Enantiopure Sulfoxides

A Highly Selective and Practical Method for Enantiopure Sulfoxides Utilizing Activated and Functionally Differentiated *N*-Sulfonyl-1,2,3-oxathiazolidine-2-oxide Derivatives

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During the past four decades, many groups have been engaged in the design and development of new synthetic methods for the generation of enantiopure sulfoxides because they are often used as chiral controllers for asymmetric C–C bond formation processes and ligands in catalytic asymmetric synthesis.[1] In addition to these synthetic uses, the chiral sulfoxide functionality plays a highly important role in a variety of medicinal targets like OPC-29030, a platelet adhesion inhibitor, and esomeprazole for the treatment of acid related disorders.[2] A literature search revealed that two distinct approaches have been applied in the preparation of optically active sulfoxides: asymmetric oxidation of prochiral sulfides,[3] and an organometallic addition to electrophilic sulfinic-acid derivatives with inversion of configuration at the sulfur atom.[4] As noted in the literature, both methods have

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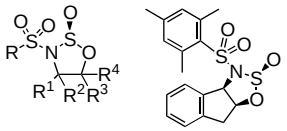
advantages and disadvantages. However, the latter method, which utilizes sulfinyl transfer agents, is widely used in the production of optically active sulfoxides.[1e,f,5] Recently, Khiar, Alcudia and co-workers have developed a practical method for the generation of both enantiomers of several valuable sulfoxides through dynamic kinetic resolution by using diacetone D-glucose (DGA) as a chiral controller.[5f–h] Because of the high biological and chemical significance of many molecules containing the sulfoxide functional group, it is clear that a search for milder asymmetric methods is very important and still needed. Herein, we disclose a highly selective, general, and mild (zinc reagents can be employed) asymmetric technology for both antipodes of sulfoxides from functionally differentiated aryl *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives **1** (ASOO; see Scheme 1).

Recently, we disclosed that simple treatment of **2b** (R = mesityl) in THF at low temperature with $SOCl_2$, followed by



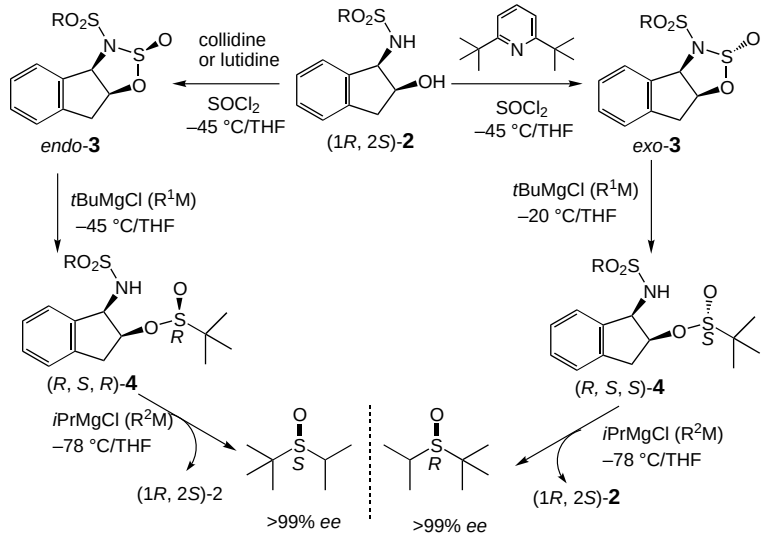
1 (ASOO) *Endo*-**3b**

Scheme 1.

