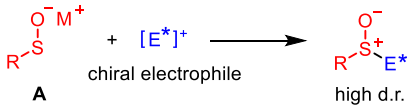
論文 / 著書情報
Article / Book Information

題目(和文)	
Title(English)	Stereoselective Transformation of Prochiral Sulfenates to Chiral Sulfoxides: Mechanism and Application
著者(和文)	ZHANGJIAN
Author(English)	Jian Zhang
出典(和文)	学位:博士(理学), 学位授与機関:東京工業大学, 報告番号:甲第12613号, 授与年月日:2023年12月31日, 学位の種別:課程博士, 審査員:大森 建,豊田 真司,後藤 敬,工藤 史貴,鷹谷 絢
Citation(English)	Degree:Doctor (Science), Conferring organization: Tokyo Institute of Technology, Report number:甲第12613号, Conferred date:2023/12/31, Degree Type:Course doctor, Examiner:,,,,
学位種別(和文)	博士論文
Category(English)	Doctoral Thesis
種別(和文)	要約
Type(English)	Outline

Thesis Outline

1. Research background.

Among the many organosulfur compounds, chiral sulfoxides are widely used as a ligand and organocatalyst for asymmetric reactions. In addition, chiral sulfinyl groups are also embedded in the structure of natural products and marketed drugs, such as sparoxomycins and esomeprazole. In this context, developing an efficient synthetic method enabling access to chiral sulfoxides is highly demanded. Among the various synthetic approaches, enantio- or diastereoselective alkylation of prochiral sulfenates is a potentially useful method for constructing chiral sulfinyl functions in a complex molecular architecture. In this thesis, the achiral sulfenates **A** were utilized in reactions with various chiral electrophiles to afford diastereomeric chiral sulfoxides with high efficiency and excellent stereoselectivities (Scheme 1).



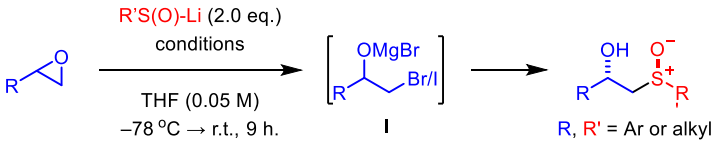
Scheme 1. This work.

2. Diastereoselective alkylation of prochiral sulfenates: efficient access to β-hydroxy sulfoxides from chiral epoxides.

First, a highly efficient method for synthesizing β-hydroxy sulfoxide was studied by using chiral epoxides and prochiral sulfenate as substrates (Scheme 2). Optimizations of reaction conditions reveled that the reaction efficiently proceeds in the presence of $MgBr_2 \cdot OEt_2$, allowing the tentative formation of a halohydrin intermediate **I** followed by the nucleophilic attack of the sulfenate species, giving β-hydroxy sulfoxides in an excellent yield with a high diastereoselectivity (Table 1). Moreover, addition of catalytic amount of LiI could improve the diastereoselectivity (entry 4). Various chiral sulfoxides were obtained with high yields and excellent stereoselectivities (up to 97% yield and >20:1 d.r.).

DFT calculations suggested that the coordination of the lithium ion and the oxygen atom on the halohydrin magnesium alkoxide constrains their conformation in the transition states for TS*anti* and TS*syn*. In the TS*syn* toward the *syn*-product generates a considerable tortional strain, while TS*anti* toward the *anti*-product have no severe tortional strain. The free energy defference between TS*anti* and TS*syn* is ca. –1.4

kcal/mol, corresponds to a 7.8/1 d.r. value which are the same as the observation in the experiments.

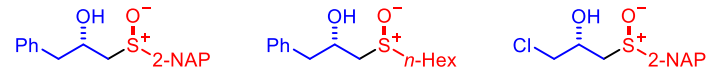


Scheme 2. Reaction with epoxides.

