Selected Paper

Novel Synthesis of α-Amino Carboxamides and Their Related Compounds via α-Oxo Sulfones Starting from 2,2-Disulfonyloxiranes

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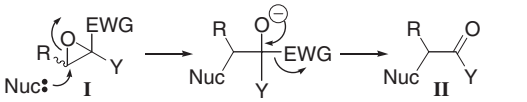
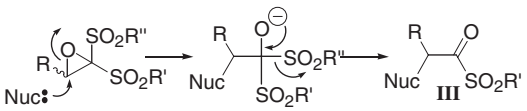
2-(Methylsulfonyl)-2-(*p*-tolylsulfonyl)oxiranes **1** are easily prepared by the condensation of methylthiomethyl *p*-tolyl sulfone (MT-sulfone) with aldehydes and the subsequent oxidation with MCPBA. They smoothly reacted with 2 molar amounts of primary or secondary amines to give α-amino carboxamides in high yield. This reaction can be suitably extended to the reaction with one molar amount of 1,*n*-diaminoalkanes ($n = 2$, 3, or 4) to form the corresponding 2,5-diazacyclohexanone, 2,6-diazacycloheptanone, or 2,7-diazacyclooctanone, respectively. The reaction of **1** with some related compounds having two nucleophilic sites are also described.

Epoxides are versatile intermediates in organic synthesis.[1] Thus, various synthetic routes via the epoxides have been developed for preparing biologically active natural products and medical supplies.[2,4a] The epoxides undergo many kinds of reaction, such as ring-opening with a nucleophile,[3] acid-promoted rearrangement,[4] and introduction of a substituent on their ring that is achieved by deprotonation and the subsequent reaction with an electrophile.[5] The easy ring-opening reaction with various nucleophiles to produce glycols, 2-aminoethanols, and 2-sulfanylethanols seems to result from high strain of the ring. When an electron-withdrawing group (EWG) is situated on the ring, the attack of a nucleophile is generally followed by elimination of the EWG to produce a carbonyl compound **II**, as depicted in Eq. 1. Thus, the epoxides having cyano, nitro, sulfonyl, or sulfinyl group are reported to give the corresponding carbonyl derivatives.[6]

If another group (Y) of the epoxide **I** in Eq. 1 has good leaving ability, the resultant carbonyl derivative **II** would be regarded as an active form of a carboxylic acid. This is the case when the epoxide having two cyano groups (**I**; EWG = Y = CN) reacts with a nucleophile.[7] Some researchers reported that 2,2-dicyanooxiranes react with halide ion to give α-haloacyl cyanides that are converted to α-halo carboxamides[7f,g] or α-halo hydroxamic acids[7e,h] by successive treatment with amines or hydroxylamine derivatives. An optically active ketene dithioacetal *S*,*S*′-dioxide (**I**; EWG + Y = –SO–$(CH_2)_3$–SO–) was reported to react with an amine.[8] In this reaction, the corresponding intermediate **II** would undergo further reaction with the amine to give an α-amino carboxamide.



(1)



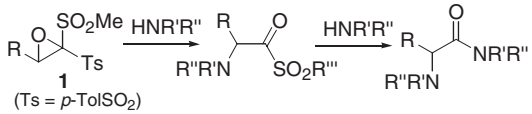
(2)

Against such background, our investigation on the reaction of 2,2-bis(alkyl- or arylsulfonyl)oxiranes with a nucleophile was initiated in expectation of developing a novel method for preparing α-oxo sulfones **III** (Eq. 2).

Some α-oxo sulfones bearing electron-donating group(s) such as OR or NRR′ as well as α-oxo sulfones bearing two aryl groups at both ends have been reported.[9] These α-oxo sulfones could be synthesized by oxidation of the corresponding α-oxo sulfides or ozonolysis of α-diazo sulfones. However, no aliphatic α-acyl sulfone has appeared in the literature. Since the corresponding aliphatic α-acyl sulfoxides were reported to exhibit significant reactivity toward various nucleophiles,[10] it is likely that the α-oxo sulfones are too reactive to be isolated. Here, we wish to report an efficient preparation of acyclic and cyclic α-amino carboxamides and their related compounds by the use of the reactivity of the α-oxo sulfones that are formed by the reaction of 2-(methylsulfonyl)-2-(*p*-tolylsulfonyl)oxiranes **1** with nucleophiles (Scheme 1).

Results and Discussion

Previously, we reported that 2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (**1**; R = Ph) was produced by oxidation of the corresponding ketene dithioacetal *S*,*S*-dioxide, derived from methylthiomethyl *p*-tolyl sulfone (MT-sulfone; **2**)[11] and benzaldehyde, with an excess amount of *m*-chloroperbenzoic acid (MCPBA).[12] In addition, some epoxides having two sulfonyl groups were reported by other researchers, but their reactivity was not examined well.[13,14] According to the procedure described in our previous paper, various 2-(methylsulfonyl)-2-(*p*-tolylsulfonyl)oxiranes **1** were prepared by the



Scheme 1.

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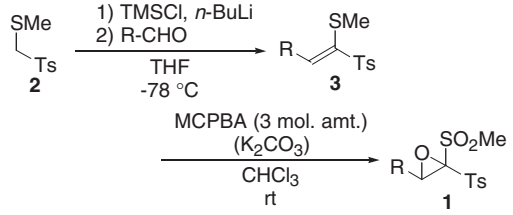
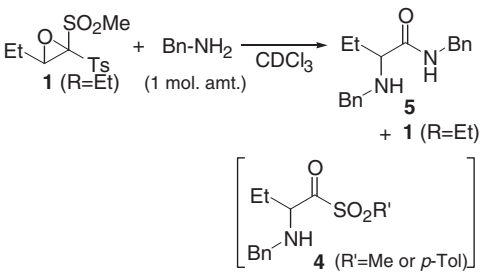
Table 1. Preparation of 2,2-Disulfonyloxiranes (**1**)



