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Published on Web 12/10/2010

Catalytic Asymmetric Oxidation of Cyclic Dithioacetals: Highly Diastereo- and Enantioselective Synthesis of the *S*-Oxides by a Chiral Aluminum(salalen) Complex

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Abstract: Aluminum(salalen) complex **1** [salalen = half-reduced salen, salen = *N*,*N*′-ethylenebis(salicylideneiminato)] was found to be a highly efficient catalyst for asymmetric oxidation of cyclic dithioacetals in the presence of 30% hydrogen peroxide as an oxidant. In the reaction of a series of 2-substituted 1,3-dithianes bearing alkyl, alkenyl, alkynyl, and aryl groups as the substituent, the *trans*-monoxides were obtained in high yields with 19:1 → >20:1 dr (diastereomeric ratio) and 98−99% ee (enamtiomeric excess). The reaction of nonsubstituted 1,3-dithiane also proceeded in a highly enantioselective manner to give the monoxide with a small formation of the *trans*-1,3-dioxide, an overoxidation product. Five-membered 1,3-dithiolanes and seven-membered 1,3-dithiepanes also underwent oxidation to give monoxides with high diastereo- and enantioselectivity. It was found that the equilibrium between the two chairlike conformers of dithianes has relevance to the observed diastereoselectivity in the first oxidation process, and the dioxide formation in the oxidation of 1,3-dithiane and its stereochemistry also can be explained by the conformational equilibrium of the product monoxide.

Introduction

Optically active sulfoxides are efficient chiral auxiliaries, organocatalysts, and ligands for metal complexes utilized in stereoselective synthesis.[1] They are also found in an important class of biologically active compounds.[2] For example, omeprazole and derivatives containing a chiral sulfoxide moiety are present in leading pharmaceuticals.[3] A reliable route to this class of compounds involves asymmetric oxidation of the corresponding sulfides. Thus, the past few decades have witnessed significant progress in the field of catalytic asymmetric sulfur oxidation.[4] Since the seminal reports by the Kagan group[5] and Modena group[6] using titanium/tartrate catalysts together with alkyl hydroperoxide as oxidant, a variety of chiral ligands have been introduced for titanium-catalyzed oxidation.[7] Other transition-metal catalysts based on vanadium,[8] manganese,[9] iron,[10] and so on,[11−15] and chemoenzymatic[16] methods have also been

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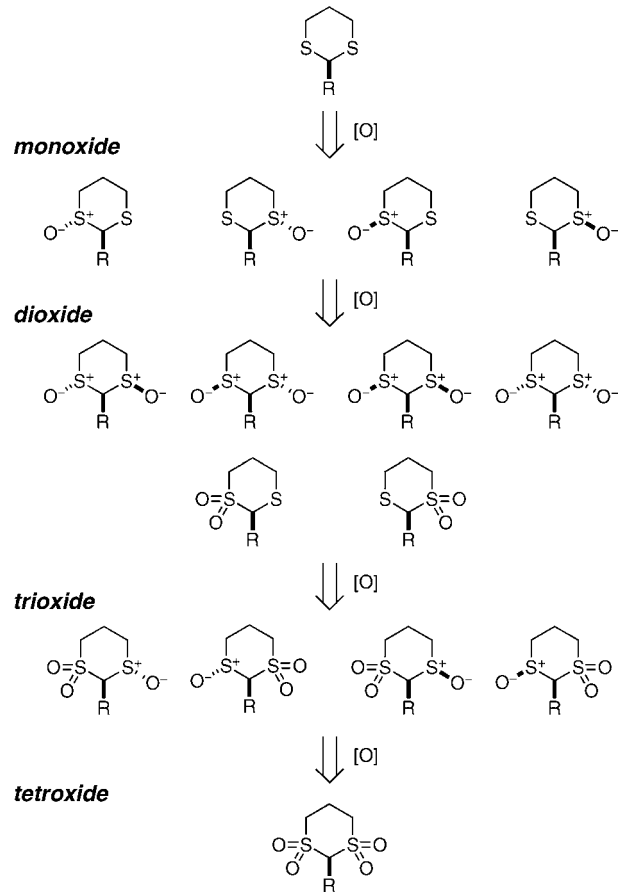
10.1021/ja106877x