Table 1. conditions optimization, R = Bn, R' = Ph

entry	conditions	yield/%	*anti* : *syn*
1	none $MgBr_2{\cdot}OEt_2$ and LiI	30	1 : 1.2
2	$MgBr_2{\cdot}OEt_2$ (2.0), none LiI	80	7.8 : 1
3	$MgI_2{\cdot}OEt_2$ (2.0), none LiI	80	6.0 : 1
4	$MgBr_2{\cdot}OEt_2$ (2.0), LiI (0.2)	86	9.0 : 1

selected examples



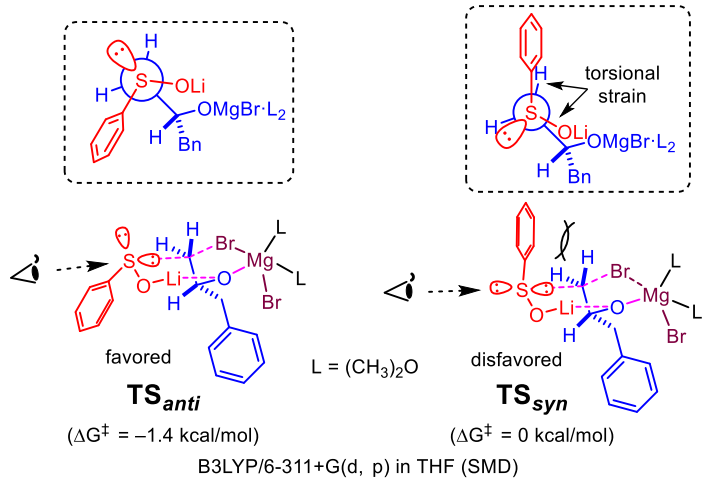
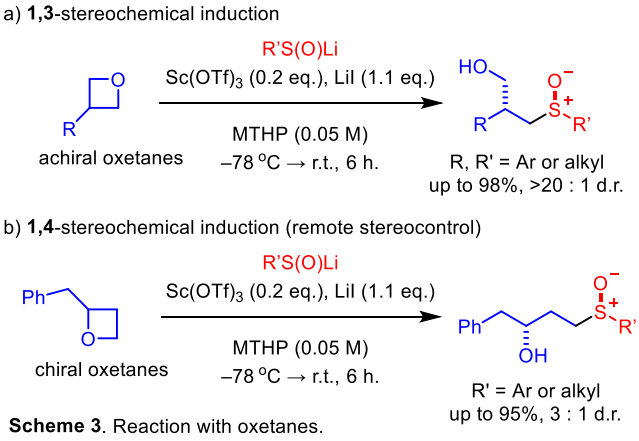


Figure 1. Computational analyses.

3. Diastereoselective alkylation of prochiral sulfenates: efficient access to γ-hydroxy sulfoxides from prochiral or chiral oxetanes.

Next, a reaction of sulfenates and oxetane derivatives was attempted. Unfortunately, the use of the optimized condition described above for the reaction with epoxide ($MgBr_2$, LiI, THF) was not applicable to this reaction. No reaction was observed. After seeking suitable Lewis acid, $Sc(OTf)_3$ gave a good result. Thus, a catalytic amount of $Sc(OTf)_3$ in the presence of stoichiometric LiI undergoes diastereoselective ring-opening of oxetanes, allowing the nucleophilic attack of the sulfenate species to give γ-hydroxy sulfoxides in high yield with excellent diastereoselectivity. Furthermore, these

reaction conditions were also applicable not only for 1,3-stereochemical induction but also 1,4-stereochemical induction (remote stereocontrol). Both of aryl and alkyl-substituted chiral oxetanes could be applied to this transformation. Various γ-hydroxy sulfoxides were obtained with high yields and excellent stereoselectivities (up to 98% yield and >20:1 d.r.) (Scheme 3).



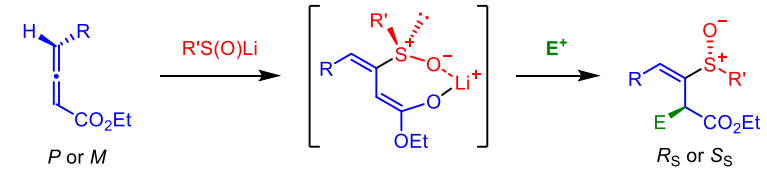
Scheme 3. Reaction with oxetanes.

