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ASYMMETRIC OXIDATION OF CYCLIC SULFIDES CATALYZED BY AN ALUMINUM(SALALEN) COMPLEX AS THE CATALYST‡

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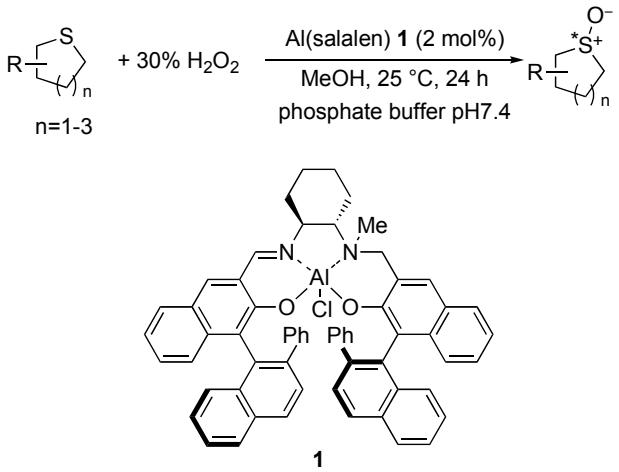
‡ Dedication to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – We report a catalytic asymmetric oxidation of cyclic sulfides that uses a combination of aluminum(salalen) complex **1** as the catalyst and aqueous hydrogen peroxide as the oxidant. Oxidations of six-membered cyclic sulfides, thiochroman-4-ones, furnish the corresponding sulfoxides in high yield with high enantioselectivity. Five-membered 2,3-dihydrobenzo[*b*]thiophene and seven-membered dibenzo[*b*,*e*]thiepin-11(6*H*)-one are also good substrates for the aluminum-catalyzed system.

Optically active sulfoxides are of great importance as chiral ligands and auxiliaries in organic synthesis. Recently Kobayashi and co-workers disclosed its excellent catalysis as a neutral coordinate-organocatalyst for the asymmetric allylation of hydrazones with allylsilanes.[1,2] Moreover, chiral sulfoxides are found in many important bioactive compounds such as omeprazole and its analogs, which are gastric proton-pump inhibitors for dyspepsia, peptic ulcer disease, etc. Enantioselective oxidation of prochiral sulfides is the most direct and effective approach to optically active sulfoxides. Thus, the development of highly efficient synthetic methods has attracted much attention from the synthetic community.[3-11] While many improvements have been achieved for asymmetric sulfur oxidation and optically active chiral sulfoxides have a potential for pharmaceuticals and chiral ligands,[12,13] there are still only a few catalytic systems for enantioselective oxidation of cyclic sulfides with a wide substrate scope.[14] Enzymatic methods are also available, but the substrates are inherently limited.[15,16] Moreover, we were intrigued with the asymmetric induction in the oxidation of cyclic sulfides. Two lone pairs on sulfur atom of cyclic sulfides are intrinsically different, because of a ring-conformational isomerism. Due to the

problem, cyclic sulfides are a difficult class of substrates for asymmetric oxidation chemistry.

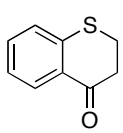
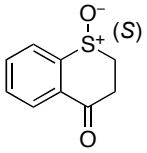
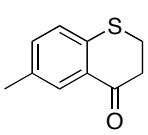
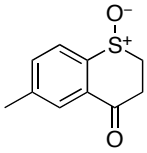
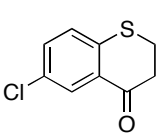
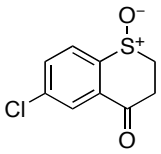
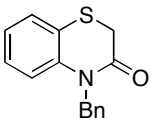
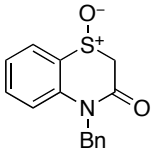
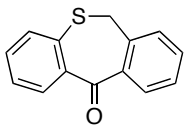
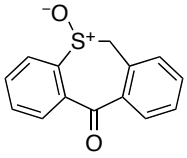
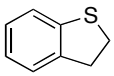
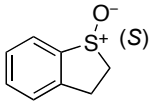
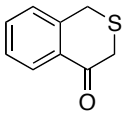
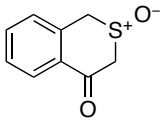
Recently, we reported an aluminum-based catalyst, Al(salalen) complex **1**, that uses aqueous hydrogen peroxide as the stoichiometric oxidant to oxidize various sulfides into the corresponding sulfoxides.[17-19] Reactions of acyclic alkyl aryl sulfides, acyclic dialkyl sulfides and cyclic thioacetals proceeded smoothly to afford the corresponding mono-oxides with high to excellent enantioselectivity. Herein, we report the highly enantioselective oxidation of cyclic sulfides using the Al(salalen) complex **1** as the catalyst (Scheme 1).