Entry	R	Yield of **3**/%	Yield of **1**/%
1	Ph	94	84
2	*p*-Br–C_6H_4	93	89
3	*p*-MeOCO–C_6H_4	89	quant.
4	*m*-MeO–C_6H_4	72	93
5	*p*-Me–C_6H_4	64	complex mixture
6	1-Naphthyl	59	complex mixture
7	Et	96	81
8	*i*-Pr	100	87

olefination of **2** with aliphatic and aromatic aldehydes, followed by oxidation with 3 molar amounts of MCPBA. The results are summarized in Table 1. It should be noted that the oxidation of **3** to give **1** was accelerated by coexisting K_2CO_3 (0.5 mol. amt.). The oxiranes were obtained as a single stereoisomer by recrystallization. The 2,2-disulfonyloxiranes having an electron-rich aromatic residue as R (for example, *p*-tolyl and 1-naphthyl groups in entries 5 and 6, respectively) were too reactive to be isolated in a pure form by column chromatography.

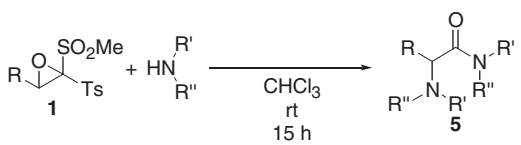
With various 2,2-disulfonyloxiranes in hand, we tested the reaction of the epoxide using benzylamine as a nucleophile in an NMR tube. About one equimolar amount of benzylamine was added to a solution of **1** (R = Et) in $CDCl_3$ and the reaction progress was monitored by ^{1}H NMR. The reaction started at an ambient temperature, but we could not detect any signal corresponding to the α-oxo sulfone **4** that would be formed as an intermediate. Instead, a smooth formation of *N*,*N*′-dibenzyl-2-aminobutanamide (**5** in Scheme 2) was observed, even though most of the starting epoxide remained unchanged. This suggests that the expected α-oxo sulfone **4** reacts with benzylamine much faster than the starting epoxide. Hence, we decided to employ more than 2 molar amounts of an amine in the reaction with **1**.



Scheme 2.

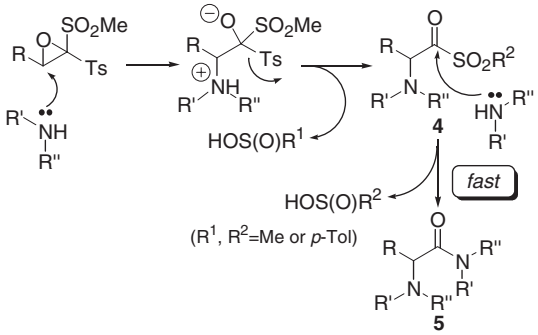
To a solution of **1** (R = Ph) in chloroform was added 2.7 molar amounts of morpholine, and the resulting mixture was stirred for 24 h at room temperature. By evaporation and column chromatography on silica gel, 4-(2-morpholino-2-phenylacetyl)morpholine was obtained in 77% yield (Table 2, entry 1). Since 4-(*p*-tolylsunfinyl)morpholine[15] and 4-(methylsulfinyl)morpholine were also detected among the reaction mixture components (30% and 10%, respectively), morpholine was shown to work not only as a nucleophile, but also as a trapping reagent of the by-products, such as *p*-toluenesulfinic acid and methanesulfinic acid.[16] This is the reason why an excess amount of morpholine improves the yield of **5** (entry 2). Interestingly, the present reaction is applicable to various primary and secondary amines, as shown in Table 2 (entries 3 and 4). Aniline also reacted with **1** to give the corresponding **5** (entry 5), though it has lower nucleophilicity.[17] The reaction with **1** (R = *i*-Pr) required a long period of time to complete the reaction, probably because of the steric hindrance of the isopropyl group against the attack of the amine (entries 10 and 11).

Table 2. Reaction of **1** with Amines



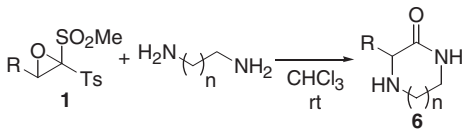
Entry	R	R′	R″	Mol. amt. of amine	Yield of **5**/%
1[a)]	Ph	–$(CH_2)_2$–O–$(CH_2)_2$–		2.7	77 (quant.)[b,c)]
2				4.2	97
3		Bn	H	4.1	99
4		Bn	Me	4.0	84
5		Ph	H	4.1	48[c)]
6	*p*-Br–C_6H_4	Bn	H	4.1	95
7	*p*-MeOCO–C_6H_4			4.1	98
8	*m*-MeO–C_6H_4			4.1	quant.
9	Et			4.0	85
10	*i*-Pr			4.0	66 (95)[b)]
11[d)]				4.0	82 (96)[b)]

a) Reacted for 24 h. b) Value in parenthesis was shown the yield based on the consumption of **1**. c) Tolyl- and methylsulfinylamides were observed. d) Reacted for 72 h.



Scheme 3.

Table 3. Reaction of **1** with Diamines

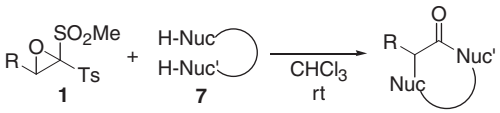


Entry	R	*n*	Mol. amt. of diamine	Time/h	Yield of **6**/%
1	Ph	1	3.6	24	90
2		2	2.5	14	96
3		3	2.0	15	trace
4		3	1.2	25	31
5	Et	1	3.9	50	92
6		2	2.5	21	92
7		3	2.5	4	72

As mentioned above, the attack of amine to the intermediary α-oxo sulfone **4** is much faster than its attack to the starting oxirane **1** (Scheme 3). This phenomenon would be favorably utilized for synthesizing cyclic α-amino carboxamides, i.e., α-azalactams **6**, from **1** and 1,ω-diaminoalkanes: in this reaction, the intermediary α-oxo sulfone has one amino group, which can react intramolecularly with the carbonyl part to give **6**.

