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Facile synthesis of enantioenriched phenol-sulfoxides and their aluminum complexes†

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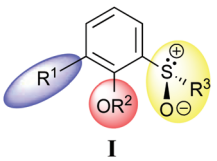
Chiral phenolic *p*-tolylsulfoxides and *t*-butylsulfoxides were prepared by several short synthetic routes starting from readily available starting materials. The key synthetic step was the reaction of lithiated arenes with menthyl sulfinates or enantioselective oxidation of a *t*-butyl sulfide. Well-defined neutral ligand–$AlMe_2$ complexes were obtained by stoichiometric treatment with $AlMe_3$.

Introduction

The preparation of optically active compounds has been a long-standing challenge in organic synthesis. Two main approaches for the synthesis of enantioenriched products starting from achiral molecules are the use of chiral auxiliaries and enantioselective catalysis.[1–3] The former requires the stepwise introduction and removal of a chiral moiety, while the latter relies on direct formation of a desired stereoisomer. Both strategies can provide access to products in high yields as well as excellent enantiomeric excess, and the choice of the synthetic route towards a specific target will depend on many factors, such as, obviously, the transformation to be performed, the availability of an enantioselective methodology, costs of materials involved, ease of operation, *etc*. The quest for improved stereoselective reactions is a remaining challenge in academic research and industry, and therefore the development of new classes of reagents that are capable of transferring stereochemical information to target compounds is still of high significance.

The research into and increased use of chiral sulfoxides as auxiliaries and ligands for enantioselective reactions over the past two decades may well be termed a success story. The sulfoxide moiety as a stereogenic unit exhibits several favorable properties: (1) configurational inertness, (2) synthetic accessability of both enantiomers and (3) creation of a chiral environment that enables reactions with exceptional enantioinduction, based on the steric and electronic differences of the lone pair, oxygen atom and organic group attached to sulfur.[4–7] Furthermore, either oxygen or sulfur can act as the coordinating atom towards metal centers when sulfoxides are used as ligands, adding an interesting facet to their chemistry.[8] In terms of chiral auxiliaries, the *t*-butane-sulfinamide group is the most prominent example of a stoichiometric sulfoxide-based reagent in the synthesis of natural products and biologically active compounds, including pharmaceuticals and agrochemicals.[9] With regard to use in catalysis, ligands binding to transition metals based on S(O)–N, S(O)–P, S(O)–S, S(O)–olefin and S(O)–Cp (Cp = cyclopentadienyl) coordination have been reported. Primarily in combination with Pd, Rh and Ru, the resulting complexes have proven to be highly effective in enantioselective transformations such as allylic alkylations as well as 1,2- and 1,4-addition reactions to carbonyl groups.[10,11]

Compared to the plethora of chiral reagents derived from naturally occurring amines/amino acids or based on chiral phosphines, the number of hitherto known sulfoxide frameworks is still limited. We therefore sought to develop a class of compounds combining a central phenolic functionality flanked by a stereogenic sulfoxide moiety and an additional substituent confining sterics (**I**, Fig. 1).[12] From this design we anticipated a tunable chiral cone around the central group. Furthermore, targeting phenol-based products, a range of



I

R^1 = Substituent confining sterics
OR^2 = (Lewis-)Acidic or (Lewis-)basic functionality
$S(O)R^3$ = Chiral sulfoxide group

Fig. 1 General framework of chiral target compounds **I** based on a stereogenic sulfoxide moiety.

