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Enantioselective desymmetrization of *meso*-*N*-sulfonylaziridines with thiols

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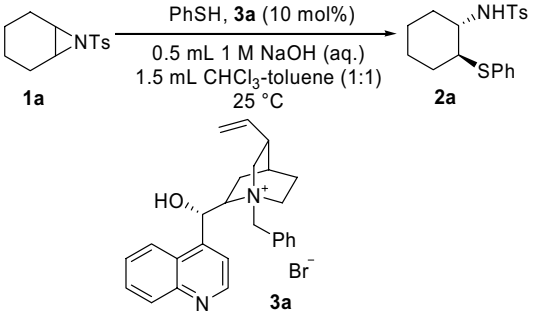
Abstract—Desymmetrization of *meso*-*N*-sulfonylaziridines with thiols was realized using cinchonine-derived chiral quaternary ammonium salts as the catalyst. The corresponding chiral thio amines were provided in high yields (80–99%) and in good enantioselectivities (40–73% ee).

1. Introduction

The synthesis of optically active organic compounds using a desymmetrization strategy has attracted much attention because it offers the opportunity to generate two stereogenic centres in a single step.[1] Many examples of the enantioselective ring-opening reaction of *meso* epoxides with nucleophiles in the presence of a chiral catalyst have been realized.[2,3] However, the catalytic asymmetric ring cleavage of symmetrical N-substituted aziridines by a nucleophile to form optically active amines is a rather more difficult task. So far, only a few examples are reported in the literature,[4,5] among them the desymmetrization of *meso*-*N*-acylaziridines by TMSCN and $TMSN_3$ using chiral Gd and Y-complex, respectively, are excellent examples.[5] On the other hand, asymmetric reactions mediated by chiral quaternary ammonium salt have been well documented.[6–8] In the reactions of imines with allylsilane and that of aziridines with TMSX (X = CN, N_3) or KF, we found that ammonium salt played an important role.[9] Therefore, we intended to use the chiral ammonium salt in this desymmetrization reaction. When cinchonium halides were used in the reaction of *N*-tosyl aziridines with thiophenols, good enantioselectivities were given. Herein we report this desymmetrization of *meso*-*N*-sulfonylaziridines with thiols mediated by a chiral quaternary ammonium salt.

2. Results and discussion

Initially, the reaction of *N*-Ts aziridine **1a** with PhSH in the presence of 10 mol % of *N*-benzylcinchoninium bromide **3a**[10] under PTC conditions provided the ring opening product **2a** in 81% yield and 9% ee (Eq. 1). Only an 8% yield of product **2a** was given in the absence of **3a**. Using toluene or CH_2Cl_2 as solvent and 1 M NaOH (aq), Cs_2CO_3 and CsF as base afforded the product with 7–16% ee. However, when 2 equiv of $CsOH{\cdot}H_2O$ was used as base and CCl_4 as solvent, the reaction gave **2a** in 34% ee. Lowering the reaction temperature from room temperature to 0 °C increased the enantiomeric excess to 40% ee, while lowering the reaction temperature to −10 °C decreased both the reactivity and enantioselectivity.



(1)

Many reports have shown that the substituent on the bridgehead nitrogen of cinchona alkaloids has a great

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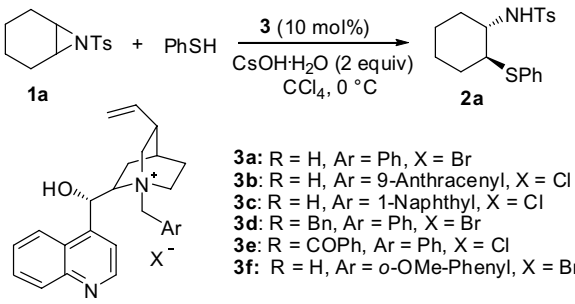
Table 1. Desymmetrization of aziridine **1a** with thiophenol[a]

Entry	Cat	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3a**	24	93	40
2	**3b**	24	85	73
3	**3c**	18	89	34
4	**3d**	7	99	19
5	**3e**	24	85	27
6	**3f**	14	99	63