Scheme 1. Al(salalen)-catalyzed asymmetric oxidation of cyclic sulfides.

We examined the asymmetric oxidation of several cyclic sulfides in methanol as the solvent with 2 mol% of catalyst in the presence of phosphate buffer at 25 °C (Figure 2).[20-27] In the oxidation of thiochroman-4-one, the corresponding sulfoxide was obtained in 64% with 97% ee (entry 1). While the highest ee value of 99% was achieved with the reaction of 6-methylthiochroman-4-one, the substitution of the methyl group by the chloro group led to diminished enantioselectivity (entries 2 and 3). The reaction of 4-benzyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one was slow and the mono-oxide was yielded in only 18% (entry 4). Although it was suspected that the produced sulfoxide might inhibit the reaction by coordination to the aluminum ion, the reaction of 6-methylthiochroman-4-one proceeded smoothly, even in the presence of 20 mol% of the racemic sulfoxide. High enantioselectivity was also achieved in the oxidation of a seven-membered substrate, dibenzo[*b*,*e*]thiepin-11(6*H*)-one (entry 5). The oxidation of the five-membered 2,3-dihydrobenzo[*b*]thiophene furnished the mono-oxide with 99% ee (entry 6). Especially, it is noteworthy that the present oxidation system can efficiently differentiate two α- and α'-methylene carbons. A cyclic dialkyl sulfide, 2-isothiochroman-4-one, was also a good substrate for this oxidation system to give the sulfoxide with 90% ee (entry 7). In these oxidations, over-oxidation of sulfoxides was observed, and the corresponding sulfones were yielded in 5-20%.

Table 1. Asymmetric oxidation of cyclic sulfides catalyzed by Al(salalen) complex **1**.

Entry	Substrate	Product		Yield/%[a]	Ee/%[b]
1			**2**	64	97
2			**3**	86	99
3			**4**	82	87
4			**5**	18	62
5			**6**	81	95
6			**7**	83	99
7			**8**	77	90

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

In summary, we found that Al(salalen) complex **1** was an efficient catalyst for asymmetric oxidation of cyclic sulfides. High to excellent enantioselectivity was obtained in the oxidation of various cyclic sulfides ranging from five- to seven-membered ones.

ACKNOWLEDGEMENTS

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20. General experimental procedure for aluminum-catalyzed asymmetric oxidation of cyclic sulfides: sulfide (0.20 mmol) was dissolved in a methanolic solution of Al(salalen) complex (2 mol%, 1.0 mL), and then pH 7.4 phosphate buffer (20 μL, 66.6 mmolL^{-1}) was added to the solution. After the addition of 30% hydrogen peroxide (1.1 equiv.), the resultant mixture was stirred at 25 °C for 24 h. The reaction was quenched with aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/EtOAc=1:1→0:1) to give the desired sulfoxide. The enantiomeric excess was determined by chiral HPLC.
21. For (*S*)-(+)-thiochlomanon-4-one oxide (**2**): colorless solid; 64%, 97% ee (CHIRALPAK IC, hexane/*i*PrOH 50:50, 0.80 mL/min, 25 °C); $[\alpha]_D^{24}$ +138.9 (*c* 0.7, acetone) [lit.,[28] $[\alpha]_D$ +96.8 (c 1, acetone), 66% ee, (*S*)-isomer].; IR (KBr): 1682 (C=O), 1038 (S→O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.19-8.17 (d, *J*=7.6 Hz, 1H), 7.91-7.89 (d, *J*=7.7 Hz, 1H), 7.80-7.77 (m, 1H), 7.70-7.66 (m, 1H), 3.55-3.46 (m, 3H), 2.97-2.86 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 191.7, 145.4, 134.4, 132.0, 129.0, 128.8, 128.3, 46.8, 30.5 ppm.
22. For (+)-6-methylthiochlomanon-4-one *S*-oxide (**3**): colorless solid; 86%, 99% ee (CHIRALPAK IC, hexane/*i*PrOH 50:50, 0.80 mL/min, 25 °C); $[\alpha]_D^{24}$ +142.9 (*c* 0.8, acetone); IR (KBr): 1684 (C=O), 1028 (S→O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 7.98 (s, 1H), 7.77-7.75 (d, *J*=7.8 Hz, 1H), 7.58-7.56 (d, *J*=7.8 Hz, 1H), 3.57-3.44 (m, 3H), 2.92-2.85 (m, 1H), 2.47 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 192.1, 142.9, 142.0, 135.0, 129.1, 128.8, 128.7, 46.5, 30.1, 21.5 ppm.
23. For (+)-6-chlorothiochlomanon-4-one *S*-oxide (**4**): colorless solid; 82%, 87% ee (CHIRALPAK AD-H, hexane/*i*PrOH 90:10, 1.0 mL/min, 40 °C); $[\alpha]_D^{24}$ +119.7 (*c* 1.1, acetone); IR (KBr): 1692 (C=O), 1043 (S→O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.12-8.12 (d, *J*=1.8 Hz, 1H), 7.85-7.83 (d, *J*=8.3 Hz, 1H), 7.75-7.73 (dd, *J*=1.8, 8.3 Hz, 1H), 3.54-3.46 (m, 3H), 2.97-2.87 ppm (m, 1H); ^{13}C NMR ($CDCl_3$): δ = 190.6, 143.6, 138.7, 134.3, 130.3, 130.0, 128.7, 46.7, 30.3 ppm.
24. For (+)-4-benzyl-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one *S*-oxide (**5**): 18%, 62% ee (CHIRALPAK IC,