In fact, the expected 2,5-diazacyclohexanone (3-azapentanelactam) (**6**; R = Ph, $n = 1$) was afforded in 90% yield when 3.6 molar amounts of ethylenediamine was added to a 0.03 M (1 M = 1 mol dm^{-3}) solution of **1** (R = Ph) in chloroform and the resulting solution was stirred at room temperature. Analogously, 3-azahexanelactam (**6**; R = Ph, $n = 2$) was obtained in 96% yield in the reaction of propylenediamine and **1** (R = Ph). Other results are summarized in Table 3. Although the formation of an eight-membered ring from an acyclic system is usually a process of great difficulty,[18] we tried to prepare an eight-membered 3-azaheptanelactam (**6**; $n = 3$). In the reaction of **1** (R = Ph) under conditions similar to those of the above reactions using an excess amount (2 mol. amt.) of 1,4-diaminobutane, the expected **6** was formed in trace amounts, but we obtained a large amount of insoluble oligomer-like solid. This was the expected result. To our delight, **6** (R = Ph; $n = 3$) was produced as a major product (31% yield) when 1.2 molar amount of 1,4-diaminobutane was dropwise added to the solution of **1** (R = Ph) (entry 4). Notably, the eight-membered 3-azaheptanelactam (**6**; R = Et, $n = 3$) was formed in 72% yield by dropwise addition of 1,4-diaminobutane to a 0.03 M solution of **1** (R = Et). Thus, the present reaction system was shown to be suitable for the α-azalactam formation.

Table 4. Formation of Various Cyclic Compounds from **1**



Entry	R	Mol. amt. of **7**	Additive (Mol. amt.)	Time/h	Product	Yield/%
1	Ph	1.2	NaOH[a] (1.1)	3		81
2	Et	1.2	NaOH[a] (1.1)	3.5	**8**	88
3	Ph	1.1	DBU (2.2)	0.5		59
4	Et	1.1	DBU (2.2)	0.5	**9**	66
5	Et	1.1	DBU (2.2)	0.5	**10**	25
6	Ph	1.5	NEt_3 (3.5)	0.5		88
7	Et	1.5	NEt_3 (3.0)	0.5	**11**	97
8	Et	1.1	NEt_3 (1.1)	2	**12**	57

a) Reacted in THF.

Furthermore, we succeeded in the formation of various cyclic compounds from **1** and the reagents **7** having two different nucleophilic sites, as summarized in Table 4. To achieve the nucleophilic attack by OH or SH group, the addition of a base was effective to promote the reaction.

In summary, we examined the reactivity of 2,2-disulfonyloxiranes **1** toward various amines. A double nucleophilic addition occurred smoothly to give the α-amino carboxamide in good yield. Especially, cyclic α-azalactams and their related compounds were effectively formed from various reagents having two nucleophilic sites.

Experimental

General. Melting points were determined with a Yanaco MP-J3 and values were uncorrected. ^{1}H NMR measurement was performed on a Varian GEMINI 300 (300 MHz) spectrometer. Chemical shifts (δ) of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard ($\delta = 0$). Multiplicities are indicated as br (broadened), s (singlet), bs (broadened singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), and m (multiplet). Coupling constants (J) are reported (Hz). Infrared (IR) spectra were recorded on JASCO A-202 or JASCO FT/IR-350 spectrometers. Elemental analyses (EA) and high-resolution mass spectroscopy (HRMS) were carried out by the Chemical Analysis Center of Chiba University. Analyt-

ical thin-layer chromatography (TLC) was performed on glass plates pre-coated with silica gel (Merck Kieselgel 60 F_{254}, layer thickness 0.25 mm). Visualization was accomplished by UV light (254 nm) and anisaldehyde or iodine. Column chromatography was performed on a Merck Silica Gel 60 (70–230 mesh). Preparative GPC was performed on JAIGEL-1H and 2H with a LC-908 (Japan Analytical Industry, Co. Ltd.). Commercially available materials were purchased from Aldrich Chemical Co., Tokyo Kasei Chemical Industry Co., Wako Pure Chemical Co., Kanto Chemical Co., and Nacalai Tesque Inc. and no further purification was employed except for otherwise noted. Tetrahydrofuran (THF) was distilled from sodium diphenylketyl immediately prior to use. Chloroform was distilled after being treated with K_2CO_3. The reaction was performed under nitrogen atmosphere unless otherwise noted.

Preparation of Epoxides. To a solution of methylthiomethyl *p*-tolyl sulfone (5.01 g, 23.7 mmol) in THF (100 mL) was added trimethylsilyl chloride (6.45 mL, 51.1 mmol) at −78 °C. To the resulting solution was dropwise added butyllithium (1.6 M in hexane, 43.5 mL, 69.6 mmol) and this mixture was stirred for 75 min at that temperature. Then, freshly distilled propanal (1.85 mL, 25.8 mmol) was added and the reaction mixture was stirred for 1.5 h. After the addition of saturated aqueous solution of NH_4Cl (5 mL) and water (50 mL), the mixture was extracted with diisopropyl ether (50 mL × 3). The combined extracts were washed with brine, dried with $MgSO_4$ and evaporated to give a colorless oil. These were subjected to column chromatography on SiO_2 (hexane:ethyl acetate = 4:1) to give (*E*)-1-methylthio-1-(*p*-tolylsulfonyl)-1-butene (5.64 g, 22.0 mmol; 96% yield) as a colorless oil. To a solution of the thus-obtained (*E*)-1-methylthio-1-(*p*-tolylsulfonyl)-1-butene (3.00 g, 11.7 mmol) in chloroform (200 mL) was added *m*-chloroperbenzoic acid (70 wt %, 10.1 g, 40.9 mmol) at 0 °C. The resulting mixture was gradually warmed up to room temperature and then stirred for 39 h. After addition of 10% aqueous solution of $NaHSO_3$ (10 mL) and 30% aqueous solution of K_2CO_3 (30 mL), the mixture was extracted with chloroform (100 mL × 3). The combined extract was dried with Na_2SO_4 and evaporated to give a colorless oil. This was subjected to column chromatography on SiO_2 (hexane:ethyl acetate = 2:1) followed by recrystallization from a mixture of hexane and ethyl acetate to give *trans*-2-ethyl-3-(methylsulfonyl)-3-(*p*-tolylsulfonyl)-oxirane (**1**; R = Et) (2.88 g, 9.48 mmol; 81% yield) as colorless crystals: mp 138.0–139.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, 3H, J = 7.5 Hz), 1.99–2.21 (m, 2H), 2.47 (s, 3H), 3.28 (s, 3H), 4.01 (dd, 1H, J = 7.8, 5.0 Hz), 7.38 (d, 2H, J = 8.3 Hz), 7.86 (d, 2H, J = 8.5 Hz); IR (KBr) 1596, 1338, 1138, 1115, 1086, 998, 812, 766, 660, 559, 575, 541, 500, 471 cm^{-1}. Anal. Found: C, 47.19; H, 5.25%. Calcd for $C_{12}H_{16}O_5S_2$: C, 47.35; H, 5.30%.