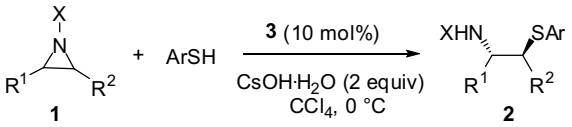
[a] Aziridine **1a** (0.25 mmol), PhSH (0.3 mmol), **3** (10 mol %), $CsOH{\cdot}H_2O$ (200 mol %), CCl_4 (2 mL).
[b] Isolated yields.
[c] Determined by HPLC analysis.

impact on the stereochemistry of the reactions.[8] Thus, several chiral quaternary ammonium salts with different substituents on nitrogen were prepared from cinchonine and applied in the desymmetrization of aziridine **1a** by thiophenol (Eq. 2). The results are shown in Table 1. As can be seen in Table 1, the stereochemical outcome was closely relevant to the substituent on the nitrogen. When catalyst **3b**, with an attachment of a 9-anthracenylmethyl to the bridgehead nitrogen, was used as catalyst, the ee value increased to 73% (entry 2).[8c] Also, using **3f** with an *o*-methoxy phenylmethyl as substituent on nitrogen afforded the ring opening product **2a** in 63% ee (entry 6).[8e] In comparison, only 40% ee was given using **3a** (entry 1). On the other hand, protection of the hydroxyl group of cinchonine decreased the enantioselectivity significantly (entries 4 and 5 vs 1 and 2, respectively).



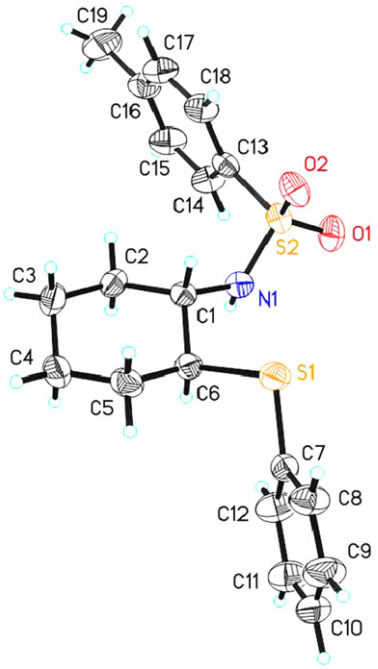
(2)

Under the above reaction conditions, different thiophenols and aziridines were tested using **3b** and **3f** as catalyst (Eq. 3).[11] The results are shown in Table 2.



(3)

It can be seen that all reactions using different aziridines and ArSH gave good enantioselectivities except when using aziridines **1b** and **1e** as substrates, which afforded ring opening products in 40% and 44% ee, respectively (entries



Scheme 1. ORTEP diagram of the X-ray structure of **2a**.

Table 2. Desymmetrization of aziridine **1** with substituted thiophenols[a]

Entry	Aziridine	R^1R^2, X	Ar	Cat	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	$(CH_2)_4$, Ts	Ph	**3b**	24	85	73
2	**1a**	$(CH_2)_4$, Ts	Ph	**3f**	14	99	61
3	**1a**	$(CH_2)_4$, Ts	*o*-Me–C_6H_4	**3b**	20	99	3
4	**1a**	$(CH_2)_4$, Ts	*o*-Me–C_6H_4	**3f**	11	99	28
5	**1a**	$(CH_2)_4$, Ts	*m*-Me–C_6H_4	**3b**	20	98	6
6	**1a**	$(CH_2)_4$, Ts	*m*-Me–C_6H_4	**3f**	13	99	60
7	**1a**	$(CH_2)_4$, Ts	*p*-Me–C_6H_4	**3b**	12	99	45
8	**1a**	$(CH_2)_4$, Ts	*p*-Me–C_6H_4	**3f**	11	99	52
9	**1a**	$(CH_2)_4$, Ts	*p*-^{t}Bu–C_6H_4	**3b**	20	98	6
10	**1a**	$(CH_2)_4$, Ts	*p*-^{t}Bu–C_6H_4	**3f**	11	99	58
11	**1b**	$(CH_2)_3$, Ts	Ph	**3b**	96	80	40
12	**1c**	$CH_2CH{=}CHCH_2$, Ts	Ph	**3b**	18	88	72
13	**1c**	$CH_2CH{=}CHCH_2$, Ts	Ph	**3f**	24	99	66
14	**1d**	$(CH_2)_4$, Ns	Ph	**3b**	36	99	55
15	**1d**	$(CH_2)_4$, Ns	Ph	**3f**	36	99	43
16	**1e**	CH_2OCH_2, Ts	Ph	**3f**	24	92	44

