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New General Sulfinylating Process for Asymmetric Synthesis of Enantiopure Sulfinates and Sulfoxides

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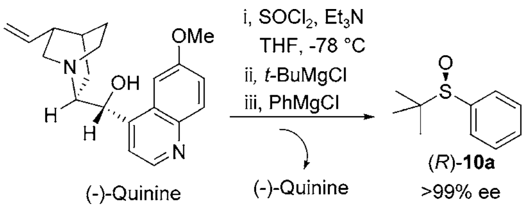
ABSTRACT



A general process for the efficient synthesis of sulfinyl transfer agents has been developed using cinchona alkaloids quinine and quinidine as chiral auxiliaries. The importance of these new and unique sulfinyl transfer agents is exemplified by the expedient synthesis of several sulfoxides in excellent enantiopurities and high yields.

Enantiopure sulfinamides and sulfoxides have stimulated great interest in recent years due to their broad scope as versatile chiral synthons for C−C and C−N bond formations.[1,2] Although the preparation of sulfoxides by catalytic asymmetric oxidation of prochiral sulfides has been reported,[3] the most frequently used precursors to access both sulfoxides and sulfinamides are chiral sulfinates.[1,2] A variety of methods have been developed for the synthesis of these important precursors, including kinetic resolution of sulfinates from reaction of racemic sulfinyl chlorides with a chiral auxiliary such as the Andersen's (*S*)-menthyl *p*-toluenesulfinate **1a**,[4] Alcudia's sulfinate **1b** derived from diacetone D-glucose,[5] Evans' *N*-sulfinyloxazolidinone **2**,[6] Oppolzer's *N*-sulfinyl sultam **3**,[7] asymmetric oxidation of disulfides such as Ellman's *tert*-butyl-*t*-butanethiosulfinate **4**,[8] and formation of cyclic sulfites or oxathiazolidines such as Wudl's 1,2,3-oxathiazolidine-2-oxide **5** derived from (−)-ephedrine,[9] Kagan's cyclic sulfite **6**,[10] etc. (Figure 1).

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(1) For recent reviews on sulfinylamines, see: (a) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984 and references therein. (b) Ellman, J. A. *Pure Appl. Chem.* **2003**, *75*, 39. (c) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (d) Senanayake, C. H.; Krishnamurthy, D.; Lu, Z.-H.; Gallou, I. *Aldrichimica Acta*, in press.

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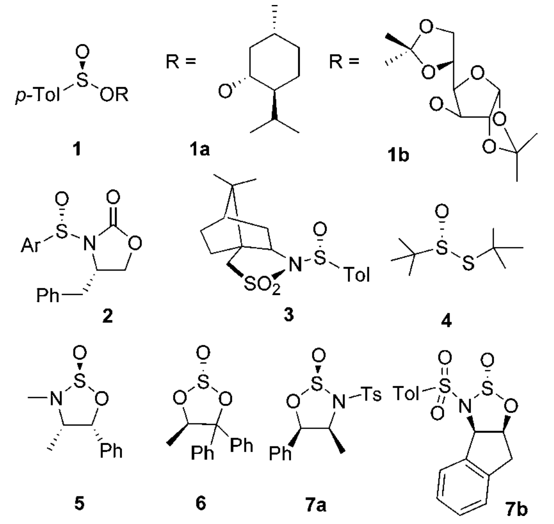
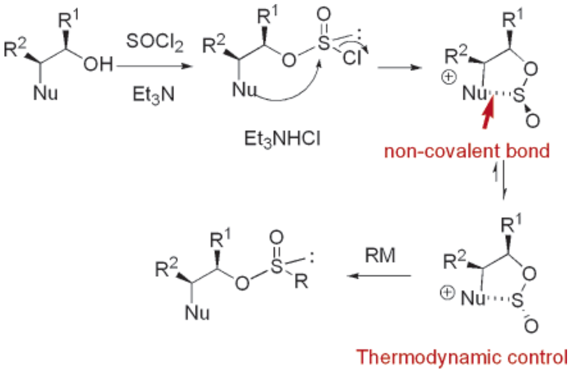


Figure 1. Selected sulfinyl transfer agents.