developed, and high enantioselectivity has already been achieved in the oxidation of simple substrates such as alkyl aryl sulfides. However, asymmetric oxidation of cyclic dithioacetals including 1,3-dithiolanes and 1,3-dithianes has been slow to develop, despite the synthetic utility of the enantiomerically enriched *S*-oxides.[17] To the best of our knowledge, there are no general catalysts that achieve high stereoselectivity (more than 20:1 dr (diastereomeric ratio), more than 95% ee (enamtiomeric excess)) in the oxidation of dithioacetals with a wide substrate spectrum. Although the titanium/tartrate systems have been applied to the oxidation of dithiolanes and dithianes, good substrates were limited with regard to both diastereo- and enantioselectivity.[18] Bolm and Bienewald's vanadium/Schiff base catalysts, which showed high enantioselectivity in the oxidation of simple sulfides, also gave insufficient results.[19] We reported significant improvements in the oxidation of 2-substituted cyclic dithioacetals by using titanium(salen) complexes as catalyst, but the stereoselectivity was strongly affected by the substituents on the 2-position. For example, the oxidation of 2-*tert*-butyl-1,3-dithiane produced the *S*-oxide with only 39% ee.[20] Enzymatic methods have also been developed for the oxidation, but the substrate scope is inherently narrow.[21]

Different from simple sulfides, cyclic dithioacetals have four sulfur lone pairs in one molecule which can participate in oxidation process, and the presence of a substituent at the 2-position raises the issue of diastereoselectivity as well as enantioselectivity (Scheme 1). Potentially, four stereoisomers of the monoxide can be produced. Thus, the discrimination of the four lone pairs by optically active catalysts is an essential qualification for achieving highly stereoselective oxidation of dithioacetals. Moreover, the produced monoxides can undergo overoxidation to give the 1,3-dioxide (disulfoxide) and 1,1-dioxide (sulfone), and these overoxidation products can also undergo further oxidation. In addition, there is a possibility of kinetic resolution in these overoxidation processes.[22] This complexity has hampered the development of asymmetric oxidation of cyclic dithioacetals. Consequently, extremely high stereorecognition ability of catalysts is essential in order to realize highly stereoselective oxidation of cyclic dithioacetals.

Scheme 1. Product Complexity in Oxidation of 2-Substituted 1,3-Dithianes

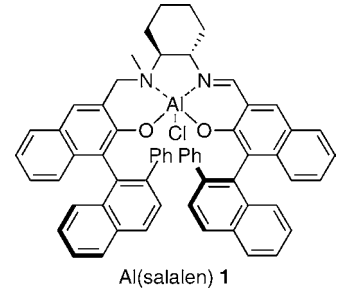


In the preceding papers, we have reported that aluminum(salalen) complex **1** (Figure 1) is an effective catalyst for asymmetric oxidation of sulfur compounds such as acyclic and cyclic sulfides in the presence of environmentally benign aqueous hydrogen peroxide as the stoichiometric oxidant[23] and preliminarily demonstrated that a few cyclic 1,3-dithianes underwent the oxidation to give the monoxides with high diastereo- and enantioselectivity.[23b] Here, we report a more detailed examination of the aluminum-catalyzed asymmetric oxidation of cyclic dithioacetals.

Results and Discussion

I. Preparation of Al(salalen) Complex 1. Al(salalen) complex **1** was prepared from Et_2AlCl and the corresponding salalen ligand according to the reported procedure.[23b]

II. Development of Al(salalen)-Catalyzed Asymmetric Oxidation of 1,3-Dithianes. We first examined asymmetric oxidation of 2-phenyl-1,3-dithiane **2a** with Al(salalen) complex



Al(salalen) **1**

Figure 1. Aluminum(salalen) complex **1**.

