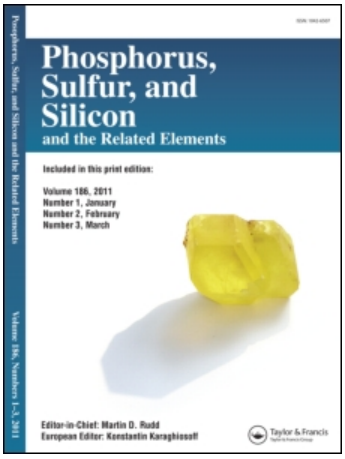

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Asymmetric Synthesis of a Xanthine Dehydrogenase Inhibitor (*S*)-(–)-BOF-4272 : Mechanism of Chiral Diaryl Sulfoxide Formation

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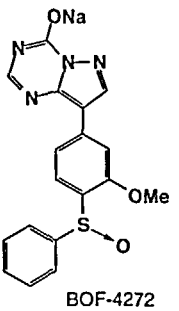
A pyrazolotriazine derivative (BOF-4272), a potent xanthine dehydrogenase inhibitor, was synthesized in good yield *via* 9 steps from vanillin. The asymmetric synthesis was achieved effectively by a modified Oae's asymmetric oxidation of diaryl sulfide. A mechanism involving pentacoordinated sulfurane intermediates was supported by the molecular modeling.

KEY WORDS ; BOF-4272, XANTHINE DEHYDROGENASE INHIBITOR, ASYMMETRIC SYNTHESIS, MECHANISM

INTRODUCTION

BOF-4272 is a pyrazolotriazine derivative which shows a potent inhibition of the biosynthesis of uric acid (UA) by interfering with the xanthine oxidase (XO) and xanthine dehydrogenase (XDH) systems.[1] These enzymes catalyze the last two steps of purine catabolism. The XO/XDH inhibitor is expected to be an effective remedy for hyperuricemia and gout. However, no clinically effective XO/XDH inhibitor was available except allopurinol which was introduced for clinical use in 1967.[2]

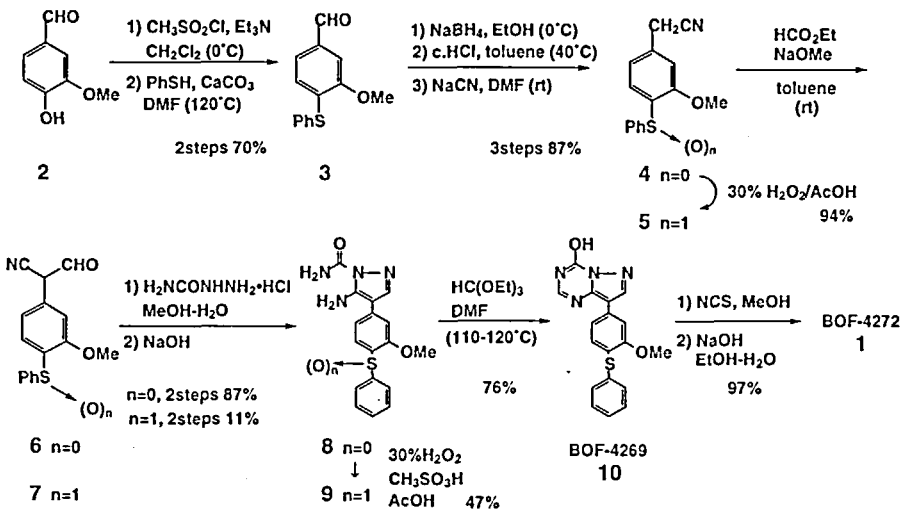


BOF-4272
1

The racemic mixture of BOF-4272 was first synthesized at Otsuka's laboratories, by late Professor S. Fujii and his colleagues in 1987.[3] In 1991, impressive biological activities such as reduction of serum UA levels were observed in human volunteers.[4] An effective asymmetric synthesis must be found in order to carry out pharmacokinetic and toxicological studies since it was soon found, employing extraordinary expensive optical isomers[5], that the (–)-isomer was 100 fold more active than was the (+)-isomer *in vitro*.[6] Results of these efforts are the subject of this article.