***trans*-2-(Methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (1; R = Ph).**[12] The titled compound was prepared in 79% overall yield (two steps) according to a procedure similar to that mentioned above: colorless crystals; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.84 (s, 3H), 5.31 (s, 1H), 7.39–7.50 (m, 7H), 7.94 (d, 2H, J = 8.4 Hz).

***trans*-2-(4-Bromophenyl)-3-(methylsulfonyl)-3-(*p*-tolylsulfonyl)oxirane (1; R = *p*-Br–C$_6$H$_4$).** To a solution of (*E*)-1-(4-bromophenyl)-2-methylthio-2-(*p*-tolylsulfonyl)ethene (0.763 g, 2.00 mmol), prepared according to a procedure similar to that mentioned above, in chloroform (20 mL) was added *m*-chloroperbenzoic acid (70 wt %, 1.594 g, 6.46 mmol) at 0 °C. The resulting mixture was gradually warmed up to room temperature and then stirred for 7 h. After addition of K_2CO_3 (0.140 g, 1.00 mmol), the resulting mixture was stirred for 10 h. After addition of 10% aqueous solution of $NaHSO_3$ (5 mL) and 30% aqueous solution of K_2CO_3 (10 mL), the mixture was extracted with chloroform (20 mL × 3). The combined extract was dried with Na_2SO_4 and evaporated to give a colorless oil. This was subjected to column chromatography on SiO_2 (hexane:ethyl acetate = 3:1) to give *trans*-2-(4-bromophenyl)-3-(methylsulfonyl)-3-(*p*-tolylsulfonyl)-oxirane (**1**; R = *p*-Br–C$_6$H$_4$) (0.762 g, 1.78 mmol; 89% yield) as colorless plate crystals. The product was furthermore purified by recrystallization from mixture of hexane and ethyl acetate: mp 121.0–122.0 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.90 (s, 3H), 5.24 (s, 1H), 7.35 (d, 2H, J = 8.5 Hz), 7.41 (d, 2H, J = 8.4 Hz), 7.55 (d, 2H, J = 8.7 Hz), 7.93 (d, 2H, J = 8.4 Hz); IR (KBr) 3008, 1593, 1489, 1309, 1188, 1149, 1117, 812, 675, 596, 536, 511 cm^{-1}. Anal. Found: C, 44.55; H, 3.41%. Calcd for $C_{16}H_{15}BrO_5S_2$: C, 44.55; H, 3.51%.

***trans*-2-(4-Methoxycarbonylphenyl)-3-(methylsulfonyl)-3-(*p*-tolylsulfonyl)oxirane (1; R = *p*-MeOCO–C$_6$H$_4$).** The titled compound was prepared in 89% overall yield (two steps) according to a procedure similar to that mentioned above: white powder; mp 178.5–178.9 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 2.90 (s, 3H), 3.93 (s, 3H), 5.32 (s, 1H), 7.42 (d, 2H, J = 8.1 Hz), 7.55 (d, 2H, J = 8.1 Hz), 7.94 (d, 2H, J = 8.4 Hz), 8.08 (d, 2H, J = 8.5 Hz); IR (KBr) 3005, 2925, 1720, 1435, 1344, 1288, 1161, 1111, 756, 675, 598, 538 cm^{-1}. Anal. Found: C, 52.60; H, 4.38%. Calcd for $C_{18}H_{18}O_7S_2$: C, 52.67; H, 4.42%.

***trans*-2-(3-Methoxylphenyl)-3-(methylsulfonyl)-3-(*p*-tolylsulfonyl)oxirane (1; R = *m*-MeO–C$_6$H$_4$).** The titled compound was prepared in 67% overall yield (two steps) according to a procedure similar to that mentioned above: white powder; mp 102.1–103.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 2.85 (s, 3H), 3.80 (s, 3H), 5.29 (s, 1H), 6.94 (dd, 1H, J = 2.3, 8.2 Hz), 7.01 (diffused s, 1H), 7.06 (dm, 1H, J = 7.6 Hz), 7.32 (t, 1H, J = 8.0 Hz), 7.40 (d, 2H, J = 8.5 Hz), 7.94 (dm, 2H, J = 8.5 Hz); IR (KBr) 3003, 2837, 1597, 1495, 1338, 1255, 1151, 1122, 1039, 661, 602, 532 cm^{-1}. Anal. Found: C, 53.26; H, 4.64%. Calcd for $C_{17}H_{18}O_6S_2$: C, 53.39; H, 4.74%.