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Scheme 2. Asymmetric Oxidation of 2-Phenyl-1,3-dithiane **2a** with Al(salalen) Complex **1**

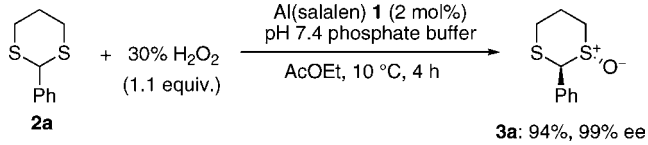
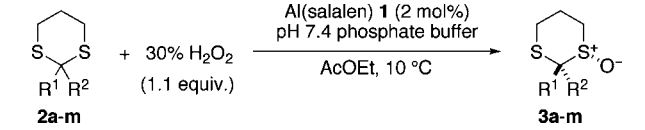


Table 1. Asymmetric Oxidation of 1,3-Dithiane Derivatives



entry	substrate	R^1	R^2	time (h)	dr[a]	yield (%)[b]	ee (%)[c]
1[d]	**2a**	Ph	H	4.5	>20:1	93	99
2	**2b**	PhCH═CH	H	4	>20:1	94	99
3[d]	**2b**	PhCH═CH	H	4	>20:1	95	99
4	**2c**	PhC≡C	H	4	19:1	72	>99 (1*S*,2*S*)[e]
5	**2d**	$PhCH_2$	H	3	>20:1	92	99
6	**2e**	$PhCH_2CH_2$	H	4	>20:1	94	99 (1*S*,2*S*)[f]
7	**2f**	$(CH_3)_2CH$	H	5	>20:1	98	>99
8[d]	**2f**	$(CH_3)_2CH$	H	6	>20:1	95	>99
9	**2g**	cC_3H_5	H	11	>20:1	95	>99
10	**2h**	cC_6H_{11}	H	12	>20:1	98	99
11	**2i**	$(CH_3)_3C$	H	12	>20:1	73	>99 (1*S*,2*S*)[g]
12	**2j**	$(CH_3)_3Si$	H	3	>20:1	91	99 (1*S*,2*S*)[g]
13	**2k**	CH_3	CH_3	24		68	99 (*S*)[g]
14	**2l**	Ph	CH_3	48	>20:1	79	>99
15	**2m**	$PhCH_2CH_2$	CH_3	4	1.2:1	47[h]/38[i]	98 (1*S*,2*R*)[j]/ 99 (1*S*,2*S*)[j]

[a] Determined by ^{1}H NMR analysis (400 MHz). [b] Isolated yield. [c] Determined by chiral HPLC analysis, see the Supporting Information for details. [d] Run on a 1 mmol scale. [e] Determined by X-ray crystallographic analysis. [f] Determined by comparison of the optical rotation with the authentic sample prepared from (−)-(*S*)-1,3-dithiane 1-oxide. [g] Determined by comparison of the optical rotation with literature value. [h] Yield of (1*S*,2*R*)-isomer **3m**. [i] Yield of (1*S*,2*S*)-isomer **3m′**. [j] Determined by comparison of the optical rotation with the authentic sample prepared from (+)-(1*S*,2*S*)-2-phenylethyl-1,3-dithiane 1-oxide.

1 in the presence of 30% hydrogen peroxide as the oxidant (Scheme 2). Addition of pH 7.4 phosphate buffer is effective for increasing the reproducibility. In the course of this study, ethyl acetate was found to be a more effective solvent with respect to the reaction rate, though the reaction was conducted in methanol in the previous study.[23b] In ethyl acetate, the dithiane **2a** was completely consumed in less than 4 h. Although only a trace amount of the *cis*-monoxide and dioxides were formed under the conditions, the *trans*-monoxide **3a** was preferentially obtained in 94% yield with 99% ee.

