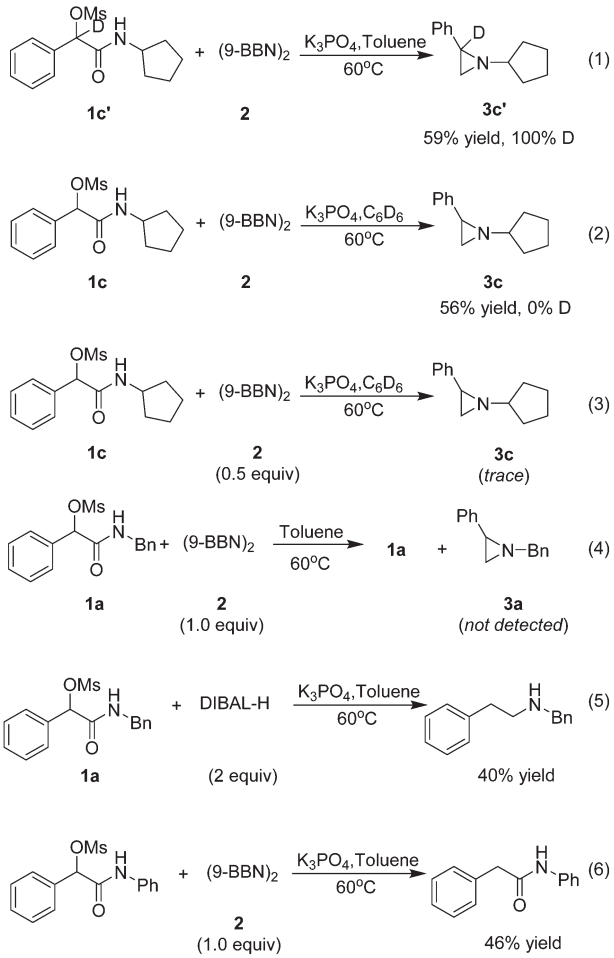
Table 2 Formation of optically active aziridines **3a–o** by reductive cyclization[a]



1 2 3



[a] Unless otherwise specified, the reactions were carried in toluene under nitrogen at 60 °C for 8 h in the presence of $(9\text{-BBN})_2$ (2 equiv.) and K_3PO_4 (2 equiv.), isolated yields, ee value of the substrate in parenthesis.

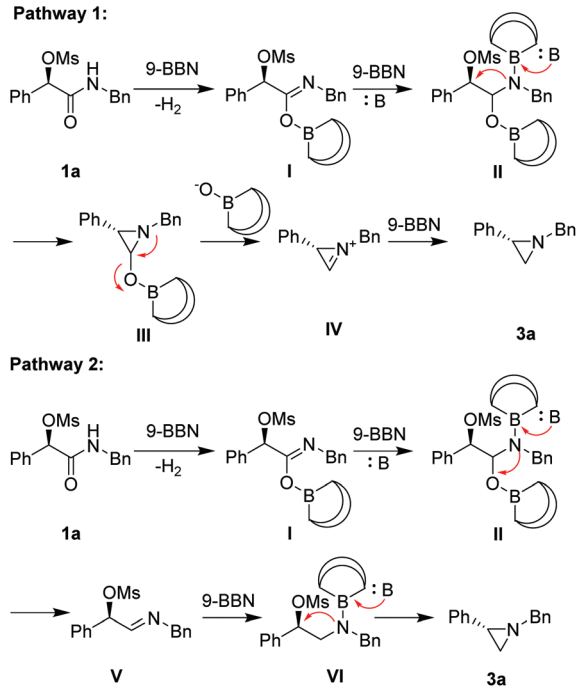


Scheme 1 Mechanistic investigation.

N-phenyl substrate was employed, a demesylate product was isolated in 46% yield (eqn (6)), indicating a facile demesylation process with an *N*-aryl substrate. This result explained the limitation of the reductive cyclization in the preparation of *N*-aryl aziridines.

On the basis of the above observation, we proposed two reaction pathways for the reductive cyclization (Scheme 2). In pathway I, 9-BBN reacts with substrate **1a** to generate imidate **I**, which further react with a 2nd equiv. of 9-BBN to form **II**. In the presence of a base, intramolecular cyclization at a S_N2-type fashion occurs to form cyclic product **III**, which can break down to a cyclic iminium **IV**. Further reduction with a 3rd equiv. of 9-BBN to form product **3a**. Alternatively in pathway **II**, intermediate **II** can give rise to the formation of imine **V** under basic conditions, which can further reduced by 9-BBN to form **VI**. In the presence of a base, cyclization of **VI** through a S_N2-type process takes place to form product **3a**.

In summary, an efficient method for the synthesis of optically active *N*-alkyl aziridines has been realized for the first time by stereospecific reductive cyclization of optically active α-mesylated acetamides. With this method, a series of optically active *N*-alkyl aziridines have been prepared in moderate to good yields with excellent ees. Mechanistic investigation has indicated an intramolecular S_N2-type process under reductive conditions and the employment of $(9\text{-BBN})_2$ has been proven to be crucial for the success of reaction. Because of the readily availability of optically active α-hydroxy acetamides, this method offers a facile and expedite preparation of optically active aziridines complementary to other existing methods. The methodology should find a number of applications in drug discovery and process chemistry.



Scheme 2 Proposed mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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