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ortho-Metalation of Enantiopure Aromatic Sulfoxides and Stereocontrolled Addition to Imines

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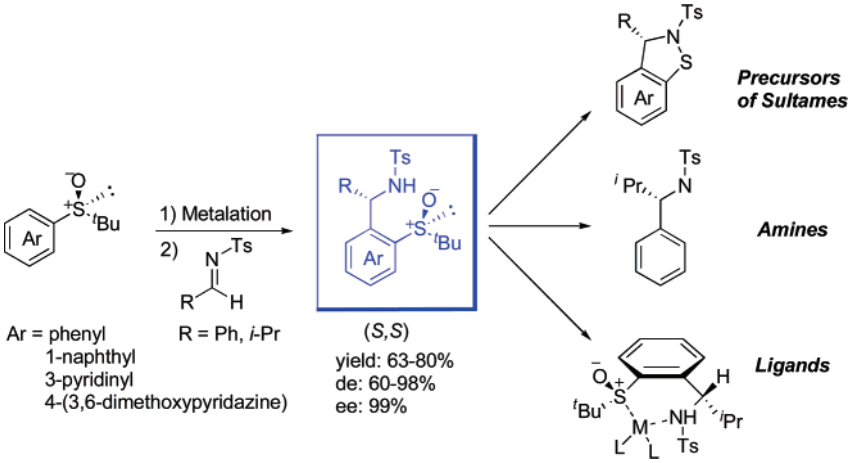

Enantiopure aromatic (phenyl, naphthyl) and heteroaromatic (pyridyl, quinolyl, diazinyl) sulfoxides have been synthesized by reaction of (*S*)-*tert*-butyl *tert*-butanethiosulfinate with aryl- or heteroaryllithium derivatives. The *ortho*-directed metalation of the sulfoxides was performed with lithium bases. Subsequent addition of the lithiated intermediates to *N*-tosylimines afforded tosylaminoalkyl *tert*-butylsulfinyl arenes. In most cases a complete asymmetric induction was highlighted in favor of (*S*,*S*) isomers. Heating the aminosulfoxides provided an original cyclization to form novel cyclic sulfenamides. A novel enantiopure synthesis of a benzylamine was described. An application of an enantiopure aminosulfoxide as *N*,*S* ligand for the asymmetric catalysis of allylic nucleophilic substitution has been successfully tested.

Introduction

An efficient and largely developed strategy for the stereocontrolled creation of C−C bonds involves a sequence of deprotonation and addition of a prochiral electrophile. The first step is activated by an electron-withdrawing group (such as a carbonyl, an imine, a hydrazone, a sulfoxide, etc.), which may incorporate a chiral auxiliary. We became interested in a similar strategy in the aromatic series, using the sulfinyl group[1−5] to provide both *ortho*-directed metalation[6] and a stereogenic element (Scheme 1).

Some stereogenic *ortho*-directing groups have been studied: oxazolines,[7] masked aldehydes,[8−10] amides,[11−13] sulfonamides,[14]

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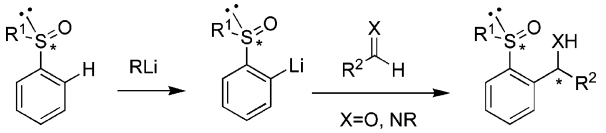
SCHEME 1. Deprotonation of Aryl Sulfoxides and Addition of Prochiral Electrophiles



and also sulfoxides.[15−17] The prochiral electrophiles used were aldehydes or ketones (leading to chiral alcohols), and the best asymmetric induction (excluding sulfoxides) was observed by Matsui[12,13] with amides (de = 80%). In the course of our studies on the synthesis and metalation of diazine and benzodiazine sulfoxides,[16,18,19] we observed that the addition of the metalated species to aldehydes took place in some cases with a remarkable asymmetric induction. Surprisingly, imines (leading to attractive chiral amines) were not used previously as prochiral electrophiles. This prompted us to use imines as electrophile with aromatic substrates, such as phenyl and naphthyl sulfoxides. This opens the way to a new class of bidentate ligands with nitrogen and sulfur coordination sites for asymmetric catalysis.[20−23]

Preparation of Sulfoxides. We wished to prepare a variety of sulfoxides bearing an aryl and a *tert*-butyl group. The latter was chosen as it provides steric hindrance, relative to the conventional *p*-tolyl group, and avoids any competition with proton abstraction of a primary or secondary alkyl group or that of another aromatic substituent.

The aromatic moieties of the sulfoxides that we selected are benzene, naphthalene, pyridine, quinoline, and diazine (Figure 1). Compounds **1** and **2** were prepared previously[24,25] in the respective (*S*) and (*R*) enantiomeric form by other methods, whereas enantiopure **3**−**5**, or their antipodes, were not reported previously.

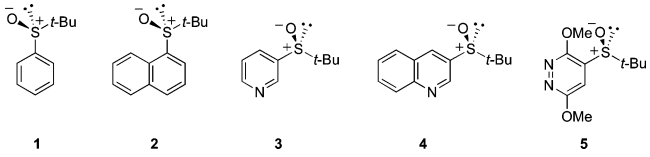
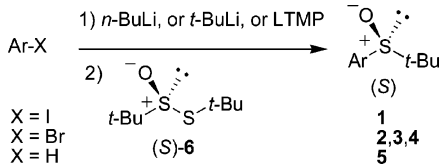


FIGURE 1. Enantiopure (*S*)-sulfoxides.

SCHEME 2. Synthesis of Enantiopure Sulfoxides 1−5



Numerous methods have been developed to prepare enantiopure sulfoxides, among which the S_N2 Andersen's reaction of menthyl sulfinate with organolithiums or Grignards is extremely popular.[2,26,27] It is however restricted to the synthesis of *p*-tolyl substrates.