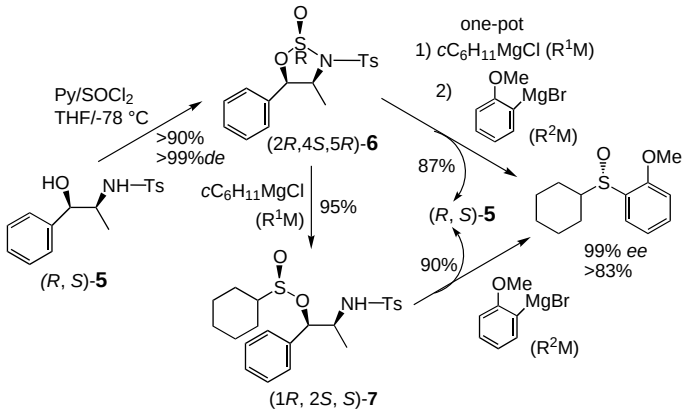
the slow addition of 3,5-lutidine provided a 97:3 ratio of *endo*-selective **3b** in excellent yield.[6] Attempts to find a proper procedure to produce highly *exo*-selective indane-derived *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide (IASOO-**3**) were unsuccessful. After the examination of many reaction conditions, it was found that high *endo* selectivity can be switched to a high *exo* selectivity by a simple change in the pyridine substitution pattern of the ring, thus increasing the steric bulk of the 2,6 positions of the pyridine ring. As indicated in Table 1, when compound **2** was subjected to 3,5-lutidine or collidine, highly *endo*-selective **3** (Table 1, entry 2 and 5) was afforded. On the other hand, sterically congested 2,6-di-*tert*-butyl pyridine provided highly *exo*-selective **3** (Table 1, entry 4 and 6). *Endo*-**3** and *exo*-**3** are highly crystalline, and are crystallized to an enantiomerically and diastereomerically pure form with excellent recovery from single antipode **2**.[7]

Having generated large quantities of *endo*- and *exo*-**3** in enantiomerically and diastereomerically pure form, we focused on the production of both enantiomers of chiral sulfoxides**.** To highlight the power of this new synthetic methodology, we first investigated the preparation of both antipodes of *t*BuS(O)*i*Pr. Exposure of either *endo*- or *exo*-**3** to *t*BuMgCl at low temperature led to the smooth chemospecific cleavage of the S–N bond to produce the corresponding diastereomer of the sulfinate, **4**, with inversion of configuration at the S atom in > 95 % yield (Scheme 2). Individual diastereomeric sulfinate **4**, upon treatment with *i*PrMgCl, provided the corresponding enantiomer of *t*BuS(O)*i*Pr (with inversion of configuration at the S atom) in excellent yield with an outstanding recovery of enantiopure **2** (> 98 %).[7b,8]

Next, our attention focused on the development of readily available and inexpensive aminoalcohol based *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives. After evaluating many chiral aminoalcohol sulfonyl derivatives, we found that inexpensive *N*-tosylnorephedrine is an ideal template for the preparation of *N*-tosyl-1,2,3-oxathiazolidine-2-oxide. Treatment of (1*R*,2*S*)-**5** in THF with thionyl chloride and pyridine at −78 °C provided > 99 % *de* and > 90 % yield of the isolated product, 4-phenyl-5-methyl-3-*N*-tosylnorephedrine-1,2,3-oxathiazolidine-2-oxide (PMTOO) **6** (Scheme 3).[7c] The single crystal analysis of **6** indicated that absolute configuration of the S center is *R*.[7b]



Scheme 2. Production of Enantiopure Sulfoxide Using IASOO-**3**.



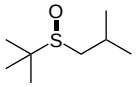
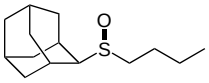
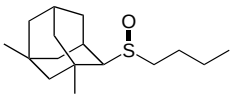
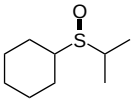
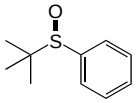
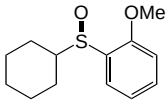
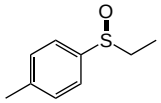
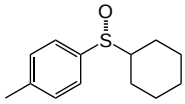
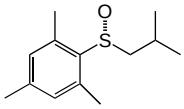
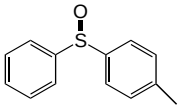
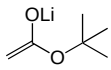
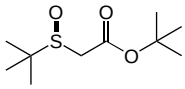
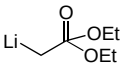
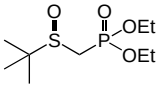
Scheme 3. Production of Enantiopure Sulfoxide Using PMTOO-**6**.