***trans*-2-Isopropyl-3-(methylsulfonyl)-2-(*p*-tolylsulfonyl)oxirane (1; R = *i*-Pr).** The titled compound was prepared in 78% overall yield (two steps) according to a procedure similar to that mentioned above: colorless cubic crystals; mp 153.1–153.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, J = 6.9 Hz), 1.16 (d, 3H, J = 6.6 Hz), 2.40–2.53 (m, 1H), 2.47 (s, 3H), 3.29 (s, 3H), 3.70 (d, 1H, J = 9.8 Hz), 7.38 (d, 2H, J = 8.5 Hz), 7.85 (d, 2H, J = 8.4 Hz); IR (KBr) 3016, 2979, 2931, 1469, 1340, 1147, 985, 764, 660, 542, 505 cm^{-1}. Anal. Found: C, 48.91; H, 5.77%. Calcd for $C_{13}H_{18}O_5S_2$: C, 49.04; H, 5.70%.

Reaction with Amines. To a solution of *trans*-2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (**1**; R = Ph) (0.177 g, 0.50 mmol) in chloroform (17 mL) was added morpholine (190 μL, 2.1 mmol) at room temperature. After the solution was stirred for 15 h, the resulting mixture was evaporated to give a colorless oil. This was subjected to column chromatography on SiO_2 (ethyl acetate) to give 4-(2-morpholino-2-phenylacetyl)morpholine (**5**; R = Ph, R′ = R″ = –$(CH_2)_2$–O–$(CH_2)_2$–) (0.142 g, 0.49 mmol; 97% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.45–2.59 (m, 4H), 3.11–3.78 (m, 12H), 4.22 (s, 1H), 7.28–7.42 (m, 5H); IR (neat) 2960, 2854, 1650, 1452, 1278, 1227, 1116, 1069, 1011, 879, 752 cm^{-1}. HRMS (FAB): m/z 291.1717 ([M + H]$^+$). Calcd for $C_{16}H_{23}N_2O_3$: m/z 291.1709.

***N*-Benzyl-2-(benzylamino)-2-phenylacetamide (5; R = Ph, R′ = Bn, R″ = H).** A colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.78

(bs, 1H), 3.74 (d, 1H, $J = 13.2$ Hz), 3.79 (d, 1H, $J = 13.2$ Hz), 4.34 (s, 1H), 4.43 (d, 2H, $J = 6.0$ Hz), 7.18–7.40 (m, 15H), 7.55 (t(br), 1H, $J = 6.0$ Hz); IR (neat) 3309, 3061, 3029, 1658, 1519, 1496, 1454, 1028, 734, 698 cm^{-1}. HRMS (FAB): m/z 331.1815 ($[M + H]^+$). Calcd for $C_{22}H_{23}N_2O$: m/z 331.1810.

***N*-Benzyl-*N*-methyl-2-[benzyl(methyl)amino]-2-phenylacetamide (5; R = Ph, R′ = Bn, R″ = Me).** A colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 1.8H), 2.72 (s, 1.8H), 3.69 (d, 0.6H, $J = 13.5$ Hz), 3.88 (d, 0.6H, $J = 13.5$ Hz), 4.56 (d, 0.6H, $J = 14.6$ Hz), 4.65 (s, 0.6H), 4.72 (d, 0.6H, $J = 14.4$ Hz), 7.21–7.47 (m, 9H); amide rotamer: δ 2.30 (s, 1.2H), 3.00 (s, 1.2H), 3.49 (d, 0.4H, $J = 13.6$ Hz), 3.81 (d, 0.4H, $J = 13.6$ Hz), 4.19 (d, 0.4H, $J = 16.8$ Hz), 4.58 (d, 0.4H, $J = 16.9$ Hz), 4.66 (s, 0.4H), 6.99 (diffused d, 0.8H, $J = 7.7$ Hz), 7.21–7.47 (m, 5.2H); IR (neat) 3028, 2931, 1653, 1493, 1452, 1400, 1254, 1209, 1107, 1028, 737, 698 cm^{-1}. Anal. Found: C, 80.30; H, 7.41; N, 7.76%. Calcd for $C_{24}H_{26}N_2O$: C, 80.41; H, 7.31; N, 7.81%.

***N*-Phenyl-2-anilino-2-phenylaceticamide (5; R = Ph, R′ = Ph, R″ = H).** A colorless spherical solid: mp 143.0–144.0 °C; ^{1}H NMR ($CDCl_3$) δ 4.48 (bs, 1H), 4.83 (d, 1H, $J = 2.1$ Hz), 6.72 (diffused d, 2H, $J = 7.7$ Hz), 6.86 (t, 1H, $J = 7.3$ Hz), 7.11 (t, 1H, $J = 7.4$ Hz), 7.23 (diffused t, 2H, $J = 7.4$ Hz), 7.30 (diffused t, 2H, $J = 7.6$ Hz), 7.36–7.44 (m, 3H), 7.50 (diffused d, 2H, $J = 8.1$ Hz), 7.53 (diffused d, 2H, $J = 7.6$ Hz), 8.74 (bs, 1H); IR (KBr) 3406, 3315, 3053, 3022, 1672, 1603, 1520, 1502, 1441, 1313, 1265, 750, 690 cm^{-1}. Anal. Found: C, 79.39; H, 6.02; N, 9.30%. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26%.

***N*-Benzyl-2-(benzylamino)-2-(4-bromophenyl)acetamide (5; R = *p*-Br–C_6H_4, R′ = Bn, R″ = H).** A colorless powder: mp 125.3–126.4 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (bs, 1H), 3.75 (s, 2H), 4.25 (s, 1H), 4.44 (d, 2H, $J = 5.9$ Hz), 7.19–7.36 (m, 12H), 7.41 (t(br), 1H, $J = 5.9$ Hz), 7.47 (dm, 2H, $J = 8.5$ Hz); IR (KBr) 3286, 3086, 3028, 1651, 1558, 1489, 1454, 1263, 1026, 827, 725, 700 cm^{-1}. Anal. Found: C, 64.50; H, 5.18; N, 6.75%. Calcd for $C_{22}H_{21}BrN_2O$: C, 64.55; H, 5.17; N, 6.84%.

