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# Enantiopure sulfoximines-catalyzed 1, 4-additions to 2-en-ketone

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ABSTRACT

An efficient chiral catalyst procedure for the preparation of β-chiral ketone via the 1, 4-additions reaction of 2-en-ketone has been developed using enantiopure sulfoximines modified with functional groups as ligands. The carefully design and synthesized functional enantiopure sulfoximines could be used as linker. In this system the formation of new chiral centers occurs with the regioselective addition of the ethyl moiety at the terminal carbon of the 2-en-ketone. In addition, aromatic substituents in the substrate promote the addition reaction.

## Introduction

Sulfoximines, which can be considered as aza analogues of sulfones, were first reported by Whitehead and Bentley in 1950 [1]. The high synthetic versatility of sulfoximine group derives from its ability to function as chiral carbanion stabilizing nucleofuge [2]. Chiral sulfoximines have a stereogenic center at the sulfur atom, and have been recognized as an interesting new class of chiral ligands, which can be applied in various asymmetric catalytic reactions [3–13]. The first application of enantiopure sulfoximine as a ligand was reported by Johnson in 1979 [11]. Later works were focused on the design and preparation of novel ligands. In which bi-dentated β-hydroxysulfoximines were the most successful sulfoximine ligands in asymmetric catalysis of a variety of reactions, such as diethylzinc addition to aldehydes [8], titanium catalysed asymmetric homoaldol reaction [9] and titanium promoted addition of TMSCN to aldehyde [12]. For example, Bolm and coworker reported using readily available β-hydroxysulfoximine ligands in catalytic asymmetric phenyl transfer reactions, gaving arylphenylmethanols with moderate to high enantioselectivities [13].

However, relatively little attention has been devoted to the use of optically-active sulfoximines as ligands in the 1, 4-addition reactions and the results were not satisfy. For example, copper complex catalyzed 1, 4-additions to 2-cyclohexenone giving lower ee (7–36%) [14].

As part of our continuing program on the exploration of sulfoxide and sulfoximine chemistry [15], we designed and synthesized novel enantiopure β-hydroxysulfoximines modified by functional groups. The functional enantiopure sulfoximines with the linkers could be grafted to solid support for recycle and reuse. Hydroxysulfoximine's nickel complex used as ligand on the 1,4-addition reactions were examined. It was pleased to note that this complex showed high activity and delivered enantioselectivities up to 70% ee.

## Results and discussion

Several methods are known for the conversion of sulfoxides into sulfoximines [14,16]. The oldest method for the oxidative imination of sulfoxides involves hydrazoic acid generated in situ from $NaN_3$ and 98% sulfuric acid [17] (Scheme 1). However, the direct preparation of enantiopure sulfoximines cannot be accomplished by this way since the racemization of the sulfoxide is faster than the formation of the sulfoximines.

In general, imination reactions between a nitrene or nitrene analogue and the sulfoxide proceed with retention of configuration at the sulphur [18–21], providing that the reaction conditions do not promote racemization of sulfoxide. The most frequently used imination reagents that allow retention of configuration at sulfoxide are o-mesitylsulfonylhydroxylamine (MSH) [20,21],N-tosylimino-phenyliodinane,[18] and N-aminophthal-imide [19]. The most flexible approach to enantiomerically pure "free" sulfoximines appears to be via the MSH-method. Therefore, we decided to convert enantiopure sulfoxides (from the biotransformation reactions [15]) into sulfoximines.

The imination of optically pure sulfoxides with mesitylsulfonylhydroxylamine(MSH) yielded the corresponding sulfoximines with the complete retention of configuration [21]. The reactive MSH had to be prepared prior to imination; once prepared, it was reasonably stable and could be kept in a freezer for up to one week (see SI). Treatment of (+)-(*R*)-methyl phenyl sulfoxide **3a** (99% ee) with MSH gave (-)-(*R*)-methyl phenyl sulfoximine **4a** in 65% yield. The resolution on chiral phase GC showed as 99% enantiopure (Scheme 2).

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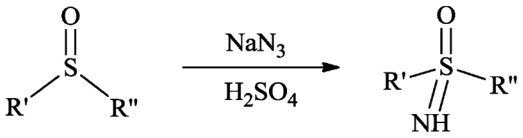