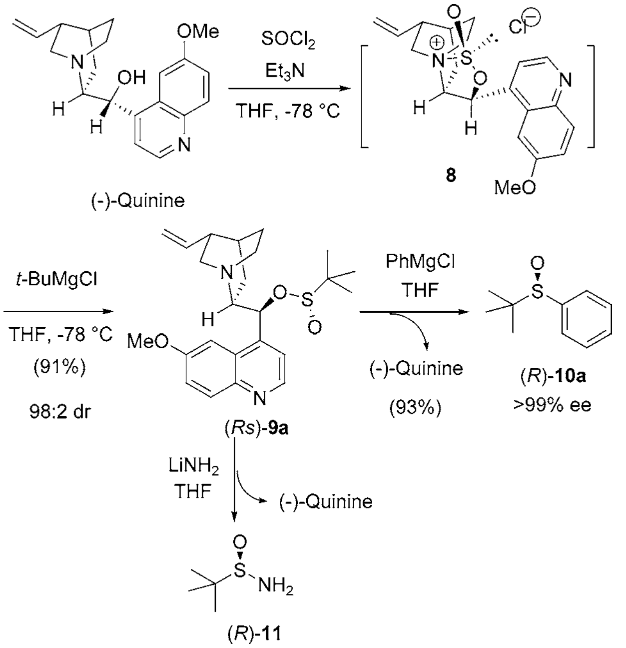
Despite the plethora of methodologies, a general, practical, and economical approach is still unavailable. We recently reported an efficient method for the preparation of enantiopure *N*-tosyl-1,2,3-oxathiazolidine-2-oxide derivatives **7a**,**b** that enabled the highly general, selective, and practical synthesis of a wide range of chiral sulfoxides and sulfinamides in high yield and excellent enantioselectivities.[11,12] The remarkable property of **7a**,**b** as a sulfinyl transfer reagent relies on the differentiation of S−N and S−O bond energies. The S−N bond of **7a**,**b** is relatively much more susceptible to nucleophilic displacement due to the electron-withdrawing effect of the tosyl group. Ideally, the desirable bond to replace the S−N σ bond is a noncovalent bond, providing that the chiral sulfinyl center could still be established. In this respect, we envisioned that it might be possible to design a more reactive sulfinylating reagent with excellent diastereoselectivity via formation of a pseudo five-member ring oxathiazolidine (Scheme 1). The integration of a noncovalent bond would allow the predominant formation of the thermodynamically stable isomer. Herein, we are pleased to report a novel and general method for the synthesis of highly enantiomerically enriched sulfoxides.

Scheme 1. Creation of Chiral Sulfur Center via a Pseudo Five-Member Ring Oxathiazolidine



We initiated our investigation with the preparation of the *tert*-butanesulfinate (*Rs*)-**9a** since it could be the precursor of *tert*-butanesulfinamide, the most widely applied chiral amine synthon.[1a,b] After screening several conventional amino alcohols as scaffolds, we found that cinchona alkaloids (−)-quinine and (+)-quinidine provided the highest diastereoselectivities. Thus, treatment of (−)-quinine with 1 equiv of thionyl chloride and 2 equiv of triethylamine in THF at −78 °C presumably afforded the pseudo oxathiazolidine-2-oxide "ate" complex **8**, as indicated by the precipitation of $Et_3N{\cdot}HCl$ salt (Scheme 2). Addition of *tert*-butylmagnesium chloride at −78 °C provided *tert*-butanesulfinate **9a** in a >98:2 ratio of diastereomers as measured by HPLC-MS. The major isomer was isolated by flash column chromatography in 91% yield, and with >99% de. Subsequently, displacement of the quinine auxiliary with a nucleophile was examined. We were initially concerned whether the enantiomeric purity of the sulfinyl group could be maintained, since epimerization of chiral sulfinyl centers are frequently observed in most of the literature procedures.[6,8a] This issue was likely caused by exposure of the sulfinate to the alkoxide moiety of the