For the preparation of alkyl sulfoxides, two main methods have emerged. Alcudia and Khiar[4,28] used DAG (diacetone-D-glucosyl) alkanesulfinates, or more recently DGG,[29] instead of menthyl sulfinate. Ellman[30−32] employed *tert*-butyl *tert*-butanethiosulfinate as a chiral source. Based upon preliminary results of the Bolm group,[33] oxidation of *tert*-butyl disulfide by hydrogen peroxide in the presence of 0.5% of an imine derived from (1*R*,2*S*)-1-amino-2-indanol and $VO(acac)_2$ and subsequent crystallization provided[32] (*S*)-*tert*-butyl *tert*-butanethiosulfinate **6** in essentially enantiopure form (ee ≥ 99%). This method has attractive features: low cost of the substrates, low loadings of the catalyst and ligand, easy procedure and scale-up, and availability of both enantiomers.

Results and Discussion

The synthesis of sulfoxides **1**−**5** was achieved (Scheme 2, Table 1) by standard halogen−lithium exchange between iodo- or bromo-arene derivatives and butyllithium at low temperature (entries 1−4), or by *ortho*-directed metalation (entry 5), followed by addition of thiosulfinate **6**.

The yields were good (76−97%, entries 1−3), except for 3-bromoquinoline (entry 4), for which some quinoline was obtained (32%). In all cases the enantiomeric excess was ≥ 99%. For products **1** and **2**, their α_D and comparison with literature data[24,25] showed that their stereochemistry is (*S*), thus arising from inversion of the thiosulfinate sulfur atom configuration, in agreement with previous observations.[31,32]

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TABLE 1. Preparation of (*S*)-Sulfoxides 1−4

entry	starting material	metalating agent	solvent	temp (°C)	time (h)	product	yield (%)	ee (*S*)
1	iodobenzene	*n*-BuLi	THF	−75	0.5	**1**	85	≥99
2	1-bromonaphthalene	*n*-BuLi	THF	−75	0.5	**2**	86	≥99
3	3-bromopyridine	*n*-BuLi	THF	−100	0.5	**3**	76	≥99
4	3-bromoquinoline	*t*-BuLi	Et_2O	−100	2	**4**	37	≥99
5	3,6-dimethoxypyridazine	LTMP	THF	−75	1.5	**5**	97	≥99

The pyridazine sulfoxide **5** was synthesized by *ortho*-directed metalation of 3,6-dimethoxypyridazine followed by reaction of thiosulfinate **6**. The yield and the enantiomeric purity were excellent.

Metalation of Aromatic Sulfoxides and Reaction with *N*-Tosylimines. Though sulfoxides have attracted a great deal of attention in asymmetric synthesis,[4,34] the metalation of the aryl substrates remains under exploited. This group is potentially enhancing the acidity of the *ortho* hydrogen atoms and stabilizing the resulting species by coordination to the metal. The first reports are by Furukawa et al. on the pyridine series.[35−37] Deprotonation was effected by LDA, and the intermediates were quenched by a variety of electrophiles. Further studies by Snieckus and his group[17,38] were carried out in the benzene series using *n*-BuLi. They reported that the sulfinyl group is a more efficient *ortho*-directing group than OMOM, $CONEt_2$, and NHBoc. The naphthalene series has also been explored but has led to moderate yields.[39,40]

The reported lithiated sulfoxides were submitted to the reaction of a variety of electrophiles. With racemic sulfoxides and aldehydes, the diastereoselectivity of the addition was usually modest: for *tert*-butylsulfinylbenzene and 2-chloro-4-tolylylsulfinylbenzene,[15] de's were in the range of 10−38%. For 2-arylsulfinylpyridines,[36] de's varied from 5% to 74%. Our group has examined two other series in the enantiopure form, 3-pyridine and pyridazine. Pollet[16] has demonstrated that the induction can be made complete by employing hindered aldehydes (de > 98%).

From these observations we anticipated that addition of the lithiated sulfoxides to imines could lead[41−43] to C−C bond formation with a higher degree of stereocontrol, as compared to aldehydes, as a result of (i) the presence of a substituent on the heteroatom of the electrophile, and (ii) the possible introduction of a lithium coordinating substituent on the nitrogen atom, such as a sulfonyl group.

Prior to the addition of imines, we needed to carry out the metalation of sulfoxides **1**−**5**. Deprotonation of racemic **1** has been reported[38] with *n*-BuLi. For the naphthalene sulfoxide **2**, the modest yields reported[39] led us to optimize the reaction conditions by carrying out deprotonation with LDA and LTMP in THF at −78 °C, followed by quenching with EtOD (Scheme 3). We observed that an excess of LTMP afforded a 90% deuterium incorporation (Table 2). The more activated pyridine sulfoxide **3** could be deprotonated at C_4 by 2.2 equiv of LDA. Diazine **5** has been previously metalated by LTMP.[16]

SCHEME 3. Metalation and Deuteration of Sulfoxides 2 and 3

2 Ar = 1-Naphthyl
3 Ar = 3-Pyridyl

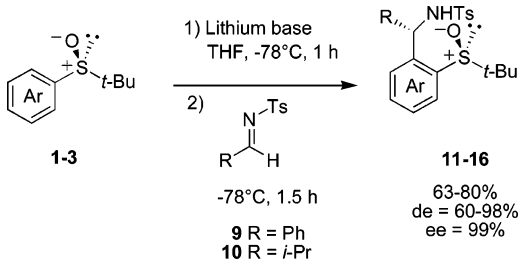
7
8

TABLE 2. Optimization of the Metalation of Naphthyl and Pyridyl Sulfoxides 2 and 3

entry	racemic sulfoxide	base	equiv	time (h)	product	deuteration incorporation[a] (%)
1	**2**	LDA	2.2	1	**7**	39
2	**2**	LTMP	2.2	1	**7**	58
3	**2**	LTMP	3.2	1	**7**	90
4	**3**	LDA	1.2	1	**8**	70
5	**3**	LDA	1.2	2	**8**	60
6	**3**	LDA	2.1	1	**8**	90

[a] Content of deuterium was determined by ^1H NMR.