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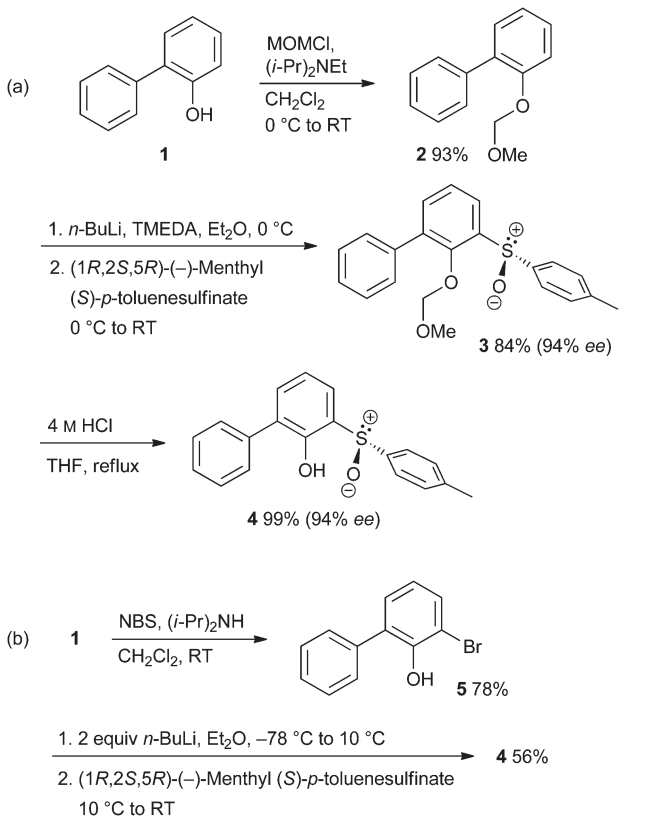
(Lewis-)acidic and (Lewis-)basic reagents should be accessible, such as phenolates, phenolate–metal complexes and phenol–phosphoric acids/phosphates or esters of other inorganic acids. In this work, we report on the synthesis of a series of novel phenol-sulfoxide products. Chiral *p*-tolylsulfoxides and *t*-butylsulfoxides were prepared by several short synthetic routes. Enantioenriched compounds were prepared by reaction of lithiated arenes with menthyl sulfinates or enantioselective oxidation of a *t*-butyl sulfide precursor as the key step. Well-defined neutral ligand–$AlMe_2$ complexes were obtained by stoichiometric treatment with $AlMe_3$.

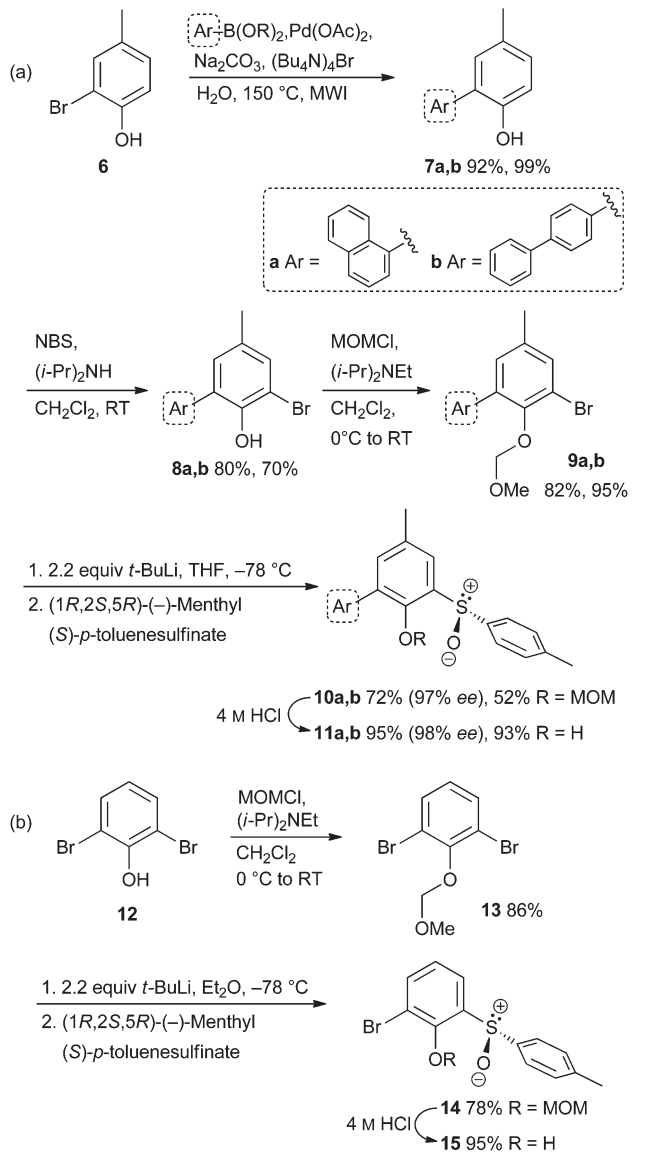
Results and discussion

Our goal was to develop synthetic routes relying on commercially available or easily accessible starting materials. Furthermore, a small number of steps and tunability of the system in terms of the nature of R^1 and R^3 of **I** were aimed at.