***N*-Benzyl-2-(benzylamino)-2-(4-methoxycarbonylphenyl)acetamide (5; R = *p*-MeOCO–C_6H_4, R′ = Bn, R″ = H).** A colorless cotton-like solid: mp 110.2–111.2 °C; ^{1}H NMR ($CDCl_3$) δ 2.06 (bs, 1H), 3.76 (s, 2H), 3.91 (s, 3H), 4.35 (s, 1H), 4.45 (d, 2H, $J = 5.9$ Hz), 7.21 (dm, 4H, $J = 7.4$ Hz), 7.27–7.35 (m, 6H), 7.45 (dm, 2H, $J = 8.4$ Hz), 7.49 (bs, 1H), 8.01 (dm, 2H, $J = 8.4$ Hz); IR (KBr) 3735, 3030, 2927, 2848, 1709, 1655, 1529, 1454, 1286, 1117, 742, 698 cm^{-1}. Anal. Found: C, 73.99; H, 6.15; N, 7.18%. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21%.

***N*-Benzyl-2-(benzylamino)-2-(3-methoxyphenyl)acetamide (5; R = *m*-MeO–C_6H_4, R′ = Bn, R″ = H).** A colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.98 (bs, 1H), 3.76 (s, 5H), 4.26 (s, 1H), 4.45 (d, 2H, $J = 6.0$ Hz), 6.84 (ddd, 1H, $J = 0.8$, 2.6, 8.2 Hz), 6.91 (t-like, 1H, $J = 2.5$ Hz), 6.96 (d(br), 1H, $J = 7.7$ Hz), 7.21–7.33 (m, 11H), 7.44 (t(br), 1H, $J = 5.1$ Hz); IR (neat) 3315, 3028, 2935, 2835, 1657, 1599, 1517, 1491, 1456, 1261, 1155, 1045, 752, 698 cm^{-1}. Anal. Found: C, 76.57; H, 6.70; N, 7.69%. Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77%.

***N*-Benzyl-2-(benzylamino)butyramide (5; R = Et, R′ = Bn, R″ = H).** A colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $J = 7.5$ Hz), 1.61–1.86 (m, 2H), 1.72 (bs, 1H), 3.15 (dd, 1H, $J = 5.1$, 7.3 Hz), 3.68 (d, 1H, $J = 13.1$ Hz), 3.74 (d, 1H, $J = 13.1$ Hz), 4.46 (d, 2H, $J = 5.9$ Hz), 7.20–7.33 (m, 10H), 7.58 (bs, 1H); IR (neat) 3297, 3029, 2965, 2930, 1651, 1523, 1454, 1228, 1122, 1030, 733, 698 cm^{-1}. HRMS (FAB): m/z 283.1805 ($[M + H]^+$). Calcd for $C_{18}H_{23}N_2O$: m/z 283.1810. Anal. Found: C, 72.55; H, 7.47; N, 9.28%. Calcd for $C_{18}H_{22}N_2O + 0.15CHCl_3$: C, 72.60; H, 7.43; N, 9.33%.

***N*-Benzyl-2-(benzylamino)isovaleramide (5; R = *i*-Pr, R′ = Bn, R″ = H).** A colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, 3H, $J = 6.9$ Hz), 0.97 (d, 3H, $J = 7.0$ Hz), 1.61 (bs, 1H), 2.16 (dsept, 1H, $J = 4.5$, 6.9 Hz), 3.03 (d, 1H, $J = 4.5$ Hz), 3.64 (d, 1H, $J = 13.1$ Hz), 3.74 (d, 1H, $J = 13.1$ Hz), 4.47 (d, 2H, $J = 5.9$ Hz), 7.19–7.37 (m, 10H), 7.55 (bs, 1H); IR (neat) 3311, 3030, 2960, 1647, 1522, 1454, 1232, 1078, 1028, 735, 698 cm^{-1}. Anal. Found: C, 76.71; H, 8.04; N, 9.40%. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45%.

Reaction with Diamines. To a solution of *trans*-2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (**1**; R = Ph) (0.103 g, 0.292 mmol) in chloroform (10 mL) was dropwise added ethylenediamine (70 μL, 1.0 mmol) at room temperature. After being stirred for 24 h, saturated aqueous solution of $NaHCO_3$ and brine were added and the resulting mixture was extracted with chloroform (30 mL × 3). The combined extracts were dried with K_2CO_3 and evaporated to give 6-phenyl-2,5-diazacyclohexanone (**6**; R = Ph, $n = 1$) (0.0463 g, 0.262 mmol; 90% yield) as colorless crystals: mp 144.0–145.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.74 (bs, 1H), 3.08 (ddd, 1H, $J = 4.3$, 8.5, 12.6 Hz), 3.17 (dt, 1H, $J = 12.6$, 4.5 Hz), 3.39 (dq-like, 1H, $J = 11.5$, 3.9 Hz), 3.55 (dddd, 1H, $J = 1.2$, 4.7, 8.7, 11.8 Hz), 4.60 (s, 1H), 6.21 (bs, 1H), 7.28–7.45 (m, 5H); IR (neat) 3854, 3752, 3677, 3651, 3202, 1677, 1491, 1338, 1261, 1092, 800, 705 cm^{-1}. Anal. Found: C, 67.96; H, 6.76; N, 15.88%. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90%.

7-Phenyl-2,6-diazacycloheptanone (6; R = Ph, $n = 2$). Colorelss crystals: mp 153.0–154.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.69–1.83 (m, 3H), 3.05 (ddd, 1H, $J = 4.7$, 8.8, 13.6 Hz), 3.33 (dt, 1H, $J = 13.6$, 4.7 Hz), 3.40 (m, 2H), 4.59 (s, 1H), 6.02 (bs, 1H), 7.28–7.38 (m, 5H); IR (KBr) 3288, 2922, 1663, 1459, 1411, 1254, 1123, 814, 746, 698 cm^{-1}. Anal. Found: C, 69.35; H, 7.41; N, 14.64%. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72%.