[a] Aziridine **1a** (0.25 mmol), ArSH (0.3 mmol), **3** (10 mol %), $CsOH{\cdot}H_2O$ (200 mol %), CCl_4 (2 mL).
[b] Isolated yields.
[c] ee value was determined by HPLC analysis.

11 and 16). It is also interesting to note that reactions of aziridine **1a** with different thiols other than thiophenol as nucleophiles using **3f** as catalyst provided better enantioselectivities than those using **3b** as catalyst (entries 3, 6, 8, 10 vs entries 3, 5, 7, 9).

The absolute configuration of the ring opening product **2a** was assigned as (*S*,*S*) by X-ray diffraction analysis and subsequent HPLC analysis of the crystal (Scheme 1).[12]

3. Conclusion

In conclusion we developed a simple protocol for desymmetrization of *meso*-aziridines by arylthiols using cinchonine-derived chiral quaternary ammonium salts as a catalyst, giving chiral thio amines in high yields and in good enantioselectivity. Applications of this methodology in the desymmetrization of aziridines by other types of nucleophile are currently underway.

Acknowledgements

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11. *Typical procedure for desymmetrization of aziridine* **1a** *with thiophenol*: To a solution of catalyst **3b** (14 mg, 0.025 mmol), $CsOH{\cdot}H_2O$ (84 mg, 0.5 mmol) and CCl_4 (2 mL) were added PhSH (30 μL, 0.3 mmol) and then aziridine **1a** (64 mg, 0.25 mmol) under an Ar atmosphere at 0 °C. The mixture was stirred under this temperature until the starting material **1a** disappeared (as monitored by TLC). Water (5 mL) was added and the mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic phase was washed with brine and then dried over anhydrous Na_2SO_4. Removal of the solvent by rotatory evaporation and subsequently chromatography (silica gel: petroleum ether/AcOEt = 5:1) afforded **2a** as a white solid, mp 125–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$/TMS) (ppm): δ = 1.24–1.37 (m, 4H), 1.56–1.59 (m, 2H), 1.99–

2.04 (m, 1H), 2.24 (m, 1H), 2.43 (s, 3H), 2.90 (ddd, $J = 3.9$, 9.3, 9.3 Hz, 1H), 2.98 (m, 1H), 5.43 (d, $J = 3.6$ Hz, 1H), 7.25–7.30 (m, 7H), 7.76 (d, $J = 8.4$ Hz, 2H). ^{13}C NMR ($CDCl_3$/TMS) (ppm): $\delta = 21.8$ (Ar–CH_3), 23.4 (CH_2), 24.7 (CH_2), 31.6 (CH_2), 32.4 (CH_2), 51.5 (S–CH), 56.4 (N–CH), 127.5 (Ar–C), 127.8 (Ar–C), 129.2 (Ar–C), 129.9 (Ar–C), 132.8 (Ar–C), 133.2 (Ar–C), 137.5 (Ar–C), 143.6 (Ar–C). EI-MS m/z: 361 (M^+). The ee of the reaction product was determined by HPLC analysis. Chiral OD column, n-hexane/^{i}PrOH = 95:5, 230 nm, 1.0 mL/min, $t_R = 20.3$, 24.2 min.

12. CCDC 632008 contains the supplementary crystallographic data for **2a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.