4. Chiral sulfoxide compounds by axial-to-central chirality transfer.

Next, the stereochemical transformation from axial chirality in allenes to stereogenicity on a sulfur atom was studied. Various alkyl- and vinyl-substituted optically-active sulfoxides were obtained in high yield with excellent enantioselectivities (up to 93% yield, >99 ee.) (Scheme 4). Proposed reaction models were given out to explain the observed stereospecificity. Several key points should be noted. First, the chelation between Li atom and the oxygen atom on the alkoxy carbonyl group is essential. Next, to avoid steric hindrance, sulfenates approach from the opposite side of R-group in allenes as in **I** and **II** instead of **III** and **IV**, and the minimizing steric repulsion between R' group of sulfenates and the vinylic hydrogen atom in allenes preferred **I** rather than **II**.

Furthermore, diastereoselective introduction of one more substituent into the α position of the carbonyl function in the addition product was also succeeded. By using the disubstituted allenes as starting materials, sulfenate addition followed by effecting an electrophile, e.g., MeI gave the double substituted product (E = CH_3) in high yield with excellent diastereoselectivity. Various multi-substituted sulfoxides could be obtained. On the other hand, by utilizing the trisubstituted allenes as starting materials, sulfenates as nucleophilic species and MeOH as proton source, various corresponding sulfoxides possessing the additional carbon chiral center with opposite configuration could be

obtained in good yield with diastereoselectivity.

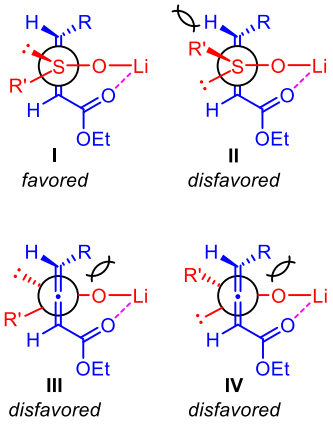


E = H, stereospecific reaction

R = Me	R' =	*c*-Hex	91%, 95% ee
^{t}Bu		*n*-dodecyl	91%, >99% ee
Ph		*c*-Hex	91%, >99% ee
Ph		*n*-dodecyl	90%, >99% ee

E = MeI, 3-component assembly

R = Me	R' =	*n*-octadecyl	81%, >20 : 1 d.r.
^{i}Pr		*n*-dodecyl	81%, 11 : 1 d.r.
^{i}Pr		*n*-octadecyl	81%, >20 : 1 d.r.
^{t}Bu		*n*-octadecyl	82%, >20 : 1 d.r.