8-Phenyl-2,7-diazacyclooctanone (6; R = Ph, $n = 3$). Pale yellow solid (purified with preparative GPC): mp 111.5–113.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.68–1.95 (m, 5H), 3.04–3.18 (m, 2H), 3.22–3.38 (m, 1H), 4.60 (s, 1H), 4.79–4.86 (m, 1H), 5.80 (bs, 1H), 7.29–7.48 (m, 5H); IR (KBr) 1655, 1560, 1543, 1508, 1459, 1420, 1303, 1262, 1118, 790, 701 cm^{-1}. HRMS (FAB): m/z 205.1345 ($[M + H]^+$). Calcd for $C_{12}H_{17}N_2O$: m/z 205.1341.

6-Ethyl-2,5-diazacyclohexanone (6; R = Et, $n = 1$). A yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, $J = 7.4$ Hz), 1.73 (ddq, 1H, $J = 8.2$, 15.7, 7.4 Hz), 1.92 (bs, 1H), 1.99 (ddq, 1H, $J = 3.7$, 15.2, 7.7 Hz), 2.98 (ddd, 1H, $J = 4.3$, 9.8, 12.9 Hz), 3.156 (dt, 1H, $J = 12.8$, 3.8 Hz), 3.26–3.46 (m, 3H), 6.63 (bs, 1H); IR (neat) 3282, 2961, 2927, 2873, 1685, 1492, 1459, 1335, 1073, 802 cm^{-1}. HRMS (FAB): m/z 128.0940 ($[M]^+$). Calcd for $C_6H_{12}N_2O$: m/z 128.0950.

7-Ethyl-2,6-diazacycloheptanone (6; R = Et, $n = 2$). Colorelss crystals: mp 95.7–97.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, $J = 7.4$ Hz), 1.53 (dquint, 1H, $J = 13.7$, 7.4 Hz), 1.60–1.75 (m, 3H), 1.90 (dquint, 1H, $J = 13.7$, 7.4 Hz), 2.92 (ddd, 1H, $J = 3.6$, 11.1, 13.7 Hz), 3.16 (dd, 1H, $J = 6.3$, 7.1 Hz), 3.24–3.45 (m, 3H), 5.96 (bs, 1H); IR (neat) 3219, 2933, 1655, 1459, 1430, 1337, 1146, 808, 569 cm^{-1}. HRMS (FAB): m/z 143.1176 ($[M + H]^+$). Calcd for $C_7H_{15}N_2O$: m/z 143.1184.

8-Ethyl-2,7-diazacyclooctanone (6; R = Et, $n = 3$). Pale yellow crystals (purified with preparative GPC): mp 93.2–94.5

°C; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, $J = 7.4$ Hz), 1.55–1.91 (m, 6H), 1.84 (dquint, 1H, $J = 13.5$, 7.6 Hz), 2.90–3.05 (m, 2H), 3.40–3.52 (m, 1H), 3.47 (dd, 1H, $J = 5.9$, 7.6 Hz), 3.66–3.76 (m, 1H), 5.81 (bs, 1H); IR (KBr) 3266, 3066, 2925, 1654, 1498, 1461, 1434, 1299, 1139, 905 cm^{-1}. HRMS (FAB): m/z 157.1338 ([M + H]$^+$). Calcd for $C_8H_{17}N_2O$: m/z 157.1341.

Reaction with Aminophenol. To a solution of *o*-aminophenol (0.130 g, 1.19 mmol) in THF (30 mL) was added NaOH (0.103 g, 1.08 mmol) at room temperature, and the resulting mixture was stirred for 15 min. After *trans*-2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (**1**; R = Ph) (0.350 g, 0.99 mmol) was added, the mixture was stirred for 3 h, and then acidified to pH ~ 3 with 1 M HCl. Water (20 mL) was added and the extraction was performed with chloroform (50 mL × 3). The combined extracts were dried with K_2CO_3 and evaporated to give a colorless oil. This was subjected to column chromatography on SiO_2 (hexane–chloroform) to give 2-phenyl-2*H*-1,4-benzoxazin-3(4*H*)-one (**8**; R = Ph) (0.182 g, 0.808 mmol; 81% yield) as colorless crystals: mp 171.5–172.5 °C (lit.[19] 169–170 °C); ^{1}H NMR ($CDCl_3$) δ 5.71 (s, 1H), 6.78–6.81 (m, 1H), 6.92–7.06 (m, 3H), 7.34–7.39 (m, 3H), 7.44–7.48 (m, 2H), 8.51 (bs, 1H); IR (KBr) 2964, 1685 (CONH), 1500, 1398, 1261, 11213, 1039, 802, 746, 700 cm^{-1}; Anal. Found: C, 74.69; H, 4.86; N, 6.13%. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%.

2-Ethyl-2*H*-1,4-benzoxazin-3(4*H*)-one (8; R = Et). Colorless solid: mp 104.0–105.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3H, $J = 7.4$ Hz), 1.83–2.02 (m, 2H), 4.52 (dd, 1H, $J = 4.7$, 8.0 Hz), 6.79 (dd, 1H, $J = 2.1$, 6.0 Hz), 6.92–7.11 (m, 3H), 8.30 (bs, 1H); IR (KBr) 3651, 3198, 2369, 2345, 1685 (CONH), 1610, 1503, 1408, 743 cm^{-1}. Anal. Found: C, 67.57; H, 6.20; N, 7.85%. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90%.