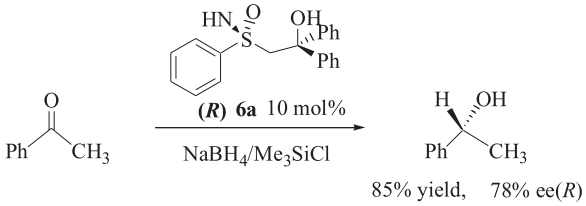

**Scheme 1.** Conversion of sulfoxides into sulfoximines.

N-protected sulfoximine was obtained by treating methyl phenyl sulfoximine **4a** with trimethylsilyl diethylamine and the product **5a** was purified by distillation. Since the by-product was a volatile diethylamine, this procedure is perfectly suitable for the product N-protected sulfoximine. In the following step, condensation with benzophenone gave TM(S)-protected β-hydroxysulfoximine; reflux of the crude product in methanol for 3–4 h gave desilylated sulfoximine **6a**. The overall yield after 3 steps was 47%. Borane reduction of a prochiral ketone was used to test the efficiency of catalytic activity of **6a** in homogeneous reaction, and **6a** (10 mol %) catalyzed the asymmetric reduction of ketone into alcohol with good selectivity (78% ee) and in high yield. The chiral ligand was recovered without loss of chirality, as described in Scheme 3.

In view of the successful performance of ligand **6a**, we proceeded with the syntheses of sulfoximines **4a, 4b,** and **4c** with the different functional groups on the aromatic rings that could be grafted to the solid support. To develop efficient protocols for imination, initial syntheses were carried out with racemic materials. Thus, sulfoximines were prepared by treating the corresponding sulfoxides with a 40% excess of o-mesitylsulfonylhydroxylamine in methylene chloride (25 mL) at room temperature [22]. Because of the relatively high acidity of free sulfoximines (pKa = 24.3) [23] the protection of the amine is necessary before further modification. Two types of protective groups were investigated: silyl and alkyl groups. It has been reported that these groups have only a minor influence on the enantioselectivity [24]. Silylation of compounds **4a** and **4b** was achieved by heating the free sulfoximine with $Et_2NSiMe_3$ [25]. The allyl-substituted compound **4c** which cannot tolerate these reaction conditions was alkylated using triethyloxonium fluoroborate [26] under milder conditions to give the ethyl N-protected **5c** (Scheme 4).

Unfortunately, numerous attempts at converting **5b** and **5c** to the target ligands **6b** and **6c** gave multiple products with very low yields. After the systematic investigation on the difficulties for the above syntheses, an alternative ligand was designed as show in Scheme 5, indeed, it was successful.

Biotansformation only could provide small quantity of enantiopure sulfoxides. A large quantity of enantiopure **(*S*)-4a** was prepared through the resolution of racemic sulfoximine **4a** with (+)-10-camphorsulfonic acid ((+)-CSA) giving **(*S*)-4a** in 41% yield and 99% ee. Large-scale preparation of enantiopure sulfoximines by the separation



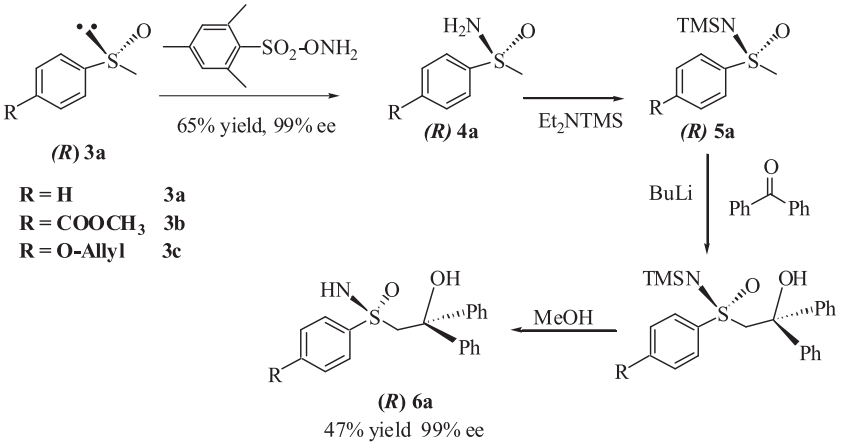

**Scheme 3.** Borane reduction of ketone.

of N-(+)-10 camphorsulfonyl-sulfoximine diastereomers followed by the removal of the resolving group by acid hydrolysis was developed by Gais and co-workers (Scheme 6) [27]. The enantiomer **(*R*)-4a** can be obtained similarly by using (-)-CSA.