Table 1: Diastereoselective Thionylation of **2**.

Entry	**3**	R	Base	*endo*-**8**:*exo*-**8**[a]
1	**3a**	4-tolyl	pyridine (Py)	80:20
2	**3a**	4-tolyl	2,4,6-collidine	91:9[b]
3	**3a**	4-tolyl	4-methyl-2,6-di-*t*BuPy	20:80
4	**3a**	4-tolyl	2,6-di-*t*BuPy	2:98[b]
5	**3b**	2,4,6-mesityl	3,5-lutidine	97:3[b]
6	**3b**	2,4,6-mesityl	2,6-di-*t*BuPy	7:93[b]

[a] *Endo*/*exo* ratio is determined by ^{1}H NMR analysis. [b] Recrystallization provided diastereo- and enantiopure **3.**

Table 2: Double Nucleophilic Displacement of *N*-Sulfonyl-1,2,3-oxathiazolidine-2-oxide to form Optically Active Sulfoxides (Scheme 3).

Entry	R^1M	R^2M	Product	Configuration[a] and % *ee*[b]	Yield[c]
1	*t*BuMgCl	*i*BuMgCl		(*S*)-99.5[d] (*R*)-99.5[e]	90 91
2	AdZnBr	*n*BuMgBr		(*S*)-99[d] (*R*)-99[e]	93 91
3	3,5-dimethyl-1-admentylZnBr	EtMgCl		(*S*)-96[d] (*R*)-$>$99[e]	90 93
4	*c*C_6H_{11}MgCl	*i*PrMgCl		(*S*)-99[d] (*R*)-98[f]	88 63
5	*t*BuMgCl	PhMgCl		(*R*)-99[d]	77
6	*c*C_6H_{11}MgCl	*o*-MeO-PhMgCl		(*R*)-98[g] (*S*)-99[f]	83 87
7	*p*-tolylMgBr	EtMgCl/CuBr·SMe2		(*S*)-95[d] (*S*)-90[d]	89 83
8	*p*-tolylMgBr	*c*C_6H_{11}MgCl		(*R*)-99[d]	97
9	2,4,6-mesitylMgBr	*i*BuMgCl		(*S*)-98[g] (*R*)-99[f]	85 86
10	PhMgBr	*p*-tolylMgBr		(*R*)-99[d]	84
11	*t*BuMgCl			(*R*)-99[d] (*S*)-99[e]	93 92
12	*t*BuMgCl			(*S*)-99[d] (*R*)-98[h]	93 83

[a] Absolute configuration was deduced from the synthetic schemes involving two consecutive inversions of configuration, and by comparison to known literature optical rotations**.** [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] All of the yields are of the isolated productss. See Supporting Information experimental procedures for [d] method A, [e] method D, [f] method E, [g] method C, and [h] method B.

First, the application of (2*R*,4*S*,5*R*)-**6** in the generation of optically active cyclohexyl 2-methoxyphenyl sulfoxide was evaluated. The treatment of *c*C_6H_{11}MgCl with (2*R*,4*S*,5*R*)-**6** in THF at −78 °C provided $>$90 % isolated yield of (1*R*,2*S*,*S*)-**7** (inversion of configuration at the S atom; Scheme 3). Diastereopure **7** was then exposed to 2-methoxyphenylmagnesium bromide at −78 °C, which underwent clean inversion of configuration at the S atom to give enantiopure cyclohexyl-2-methoxyphenyl sulfoxide. Importantly, this product can also be generated in excellent yield utilizing a one-pot operation by adding sequentially *c*C_6H_{11}MgCl and 2-methoxyphenylmagnesium bromide to (2*R*,4*S*,5*R*)-**6** at −78 °C. Furthermore, the chiral template (*R*,*S*)-**5** can be effectively isolated from the reaction mixture and recycled.

