Synthesis of C_2-Symmetric Sulfide and Its First Application in Highly Enantioselective Synthesis of Chiral Aziridines

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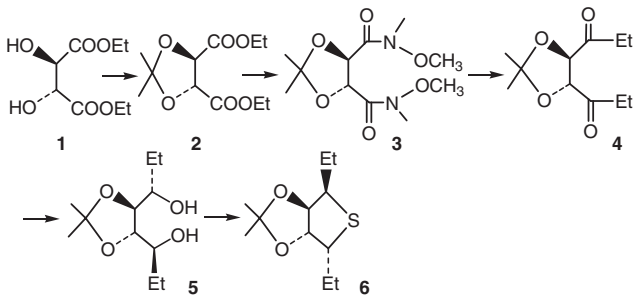
A C_2-symmetric sulfide **6** has been synthesized from cheap L-tartaric acid. It was found that sulfide **6** could perform a tandem reaction with benzyl bromide and tosyl imines to give (2*S*,3*S*)-aziridines **9a**–**9g** with good to excellent enantioseletivities (up to 96% ee).

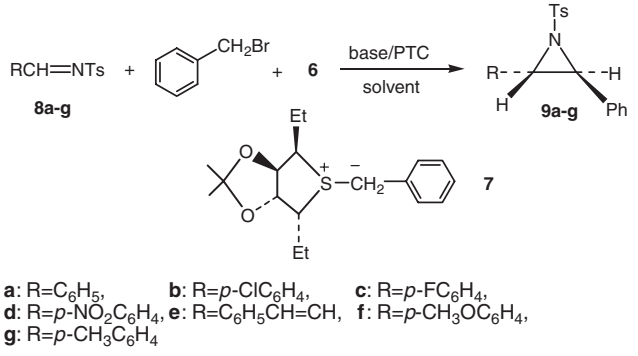
Chiral aziridines are important moieties in many biologically active compounds and versatile building blocks for the synthesis of many biologically important compounds, such as amino acids, alkaloids, amino sugars, and β-lactamic antibiotics.[1] Recently, the chiral ylide route was envisaged to become possibly one of the most important methods for the asymmetric synthesis of aziridines as well as the asymmetric synthesis of epoxides and cyclopropanes.[2] There are some excellent examples on the utilities of chiral sulfonium ylides in the synthesis of chiral aziridines.[3] However, the development of new methods for highly enantioselective synthesis of aziridines via chiral ylide is still a challenging subject. C_2-symmetric sulfide or telluride generates only one diastereomeric sulfonium or telluronium salt as the precursor of corresponding ylide. The chiral ylides derived from C_2-symmetric sulfides and tellurides have proved very effective in asymmetric epoxidation and cyclopropanation with high enantioselectivities (up to 99% ee).[4] Nevertheless, to our knowledge, few literatures revealed the application of C_2-symmetric chalcogenide derived chiral ylide in asymmetric aziridination. Therefore, we started to synthesize C_2-symmetric sulfide and explore its utility in the highly enantioselective synthesis of aziridines via chiral sulfonium ylide.

We chose readily available L-tartaric acid **1** as the starting material for the synthesis of C_2-symmetric sulfide **6**. Initailly, **1** was esterified with ethanol, followed by the condensation with acetone to give diethyl diester **2** (Scheme 1).[5a] Diester **2** then reacted with Me(MeO)NH·HCl and the Grignard reagent to generate bis-Weinreb amide **3**.[5b] The reaction of amide **3** with the ethyl Grignard reagent afforded diethyl diketone **4**.[5c] Diketone **4** could be reducted smoothly by sodium borohydride to afford C_2-symmetric diol **5**[5c] and the structure of diol **5** was determined by single-crystal X-ray diffraction.[6] Finally, a one-pot reaction of chiral diol **5** with methanesulfonyl chloride and then sodium sulfide afforded the desired C_2-symmetrical sulfide **6**.[7] Metzner et al. prepared a similar C_2-symmetrical sulfide with a locked comformation using D-mannitol instead of L-tartaric acid as starting material, which has been used successfully in asymmetric epoxidation with excellent enantioselectivities.[7]



Scheme 1. Synthetic route for C_2-symmetric sulfide **6**.

With the C_2-symmetric sulfide **6** in hand, we chose phenyl-*N*-tosylmethanimine (**8a**) as a model substrate to search the reaction conditions for asymmetric aziridination (Scheme 2). We were pleased to find that the sulfide **6** and benzyl bromide could react with potassium carbonate in dichloromethane to generate chiral sulfonium ylide **7** in situ, followed by the reaction with *N*-tosyl imine **8a** to give the desired aziridines **9a** in 52% yield with 85% ee (Entry 1, Table 1). Encouraged by the result, we examined other solvents in the tandem aziridination reaction. It was found that acetonitrile is the best solvent in comparison with dichloromethane and *tert*-butanol (Entries 1–3, Table 1). Then, other bases were also examined in the reaction in acetonitrile. Experiments showed that sodium hydroxide and sodium hydride could not lead to the aziridination and cesium carbonate led to lower yield and enantioselectivity of **8a** (Entry 4, Table 1), compared with potassium carbonate. It was further found that, when 0.1 equiv. of tetrabutylammonium iodide (TBAI) relative to imine **8a** was added as a phase-transfer catalyst (PTC), both the yield and enantioselectivity were improved (Entries 3 and 6, Table 1).[8] When the amount of sulfide **6** was increased from 1.0 equiv. to 1.5 equiv. relative to imine **8a**, the yield of aziridine **9a** was further improved with increasing enantioselectivity slightly (Entry 7, Table 1). Using 2.0 equiv. of sulfide **6** led to a little increase in yield with keeping excellent enantioselectivity (Entries 7 and 8, Table 1). Decreasing the amount of sulfide **6** from 1.0 equiv. to 0.5 equiv. led to the reduction of both yield and enantioselectivity (Entries 5 and 6, Table 1). Thus, the optimal conditions of the asymmetric aziridination were chosen as



