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One-Pot Synthesis of Chiral Aziridines by a Domino Reaction by Using Desulfonylative Formation on the *N*-Tosyl Imine of Chloroacetaldehyde with an Asymmetric Mannich Reaction as a Key Step

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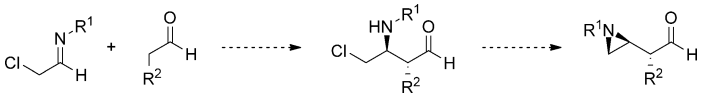
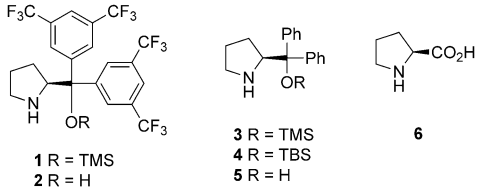
Aziridine is a versatile building block in organic synthesis because of its facile transformation to other useful compounds by ring-expansion and ring-opening reactions. Aziridine is also found as a key structural unit in natural products. Thus, the development of an efficient method for the preparation of chiral aziridines is synthetically important.[1] There are several successful asymmetric, catalytic aziridinations, such as nitrene addition to alkene and carbene addition to imine catalyzed by organometallic reagents. Organocatalysts[2] are known to catalyze aziridination, most of which involve the reaction of α,β-enal or α,β-enone with hydroxyamine derivatives through an iminium ion intermediate.[3]

Recently, we have reported the one-pot synthesis of chiral β,γ-epoxyaldehyde through uninterrupted sequential reactions including an asymmetric aldol reaction of chloroacetaldehyde as a key step.[4] If the asymmetric Mannich reaction of the imine derived from chloroacetaldehyde and unmodified aldehyde proceeds, followed by an intramolecular nucleophilic substitution, a chiral aziridine derivative would be generated (Scheme 1). The Mannich reaction of imines derived from aliphatic aldehydes with α-hydrogens is thought to be difficult because of the equilibrium between imine and enamine,[5] and there are only four examples of the organocatalyst-mediated, asymmetric cross-Mannich reaction of an unmodified aldehyde as the Mannich donor and imines derived from aliphatic aldehydes with α-hydrogens.[5d,f,h] Because imines derived from chloroacetaldehyde possess α-hydrogens, their Mannich reaction is expected to be very difficult. Just recently, we have found that the asymmetric catalytic Mannich reaction of imines derived from aliphatic aldehydes with α-hydrogens is catalyzed by diarylprolinol silyl ether **1**.[6,7] In this communication, we describe the successful synthesis of chiral aziridine derivatives by an asymmetric Mannich reaction catalyzed by **1**, followed by intramolecular cyclization in a one-pot operation.

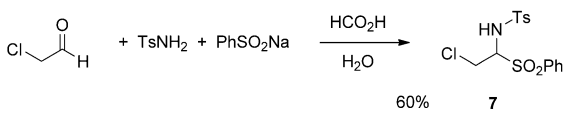


Scheme 1.



First, we chose *N*-(2-chloroethylidene)-*p*-toluenesulfonamide as the imine, which can be obtained from *N*-(2-chloro-1-phenylsulfonylethyl)-*p*-toluenesulfonamide (**7**) by treatment with a base. α-Amidosulfone **7** was prepared from an aqueous solution of chloroacetaldehyde, *p*-toluenesulfonamide ($TsNH_2$), and $PhSO_2Na{\cdot}2H_2O$ in aqueous formic acid (Scheme 2).

Because all of the trials for the isolation of the desired imine were unsuccessful as a result of its rapid degradation, we investigated the domino reaction of the in situ desulfonylative generation of *N*-Ts imine and the enantioselective Mannich reaction.[8] The reaction was performed as follows: organocatalyst, base, α-amidosulfone **7** and aldehyde were all mixed together in the presence of solvent at 0 °C, and the reaction mixture was stirred for 24 h. Because trifluoromethyl-substituted diarylprolinol silyl ether **1** gave good results in



Scheme 2.