The scope and limitations of cyclic 1,3-dithianes are shown in Table 1. Most of the 2-substituted 1,3-dithianes examined gave the monoxides with almost complete diastereo- and enantioselectivity. 1,3-Dithianes with unsaturated groups such as cinnamyl and phenylethynyl groups underwent the oxidation with excellent stereoselectivity (entries 2−4). Substitution with primary, secondary, and tertiary alkyl groups also led to the production of the monoxides in a highly stereoselective manner (entries 5−11), but the reactions with bulkier groups including cyclopropyl, cyclohexyl, and *tert*-butyl required longer reaction times to completion (entries 9−11). A silylated dithiane **2j** smoothly underwent the oxidation with excellent diastereo- and enantioselectivity (entry 12). These results indicate that the steric hindrance of the 2-substituents had little impact on the diastereo- and enantioselectivity. The relative configuration of the major monoxides was determined as the *trans*-isomers, based on the ^{1}H and ^{13}C NMR analysis.[18b,24] The absolute configuration of *trans*-2-phenylethynyl-1,3-dithiane 1-oxide **3c** was unequivocally determined to be 1*S*,2*S* by X-ray crystallographic analysis (Figure 2).[25] In addition to 2-monosubstituted dithioacetals, 2,2-disubstituted ones are also good substrates for the Al(salalen)-catalyzed asymmetric oxidation. The reaction of 2,2-dimethyl-1,3-dithiane **2k** produced the monoxide **3k** with 99% ee, but the reaction was slow (entry 13). 2-Methyl-2-phenyl-1,3-dithiane **2l** also underwent the oxidation to give the *trans*-oxide **3l** in 79% yield with >20:1 dr and 99% ee (entry 14). Although the reaction of 2-methyl-2-(2-phenylethyl)-1,3-dithiane **2m** furnished the monoxides as a 1.2:1 diastereomer mixture, both the diastereomers were obtained in high enantiomeric excesses (entry 15). The cause of this low diastereoselectivity is discussed in the next section.

Surprisingly, the oxidation of 1,3-dithiane **2n** with no substituent was also highly enantioselective (Scheme 3).[26] The monoxide **3n** was obtained in 70% yield with 95% ee. This high enantioselectivity further emphasizes the high utility of the Al(salalen)-catalyzed system. It is of note that an overoxidation product, 1,3-dithiane *trans*-1,3-dioxide **4n**, was formed in 15% yield with 99% ee under the reaction conditions.

Although the dioxide formation was difficult to suppress, employment of 2.2 equiv of aqueous hydrogen peroxide enabled the selective formation of the *trans*-dioxide **4n** in 71% yield with >99% ee (Scheme 4). The dioxide is known as an important chiral auxiliary, and it can be transformed to a variety of chiral-modified compounds.[27] Although Aggarwal and co-workers have reported an effective procedure for the preparation in an enantiopure form using Modena's protocol [$Ti(OiPr)_4$ (0.5 equiv), DET (2 equiv), and CHP (4 equiv)], the procedure is indirect and includes the steps of the asymmetric oxidation of 2-carbethoxy-1,3-dithiane and the subsequent hydroxylation and decarboxylation.[28] In contrast, the Al(salalen)-catalyzed system makes the direct preparation of enantiopure *trans*-1,3-dithiane 1,3-dioxide **4n** possible.

III. Mechanistic Consideration of Al(salalen)-Catalyzed Asymmetric Oxidation of 1,3-Dithianes. We postulate that Al(salalen) complex **1** and hydrogen peroxide give a hydrop-

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(25) CCDC 766991 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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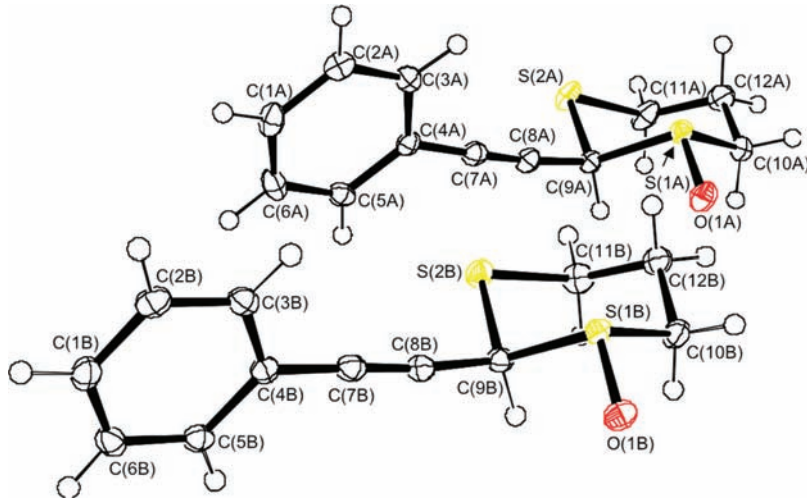
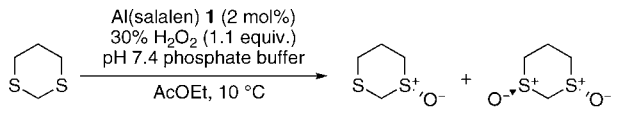
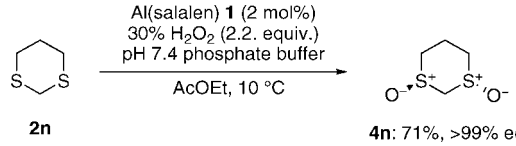