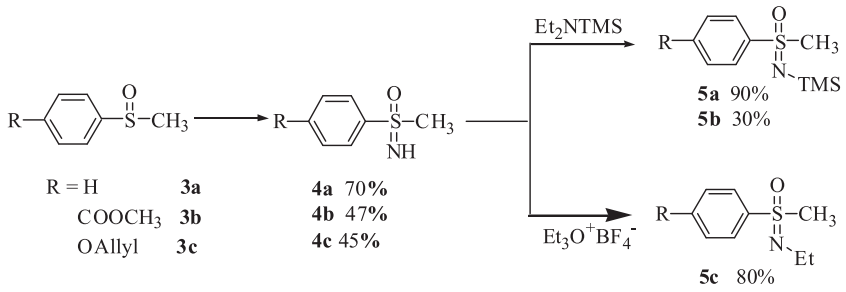
The N-methylation of **(*S*)-4a** occurred with retention of the configuration at sulfur center. The following condensation gave a diastereomeric *cis/trans* mixture of **6d** in good yield. The *cis*- and *trans*- mixture was separated by column chromatography to give enantiopure *cis* **6-d** and *trans* **6-d** (> 99% ee). The structure of ***cis*-(*S*)-6d** was unambiguously established by X-ray crystallography. The crystal data and the crystallographic details were shown in the experimental section. The absolute configuration of the compound was confirmed by the low Flack parameter and lower R factors. The *cis* geometry of the product was verified by the X-ray data. The crystal structure showed the presence of two independent molecules in the unit cell. These two molecules have different conformations of COOEt group, which was clearly displayed on the right-hand side of two drawings in Fig. 1.

The cyclohexane ring has the expected chair conformation with torsion angles between 52 and 59° (+and – alternating). The C═O bond (avg. 1.209(3) Å) is shorter than the C–O bond (avg. 1.333(2) Å) of the ester group, while the C—O of the hydroxyl group is much longer (avg. 1.429(2) Å). The environment around the S atom is tetrahedral, with the angle O—S—N the largest (avg. 121.5(1) o). The avg. S═O distance is 1.451(1) Å, while the avg. S—N bond is 1.522(2) Å. The S—C bond distances vary between 1.7762(17) and 1.7955(17) Å.

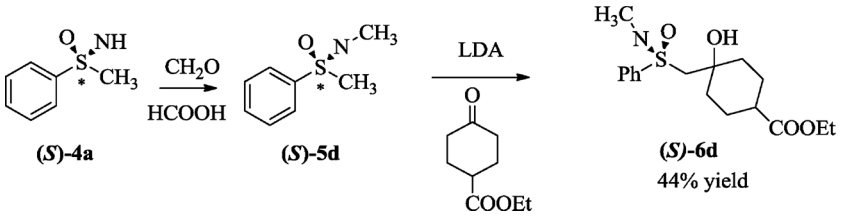
We conducted asymmetric 1, 4 addition reaction to 2-en-ketones achieved by reaction of diethyl zinc in the presence of nickel acetylacetonate [Ni(acac)$_2$] and chiral β-hydroxysulfoximines as chiral ligands. Several influence factors have been evaluated, such as the concentration of the catalyst and the solvent on the conjugate addition. All reactions were carried out in propionnitrile at −30 °C as these proved to be optimal conditions. In toluene, THF, products with lower yields were obtained. All reactions were carried with a ligand: Ni ratio of 20:1. Control experiments were processed. Several conclusions were achieved: Ni was necessary to promote the reaction. Sulfoximines ligand did not catalyzed the conjugate addition of $ZnEt_2$ to 2-en-ketones in the absence of Ni(acac)$_2$.