At the outset of our studies, we investigated the synthesis of phenol-oxide **4**. 2-Phenylphenol (**1**) was first protected as its MOM (methoxymethyl) ether, lithiated at the free *ortho* position and treated with commercially available (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate to introduce the chiral sulfoxide moiety (Scheme 1a). Subsequent deprotection with hydrochloric acid in tetrahydrofuran afforded product **4**. Each of the steps proceeded in high yield, and the phenol-sulfoxide was obtained with 94% ee. Only in the sulfination step a slight erosion of enantiomeric excess was observed.[13] Product **4** could also be prepared applying a two-step procedure starting from **1**. Bromination of the free phenol with NBS (*N*-bromosuccinimide) gave bromophenol **5** in 78% yield (Scheme 1b).[14] OH-Deprotonation/Br–Li exchange of this intermediate followed by sulfination gave **4** in 56% yield. Even though this second route is shorter as it does not require protection–deprotection steps, the overall yield was found to be lower (44% *vs.* 77%). Furthermore, over-bromination of **1** must be prevented by slow addition of NBS and careful monitoring of the reaction.[15] Commercially available 2-bromo-4-methylphenol (**6**) provided a more versatile access to phenol-sulfox-



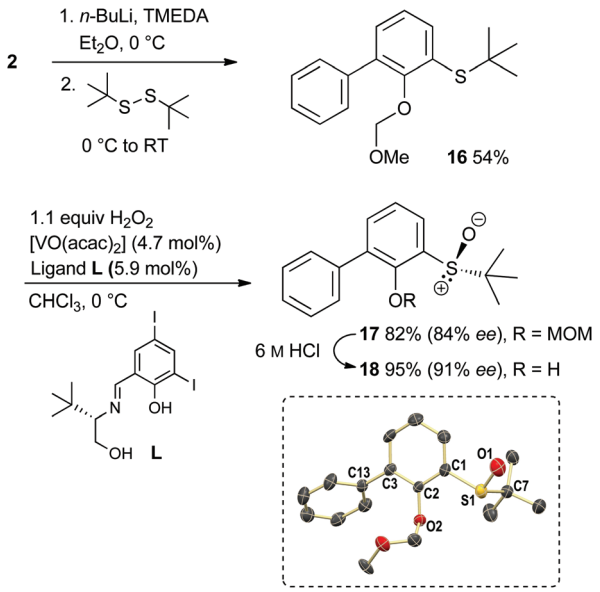
Scheme 1 Synthesis of phenol-sulfoxide **4** by protection–sulfination–deprotection (a) and bromination–sulfination (b).



Scheme 2 Synthesis of phenol-sulfoxides **11** and **15**.

ides **I**. Introduction of an aryl substituent was accomplished by microwave-assisted Pd-catalyzed cross-coupling of **6** with arylboronic acids (Scheme 2a).[16] The coupling with 1-naphthylboronic acid and 4-biphenylboronic pinacol ester was tested. These reactions proceeded efficiently with 0.4 mol% $Pd(OAc)_2$ and a phase-transfer catalyst in water, giving **7a** and **b** in 92% and 99% yield, respectively. Bromination and subsequent MOM protection afforded products **8a,b** and **9a,b** in good overall yields. The 4-methyl substituent in **7a,b** prevented overbromination of the central ring effectively. Br–Li exchange followed by sulfination gave **10a,b**, and final deprotection afforded phenol-oxides **11a,b** in moderate to good yields and high enantiomeric excess (97% and 98% ee, respectively). Bromination of **7a,b** was a necessary step; *ortho*-lithiation of MOM-protected **7a,b** and direct reaction with menthyl sulfinate did not give satisfactory yields; control experiments in which the putative lithiate was quenched with D_2O or I_2 showed little incorporation of iodine or deuterium.

Alternatively, 2,6-dibromophenol (**12**) allowed for a similar synthesis of the target scaffold. MOM protection to give **13**, followed by Br–Li exchange, sulfination and deprotection yielded compound **15** in 65% yield over three steps (Scheme 2b). With the sulfoxide moiety already in place, **15** is a promising compound to undergo Pd-catalyzed cross-coupling reactions at the C–Br position similar to those from **6** to **7**, and we are currently investigating its potential to form phenol-sulfoxides. Crystals suitable for X-ray diffraction were obtained for **10a** and **15**. The observed absolute (*S*) configurations were in agreement with inversion at the sulfur center in the sulfination step using (–)-menthyl (*S*)-*p*-toluenesulfinate. In the solid state, both products prefer a conformation that results in reduced repulsion of the tolyl ring with the OR group of the central ring (Fig. 2). The respective torsion angles for **10a** and **15** are C1–S1–C8–C9 = −78.8° and C7–S1–C6–C1 = −81.5°. Likewise, in **10a** the naphthyl moiety exhibits an orientation with a dihedral angle of 70.8° between the best-fit planes through the naphthyl system and the central ring; the *S*-tolyl and naphthyl substituents are oriented in an *anti* fashion. For **10a** and **11a**, the ^1H and $^{13}C\{^1H\}$ NMR spectra indicated slow rotation about the naphthyl–aryl bond. Because of the stereogenicity at sulfur, the *syn* and *anti* forms gave rise to diastereomers with two sets of signals (see the ESI† for details).