SYNTHESIS OF BOF-4272

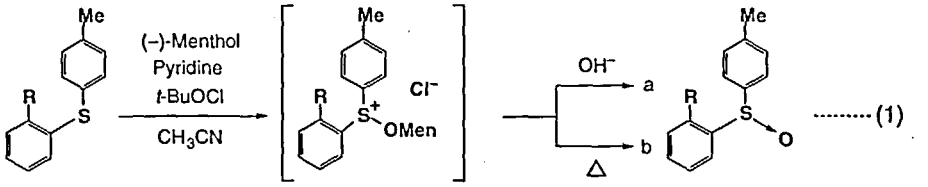
The known synthesis[2,3] of BOF-4272 **1** involves 2-(3-methoxy-4-phenylsulfenylphenyl) acetonitrile **4** which requires 8 step synthesis from 4-chloro-3-nitrobenzoic acid. Our new approach to obtain compound **4** is shown in Scheme 1. Employing vanillin **2** as a starting material, a straightforward nucleophilic displacement of its activated hydroxyl group with thiophenol has become possible with $CaCO_3$ as the base. Sodium or potassium bases, *e.g.*, Na_2CO_3, NaH or K_2CO_3, were ineffective. Thus 3-methoxy-4-phenylsulfenylbenzaldehyde **3** was obtained in good yield by treating of the mesylate with thiophenol and $CaCO_3$ in *N,N*-dimethylformamide (DMF). The triflate, tosylate or p-nitrobenzenesulfonate of **2** gave low chemical yields along with recovery of vanillin **2**. The reduction of **3** with $NaBH_4$ in ethanol followed by chlorination with c.HCl in toluene at 40°C produced the corresponding benzyl chloride which was then treated with NaCN in DMF to give **4** in 60% yield from **2**. Following the literature procedures[7], pyrazolotriazine skeleton then was constructed. The oxidation of the sulfide BOF-4269 **10** with *N*-chlorosuccinimide in methanol afforded BOF-4272 **1** in high yield (Scheme 1).



SCHEME 1. Synthetic route of BOF-4272

SYNTHETIC STRATEGY OF OPTICALLY ACTIVE BOF-4272

It must be pointed out that in the above reaction sequence neither the final product **1** nor any synthetic intermediate was suitable for optical resolution. In addition, transformation of **5** to give **9** or oxidation of sulfide **8** to the corresponding sulfoxide **9** gave very poor yields. Therefore, we have chosen a synthetic route involving an asymmetric oxidation of BOF-4269 **10**.



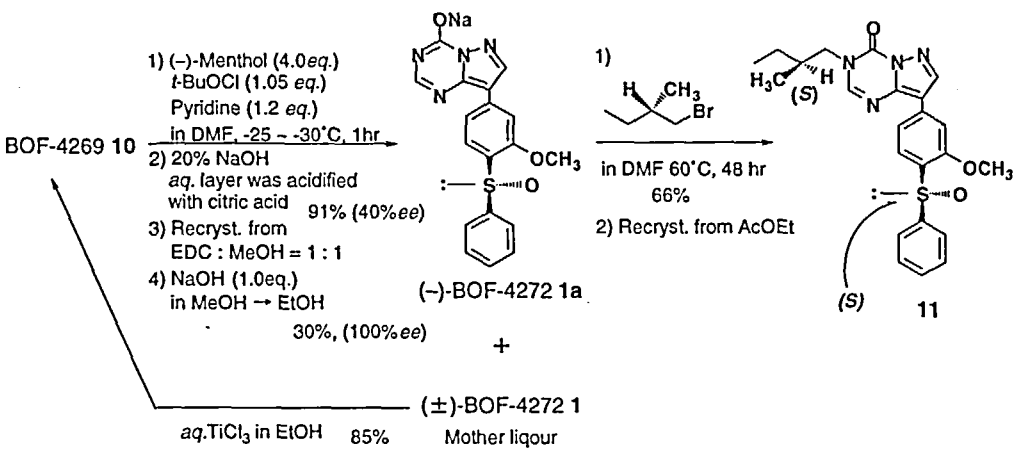
	R = OMe	R = Me
a: (*S*)-(–)	22%*ee*	26%*ee*
b: (*R*)-(+)	14%*ee*	15%*ee*