Figure 2. X-ray structure of *trans*-2-phenylethynyl-1,3-dithiane 1-oxide **3c**. ORTEP view (50% probability).

Scheme 3. Asymmetric Oxidation of 1,3-Dithiane **2n**



Scheme 4. Asymmetric Synthesis of *trans*-1,3-Dithiane 1,3-Dioxide **4n**



eroxo species,[23c,29] which oxidizes sulfides to the sulfoxides, and that the highly elaborated salalen ligand with two binaphthyl units constructs an effective cavity around the hydroperoxo species for the asymmetric induction. However, a detailed discussion regarding the asymmetric induction is difficult because the actual structure of the active species is unclear at present. Nonetheless, the observed absolute configuration of the produced 1,3-dithiane monoxides and its extremely high diastereo- and enantioselectivity indicate that, among the four lone pairs on the sulfur atoms, the optically active oxidant exclusively reacts with lone pair *a*, an equatorial lone pair on the *pro-S* sulfur atom, irrespective of substituents at the C2-position (Figure 3). Axial lone pairs *b* and *ent-b* are inherently less reactive, due to the hyperconjugative interactions with σ^*_{C-H} orbitals,[30] and the enantiotopic lone pairs *a* and *ent-a* could be effectively differentiated by the highly elaborated Al(salalen) complex.

If based on the premise that only lone pair *a* can attack the optically active oxidant to give the corresponding sulfoxide, not only the high diastereomer ratio of the produced monoxides but also almost no formation of overoxidation products in the oxidation of 2-substituted 1,3-dithiane and the formation of

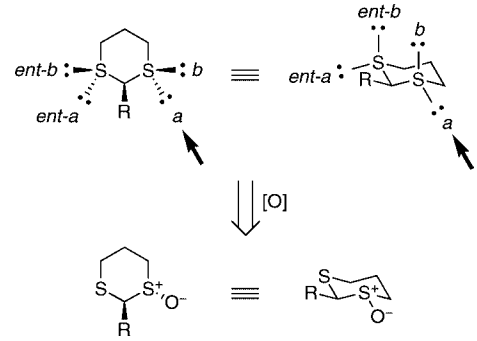
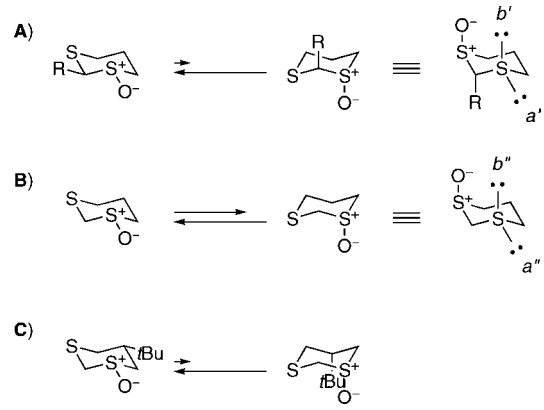


Figure 3. Reaction sites in 1,3-dithianes: four lone pairs.