a: R=C_6H_5, **b**: R=*p*-ClC_6H_4, **c**: R=*p*-FC_6H_4, **d**: R=*p*-$NO_2C_6H_4$, **e**: R=C_6H_5CH=CH, **f**: R=*p*-$CH_3OC_6H_4$, **g**: R=*p*-$CH_3C_6H_4$

Scheme 2. Asymmetric synthesis of (2*S*,3*S*)-aziridines **9a**–**9g** via chiral sulfonium ylide **7**.

Table 1. Optimization of the aziridination in different experimental conditions

Entry	Reaction conditions[a]	Sulfide /equiv.	Yield /%[b]	Trans/cis[c]	Trans ee /%[d]
1	CH_2Cl_2/K_2CO_3	1.0	52	76:24	85
2	*t*-BuOH/K_2CO_3	1.0	43	72:28	90
3	MeCN/K_2CO_3	1.0	58	75:25	92
4	MeCN/Cs_2CO_3	1.0	38	70:30	80
5	MeCN/K_2CO_3/TBAI	0.5	43	75:25	87
6	MeCN/K_2CO_3/TBAI	1.0	62	76:24	95
7	MeCN/K_2CO_3/TBAI	1.5	70	75:25	96
8	MeCN/K_2CO_3/TBAI	2.0	72	75:25	96

[a]Reactions were performed at room temperature for 2 days. [b]Isolated yields. [c]Determined by ^{1}H NMR or HPLC. [d]Determined by chiral HPLC on a chiralcel OD-H column.

Table 2. Aziridination of various *N*-tosyl imines via chiral ylide **7**[9]

Entry	R	Yield[a]	Trans/cis[b]	Trans ee /%[c]
1	Ph	72	75:25	96
2	*p*-ClC_6H_4	62	80:20	87
3	*p*-FC_6H_4	65	75:25	93
4	*p*-$NO_2C_6H_4$	50	65:35	85
5	PhCH=CH	75	90:10	90
6	*p*-$OCH_3C_6H_4$	60	60:40	80
7	*p*-$CH_3C_6H_4$	68	80:20	91

[a]Isolated yields. [b]Determined by ^{1}H NMR or HPLC. [c]Determined by chiral HPLC on a chiralcel OD-H column.

follow: the amount of sulfide **6** was 2.0 equiv., the base was potssium carbonate, the solvent was acetonitrile and TBAI was used as a PTC.

Following this optimization, a variety of *N*-tosyl imines **8a**–**8g** were examined in the asymmetric aziridination reaction (Table 2). We found that, in the presence of potassium carbonate and TBAI, the sulfide **6** and benzyl bromide could react with various *N*-tosyl imines **8a**–**8g** via chiral sulfonium ylide **7**, giving the desired chiral aziridines **9a**–**9g** in the yields of 50–75% with dominant trans isomers. As expected, C_2-symmetric sulfide **6** could lead to good to excellent enantioselectivities (80–96% ee) in the asymmetric aziridination of various tosyl imines. The absolute configurations of **9a**–**9g** were assigned by comparison of the sign of optical rotation with that of the known compounds and all (2*S*,3*S*)-isomers of **9a**–**9g** are levorotatory in $CHCl_3$.[3a] Electron-withdrawing or electron-donating groups on the benzene ring seem to have no significant effects on yields, diastereoselectivities and enantioselectivities in the asymmetric aziridination.

In conclusion, we have synthesized C_2-symmetric sulfide **6** from cheap L-tartaric acid. Further experiments showed that the chiral sulfide could conduct the tandem reaction with benzyl bromide and tosyl imine to give the desired (2*S*,3*S*)-aziridines **9a**–**9g** in moderate yields with dominant trans isomers and good to excellent enantioseletivities (up to 96% ee). Further investigations on the extension and mechanism of the method for the highly enantioselective synthesis of aziridines using the C_2-symmetric sulfide **6** and a C_2-symmetric telluride are currently underway.

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9 General procedure for the synthesis of *trans*-(2*S*,3*S*)-aziridines **9a**–**9g**. The mixture of sulfide **6** (1.0 mmol), benzyl bromide (1.5 mmol), tosyl imines **8** (0.5 mmol), K_2CO_3 (1.5 mmol), and TBAI (0.05 mmol) in CH_3CN (20 mL) was stirred for 2 days at room temperature. Common workup/isolation afforded the desired chiral aziridines **9a**–**9g**.

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