SCHEME 4. Metalation of Sulfoxides 1−3 and Addition of *N*-Tosylimines



1-3

-78°C, 1.5 h

9 R = Ph
10 R = *i*-Pr

11-16

63-80%
de = 60-98%
ee = 99%

The reactivity of the resulting metalated sulfoxides was first tested with unactivated *N*-alkyl or phenyl imines. The addition did not take place. We pursued our study with imines bearing an electron-withdrawing group on the nitrogen atom. We chose the *N*-tosyl group, in connection with its steric hindrance (sp^3 tetrasubstituted sulfur atom) and presence of oxygen atoms for coordination to lithium with potentially ordered transition states.

Phenyl sulfoxide **1** was lithiated as indicated above and submitted to *N*-tosyl imines[44] of benzaldehyde **9** (R = Ph) or isobutyraldehyde **10** (R = *i*-Pr) for 1.5 h at −78 °C (Scheme 4). The awaited tosylamino-sulfoxides **11** and **12** were obtained in 63−80% yields (Table 3, entries 1 and 2).

With the tosylimine of benzaldehyde **9** (R = Ph, entry 1), a modest diastereoisomeric excess of 60% was observed, and the

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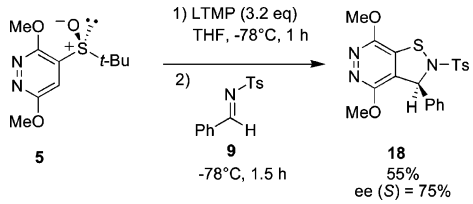
TABLE 3. Metalation of Sulfoxides 1−3 and Addition of *N*-Tosylimines

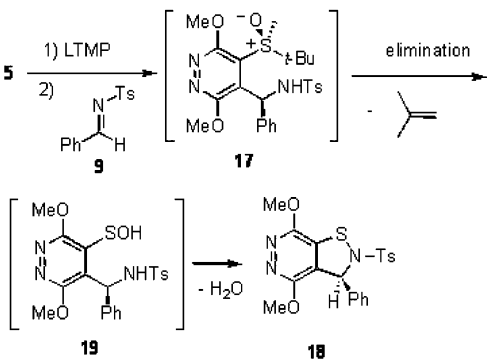
entry	sulfoxide	deprotonation conditions[a]	imine[b] R	product	yield (%)	de[c] (%)	ee[d] (%)
1	**1**	*n*-BuLi (1.2 equiv)	Ph	**11a**, **11b**	63	60[e]	99
2	**1**	*n*-BuLi (1.2 equiv)	*i*-Pr	**12**	80	>98	99
3	**2**	LTMP (3.2 equiv)	Ph	**13**	64	>98	99
4	**2**	LTMP (3.2 equiv)	*i*-Pr	**14**	66	>98	99
5	**3**	LDA (2.1 equiv)	Ph	**15**	79	>98	99
6	**3**	LDA (2.1 equiv)	*i*-Pr	**16**	67	>98	99

[a] −78 °C for 1 h. [b] −78 °C for 1.5 h. [c] Diastereomeric excess (*SS*/*SR*) was measured by ^{1}H NMR on the crude product. [d] Enantiomeric excess (*SS*/*RR*) was determined by enantioselective HPLC (Chiralpak AD column). [e] Diastereomers were separated by column chromatography.

SCHEME 5. Metalation of Sulfoxide 5 and Addition of *N*-Tosylimine 9



SCHEME 6. Formation of 18



two diastereoisomers **11a** and **11b** were easily separated by column chromatography with silica gel. Furthermore the enantiomeric excess measured for each diastereoisomer was 99%. Thus, no racemization of the sulfoxide occurred during the metalation process.[45] With an aliphatic tosylimine **10** (R = *i*-Pr, entry 2), the yield was increased and the asymmetric induction was excellent (de >98%). The (*S*) configuration of the new stereogenic center will be established hereunder.

Naphthyl and pyridyl sulfoxides **2** and **3** were deprotonated and imines **9** and **10** were added to the reaction mixture. Good yield of adducts **13**−**16** were isolated. We were rewarded to observe that a single diastereomer was detected by NMR. Their enantiomeric purity is 99%.

A similar sequence was carried out with pyridazine sulfoxide **5**. Instead of the expected adduct **17**, we isolated a cyclic sulfenamide **18** (Scheme 5).

The formation of **18** can be explained by the following pathway (Scheme 6). The aminosulfoxide **17** undergoes a 1,2-elimination or [2,3] sigmatropic process[46] leading to isobutene and a sulfenic acid **19**, The amino group attacks the electrophilic sulfenic acid, followed by elimination of H_2O. The formation of sulfenic acids from sulfoxides is classical but normally takes place at higher temperatures. The present structure may present specific features, possibly an electronic effect and/or a hydrogen bond stabilizing[47] the intermediate **19**.