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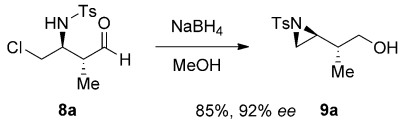
the Mannich reaction of imines derived from aliphatic aldehydes with an α-hydrogen,[6] compound **1** was employed as the organocatalyst in this transformation. Propanal and $NaHCO_3$ were chosen as the Mannich donor and base, respectively. When CH_2Cl_2 was employed as the solvent, the reaction proceeded and afforded the Mannich product **8a** in 59% yield with predominant formation of the *anti* isomer. When **8a** was treated with $NaBH_4$, not only reduction but also aziridination reaction proceeded to afford the desired 2-aziridinylpropanol **9a** in 85% yield, and the enantiomeric excess (*ee*), which was found to be excellent (92% *ee*), was determined by HPLC using a chiral phase (Scheme 3).

First, the domino desulfonylation/Mannich reaction was investigated and the effect of the solvent was examined; the results are summarized in Table 1. The reaction proceeds in

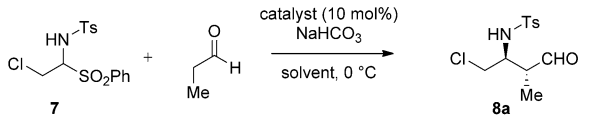


8a **9a**

Scheme 3.

most of the solvents under investigation. Even in the presence of brine without organic solvent, the desired product was obtained in 61% yield (Table 1, entry 5). The yield and diastereoselectivity are dependent on the solvent; a good yield and excellent diastereo- and enantioselectivities were obtained when toluene or 1,4-dioxane was employed (Table 1, entries 3 and 4). Next, the catalyst was examined. Diphenylprolinol silyl ethers **3** and **4** are more reactive, promoting the reaction in much shorter time (6 h) than **1**. In particular, *tert*-butyldimethylsilyl ether **4** gave the product in excellent yield (95%) and enantioselectivity (92% *ee*) in a short reaction time (6 h), although the diastereoselectivity (d.r.) was modest (d.r. = 2.3:1; Table 1, entry 8). It should be noted that the corresponding alcohol **2** gave the other *syn* diastereomer predominantly, although the yield is insufficient (Table 1, entry 6). Low yield and enantioselectivity were obtained in the presence of proline (Table 1, entry 10).

Table 1. Effect of solvent and catalyst in the domino desulfonylation/Mannich reaction.[a]



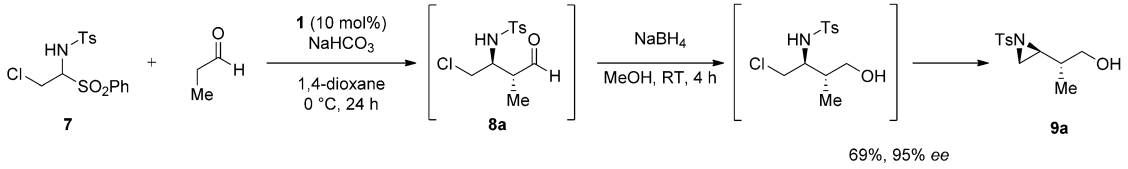
7 **8a**

Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1	**1**	CH_2Cl_2	24	59	15:1	92
2	**1**	CH_3CN	24	70	4:1	88
3	**1**	toluene	24	81	16:1	97
4	**1**	1,4-dioxane	24	82	16:1	96
5	**1**	brine	24	61	5:1	90
6	**2**	1,4-dioxane	72	27	1:10	nd
7	**3**	1,4-dioxane	6	93	4:1	74
8	**4**	1,4-dioxane	6	95	2.3:1	92
9	**5**	1,4-dioxane	24	12	1.6:1	nd
10	**6**	1,4-dioxane	24	23	2.3:1	22

[a] Reactions were performed employing α-amidosulfone **7** (0.4 mmol), propanal (2.0 mmol), catalyst (0.04 mmol), $NaHCO_3$ (1.2 mmol), and solvent (0.8 mL) at 0 °C. nd = not determined. [b] Isolated product yield. [c] Diastereomer ratio was determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of *anti* isomer was determined by HPLC analysis on chiral column material after conversion to **9a** by the reduction and aziridination with $NaBH_4$.