Scheme 5. Conformational Issue of 2-Substituted 1,3-Dithiane 1-Oxide (A), 1,3-Dithiane 1-Oxide (B), and 5-*tert*-Butyl-1,3-dithiane 1-Oxide (C)

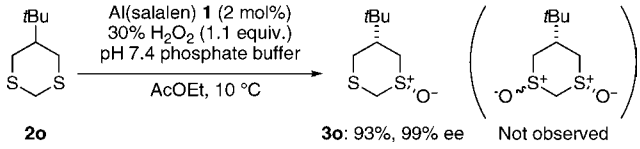


trans-1,3-dioxide in the oxidation of 1,3-dithiane are clearly explained by the respective conformational equilibriums of 1,3-dithianes and the monoxides. It is known that 1,3-dithianes take a chairlike conformation in which substituents prefer to occupy equatorial positions similar to cyclohexane chemistry.[30] In the oxidation of 2-substituted 1,3-dithianes, lone pair *a*′ of the product monoxide which is hypothetically identical to lone pair *a* can also participate in the oxidation (Scheme 5A). However, the chair conformer in which two substituents (R and O^-) occupy axial positions is disfavored. As the result, the second oxidation is significantly retarded. On the other hand, the oxygen atom of 1,3-dithiane 1-oxide also tends to occupy the equatorial

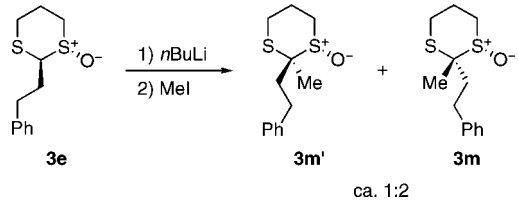
(29) (a) Rinaldi, R.; Fujiwara, F. Y.; Hölderich, W.; Schuchardt, U. *J. Catal.* **2006**, *244*, 92–101. (b) van Vliet, M. C. A.; Mandelli, D.; Arends, I. W. C. E.; Schuchardt, U.; Sheldon, R. A. *Green Chem.* **2001**, *3*, 243–246. (c) Rebek, J.; McCready, *Tetrahedron Lett.* **1979**, *45*, 4337–4338.

(30) Freeman, F.; Le, K. T. *J. Phys. Chem. A* **2003**, *107*, 2908–2918.

Scheme 6. Asymmetric Oxidation of 5-*tert*-Butyl-1,3-dithiane **2o**



Scheme 7. Conversion of (1*S*,2*S*)-2-(2-Phenylethyl)-1,3-dithiane 1-Oxide **3e** to 2-Methyl-2-(2-phenylethyl)-1,3-dithiane 1-Oxide



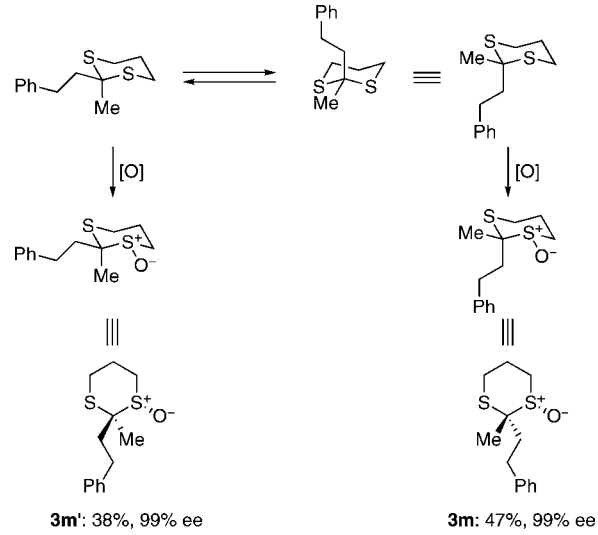
position, but the energy difference between the equatorial and axial conformers is rather small. The axial conformer is reported to be only 7.1 kJ mol^{-1} higher in energy by theoretical calculations, and the experimental value of 2.7 kJ mol^{-1} was also reported.[31] These studies indicate easy ring flipping of 1,3-dithiane 1-oxide at the reaction temperature. Thus, the lone pair *a″* of the S^+-O^- axial conformation (Scheme 5B), which is identical in a spatial arrangement to lone pair *a*, participates in the second oxidation to give the *trans*-1,3-dioxide with high diastereo- and enantioselectivity (Schemes 3 and 4).