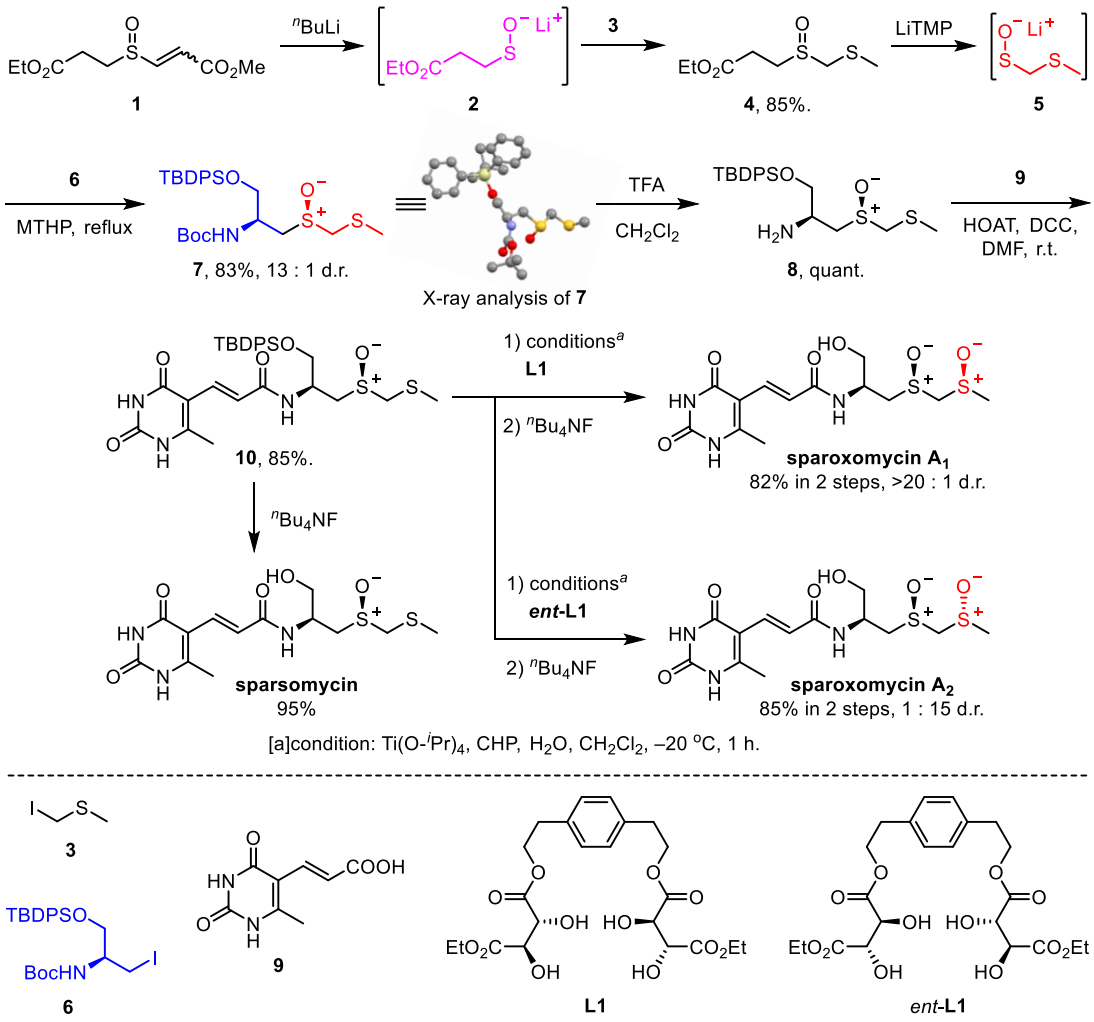


Scheme 4. Reaction with allenes.

5. Asymmetric total synthesis of sparsomycin, sparoxomycin A_1 and sparoxomycin A_2.

Asymmetric total synthesis of sparsomycin and the first asymmetric total synthesis of sparoxomycin A_1 and sparoxomycin A_2 were successfully achieved. α,β-Unsaturated sulfinyl ester **1** was treated with ^{n}BuLi to generate sulfenates **2** in-situ, which could further be reacted with iodomethyl methyl sulfide **3** to afford sulfinyl ester **4** in 85% yield. The sulfenate **5** was generated in-situ by treating **4** with LiTMP. After that, the reaction of **5** with **6** underwent diastereoselective alkylation to afford β-amino sulfoxides **7** in 83% yield with 13:1 d.r. The X-ray diffraction analysis confirmed the relative stereochemistry of **7** to be *anti*. Detachment of the Boc group followed by the condensation with 6-methyluracil-drived carboxylic acid **9** gave the key intermediate **10**. Removal of TBDPS group by using ^{n}Bu$_4$NF successfully afforded sparsomycin in 95% yield. On the other hand, the diastereoselective oxidation of **10** was successful based on the reagent-control manner. Final detachment of TBDPS group successfully gave sparoxomycins A_1 and A_2, respectively. In summary, the convergent synthetic route includes the longest linear step count (8 steps) and the total step count (15 steps) with 11.7% overall yield for sparsomycin and the longest linear step count (9 steps) and the total step count (16 steps) with 10.1% for sparoxomycin A_1 and 10.5% overall yield for sparoxomycin A_2 from the normal commercially available starting materials

(Scheme 5). This new convergent approach will improve the synthetic efficiency of obtaining the natural product sparsomycin, sparoxomycin A_1 and sparoxomycin A_2, which will provide a strong base for the future bioactive test of these natural products.



Scheme 5. Total synthesis of sparsomycin, sparoxomycins A_1 and A_2.

In conclusion, we have successfully developed a series of stereoselective conversions between sulfenate anions and diverse chiral electrophiles, resulting in the efficient synthesis of various chiral sulfoxides. These innovative conversions have opened new synthetic pathways to access chiral sulfoxides. Our laboratory remains committed to further research on the potential conversions and applications in this domain.