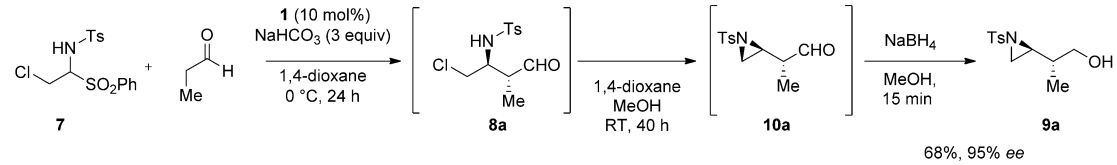
Next, the one-pot synthesis of 2-aziridinylpropanol **9a** was investigated (Scheme 4). After the domino reaction of desulfonylative formation of imine and Mannich reaction, addition of $NaBH_4$ and MeOH in the same pot gave **9a** in 69% yield with excellent enantioselectivity (95% *ee*). In the reaction with $NaBH_4$, first reduction of aldehyde occurs and then the aziridine is formed.

Because aziridinylaldehyde is also a useful chiral building block, its generation was investigated. When three equivalents of $NaHCO_3$ were employed in the desulfonylative generation of imine and the addition of MeOH to the reaction mixture of Mannich product **8a**, which was gradually converted into aziridinylaldehyde **10a** (40 h) as detected by ^{1}H NMR spectroscopy. Because **10a** is difficult to purify, it was reduced to alcohol **9a**, which was isolated in 68% yield from **7** with excellent enantioselectivity (95% *ee*, Scheme 5).



7 **8a** **9a**

Scheme 4.



7 **8a** **10a** **9a**

Scheme 5.

This result indicates that aziridinylaldehyde can be synthesized in moderate yield with excellent enantioselectivity in a one-pot reaction.

The generality of both the desulfonylative Mannich reaction and the one-pot synthesis of 2-hydroxyethylaziridine **9**, using the method in Scheme 5, was investigated and the results are summarized in Tables 2 and 3, respectively.

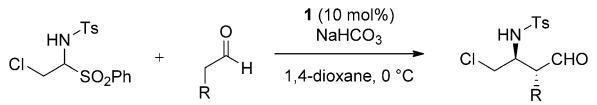
In both the domino reaction and the one-pot reaction for the synthesis of 2-hydroxyethylaziridine **9**, there is a wide generality: the domino reaction product **8** and 2-hydroxyethylaziridine derivative **9** are obtained with excellent diastereo- and enantioselectivities. In most of the reactions, moderate to good yields were obtained. In the reaction of isovaleraldehyde, the reaction is slow because of the steric bulkiness of the aldehyde. Double and triple bonds do not interfere with the reaction, affording the products **8** and **9** in good yield. It is noteworthy that the (2-hydroxy-1-methylethyl)aziridine derivative, which was prepared in good yield with excellent diastereo- and enantioselectivities in a single-pot reaction (Table 3, entry 1), is an enantiomer of the key intermediate of (−)-deoxynupharidine, previously synthesized in five steps from (*R*)-aspartic acid.[9]

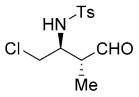
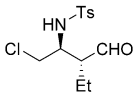
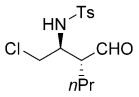
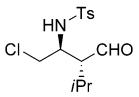
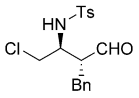
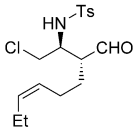
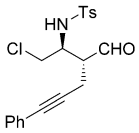
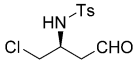
Other synthetically useful chiral compounds can also be prepared with excellent enantioselectivity based on the present reaction, as follows. The ethyl 4-aziridinyl-2-pentenoate derivative was prepared in a one-pot reaction in good yield with excellent enantioselectivity with the domino reaction, followed by the successive Wittig reaction and aziridine formation (Scheme 6).

The aziridine dimethylacetal derivative was also prepared in a one-pot reaction by using the domino reaction, followed by acetalization and aziridine formation (Scheme 7).