Scheme 2. Asymmetric Synthesis of Sulfinyl Transfer Agents



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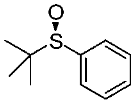
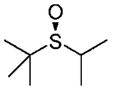
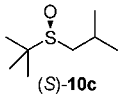
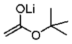
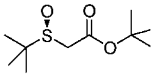
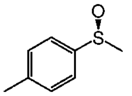
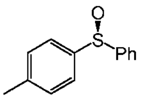
[12] (a) A similar strategy for the preparation of chiral sulfoxides obtained from *N*-benzyloxycarbonyl sulfamidite of (1*R*,2*S*)-(−)-norephedrine was recently reported: García-Ruano, J. L.; Alemparte, C.; Aranda, M. T.; Zarzuelo, M. M. *Org. Lett.* **2003**, *5*, 75. (b) Other *N*-carbamate-activated oxathiazoline oxides have been studied: Qin, Y.; Wang, C.; Huang, Z.; Xiao, X.; Jiang, Y. *J. Org. Chem.* **2004**, *69*, 8533.

auxiliary itself, a byproduct of the nucleophilic displacement. In addition, the alkoxides could impact the rate of nucleophilic addition by coordination with the nucleophilic reagent to form new aggregates. The addition usually became more sluggish with the increasing formation of the displaced auxiliary. To avoid this inherent problem, an excess amount of Grignard reagent was used. Thus, treatment of the *tert*-butanesulfinate **9a** with 2 equiv of phenylmagnesium chloride in THF gave (*R*)-*tert*-butylphenyl sulfoxide, **10a**, in 93% isolated yield and >99% ee.[13] The absolute configuration of **10a** was assigned by comparison of HPLC retention time with authentic samples prepared according to literature procedure.[8a] Since each nucleophilic substitution inverts the conformation of the sulfinyl center,[8a] it was concluded that the sulfur atom of the *tert*-butanesulfinate **9a** has the (*R*)-configuration.

To investigate the scope of this methodology, the *tert*-butanesulfinate **9a** was treated with a variety of alkyl Grignard reagents. The results are summarized in Table 1.

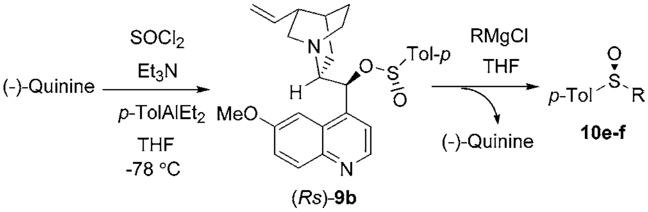
Table 1. Synthesis of Chiral Sulfoxides Using (−)-Quinine as a Chiral Auxiliary

entry	R¹M	R²M	Product[a]	Yield[b] (%)	e.e.[c] (%)
1	*t*-BuMgCl	PhMgCl	 (*R*)-**10a**	93	99
2	*t*-BuMgCl	*i*-PrMgCl	 (*S*)-**10b**	91	99
3	*t*-BuMgCl	*iso*-BuMgCl	 (*S*)-**10c**	95	99
4	*t*-BuMgCl		 (*S*)-**10d**	81	99
5	*p*-TolylAlEt$_2$	MeMgCl	 (*S*)-**10e**	88	96
6	*p*-TolylAlEt$_2$	PhMgCl	 (*S*)-**10f**	83	97

[a] Absolute configurations of **10b−f** were deduced from the corresponding sulfinates assuming that each nucleophilic substitution inverts the conformation of the sulfinyl center. [b] Isolated yield after purification by column chromatography. [c] Enantiomeric excess was determined by chiral HPLC analysis.