In recent years, a variety of synthetic methods to obtain optically active sulfoxides have been reported.[8] However, none of these methods were effective for the preparation of the chiral diaryl sulfoxides such as **1**. The scope of the successful asymmetric oxidation seems to be limited to rigid (e.g. cyclic) sulfides or sulfides bearing two substituents of very different size (e.g. aryl methyl sulfides). A substitution reaction[9] of enantiomerically pure sulfinate analogues represented by Andersen's synthesis appear to be promising for the achievement of high stereocontrol. The application for BOF-4272, however, was not successful apparently due to the heterocyclic ring involved in the molecule. In 1976, a convenient method for asymmetric oxidation of diaryl sulfides using (–)-menthol, pyridine and *t*-butylhypochlorite was reported by Oae's group (eq.1).[10]

An interesting observation was that the opposite enantiomers could be produced depending on the work-up treatment of the intermediate sulfonium salt. This suggests a possibility for asymmetric production of a sulfoxide in its desired configuration. In addition, in 1972, Johnson et al. reported[11] a preparation of benzyl menthoxy phenyl sulfonium tetrafluoroborate. Recrystallization of the sulfonium salt increased the optical purity and subsequent hydrolysis with *aq.* sodium hydroxide produced benzyl p-tolyl sulfoxide in 87%*ee*. However, the report did not mention the chemical yield. If the diastereomeric alkoxysulfonium salts could be separated as stable salts, the optically pure BOF-4272 enantiomer should be obtainable.[12]

SYNTHESIS OF (*S*)-(–)-BOF-4272

The oxidation of BOF-4269 under a modified Oae's condition (acetonitrile was replaced with DMF) took place at the sulfur atom chemoselectively in good chemical yield (91%), but with only 40%*ee* (Scheme 2). Interestingly, this enantiomerically enriched (–)-isomer showed poor solubility in organic solvents compared to the racemate. Thus subsequent recrystallization gave the optically pure (–)-isomer **1a** with an overall yield of 30% (Scheme 2). The optically active sodium salt is very soluble in water (over 50% *w/v*), whereas the racemic salt is poorly soluble in water (0.29% *w/v*). These results suggest BOF-4272 **1** to be a conglomerate. Use of (+)-menthol in the above oxidation gave (+)-isomer with similar enantioselectivity. Sulfide **10** was recovered in reusable form by the reduction of racemic sulfoxide **1** with *aq.*$TiCl_3$ in ethanol in 85% yield. Although each reaction is a reliable synthetic method, the efficiency is too low for the reaction to be of practical use. Further investigation was mandatory for our needs.



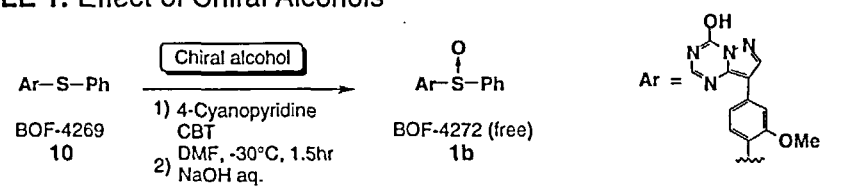
SCHEME 2. Asymmetric Synthesis of BOF-4272

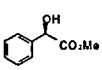
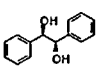
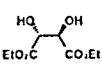
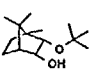
As shown in Scheme 2, (–)-**1a** was alkylated chemoselectively only at the N-3 position. The absolute configuration of (–)-**1a** was determined by a single crystal X-ray analysis using an N-alkyl derivative **11** bearing a chiral auxiliary (*S*)-(+)-2-methylbutyl moiety. The absolute configuration of (–)-**1a** was confirmed to be (*S*).

ASYMMETRIC OXIDATION BY A MODIFIED OAE'S METHOD

The variation of halo-cation oxidants such as 1-chlorobenzotriazole, trichloroisocyanuric acid and *t*-butylhypochlorite gave similar degree of enantioselectivity and chemical yields, 43%*ee* (87%), 39%*ee* (83%) and 38%*ee* (87%) respectively. However, 1-bromobenzotriazole or *N*-chlorosuccinimide gave the undesired sulfone or chlorinated aromatic ring product respectively. Therefore, 1-chlorobenzotriazole was chosen in view of the chemical yield, safety and convenience in handling compared to *t*-butylhypochlorite originally used. The solvent properties in the presence of 4-cyanopyridine affected the enantioselectivities. For example, DMF gave 63%*ee* (93% chemical yield), CH_2Cl_2 60%*ee* (84%), CH_3CN 44%*ee* (87%) and THF 0%*ee* (95%). As for the solvents, DMF was found to be the most adequate in terms of the optical and chemical yields.