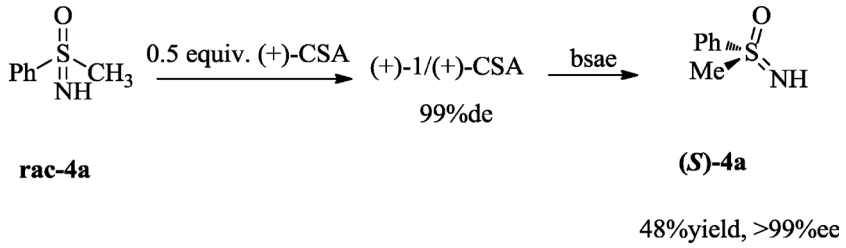

**Scheme 2.** Synthesis of chiral sulfoximine ligands.




**Scheme 4.** Preparation of N-protected sulfoximines.




**Scheme 5.** Synthesis of chiral β-hydroxysulfoximine ligands.




**Scheme 6.** Preparation of chiral sulfoximines by resolution with CSA.

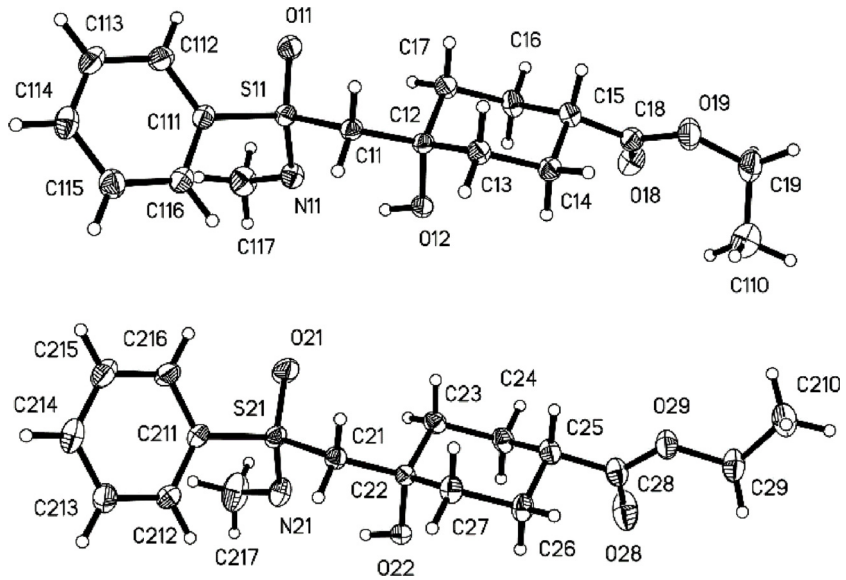
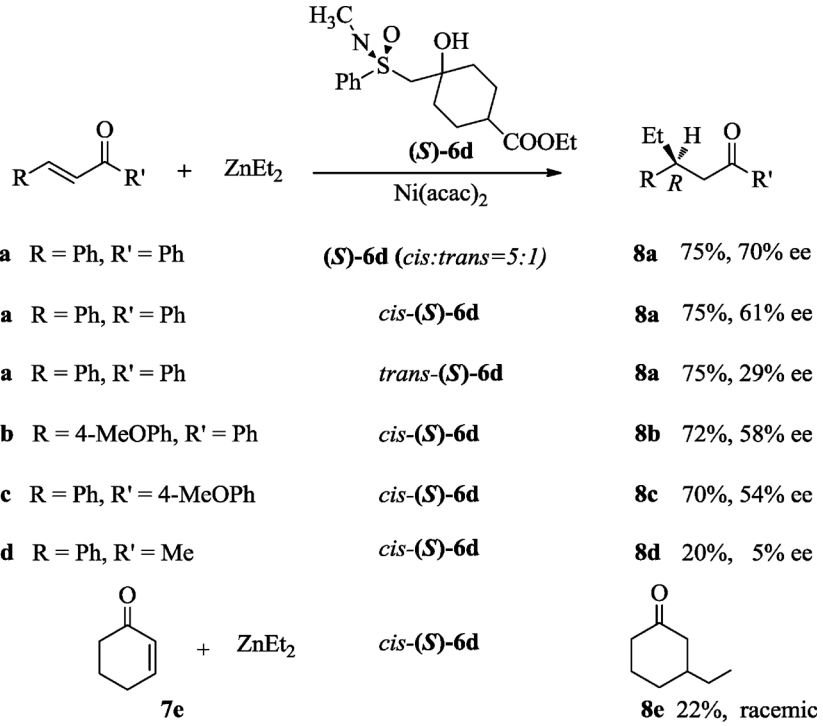



**Fig. 1.** Labelled diagrams of the two independent molecules in the crystal of compound *cis*-(S)-6d. Ellipsoids correspond to 30% probability.

Under the optimized conditions, pure *cis*-(*S*)-6d and pure *trans*-(*S*)-6d were tested as the ligands with increased amount of sulfoximine from 20 mol% to 30 mol%, but without any improvement on either the yield or enantioselectivity. The maximum enantiomeric excess of product (*R*)-1,3-diphenylpentan-1-one **8a** (75% yield, 70% ee) was achieved by using *cis : trans* = 5 : 1 mixture of **(*S*)-6d** as a ligand. The reactions catalyzed by the pure *cis*- and pure *trans*-6d were less selective giving 61%ee and 29%ee respectively (Scheme 7).

The catalyst **(*S*)-6d** could be easily recovered without any change from the reaction mixture in greater than 80% yield. The addition of several other conjugate ketones was completed under the optimized conditions with ***cis*-(*S*)-6d** as a catalyst. Interestingly, conjugate addition to methoxy-chalcone **7b** and **7c** afforded **8b** and **8c** with an enantiomeric excess of 58% and 54% respectively in good yields. The presence of an arylketone moiety seems to be important to reach high ee, as in the case of the methyl-substituted derivative **7d**; the product was obtained in low yield 20% but was essentially racemic. Alkylation of **7d** and **7e** gave essentially racemic products in low yields (Scheme




**Scheme 7. 7**. 1, 4 addition to 2-en-ketones.

7), which indicated that the presence of aryl groups is necessary to achieve reasonable enantioselectivity.

## Conclusion

In summary, more complex enantiopure β-hydroxy sulfoximines modified by functional groups have been synthesized. The structure was unambiguously established by X-ray crystallography. An efficient chiral catalyst procedure for the preparation of β-chiral ketones which were potential drug building blocks has been developed using enantiopure sulfoximines as ligands. In this system the formation of new chiral centers occurs with the regioselective addition of the ethyl moiety at the terminal carbon of the 2-en-ketone. Our current study is beneficial for future applications.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2018.06.011.

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