Both isopropylmagnesium chloride and *iso*-butylmagnesium chloride reacted uneventfully with **9a** to provide the corresponding enantiopure sulfoxides in excellent yield (Table 1, entries 2 and 3). Addition of a lithium enolate to the sulfinate **9a** was also examined, giving rise to enantiopure α-(*tert*-butoxyl-carbonyl)methyl-*tert*-butylsulfoxide in 81% yield (entry 4). On the other hand, we noticed that addition of *p*-tolylmagnesium chloride to the "ate" complex **8** under identical conditions resulted exclusively in formation of racemic di(*p*-tolyl)sulfoxide, regardless of whether 2 or 1 equiv of the Grignard reagent was used. Fortunately, this issue was circumvented by using *p*-tolyldiethylaluminum, prepared in situ by treatment of *p*-tolylmagnesium bromide and diethylaluminum chloride. The addition proceeded smoothly at −78 °C, affording the (*Rs*)-*p*-toluenesulfinate **9b** in 78% isolated yield and 99% dr (Scheme 3). Treatment of (*Rs*)-*p*-toluenesulfinate **9b** with methylmagnesium chloride afforded the sulfoxide (*S*)-**10e** in 88% yield and 96% ee (entry 5). Similarly, treatment of (*Rs*)-*p*-toluenesulfinate **9b** with phenylmagnesium chloride afforded the sulfoxide (*S*)-**10f** in 83% yield and >97% ee (entry 6). In addition, (*Rs*)-*tert*-butanesulfinate **9a** is the precursor to the well-known *tert*-butanesulfinamide (*R*)-**11**.[11] The results will be reported subsequently.

Scheme 3. Asymmetric Synthesis of Enantioenriched Sulfoxides



In conclusion, we have developed a novel, practical, and general method for the asymmetric synthesis of enantioenriched sulfoxides and *tert*-butanesulfinamide in high yields and excellent enantioselectivities. It is noteworthy that the method is superior to the traditional approaches for the preparation of enantiopure sulfinates utilizing resolution as result of its excellent stereoselectivity, generality, and

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[13] **Typical Experimental Procedure.** A three-neck 500 mL round-bottom flask was charged with (−)-quinine (3.0 g, 9.25 mmol, 1.0 equiv) and Et$_3$N (2.9 mL, 20.85 mmol, 2.2 equiv) in THF (150 mL). The solution was chilled to −78 °C, and thionyl chloride (0.75 mL, 10.28 mmol, 1.1 equiv) was added. The resultant slurry was stirred at −78 °C for 1 h, followed by addition of *tert*-butylmagnesium chloride (19 mL, 1.0 M in THF, 19.0 mmol, 2.05 equiv) at −78 °C. The mixture was stirred at −75 °C for 0.5 h and quenched with saturated NH$_4$Cl aqueous solution (90 mL), and the mixture was diluted with ethyl acetate (150 mL). The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were washed with brine, dried, and evaporated to give a yellowish oil. Purification of the crude by flash column chromatography (eluent with 5% MeOH in AcOEt) gave pure (*Rs*)-**9a** as a colorless oil, which turned into a white solid after standing at ambient temperature (3.6 g, 91% yield). A solution of (*Rs*)-**9a** (1.79 g, 4.14 mmol, 1.0 equiv) in THF (20 mL) at −78 °C under argon was charged dropwise with phenylmagnesium bromide (2.8 mL, 3.0 M in Et$_2$O, 8.3 mmol, 2.0 equiv). After complete addition, the dry ice bath was removed and the reaction mixture was warmed to 25 °C within 1 h. After complete consumption of the starting material, the reaction was quenched with aq NH$_4$Cl solution (15 mL) and diluted with EtOAc (30 mL). After phase separation, the organic phase was extracted once with EtOAc. The combined organic phases were washed with 20% NaCl (10 mL) aqueous solution, dried, and concentrated to give a mixture of (*R*)-*tert*-butyl phenylsulfoxide **10a** and (−)-quinine, which was purified by chromatography eluted with EtOAc to afford (*R*)-**10a** (0.76 g, 93%) in >99% ee (chiral HPLC: column, Chiralpark AS; mobile phase, 90:10 hexanes/ethanol; rate, 1 mL/min; wavelength, 256 nm).

practicability. The presented results suggest that it is not essential to establish the sulfinyl chiral center by forming both the S−O and S−N σ bonds. Indeed, formation of a pseudo five-member ring oxathiazolidine via a noncovalent bond provides an active but conformationally stable sulfur center, allowing easy access to a variety of sulfinates and sulfoxides. Further work on the scope of this process is under investigation and will be reported in due course.

Supporting Information Available: Reaction procedures and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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