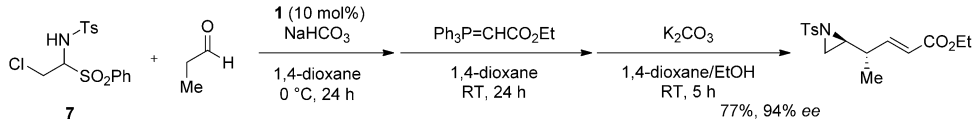
In conclusion, we have developed a one-pot synthesis of 1-substituted-2-hydroxyethylaziridine derivatives through uninterrupted sequential reactions including desulfonylative formation of *N*-Ts imine, an asymmetric, direct Mannich reaction catalyzed by diarylprolinol silyl ether **1**, reduction, and aziridine formation. Synthetically useful chiral aziridines with a hydroxyethyl moiety can be prepared in a single flask with good *anti* selectivity and excellent enantioselectivity. Aziridines with an α,β-unsaturated ester moiety or acetal moiety were also synthesized in a one-pot procedure. Because the generated product possesses several functional groups, with excellent diastereoselectivity and enantioselectivity and the synthetic proce-

Table 2. The domino reaction of desulfonylative formation of imine and Mannich reaction catalyzed by organocatalyst **1**.[a]

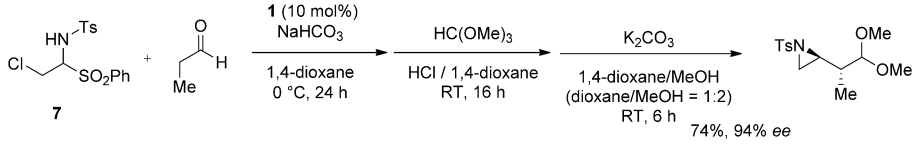


Entry	Product	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1		24	83	9:1	96
2		24	89	>20:1	99
3		24	90	>20:1	99
4		72	65	>20:1	99
5		24	62	>20:1	99
6		24	90	>20:1	99
7		24	67	>20:1	99
8[e]		24	70	–	80

[a] Unless otherwise shown, the reaction was performed employing α-amidosulfone **7** (0.4 mmol), aldehyde (1.2 mmol), catalyst **1** (0.04 mmol), $NaHCO_3$ (1.2 mmol), and 1,4-dioxane (0.8 mL) at 0 °C for the indicated time. [b] Isolated product yield. [c] Diastereomer ratio was determined by ^1H NMR spectroscopy. [d] The enantiomeric excess of *anti* isomer was determined by HPLC analysis on chiral column material after reduction and aziridination with $NaBH_4$. [e] Acetaldehyde (2.0 mmol) was employed.

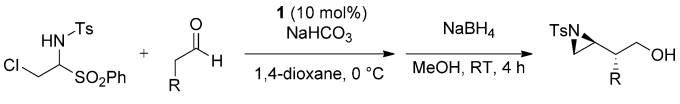


Scheme 6.

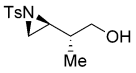
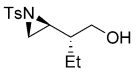
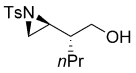
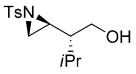
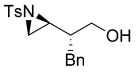
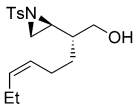
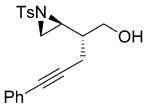
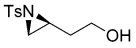
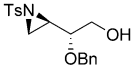


Scheme 7.

Table 3. The asymmetric one-pot synthesis of 2-hydroxyethylaziridine **9**.[a]



7 **9**

Entry	Product	Time [h]	Yield [%][b]	*anti*/*syn*[c]	*ee* [%][d]
1		24	69	8:1	96
2		24	90	>20:1	99
3		24	88	>20:1	99
4		72	69	>20:1	99
5		24	60	>20:1	99
6		24	65	>20:1	99
7		24	60	>20:1	99
8[e]		24	69	–	80
9[f]		24	48	7:1	94

[a] Reactions were performed employing α-amidosulfone **7** (0.4 mmol), aldehyde (1.2 mmol), catalyst **1** (0.04 mmol), $NaHCO_3$ (1.2 mmol) and 1,4-dioxane (0.8 mL) for the indicated time. [b] Isolated product yield. [c] Diastereomer ratio was determined by ^1H NMR spectroscopy. [d] The enantiomeric excess of *anti* isomer was determined by HPLC analysis on chiral column material after reduction and aziridination with $NaBH_4$. [e] Acetaldehyde (2.0 mmol) was employed. [f] Catalyst **3** (0.04 mmol) was employed.

dure is simple, this method offers an efficient route for the preparation of chiral aziridine derivatives.

Keywords: asymmetric reaction · domino reactions · enantioselectivity · Mannich reaction · one-pot reaction · organocatalysis

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