TABLE 1. Effect of Chiral Alcohols



Chiral alcohol	ee (%)	Yield (%)	Configuration of 1b	Chiral alcohol	ee (%)	Yield (%)	Configuration of 1b
	0	95	–		20	50*	*R*
	11	87	*S*		22	80	*R*
	20	39	*S*		43	54*	*S*
	5	96	*S*		73	78*	*S*
	20	68	*S*		18	78	*S*
	11	39*	*S*		15	89	*S*
	12	63*	*S*		48	38*	*S*
	63	93	*S*		6	27*	*S*

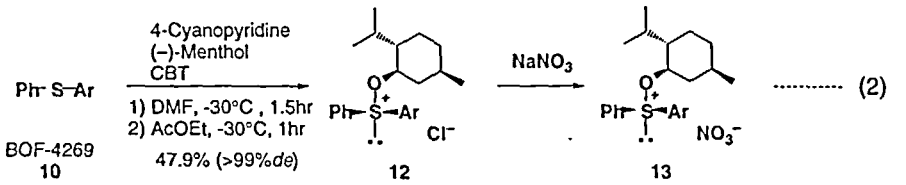
*) Chlorination on Ar ring took place as a side reaction.

Oae's oxidation recipe involves pyridine. We found an intricate dependence of the enantiomeric excess on the p*K*a value of pyridine bases. The enantiomeric excess appears to increase with decreasing basicity of pyridines. For example, 4-methylpyridine (p*K*a 6.03) gave 22%*ee*, pyridine (p*K*a 5.23) 40%*ee*, 4-chloropyridine (p*K*a 3.83) 43%*ee*, methylisonicotinate (p*K*a 3.26) 52%*ee*, 3-cyanopyridine (p*K*a 1.50) 58%*ee* and 4-cyanopyridine (p*K*a 1.90) 63%*ee*. Linear correlation was observed between the enantiomeric excess and p*K*a value for a group of pyridine bases.[13] However, this correlation does not hold for some pyridine bases. For example, 3-chloropyridine (p*K*a 2.81) and 4-acetylpyridine (p*K*a 3.57) gave 36%*ee* and 34%*ee* respectively. In case of 4-cyanopyridine, we were able to obtain the best result, a value of 63%*ee*.

We also studied the variation of chiral alcohols. Chiral 2-substituted cyclohexanol was found to be more effective. The enantiomeric excess of 73% was obtained with (1*R*,2*S*)-(–)-2-phenylcyclohexanol (Table 1), a high value for the asymmetric oxidation of a diaryl sulfide. On the other hand, we found poor enantioselectivity in the case of diols, acyclic secondary and primary alcohols.

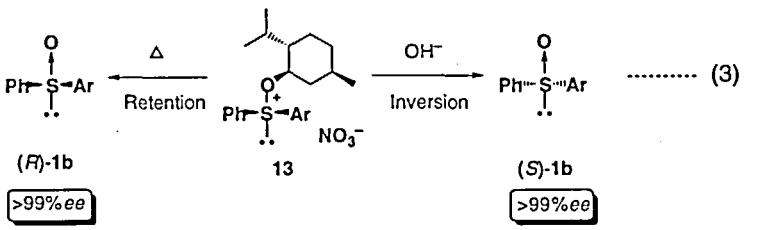
UTILITY OF MENTHOXY SULFONIUM SALTS

We were able to isolate the intermediate menthoxy sulfonium chloride **12** (>99%*de*) by choosing an appropriate solvent system (eq.2). Thus the reaction sequence involving a sulfonium salt postulated by Oae *et al.* was verified. We were able to transform the sulfonium chloride **12** into a more moisture-stable nitrate **13** by replacing the chloride anion with sodium nitrate (eq.2).



(2)

The most interesting property of the isolated salt **13** is the ability which allows its stereospecific transformation into the enantiomerically pure sulfoxides. Thus the (*S*)-(–)-isomer of **1b** was isolated in >99%*ee* by alkaline hydrolysis whereas (*R*)-(+)-isomer of **1b** was obtained with >99%*ee* by thermolysis (eq.3).