Scheme 3 Synthesis of phenol-sulfoxide **18** by enantioselective oxidation of sulfane **16** and the X-ray crystal structure of **17**; H atoms are omitted for clarity, thermal ellipsoids are drawn at the 30% probability level.

Introduction of a *t*-butyl sulfoxide group was accomplished by sulfane formation and enantioselective oxidation (Scheme 3). Reaction of lithiated **2** with di-*t*-butyl disulfide gave sulfane **16** in 54% yield. This compound was then subjected to mono-oxidation using hydrogen peroxide and the chiral vanadium catalyst derived from $VO(acac)_2$ (acac = acetylacetonate) and Schiff base ligand **L** to afford **17**.[17] The free phenol **18** was obtained in 95% yield and 91% ee after deprotection; the yield over three steps for this route was 42%.[18] The absolute configurations (*R*) were inferred from an X-ray structural analysis of **17**. In the solid state, two molecules of **17** of similar geometry were found in the asymmetric unit with torsion angles of C7–S1–C1–C2 = 90.6°/94.1°, showing conformations comparable to those found for **10a** and **15**.

We then tested the ability of some products to form complexes with Lewis acids. Bromo- and aryl-substituted **15**, **4**, **11b** and **18** underwent a clean reaction with $AlMe_3$ to give 1 : 1

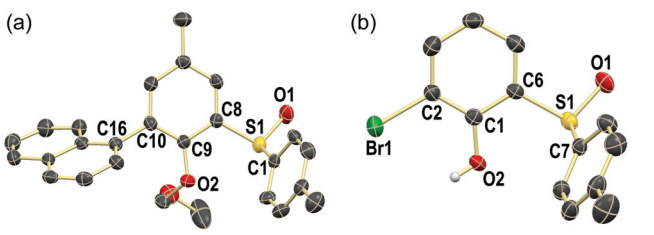
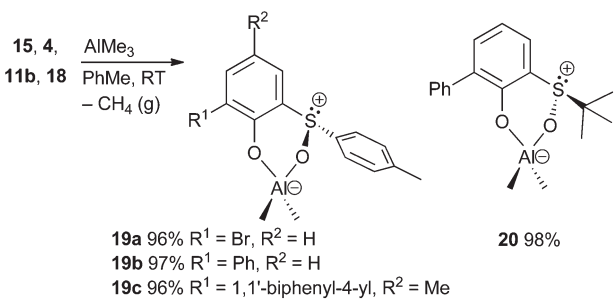


Fig. 2 X-ray crystal structures of **10a** (a) and **15** (b); H atoms are omitted for clarity except for O–H, thermal ellipsoids are drawn at the 30% probability level.



Scheme 4 Synthesis of aluminum-phenolate complexes **19** and **20**.

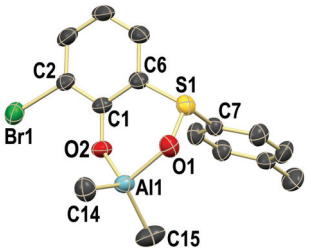


Fig. 3 X-ray crystal structure of aluminum complex **19a**; H atoms are omitted for clarity, thermal ellipsoids are drawn at the 30% probability level.