hexane/*i*PrOH 50:50, 0.80 mL/min, 30 °C); $[\alpha]_D^{24}$ +145.9 (*c* 0.8, acetone); IR (KBr): 1668 (C=O), 1024 (S→O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.74-7.72 (dd, *J*=1.0, 7.6 Hz, 1H), 7.47-7.42 (m, 1H), 7.35-7.14 (m, 7H), 5.48-5.44 (d, *J*=16.6 Hz, 1H), 5.22-5.18 (d, *J*=16.6 Hz, 1H), 4.33-4.29 (d, *J*=14.8 Hz, 1H), 3.87-3.84 ppm (d, *J*=14.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 160.9, 138.3, 135.5, 133.7, 129.7, 128.8, 127.3, 127.2, 126.3, 124.0, 118.3, 52.7, 48.0 ppm.

25. For (+)-dibenzo[*b*,*e*]thiepin-11(6*H*)-one *S*-oxide (**6**): colorless solid; 81%, 95% ee (CHIRALCEL OD-H, hexane/*i*PrOH 90:10, 1.0 mL/min, 25 °C); $[\alpha]_D^{24}$ +219.0 (*c* 1.0, acetone); IR (KBr): 1638 (C=O), 1034 (S→O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.21-8.16 (m, 2H), 8.04-8.02 (dd, *J*=1.0, 7.8 Hz, 1H), 7.80-7.76 (m, 1H), 7.65-7.60 (m, 2H), 7.53-7.49 (m, 1H), 7.41-7.39 (d, *J*=7.6 Hz, 1H), 4.88-4.84 (d, *J*=13.9 Hz, 1H), 4.31-4.28 ppm (d, *J*=13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 189.9, 146.6, 137.7, 133.9, 133.7, 133.1, 132.3, 131.7, 131.1, 130.5, 128.8, 127.7, 124.0, 61.0 ppm.
26. For (*S*)-(+)-2,3-dihydrobenzo[*b*]thiophene *S*-oxide (**7**): colorless solid; 83%, 99% ee (CHIRALPAK AD-H, hexane/*i*PrOH 90:10, 1.0 mL/min, 40 °C); $[\alpha]_D^{24}$ +301.9 (*c* 1.3, acetone) [lit.,[13] $[\alpha]_D$ -310 (c 1.5, acetone), 98% ee, (*R*)-isomer]; IR (KBr): 1022 (S→O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 7.85-7.83 (d, *J*=7.8 Hz, 1H), 7.53-7.41 (m, 3H), 3.92-3.82 (m, 1H), 3.40-3.22 ppm (m, 3H); ^{13}C NMR ($CDCl_3$): δ = 144.5, 143.0, 132.1, 128.1, 126.6, 125.9, 52.7, 31.5 ppm.
27. For (+)-isothiochroman-4-one *S*-oxide (**8**): colorless solid; 77%, 90% ee (CHIRALPAK AS-H, hexane/*i*PrOH 50:50, 0.80 mL/min, 35 °C); $[\alpha]_D^{24}$ +304.8 (*c* 0.4, acetone); IR (KBr): 1682 (C=O), 1024 (S→O) cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.15-8.13 (dd, *J*=1.0, 7.8 Hz, 1H), 7.68-7.64 (ddd, *J*=1.1, 7.6, 7.6 Hz, 1H), 7.52-7.49 (dd, *J*=7.6, 7.8 Hz, 1H), 7.38-7.36 (d, *J*=7.6 Hz, 1H), 4.37-4.33 (d, *J*=15.1 Hz, 1H), 4.32-4.28 (d, *J*=15.1 Hz, 1H), 4.05-4.01 (dd, *J*=1.0, 15.6 Hz, 1H), 3.99-3.95 ppm (dd, *J*=1.0, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 187.6, 135.2, 131.5, 131.2, 131.0, 129.1, 128.2, 59.1, 52.6 ppm.
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