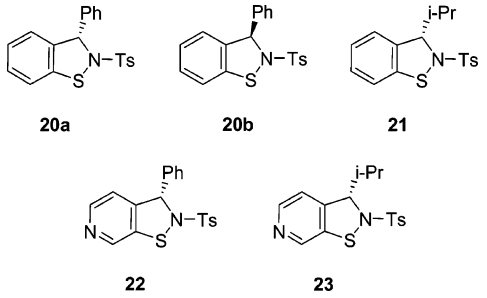


FIGURE 2. Enantioenriched isothiazolines.

TABLE 4. Cyclization of the Aminosulfoxides 11, 12, 15, and 16 into Isothiazolines 20−23

aminosulfoxide	product	yield (%)	configuration	ee (%)
11a (*S*,*S*)	**20a**	93	(*S*)	98
11b (*S*,*R*)	**20b**	93	(*R*)	99
12 (*S*,*S*)	**21**	85	(*S*)	97
15 (*S*,*S*)	**22**	83	(*S*)	99
16 (*S*,*S*)	**23**	89	(*S*)	95

This unprecedented and facile formation of isothiazolines and the interest of this structure led us to investigate the thermolytic behavior of previous aminosulfoxides **11**−**16**. Heating in toluene for 20 min nicely provided cyclic sulfenamides **20**−**23** in very good yields and excellent enantiomeric excesses (Table 4, Figure 2).

The new structures **11**−**16**, **18**, and **20**−**23** offer interesting synthetic possibilities. We have briefly explored the reductive cleavage of the stereogenic sulfur moiety as a synthesis of enantiopure amines. The reaction of sulfoxide **12** with freshly prepared Raney nickel in boiling ethanol was very slow. We then attempted the Raney nickel reduction of sulfenamide **21** and observed that it took place rapidly at room temperature to afford amine **24** in quantitative yield (the sulfonamide being untouched) and 99% ee. The overall transformation of **12** into **24** could also be performed without isolation of **21** in 81% yield (Scheme 7).

Tosylamine **24** is a known product[48] and the optical rotation indicated that we obtained the (*S*) isomer. As the initial sulfur configuration is (*S*), we assign an (*S*,*S*) structure to the aminosulfoxide **12** and propose by analogy that the major diastereomer **11** and compounds **12**−**16** have the same (*S*,*S*) stereochemistry.

A preliminary test was carried out to show that aminosulfoxides could be used as *N*,*S* chiral ligands for asymmetric organometallic catalysis (Figure 3). This type of bidentate coordination for soft transition metals is still underdeveloped.[23,49−57]

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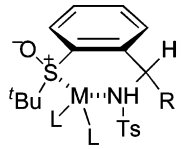
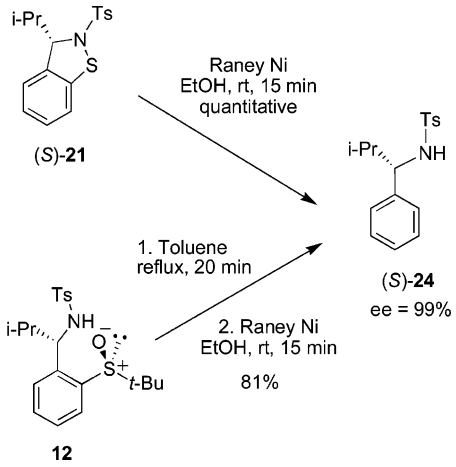
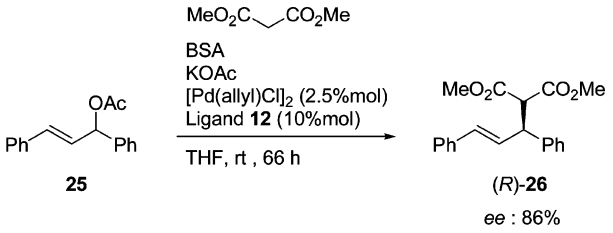


FIGURE 3. Complexes of *N*,*S*-bidentate ligands.

SCHEME 7. Synthesis of an Enantiopure Tosylamine



SCHEME 8. Enantioselective Allylic Nucleophilic Substitution



We tested **12** as a ligand for the catalytic asymmetric allylic nucleophilic substitution.[58−61] 1,3-Diphenyl-2-propenyl acetate **25** was reacted with the anion of methyl malonate under standard conditions in the presence of a palladium catalyst and 10% of our ligand **12** (Scheme 8). Allylic ester **26** was indeed produced with a 95% substitution rate (determined by ^{1}H NMR spectroscopy of the crude product), and enantioselective HPLC showed a good enantiomeric excess (86%) in favor of the (*R*) isomer.

Discussion

We have used with success the sequence of aromatic sulfoxide deprotonation and addition to activated imines. The *ortho*-metalation was applied to a variety of sulfoxides using *n*-BuLi or lithium dialkylamides.

We have reported the first investigation of the behavior of sulfinylaryllithiums toward imines. As anticipated, it was necessary to activate the electrophiles. The choice of *N*-tosyl imines led to good yields (63−80%) of aminosulfoxides **11**−**16**.

Except for the case of phenyl sulfoxide **1** and the imine **9** of benzaldehyde, the adducts **12**−**16** were produced as single diastereoisomers and enantiomers. This stands in contrast with the known reaction of aldehydes, which does lead to an efficient C−C bond formation, but with poorer diastereoselectivities.

The (*S*) stereochemistry of the newly formed carbon center was established by chemical correlation. Reductive desulfinylation of sulfenamide **21** provides a new access to amine **24** and potentially to a variety of benzylic amines.