In order to confirm this assumption, we examined the oxidation of 5-*tert*-butyl-1,3-dithiane **2o**, where a bulky *tert*-butyl group occupies the equatorial position exclusively and locks the conformation (Scheme 5C). As we expected, no formation of the dioxides was observed and the monoxide **3o** was obtained in 93% yield with 99% ee (Scheme 6). It was confirmed that conformational rigidity of 2-substituted 1,3-dithiane 1-oxides is associated with the suppression of the overoxidation.

This conformational analysis also elucidates the very low diastereoselectivity observed in the oxidation of 2-methyl-2-(2-phenylethyl)-1,3-dithiane **2m** (Table 1, entry 15). Treatment of *trans*-(1*S*,2*S*)-2-phenylethyl-1,3-dithiane 1-oxide **3e**, which was obtained in the asymmetric oxidation of 2-phenylethyl-1,3-dithiane **2e**, with *n*-butyllithium and then methyl iodide gave a ca. 1:2 diastereomeric mixture of 2-methyl-2-phenylethyl-1,3-dithiane 1-oxide, in which the *S*-stereogenic center is retained during the process (Scheme 7).[32]

It is of note that the absolute configurations of both of the diastereomers obtained with this procedure were identical with those of the diastereomers obtained in the asymmetric oxidation of 2-methyl-2-(2-phenylethyl)-1,3-dithiane **2m**. Thus, a plausible reaction pathway based on the accord of the absolute configuration can be proposed as illustrated in Scheme 8. The small difference in the steric requirements of the methyl and phenylethyl groups allows both of the chairlike conformers to participate in the oxidation. As the result, the low diastereoselectivity was observed. Since, however, the Al(salalen) complex discriminates only an enantiotopic equatorial lone pair in each of the conformers as shown in Figure 3, the monoxides with the same *S*-stereogenic center were obtained in high enantiomeric excesses.

Scheme 8. Reaction Pathway in the Oxidation of 2-Methyl-2-(2-phenylethyl)-1,3-dithiane



The conformational study of 1,3-dithianes explains the induction of diastereoselectivity in the first oxidation process. Nevertheless, there is room for discussion on the observed *excellent* diastereoselectivity. Considering the small *A* value of the phenylethynyl group that indicates a small energy difference between the two chairlike conformers,[33] the diastereomer ratio of 19:1 observed in the oxidation of 2-phenylethynyl-1,3-dithiane is higher than expected. Moreover, it has been reported that the axial conformer of 2-phenylethynyl-1,3-dithiane is preferred over the equatorial one.[34] If based on the above conformational discussion, the *cis*-oxide should be obtained preferentially from the axial conformer. In fact, however, the *trans*-oxide was obtained with high diastereo- and enantioselectivity (Table 1, entry 4). In order to explain this result, we consider that the Curtin−Hammett principle is applicable to this system, where the equatorial and axial conformers are rapidly interconvertible and the axial one reacts much slower than the equatorial one (Scheme 9).[35] Bulkier axial substituents might retard the reaction progress by a steric repulsion with catalyst. Synergistic combination of high stereorecognition ability of the aluminum catalyst and conformational flexibility of 2-substituted 1,3-dithianes explains the induction of the *excellent* diastereoselectivity.

IV. Al(salalen)-Catalyzed Asymmetric Oxidation of Other Dithioacetals. The Al(salalen) complex **1**/H_2O_2 system has a broad spectrum for cyclic dithioacetals. Five-membered 1,3-dithiolanes underwent the oxidation with high enantioselectivity (Scheme 10). The reactions of dithiolanes **5** with 2-phenyl and 2-*tert*-butyl groups smoothly proceeded to give the *trans*-monoxides **6** and small amounts of the *trans*-1,3-dioxides **7** with high enantiomeric excesses. Although conformational study of

(31) (a) Von Acker, L.; Anteunis, M. *Tetrahedron Lett.* **1974**, *15*, 225–228. (b) Khan, S. A.; Lambert, J. B.; Hernandez, O.; Carey, F. A. *J. Am. Chem. Soc.* **1975**, *97*, 1468–1473. (c) Juaristi, E.; Guzmán, J.; Kane, V. V.; Glass, R. S. *Tetrahedron* **1984**, *40*, 1477–1485. (d) Roux, M. V.; Temprado, M.; Jiménez, P.; Dávalos, J. Z.; Notario, R.; Martín-Valcárcel, G.; Garrido, L.; Guzmán-Mejía, R.; Juaristi, E. *J. Org. Chem.* **2004**, *69*, 5454–5459. (e) Juaristi, E.; Notario, R.; Roux, M. V. *Chem. Soc. Rev.* **2005**, *34*, 347–354.

