Novel Asymmetric Ring-opening Reactions of Symmetrical *N*-Acylaziridines with Arenethiols Catalysed by Chiral Dialkyl Tartrate–Diethylzinc Complexes

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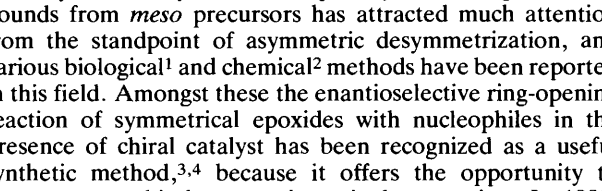
The asymmetric ring-opening reaction of *N*-acylaziridines with arenethiols proceeds in the presence of chiral zinc complexes prepared from diethylzinc and L-(+)-diisopropyl tartrate (dipt) to afford *trans*-2-thio-(*N*-acylamino)cyclohexane in up to 88% enantiomeric excess (e.e.).

The asymmetric synthesis of optically active organic compounds from *meso* precursors has attracted much attention from the standpoint of asymmetric desymmetrization, and various biological[1] and chemical[2] methods have been reported in this field. Amongst these the enantioselective ring-opening reaction of symmetrical epoxides with nucleophiles in the presence of chiral catalyst has been recognized as a useful synthetic method,[3,4] because it offers the opportunity to generate two chiral centres in a single operation. In 1985, Mukaiyama *et al.* first reported[3] the asymmetric ring opening of cyclohexene oxide with thiols by the use of a heterogeneous chiral catalyst. Since then, several reactions have been published, including our recent reports[5] on the asymmetric ring opening of symmetrical epoxides with trimethylsilyl azide using chiral dialkyl tartrate–titanium alkoxide complexes. However, the asymmetric ring cleavage of symmetrical *N*-substituted aziridines with some nucleophiles has not been reported so far.[6]

Here, we report the highly enantioselective ring-opening reaction of the symmetrical *N*-acylaziridines with thiols catalysed by diethylzinc–chiral dialkyl tartrate complexes (Scheme 1).

At first, the reactions of 7-(4′-nitrobenzoyl)-7-azabicyclo[4,1,0]heptane **1a** with *p*-*tert*-butylbenzenethiol were examined by using equimolar amounts of chiral zinc complexes prepared *in situ* from Et_2Zn and L-(+)-dipt in CH_2Cl_2 at 0 °C.



1a; R = *p*-$NO_2C_6H_4$
b; R = C_6H_5

2

Scheme 1

Table 1 Asymmetric ring opening of 7-(4′-nitrobenzoyl)-7-azabicyclo[4,1,0]heptane **1a** with *p*-*tert*-butylbenzenethiol promoted by L-(+)-dipt–Et_2Zn complex[a]

	Molar ratio			Product	
Entry	L-(+)-Dipt	Et_2Zn	Thiol	Yield[b] (%)	E.e.[c,d] (%)
1	1	1	1	83	22
2	1	1	2	95	66
3	1	2	2	96	12
4	1	2	3	96	70
5	1	2	3.6	97	82
6	1	2	4.0	97	67
7	1	3	3	90	29
8	1	3	4.8	98	88
9	1	3	5	98	85
10	1	3	5.2	98	85
11	1	3	6	94	69

[a] All reactions were carried out in CH_2Cl_2 at 0 °C for 14–96 h. [b] Isolated yield after column chromatography. [c] HPLC (SUMIPAX OA-4000). [d] Absolute configuration of the product was (1*S*,2*S*).

It was found that the enantioselectivity of the reaction was influenced by the molar ratio of the reactants, *i.e.* substrate, Et_2Zn, L-(+)-dipt and thiol (Table 1). The highest enantioselectivity was achieved when using 1:3:1:4.8 molar ratio of **1a**:Et_2Zn:L-(+)-dipt:thiol, *e.g.* *trans*-2-(*p*-*tert*-butylbenzenethio)-[*N*-(*p*-nitrobenzoyl)amino]cyclohexane **2a** was obtained in 88% e.e. and in 98% yield (entry 8).

The reaction using *N*-benzoylaziridine **1b** resulted in a low optical yield (23% e.e.). The reaction by promotion of diethylzinc with chiral tartrates other than L-(+)-dipt was also investigated. The results were as follows: L-(+)-diethyl tartrate (47% yield, 50% e.e.), L-(+)-diisobutyl tartrate (60% yield, 72% e.e.) and L-(+)-dicyclohexyl tartrate (67% yield, 10% e.e.).