Our results confirm the power of the sulfinyl group to direct the metalation and to control the approach of an electrophile. As indicated in the introduction, this strategy has been developed in the aliphatic series, including reaction with imines.[41,62−68] For aromatic compounds, the closest structures are those investigated by Garcia-Ruano and his group,[69,70] which involved sulfinylbenzenes, but the metalation was achieved in a benzylic position and then reacted with tosylimine **9**. In this case the diastereoselectivity is modest (de = 38%).

Our access to aminosulfoxides **11**−**16**, with (*S*,*S*) configuration, deserves some comment. Examination of possible approaches of the sulfinyl carbanion and the imine led us to the observation that a pseudo-cyclic chair type transition state does not lead to the observed configuration. We propose a different model, involving (i) a concerted four-membered transition state, as proposed by Garcia Ruano for the reaction of a sulfinyl benzylic carbanion with imines,[69,71] and (ii) coordination of the lithium atom with both the *tert*-butylsulfinyl oxygen atom and one of the two sulfonylimine oxygen atoms.

We shall take as model the simplest sulfoxide: (*S*)-*tert*-butylsulfinylbenzene **1**. Figure 4 represents the isolated lithiated molecule in the most stable conformation according to ab initio DFT calculations. A strong lithium−oxygen interaction was noticed (O−Li bond order, 0.49). The sulfoxide and the lithium

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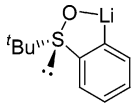

FIGURE 4. Lithiated sulfoxide **1**.

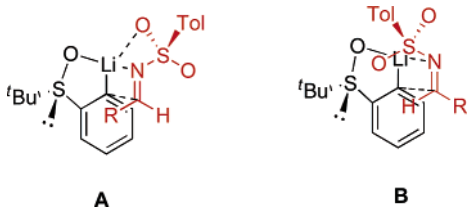

FIGURE 5. Proposed model.

atom form a flat five-membered ring, coplanar with the benzene ring. The lower face of these rings is clearly hindered by the *tert*-butyl group, so that an electrophile will approach from the upper face.

The imine has an (*E*)-configuration and a conformation in which the tolyl group is *anti* to the N=C bond (along the N−S bond).[72] With these elements, we assume two modes of attack, **A** and **B** (Figure 5).

The face of attack of the imine does not appear well differentiated by the interaction of R imine group with the aromatic ring of the sulfoxide. The tolylsulfonyl group provides a significant difference between **A** and **B**. It is a bulky group, as suggested by the conformational energy[73] of 2.5 kcal/mol for SO_2Me.[74] For the approach **B** the interaction is severe with the sulfinyl group. In a model **A** the tolylsulfonyl is located away from the sulfinyl favoring such an approach, leading to the (*S*,*S*) diastereomer, in agreement with the experimental.

The results reported here provide a nice entry to the new aminosulfoxides **12**−**16**. The sequence is rather straightforward (2 steps from the sulfoxide) and practical. The Ellman enantioenriched thiosulfinate **6** is available[32] in large scale and is easily prepared in the laboratory with low cost (0.52% ligand loading for the enantioselective oxidation).

The only precedent of structures **12**−**16** that we are aware of is in the naphthyl series. The Toru group[75] investigated the addition of methyllithium to racemic [1-(2,4,6-triisopropylphenylsulfinyl)-2-naphthyl]methanimines. They obtained a structure, similar to **13** and **14**, interestingly possessing an opposite relative stereochemistry.

Aminosulfoxides **12**−**16** are potential bidentate ligands for asymmetric synthesis mediated by transition metals. One example has been reported here, showing an enantioselectivity that is one of the highest among *N*,*S*(*O*) ligands.[23,49,76] One of the present strategies to improve catalytic systems is to develop ligands, which are not phosphines, to avoid some of the difficulties that can be met.[77] Among novel ligands, the choice of *N*,*S*(*O*) moieties has been rarely examined.[50−57]More *N*,*S* ligands have been reported recently,[20,22] but their potential has not yet been fully explored.

The unexpected conversion of amino sulfoxides into isothiazolines **20**−**23** brings a promise for further transformations, including reductive cleavage of the sulfenamide moiety to chiral amino thiols.[78−83]

Aminosulfoxides **12**−**16** are also potential precursors of enantioenriched sultames, after oxidation of the sulfur atom and deprotection of the *N*-tosyl group. The latter compounds represent an important class of chiral auxiliaries[84−87]

Conclusion

We have synthesized various aromatic enantiopure sulfoxides by reaction of lithio derivatives with *tert*-butanethiosulfinate with moderate to good yields with an excellent optical purity (≥99%). The enantiopure sulfoxides have been metalated and reacted with *N*-tosylated imines for the first time. Excellent asymmetric inductions have been observed on the new chiral center, except in one case. We have highlighted an original thermal cyclization to analogues of benzisothiazoline. The reduction of the cyclized product allowed the preparation of an enantioenriched amine with a good yield. An example of use as *N*,*S*(*O*) chiral ligand for asymmetric catalysis has also been described. Further studies and applications are in due course.