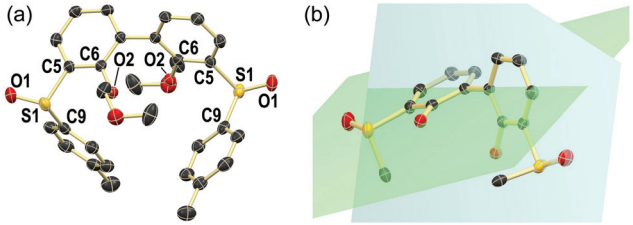


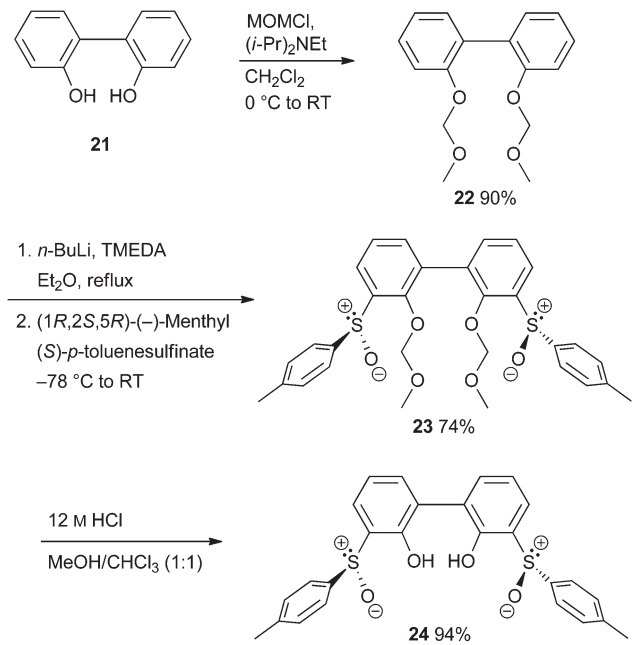
Fig. 4 X-ray crystal structure of protected bis-sulfoxide **23**; H atoms are omitted for clarity, thermal ellipsoids are drawn at the 30% probability level. ORTEP representation showing all C, O and S atoms (a); side view with best-fit planes through the biaryl rings showing only C9 of the tolyl rings and O2 of the MOM groups (b).

O–S(O)–$AlMe_2$ aluminates **19a–c** and **20** in toluene at room temperature (Scheme 4). Their identity and ligand : Al ratio were elucidated by NMR spectroscopy and an X-ray structural analysis of **19a**. ^{1}H, $^{13}C\{^{1}H\}$ and 2D (HSQC, HMBC) NMR spectra showed no unusual features apart from line broadening of certain signals because of coupling to ^{27}Al, which has a quadrupole moment owing to its nuclear spin of $I = 5/2$.

Single crystals of **19a** were obtained by slow evaporation of a diethyl ether solution at room temperature. The sulfoxide moiety showed coordination to the Al center through oxygen with bond distances of O1–Al1 = 1.860(4) Å, O2–Al1 = 1.786(3) Å and S1–O1 = 1.545(4) Å (S1–O1 = 1.501(2) Å for **15**) (Fig. 3). The Al1–O1–S1–C6–C1–O2 unit forms a puckered five-membered ring, and the observed torsion angles are O1–S1–C6–C1 = −31.5° and S1–C6–C1–O2 = −4.6°.

In an extension of the synthesis of phenol-sulfoxide products, we also investigated the feasibility of synthesizing a bis-sulfoxide ligand.[21] Biphenol **21** was protected at both OH positions to give **22** in 90% yield (Scheme 5). Subsequent di-*ortho*-lithiation and treatment with (−)-menthyl (*S*)-*p*-toluenesulfinate furnished bis-sulfoxide **23** in 74% yield. Final deprotection with concentrated aqueous HCl gave biphenol-bis-sulfoxide **24** in 94% yield. Thus, starting from the commercially available biphenol, this three-step route provided access to the desired chiral ligand system in 63% overall yield.

Single crystals of **23** were obtained by slow evaporation of a dichloromethane solution at room temperature. The molecular structure exhibited C_2 symmetry with bond distances of S1–O1 = 1.491(3) Å, S1–C5 = 1.810(4) Å and S1–C9 = 1.798(4) Å, comparable to the ones found in **17** (Fig. 4). The central biaryl moiety showed a dihedral angle of 65.3° between the respective best-fit planes. The observed torsion angle of C9–S1–C5–C6 = −80.4° indicated an orientation of the sulfoxide group with respect to the biaryl ring which is almost identical to that found for **10a** and **15**.



Scheme 5 Synthesis of biphenol-bis-sulfoxide **24** starting from biphenol **21**.

Conclusions

In conclusion, we have developed several strategies to prepare phenol-sulfoxides of the general structure **I** based on short syntheses, featuring moderate to good overall yields and high enantiomeric excesses. Aluminate complexes were formed cleanly with four of the free phenols, demonstrating their ability to undergo complex formation with Lewis acids. In addition, a biphenol-bis-sulfoxide system was elaborated and obtained in good overall yield starting from commercially available starting materials. Further research into the versatility of the synthetic procedures, the potential of the phenols to afford complexes with transition metals or esters of inorganic acids and application of the products in catalysis is currently ongoing in our laboratory.

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Tianjin University (P.R. China) for giving us a sample of the ligand for the enantioselective oxidation.

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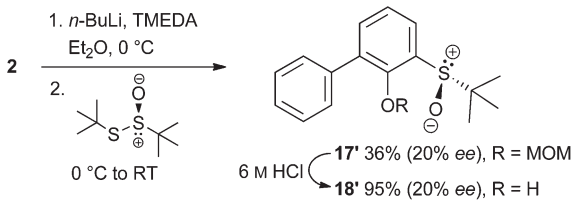

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