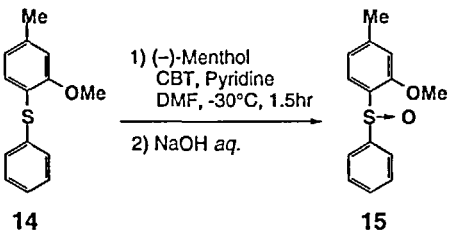


..... (3)

Furthermore, the absolute configuration of the sulfonium salt **12** and **13** obtained could be determined by its stereospecific transformation into enantiomerically pure sulfoxides. The alkaline hydrolysis of the chiral sulfonium salt is known to proceed through S_N2 type reaction.[10] In accordance with this mechanism, we recovered (–)-menthol. In contrast, the thermal reaction gave menthene. Since the absolute configuration (–)-BOF-4272 has been established to be (*S*), the stereochemistry of these transformations can be depicted (eq.3). An effective synthesis of (*S*)-(–)-BOF-4272 **1a** was achieved by the new methodology,[13] "conversion of both diastereomeric intermediates into one enantiomerically pure product, a sulfoxide enantiomer". Recently, the usage of these optically pure enantiomers for pharmacological studies has been reported[14]. The inactive (+)-isomer was also used as a valuable control reagent for study of the role of XO/XDH in pathogenesis.

MECHANISM OF CHIRAL DIARYL SULFOXIDE FORMATION

The mechanism of chiral diaryl sulfoxide formation was studied using simple model compounds (eq.4). Our proposed mechanism of asymmetric oxidation was summarized in Scheme 3. The reaction of diaryl sulfide **14** with 1-chlorobenzotriazole (CBT) presumably leads to the sulfurane derivative **16**.[11] It is well known that the pentacoordinated sulfurane is stabilized by electro-negative groups at the apical positions forming a pseudo C_{2v} geometry.[15] If the reaction system contains an organic base such as pyridine, the chloride ion of **16** will be replaced with the more electron-donating base like pyridine leading to sulfurane **17**.



..... (4)

14 15

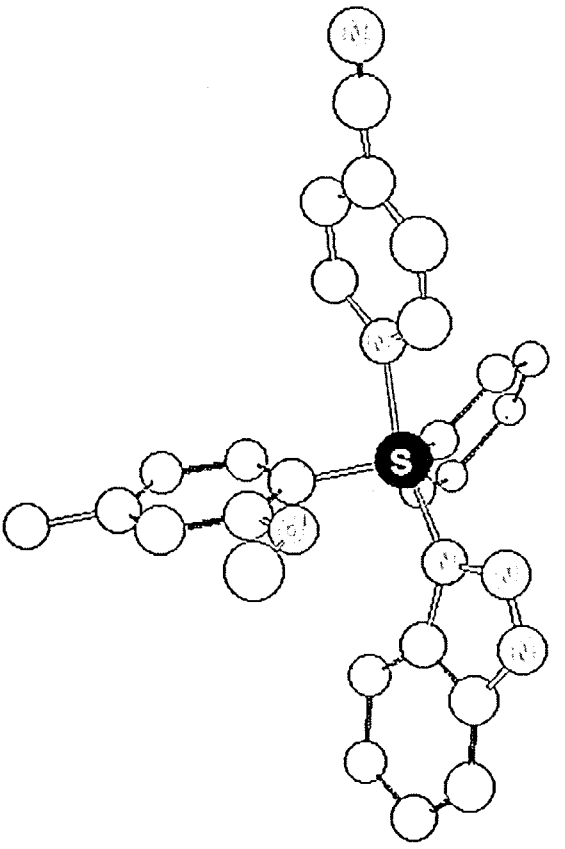
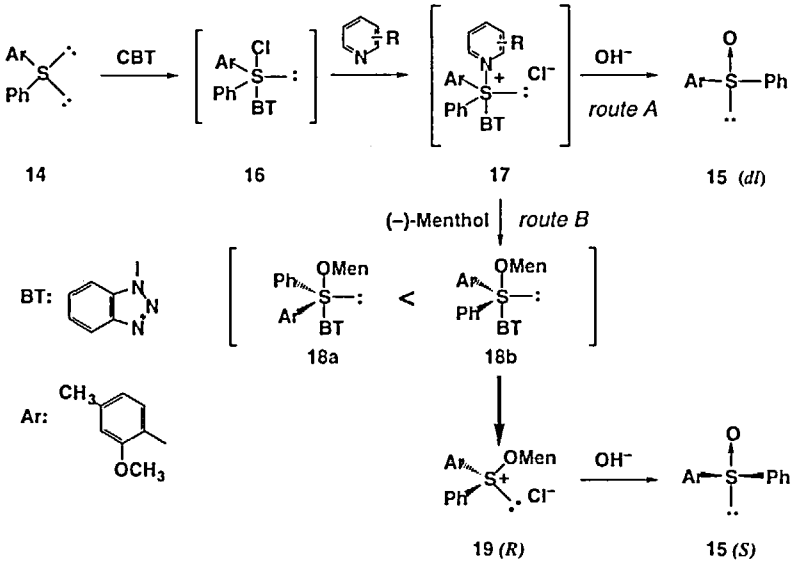