Experimental Section

General Procedure for Direct Lithiation by Lithium Alkylamide (LTMP or LDA). A solution of *n*-butyllithium (1.6 or 2.5 in hexane) was added to cold (−50 °C), stirred, and anhydrous tetrahydrofuran (10 mL) under an atmosphere of nitrogen. Then 2,2,6,6-tetramethylpiperidine (TMPH) or diisopropylamine (DIPAH) was added. The mixture was warmed to 0 °C. After 20 min, the temperature was lowered to −78 °C, and the substrate to metalate dissolved in 5 mL of THF was added. After stirring for 1 h at −78 °C, the corresponding sulfonylimine was introduced, and stirring was continued for 1.5 h at −78 °C. Hydrolysis was then carried out at −78 °C using a mixture of water, ethanol, and tetrahydrofuran (1/4/5). The reaction solution was warmed to room temperature, and the solvent was evaporated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

[1*S*,(S)*S*]-(−)-*N*-[(2-*tert*-Butylsulfinylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (11a) and [1*R*,(S)*S*]-(−)-*N*-[(2-*tert*-Butylsulfinylphenyl)phenylmethyl]-4-methylbenzenesulfonamide (11b). Metalation of **1** (0.2 g, 1.10 mmol) according to the general procedure for direct lithiation with 1.6 M *n*-BuLi (0.83 mL, 1.32 mmol), followed by reaction with the sulfonylimine **9** (R = Ph) (0.43 g, 1.65 mmol), gave after purification by column

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chromatography (silica gel with Et2O/cyclohexane (4/1) as eluent) a mixture of two diastereoisomers (ratio 80:20 determined by ^{1}H NMR). A subsequent purification by column chromatography (silica gel with dichloromethane/ethyl acetate (9/1) as eluent) gave in a first fraction the major diastereoisomer **11a** (243 mg, 50%) as a white solid, mp 160 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)R}$ = 15.4 min, $t_{1S,(S)S}$ = 18.7 min). $[\alpha]^{20}_D = -149$ (*c* 0.68, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.79 (m, 1H); 7.67 (m, 1H); 7.52 (d, *J* = 8.3 Hz, 2H); 7.37 (m, 2H); 7.10 (d, *J* = 7.9 Hz, 2H); 7.03 (m, 3H); 6.92 (m, 2H); 6.10 (d, *J* = 6.8 Hz, 1H); 6.01 (d, *J* = 6.8 Hz, 1H); 2.36 (s, 3H); 1.22 (s, 9). ^{13}C NMR ($CDCl_3$): δ 143.4 (C); 140.6 (C); 139.6 (C); 137.5 (C); 131.7 (CH); 129.4 (CH); 128.7 (CH); 128.0 (CH); 127.8 (CH); 127.4 (CH); 127.1 (CH); 127.0 (CH); 126.8 (CH); 58.0 (CH); 57.8 (C); 23.2 (CH_3); 21.5 (CH_3). IR (KBr) (cm^{-1}): 2868−3085, 1458, 1332, 1160, 1003, 670. Anal. Calcd for $C_{24}H_{27}NO_3S_2$: C, 65.28; H, 6.16; N, 3.17; S, 14.52. Found: C, 65.51; H, 5.64; N, 2.96; S, 12.80.

A second fraction gave the minor diastereoisomer **11b** (62 mg, 13%) as a white solid, mp 160 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)S}$ = 15.6 min, $t_{1S,(S)R}$ = 19.8 min). $[\alpha]^{20}_D = -135$ (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 1H); 7.47 (d, *J* = 8.3 Hz, 2H); 7.25 (m, 8H); 7.05 (d, *J* = 8.3 Hz, 2H); 6.07 (d, *J* = 6.8 Hz, 1H); 5.39 (d, *J* = 6.8 Hz, 1H); 2.28 (s, 3H); 0.89 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 143.5 (C); 139.9 (C); 139.7 (C); 139.3 (C); 137.2 (C); 131.6 (CH); 129.9 (CH); 129.5 (CH); 129.0 (CH); 128.9 (CH); 128.4 (CH); 128.4 (CH); 127.6 (CH); 127.5 (CH); 57.5 (C); 56.5 (CH); 23.5 (CH_3); 21.9 (CH_3). IR (KBr) (cm^{-1}): 2922−3253, 1440, 1328, 1159, 1057, 1028, 669. Anal. Calcd for $C_{24}H_{27}NO_3S_2$: C, 65.28; H, 6.16; N, 3.17; S, 14.52. Found: C, 64.97; H, 6.47; N, 2.92; S, 12.96.

[1*S*,(S)*S*]-(−)-*N*-[2-Methyl-1-(2-*tert*-butylsulfinylphenyl)-propyl]-4-methylbenzenesulfonamide (12). Metalation of **1** (0.15 g, 0.82 mmol) according to the general procedure for direct lithiation with 1.6 M *n*-BuLi (0.62 mL, 0.99 mmol), followed by reaction with the sulfonylimine **10** (R = *i*-Pr) (0.27 g, 1.2 mmol), gave after purification by column chromatography (silica gel with Et_2O as eluent) **12** (264 mg, 80%) as a single diastereoisomer (ratio >99:1 determined by ^{1}H NMR) and as a white solid, mp 70 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1S,(S)S}$ = 10.7 min, $t_{1R,(S)R}$ = 12.2 min). $[\alpha]^{20}_D = -150$ (*c* 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.78 (d, *J* = 7.7 Hz, 1H); 7.64 (d, *J* = 8.3 Hz, 2H); 7.33 (m, 3H); 7.12 (d, *J* = 8.3 Hz, 2H); 5.75 (d, *J* = 7.5 Hz, 1H); 4.74 (dd, *J* = 7.9 and 3.4 Hz, 1H); 2.33 (s, 3H); 2.17 (m, 1H); 1.14 (s, 9H); 0.78 (d, *J* = 6.8 Hz, 3H); 0.55 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 143.8 (C); 141.6 (C); 138.3 (C); 137.8 (C); 131.4 (CH); 129.9 (CH); 127.9 (CH); 127.3 (CH); 127.3 (CH); 127.0 (CH); 59.4 (CH); 57.9 (C); 34.8 (CH); 23.5 (CH_3); 21.9 (CH_3); 20.4 (CH_3); 15.5 (CH_3). IR (KBr) (cm^{-1}): 2894−3138, 1459, 1323, 1158, 1017, 662. Anal. Calcd for $C_{21}H_{29}NO_3S_2$: C, 61.88; H, 7.17; N, 3.44; S, 15.73. Found: C, 61.89; H, 7.29; N, 3.61; S, 15.42.