Furthermore, the reaction with a catalytic amount of the catalyst induced the decrease of enantioselectivity in comparison with that of the equimolar reaction (Table 2), *e.g.* products of 74 and 58% e.e. were obtained by the use of 50 and 20 mol% of catalyst, respectively.

The e.e. of the product was determined by HPLC using a chiral stationary phase (SUMIPAX OA-4000). The absolute configuration of the product, (1*S*,2*S*)-**2a** was obtained predominantly when L-(+)-dialkyl tartrate was used which was confirmed by the correlation of the optical rotation value after converting **2a** into *trans*-(2-*tert*-butylbenzenethio)-cyclohexanol, whose absolute configuration was known.†‡

The reaction of **1** with 4-methylbenzenethiol and benzenethiol gave the ring opening products in 69% e.e. {$[\alpha]_D^{25}$ +49.4 (*c* 1.0, $CHCl_3$)} and 3% e.e., respectively. The reaction proceeds *via* the reaction of zinc–thiolate complex with aziridines, and the enantioselectivity is influenced by the bulkiness of the reactive groups. Therefore, the use of the bulkier arenethiols resulted in the higher enantioselectivity.

Typical experimental procedure is as follows: in a Schlenk tube were placed L-(+)-dipt (0.96 g, 4.08 mmol) and dry CH_2Cl_2 (35 ml). The mixture was cooled to 0 °C and Et_2Zn (1.24 ml, 12.2 mmol) was added slowly. After stirring at 0 °C for 30 min, *p*-*tert*-butylbenzenethiol (3.3 ml, 19.6 mmol and **1a** (1.0 g, 4.06 mmol) in CH_2Cl_2 (5 ml) were added at 0 °C and the mixture stirred for a further 14 h at 0 °C. Brine (100 ml) was added to the mixture, and stirred vigorously for 30 min at room temp. The mixture was filtered through a pad of Celite, then extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with brine then dried (Na_2SO_4). After evaporation, the residue was chromatographed on silica

Table 2 Catalytic reaction of **1a** with *p*-*tert*-butylbenzenethiol[a]

		Product	
Entry	Catalyst/mol%	Yield[b] (%)	E.e.[c] (%)
1	100[d]	98	88
2[e]	50[f]	80	74
3[e]	20[f]	80	58

[a] All reactions were carried out in CH_2Cl_2 at 0 °C for 14–96 h days using 4.8 equiv. of thiol per **1a** unless otherwise noted. [b] Iolated yield. [c] HPLC. [d] Et_2Zn/L-(+)-dipt = 3:1. [e] Three equiv. of thiol were used per **1a**. [f] Et_2Zn:L-(+)-dipt, 2:1.

gel (eluent $CHCl_3$) to give **2a** (1.66 g, 98% as yellow crystals {mp 67–73 °C; $[\alpha]_D^{25}$ +44.4 (*c* 1.0, $CHCl_3$)}. The e.e. of the reaction product was determined as 88% by HPLC. t_R 13 min [(1*R*,2*R*)-isomer], 14 min [(1*S*,2*S*)-isomer] [column; SUMI-PAX OA-4000, eluent hexane : ethanol (97 : 3), 1.0 ml min^{-1}, 254 nm].

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Footnotes

† Procedure for transformation of **2a** into *trans*-(2-*tert*-butylbenzenethio)cyclohexanol **3**: treatment of **2a** with LAH in THF afforded *trans*-(2-*tert*-butylbenzenethio)cyclohexylamine, which was then treated with $NaNO_2$ in acetic acid to give **3** whose absolute configuration was confirmed by derivatizing to optically active 2-cyclohexen-1-ol.[3]

‡ During the investigation, we found the optical purity of the product could be increased to >99% e.e. by a simple extraction. The typical procedure is as follows: enantio-enriched **2a** (38% e.e.; 1.0 g) was soaked in a mixture of hexane–EtOH (97 : 3) (80 ml), then insoluble solid {0.62 g; mp 178–180 °C; $[\alpha]_D^{25}$ +5.4 (*c*. 1.1, $CHCl_3$); 10% e.e.} was separated. Evaporation of supernatant solution followed by drying *in vacuo* afforded pale-yellow crystals {0.34 g; mp 86–92 °C; $[\alpha]_D^{25}$ +49.5 (*c*. 0.8, $CHCl_3$)}, whose optical purity was proved to be >99% e.e by HPLC.

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