FIGURE 1. Computer-generated structure of **17**



SCHEME 3. Mechanism of Chiral diaryl sulfoxide formation

The structure of the pentacoordinated sulfurane **17** was studied with MO calculation[16] to obtain the optimized configuration (Fig. 1). It is apparent that the four bulky substitutents present a very crowded environment around the central sulfur atom. Therefore, the approach of the chiral auxiliary (–)-menthol to the sulfur atom would be prevented. Facile dissociation of the weak base like 4-cyanopyridine invites the formation of a menthoxy intermediate **18** (route B). In contrast, the strong base like 4-methylpyridine at the apical position would resist the substitution by a nucleophile like the menthoxy moiety. Then the substitution of the racemate **17** would occur with a stronger base like hydroxy ion resulting in a racemic mixture **15** (*dl*) (route A).

This view was confirmed by MO calculations. Briefly, results are as follows: the higher the LUMO levels of **17** the smaller the *ee* values of the sulfoxide **15** (*S*) produced (Fig. 2). This is because the nucleophilic attack of the bulky menthoxy moiety would be unfavorable. In contrast, facile substitution of the labile ligand (*e.g.* 4-cyanopyridine characterized with a low LUMO's) with menthoxy anion will lead to the formation of (–)-menthoxy sulfurane **18a** or **18b**. The menthoxy sulfurane **18** will be transformed into a menthoxy sulfonium ion **19**. The stereochemistry of this step should be governed by the sterical environment of the chiral structure of **18a** or **18b**.

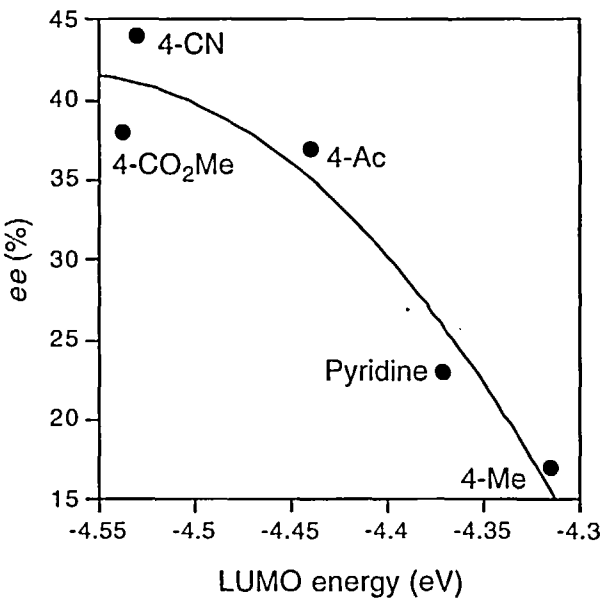


FIGURE 2. Relationship of LUMO energies of sulfurane **17** and *ee* values of Sulfoxide **15** (*S*). (n=5, r^2=0.934)

The structure of **18** bearing benzotriazole anion at the apical position was inferred by the MO calculation [16]; note the apical ligation is switched from a pyridine base to the menthoxy anion of a higher basicity. Comparison of **18a** (*S*-configuration) and **18b** (*R*-configuration) with their heat of formation obtained by the MO calculation[16] indicated the stable conformation of **18b** preferable to **18a** (ΔH = 1.98 kcal/mol) in agreement with the experimental observation. Thus, the reaction of the chiral intermediate **19** with OH^- gave the optically active diaryl sulfoxide **15** (*S*).

The above explanation based on the electronic effect holds for a certain group of pyridine bases. It must be added the necessity of their steric factor.

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