[1*S*,(S)*S*]-(−)-*N*-[(1-*tert*-Butylsulfinylnaphthalen-2-yl)phenylmethyl]-4-methylbenzenesulfonamide (13). Metalation of **2** (0.15 g, 0.65 mmol) according to the general procedure for direct lithiation with 2.5 M *n*-BuLi (0.83 mL, 2.07 mmol) and TMPH (0.35 mL, 2.07 mmol), followed by reaction with the sulfonylimine **9** (R = Ph) (0.59 g, 2.28 mmol), gave after purification by column chromatography (silica gel with dichloromethane/Et_2O (9/1) as eluent) **13** (203 mg, 64%) as a single diastereoisomer (ratio >99:1 determined by ^{1}H NMR) and as a white solid, mp 210 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)R}$ = 31.9 min, $t_{1S,(S)S}$ = 36.0 min). $[\alpha]^{20}_D = -142$ (*c* 0.65, DMSO). ^{1}H NMR (DMSO-d_6): δ 9.07 (d, *J* = 8.7 Hz, 1H); 8.77 (m, 1H); 7.90 (d, *J* = 8.7 Hz, 1H); 7.71 (d, *J* = 7.2 Hz, 1H); 7.64 (d, *J* = 8.7 Hz, 1H); 7.32 (m, 4H); 7.00 (d, *J* = 7.9 Hz, 2H); 6.90 (m, 3H); 6.82 (m, 2H); 6.28 (m, 1H); 2.08 (s, 3H); 1.01 (s, 9H). ^{13}C NMR (DMSO-d_6): δ 142.9 (C); 142.6 (C); 141.0 (C); 138.7 (C); 133.3 (C); 133.0 (CH); 132.4 (C); 129.7 (C); 129.6 (CH); 128.8 (CH); 128.7 (CH); 127.5 (CH); 127.3 (CH); 127.1 (CH); 126.8 (CH); 126.5 (CH); 126.0 (CH); 124.6 (CH); 60.0 (C); 57.4 (CH); 25.4 (CH_3); 21.3 (CH_3). IR (KBr) (cm^{-1}): 2786−3027, 1340, 1163, 1007. Anal. Calcd for $C_{28}H_{29}NO_3S_2$: C, 68.40; H, 5.94; N, 2.85; S, 13.04. Found: C, 68.10; H, 6.12; N, 3.04; S, 12.79.

[1*S*,(S)*S*]-(−)-*N*-[2-Methyl-1-(1-*tert*-butylsulfinylnaphthalen-2-yl)propyl]-4-methylbenzenesulfonamide (14). Metalation of **2** (0.15 g, 0.65 mmol) according to the general procedure for direct lithiation with 2.5 M *n*-BuLi (0.83 mL, 2.07 mmol) and TMPH (0.35 mL, 2.07 mmol), followed by reaction with the sulfonylimine **10** (R = *i*-Pr) (0.47 g, 2.1 mmol), gave after purification by column chromatography (silica gel with dichloromethane/acetone (95/5) as eluent) **14** (197 mg, 66%) as a single diastereoisomer (ratio >99:1 determined by ^{1}H NMR) and as a white solid, mp 170 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)R}$ = 14.4 min, $t_{1S,(S)S}$ = 17.8 min). $[\alpha]^{20}_D = -157$ (*c* 0.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.34 (m, 1H); 7.69 (m, 4H); 7.51 (d, *J* = 8.7 Hz, 1H); 7.41 (m, 2H); 7.15 (d, *J* = 8.3 Hz, 2H); 5.75 (d, *J* = 8.3 Hz, 1H); 5.22 (m, 1H); 2.31 (m, 4H); 1.24 (s, 9H); 0.82 (d, *J* = 6.8 Hz, 3H); 0.55 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 143.9 (C); 143.4 (C); 138.3 (C); 133.8 (C); 133.6 (C); 132.4 (CH); 130.4 (C); 129.9 (CH); 128.6 (CH); 127.3 (CH); 127.2 (CH); 126.9 (CH); 126.9 (CH); 124.1 (CH); 61.0 (C); 59.6 (CH); 36.0 (CH); 26.2 (CH_3); 21.9 (CH_3); 20.7 (CH_3); 15.8 (CH_3). IR (KBr) (cm^{-1}): 3140, 2898−2965, 1474, 1330, 1162, 1095, 1045, 1012, 670. Anal. Calcd for $C_{25}H_{31}NO_3S_2$: C, 65.61; H, 6.83; N, 3.06; S, 14.01. Found: C, 66.06; H, 6.97; N, 3.08; S, 14.45.