The double inversion organometallic displacement process was extended to produce other structurally unique optically active sulfoxides. Either enantiomer of alkyl–alkyl sulfoxides can be obtained in excellent yields (Table 2, entries 1–4). Importantly, mild reagents such as organozinc reagents, cleave the S–N bond of either *endo*-**3b** or (2*R*,4*S*,5*R*)-**6**, thus resulting in high yields. For example, sterically congested 1-adamantylzinc bromide or 3,5-dimethyl-1-adamantylzinc bromide can be added to *endo*-**3b**, or (2*R*,4*S*,5*R*)-**6** to provide the corresponding sulfinates, which upon treatment with *n*BuMgBr or EtMgCl, provided either enantiomer of the appropriate new sulfoxides in high yields (Table 2, entries 2 and 3). The success of this methodology is also exemplified by the preparation of optically active alkyl–aryl (Table 2, entries 5 and 6) and aryl–alkyl (Table 2, entries 7–9) sulfoxides in excellent yields. The one-pot addition of *p*-tolylmagnesium bromide followed by EtMgCl to *endo*-**3** provided only 90% *ee*. However, a sequential addition of *p*-tolylmagnesium bromide, followed by EtMgCl/$CuBr{\cdot}SMe_2$ to *endo*-**3** provided increased selectivity (95% *ee*, Table 2, entry 7).[7b] Interestingly, enantiopure phenyl *p*-tolylsulfoxide can be prepared without any complications (Table 2, entry 10). As noted in the literature, attempts to prepare enantiopure *tert*-butyl(*tert*-butylsulfinyl)acetate were unsuccessful.[11f] Gratifyingly, the addition of *tert*-butylacetate enolate to (*R,S,R*)-**4b** provided enantiopure *t*ert-butyl(*tert*-butylsulfinyl)acetate in 93% yield (Table 2, entry 11).[9] Furthermore, this methodology can be applied to generate either enantiomer of the novel diethyl (*tert*-butylsulfinyl)-methyl-phosphonates in high yields (Table 2, entry 12).[1g]

In conclusion, a new and highly general method for the preparation of enantiopure sulfoxides from diastereopure *N*-sulfonyl-1,2,3-oxathiazolidine-2-oxide derivatives[10] has been developed. The application of this new and powerful methodology for identification of sulfoxide containing novel biological targets, and sulfoxide derived chiral ligands for asymmetric catalysis will be reported in due course.

For experimental details and molecular structures of (2*R*,4*S*,5*R*)-**6,** *endo*- and *exo*-**3** see Supporting Information.

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[7] a) The absolute stereochemistry of *endo*-**3** and *exo*-**3** was unambiguously established by single crystal X-ray analysis; b) For the detailed experimental procedure, see Supporting Information; c) As in the case of aminoindanol series, *exo* isomer of PMTOO can be obtained in 90% yield (with *exo*:*endo* = 9:1) using 2,6-di-*tert*-butylpyridine as a base.

[8] Absolute configuration was deduced from the synthetic Scheme 3, involving two consecutive inversions of configuration and X-ray analysis of (*R,S,R*)-**4b.**

[9] Use of *tert*-butyl (*p*-tolylsulfinyl)acetate in asymmetric synthesis, see G. Solladic, C. Bauder, E. Arce-Dubois, P. Y. Jacope, *Tetrahedron Lett.* **2001**, *42*, 2923–2925.

[10] a) Polymer bound aryl *N*-sulfonyl 1,2,3-oxathiazolidine-2-oxide derivatives are under investigation; b) The application of PMTOO **6** in the synthesis of valuable sulfinamides and polymer-supported sulfinamides are under investigation.