Reaction with Thiols. To a solution of *trans*-2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)oxirane (**1**; R = Ph) (0.352 g, 1.00 mmol) in chloroform (30 mL) was added 1,2-ethanedithiol (92 μL, 1.10 mmol) at room temperature. Then, DBU (330 μL, 2.21 mmol) was added at that temperature. After the solution was stirred for 30 min, the resulting mixture was washed with saturated aqueous solution of $NaHCO_3$ (30 mL × 3). The washings were extracted with chloroform (30 mL × 3). The combined organic layer was dried with $MgSO_4$ and evaporated to give a colorless oil. These were subjected to column chromatography on SiO_2 (chloroform), followed by preparative GPC to give 3-phenyl-1,4-dithian-2-one (**9**; R = Ph) (0.125 g, 0.594 mmol; 59% yield) as colorless crystals: mp 111.0–112.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.14–3.37 (m, 3H), 3.39–3.49 (m, 1H), 4.83 (s, 1H), 7.29–7.44 (m, 5H); IR (KBr) 1671, 1455, 1430, 1270, 1031, 1020, 796, 728, 696, 599 cm^{-1}. Anal. Found: C, 56.04; H, 5.04%. Calcd for $C_{10}H_{10}OS_2 + 0.25H_2O$: C, 55.91; H, 4.93%.

3-Ethyl-1,4-dithian-2-one (9; R = Et). A yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, $J = 7.5$ Hz), 1.61 (septet like, 1H, $J = 7.2$ Hz), 2.06 (ddq, 1H, $J = 6.2$, 7.3, 14.4 Hz), 2.99–3.12 (m, 1H), 3.29–3.48 (m, 3H), 3.60 (t, 1H, $J = 6.6$ Hz); IR (neat) 2966, 2928, 1668, 1455, 1432, 1113, 1016, 999, 776 cm^{-1}. Anal. Found: C, 44.35; H, 6.12%. Calcd for $C_6H_{10}OS_2$: C, 44.41; H, 6.21%.

3-Ethyl-1,4-dithiepan-2-one (10). Colorless solid: mp 67.0–67.5 °C (lit.[20] 65–65.5 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, 3H, $J = 7.4$ Hz), 1.62 (sept-like, 1H, $J = 7.3$ Hz), 1.96 (sept-like, 1H, $J = 7.0$ Hz), 2.03–2.17 (m, 1H), 2.53–2.63 (m, 1H), 2.86–3.08 (m, 3H), 3.23 (ddd, 1H, $J = 1.5$, 11.5, 15.4 Hz), 3.60 (t, 1H, $J = 7.1$ Hz); IR (KBr) 2970, 2930, 1644, 1457, 1421, 1243, 1113, 1020, 907, 786 cm^{-1}.

3-Phenyl-1,4-benzodithiin-2(3*H*)-one (11; R = Ph). To a solution of *trans*-2-(methylsulfonyl)-3-phenyl-2-(*p*-tolylsulfonyl)-oxirane (**1**; R = Ph) (0.203 g, 0.575 mmol) in chloroform (20 mL) were dropwise added 1,2-benzenedithiol (98 μL, 0.851 mmol) and triethylamine (235 μL, 2.01 mmol) at room temperature. After the solution was stirred for 30 min, the resulting mixture was washed with water (50 mL × 3) and 0.5 M HCl (50 mL). The organic layer was dried with $MgSO_4$ and evaporated to give a pale yellow solid. This solid was subjected to column chromatography on SiO_2 (chloroform) to give 3-phenyl-1,4-benzodithiin-2(3*H*)-one (**11**; R = Ph) (0.131 g, 0.507 mmol, 88% yield) as a colorelss solid: mp 123.3–124.1 °C; ^{1}H NMR ($CDCl_3$) δ 4.59 (s, 1H), 7.18 (dd, 1H, $J = 1.8$, 7.3 Hz), 7.22–7.33 (m, 7H), 7.53 (diffused dd, 1H, $J = 1.8$, 7.1 Hz); IR (KBr) 1683, 1451, 1053, 1011, 804, 747, 737, 698, 602, 440 cm^{-1}. Anal. Found: C, 65.07; H, 4.02%. Calcd for $C_{14}H_{10}OS)_2$: C, 65.08; H, 3.90%.

3-Ethyl-1,4-benzodithiin-2(3*H*)-one (11; R = Et). A colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.04 (t, 3H, $J = 7.5$ Hz), 1.57 (sept-like, 1H, $J = 7.7$ Hz), 1.90 (sept-like, 1H, $J = 7.3$ Hz), 3.35 (dd, 1H, $J = 6.5$, 8.1 Hz), 7.24–7.31 (m, 3H), 7.53 (diffused dd, 1H, $J = 1.6$, 6.6 Hz); IR (neat) 2967, 2932, 1681, 1454, 1428, 1113, 1053, 991, 749, 437 cm^{-1}. Anal. Found: C, 57.18; H, 4.85%. Calcd for $C_{10}H_{10}OS_2$: C, 57.11; H, 4.79%.

2-Ethyl-2*H*-1,4-benzothiazin-3(4*H*)-one (12). Orange solid; mp: 100.0–101.0 °C (lit.[19] 103–104 °C); ^{1}H NMR ($CDCl_3$) δ 1.07 (t, 3H, $J = 7.4$ Hz), 1.64 (ddq, 1H, $J = 8.8$, 14.4, 7.1 Hz), 1.95 (ddq, 1H, $J = 5.9$, 14.4, 7.3 Hz), 3.32 (dd, 1H, $J = 5.9$, 8.8 Hz), 6.88 (dd, 1H, $J = 1.2$, 8.0 Hz), 7.01 (dt, 1H, $J = 1.4$, 7.7 Hz), 7.17 (dt, 1H, $J = 1.5$, 7.8 Hz), 7.32 (dd, 1H, $J = 1.5$, 7.8 Hz), 8.97 (bs, 1H); IR (KBr) 3193, 3052, 2975, 1679 (CONH), 1583, 1479, 1369, 755, 696, 549 cm^{-1}.

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