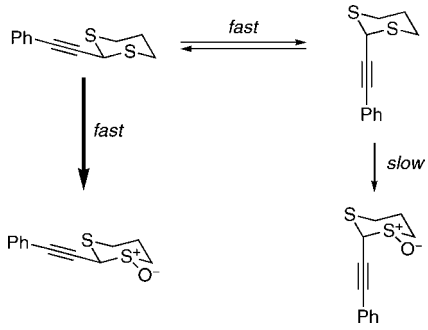
(32) Carey, F. A.; Dailey, O. D., Jr.; Hernandez, O. *J. Org. Chem.* **1976**, *41*, 3979–3983.

(33) *A* values represent free energy differences between equatorial and axial substituents on a cyclohexane ring: $\Delta G°$/kJ mol^{-1} 1.7 (C≡CH), 7.1 (CH=CH_2), 11 (Ph), and 21 (*t*Bu).

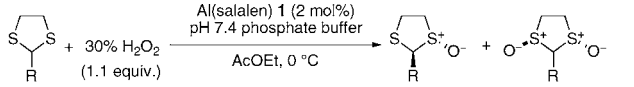
(34) Arai, K; Iwamura, H.; Ōki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3319–3323.

(35) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

Scheme 9. Stereochemical Course with 2-Phenylethynyl-1,3-dithianes



Scheme 10. Asymmetric Oxidation of 1,3-Dithiolanes **5**



5a (R = Ph)
5b (R = *t*Bu)

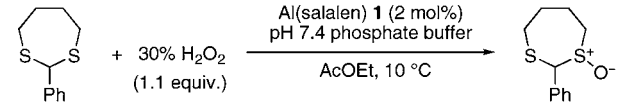
6a: 74%, 99% ee **7a**: 23%, >99% ee
6b: 83%, >99% ee **7b**: 14%, >99% ee

1,3-dithiolane 1-oxides has been unexplored, the ring conformation of the 1,3-dithiolane 1-oxides is more flexible than that of 1,3-dithiane 1-oxides.[36] The dioxide formation observed in the oxidation of 1,3-dithiolanes is considered to be due to the conformational flexibility. A seven-membered substrate, 2-phenyl-1,3-dithiepane **8**, was also a good substrate for the aluminum-catalyzed oxidation, and the monoxide **9** was obtained in 96% yield with >99% ee (Scheme 11).

Unfortunately, however, the reaction of acyclic dithioacetals was sluggish and poorly enantioselective (Scheme 12). We assumed that conformational flexibility led to the low enantioselectivity and chelate formation with products delayed the reaction progress.

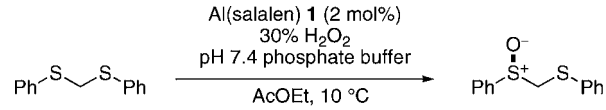
(36) Sternson, L. A.; Coviello, D. A.; Egan, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 6529–6532.

Scheme 11. Asymmetric Oxidation of 2-Phenyl-1,3-dithiepane **8**



8 **9**: 96%, >99% ee

Scheme 12. Oxidation of an Acyclic Dithioacetal **10**



10 **11**: 8%, 64% ee

Conclusion

We achieved highly diastereo- and enantioselective oxidation of cyclic dithioacetals with Al(salalen) complex **1** as catalyst and aqueous hydrogen peroxide as an oxidant. In this study, we found that a conformational issue of the substrates and produced monoxides as well as the stereorecognition ability of the aluminum catalyst is closely connected with the control of the stereoselectivity.

Acknowledgment. We are grateful to a Grant-in-Aid for Scientific Research (Specially Promoted Research 18002011) and the Global COE Program, "Science for Future Molecular Systems" from MEXT, Japan for generous financial support.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA106877X