[1*S*,(S)*S*]-(−)-*N*-[(3-*tert*-Butylsulfinylpyridin-4-yl)phenylmethyl]-4-methylbenzenesulfonamide (15). Metalation of **3** (0.15 g, 0.82 mmol) according to the general procedure for direct lithiation with 2.5 M *n*-BuLi (0.72 mL, 1.8 mmol) and DIPAH (0.25 mL, 1.8 mmol), followed by reaction with the sulfonylimine **9** (R = Ph) (0.52 g, 2 mmol), gave after purification by column chromatography (silica gel with ethyl acetate as eluent) **15** (287 mg, 79%) as a single diastereoisomer (ratio >99:1 determined by ^{1}H NMR) and as a pale yellow solid, mp 100 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 75:25 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)R}$ = 9.9 min, $t_{1S,(S)S}$ = 12.4 min). $[\alpha]^{20}_D = -65$ (*c* 1.17, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.83 (s, 1H); 8.61 (d, *J* = 4.9 Hz, 1H); 7.64 (d, *J* = 5.3 Hz, 1H); 7.52 (d, *J* = 8.3 Hz, 2H); 7.15 (m, 6H); 6.77 (d, *J* = 7.5 Hz, 2H); 5.76 (d, *J* = 6.0 Hz, 1H); 5.58 (d, *J* = 6.0 Hz, 1H); 2.37 (s, 3H); 1.21 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 152.7 (CH); 149.6 (C); 149.2 (CH); 144.5 (C); 138.1 (C); 137.3 (C); 133.9 (C); 130.1 (CH); 129.7 (CH); 129.2 (CH); 128.0 (CH); 127.5 (CH); 121.3 (CH); 58.6 (C); 58.4 (CH); 23.4 (CH_3); 22.0 (CH_3). IR (KBr) (cm^{-1}): 2861−3061, 1720, 1333, 1166, 1089, 1027, 577. Anal. Calcd for $C_{23}H_{26}N_2O_3S_2$: C, 62.42; H, 5.92; N, 6.33; S, 14.49. Found: C, 62.74; H, 5.89; N, 6.41; S, 14.56.

[1*S*,(S)*S*]-(−)-*N*-[2-Methyl-1-(3-*tert*-butylsulfinylpyridin-4-yl)-propyl]-4-methylbenzenesulfonamide (16). Metalation of **3** (0.15 g, 0.82 mmol) according to the general procedure for direct lithiation with 2.5 M *n*-BuLi (0.72 mL, 1.8 mmol) and DIPAH (0.25 mL, 1.8 mmol), followed by reaction with the sulfonylimine **10** (R = *i*-Pr) (0.45 g, 2 mmol), gave after purification by column chromatography (silica gel with ethyl acetate as eluent) **16** (223 mg, 67%) as a single diastereoisomer (ratio >99:1 determined by ^{1}H NMR) and as a pale yellow solid, mp 170 °C. The ee was 99% by HPLC (Chiralpak AD column, 1 mL/min, 80:20 heptane/*i*-PrOH, λ = 230 nm, $t_{1R,(S)R}$ = 9.8 min, $t_{1S,(S)S}$ = 18.3 min). $[\alpha]^{20}_D = -118$ (*c* 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 9.14 (s, 1H); 8.74 (d, *J* = 5.3 Hz, 1H); 7.85 (d, *J* = 8.3 Hz, 2H); 7.57 (d, *J* = 4.9 Hz, 1H); 7.41 (d, *J* = 7.9 Hz, 2H); 6.49 (d, *J* = 7.9 Hz, 1H); 4.83 (m, 1H); 2.57 (s, 3H); 2.47 (m, 1H); 1.43 (s, 9H); 1.07 (d, *J* = 6.8 Hz, 3H); 0.79 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 152.1 (CH); 151.0 (C); 149.0 (CH); 144.2 (C); 137.7 (C); 133.7 (C); 130.0 (CH); 127.3 (CH); 121.4 (CH); 59.2 (CH); 58.4 (C); 34.1 (CH); 23.4 (CH_3);

22.0 (CH_3); 20.6 (CH_3); 15.3 (CH_3). IR (KBr) (cm^{-1}): 2967−3166, 1474, 1331, 1159, 1046, 1012, 670. Anal. Calcd for $C_{20}H_{28}N_2O_3S_2$: C, 58.79; H, 6.91; N, 6.86; S, 15.70. Found: C, 59.19; H, 7.28; N, 7.02; S, 15.15.

(*S*)-(−)-4,7-Dimethoxy-3-phenyl-2-(toluene-4-sulfonyl)-2,3-dihydro-isothiazolo[4,5-*d*]pyridazine (18). Metalation of **5** (0.16 g, 0.66 mmol) according to the general procedure for direct lithiation with 2.5 M *n*-BuLi (0.85 mL, 2.12 mmol) and TMPH (0.35 mL, 2.12 mmol), followed by reaction with the sulfonylimine **9** (R = Ph) (0.57 g, 2.2 mmol), gave after purification by column chromatography (silica gel with dichloromethane/cyclohexane (8/2) as eluent) **18** (155 mg, 55%) as a pale yellow solid, mp < 50 °C. The ee was 75% by HPLC (Chiralcel OD column, 1 mL/min, 90:10 heptane/*i*-PrOH, $\lambda = 230$ nm, $t = 8.1$ min, $t = 10.3$ min). $[\alpha]^{20}_D = -292$ (*c* 0.73, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.68 (d, $J =$ 8.2 Hz, 2H); 7.25 (m, 5H); 7.04 (d, $J = 8.2$ Hz, 2H); 6.37 (s, 1H); 3.92 (s, 3H); 3.89 (s, 3H); 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 158.1 (C); 156.4 (C); 145.9 (CH); 135.8 (C); 134.2 (C); 130.9 (C); 129.5 (CH); 129.5 (CH); 129.2 (CH); 128.9 (CH); 127.4 (CH); 127.0 (C); 71.1 (CH); 55.4 (CH_3); 55.3 (CH_3); 22.0 (CH_3). IR (KBr) (cm^{-1}): 2922−3059, 1468, 1373, 1171, 1029, 673. Anal. Calcd for $C_{20}H_{19}N_3O_4S_2$: C, 55.93; H, 4.46; N, 9.78. Found: C, 56.28; H, 4.77; N, 9.46.

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Supporting Information Available: Detailed experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of compounds **1**−**5**, **11**−**16**, **18**, **20**−**23**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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