

Atropisomerism at C–S Bonds: Asymmetric Synthesis of Diaryl Sulfones by Dynamic Resolution Under Thermodynamic Control**

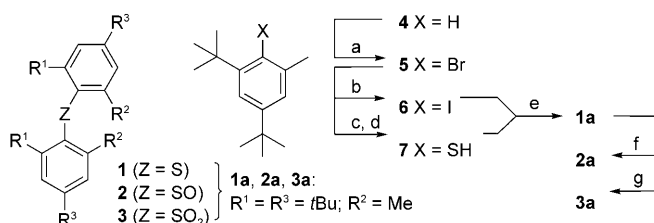
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Dedicated to Professor Marc Julia on the occasion of his 87th birthday

The family of atropisomeric compounds—those containing a bond about which the rotation is sufficiently slow that conformers are separable—includes numerous natural products^[1] and valuable ligands.^[2] Atropisomerism is associated principally with single bonds joining two planar substituents.^[3] The most common of these are the biaryls,^[4] but the last 15 years have seen non-biaryl atropisomers^[5] based on the C–CO bond of amides,^[5a] the C–N bond of anilides^[5b] or urea derivatives,^[5c] and the C–O bond of ethers^[6] come forward as compounds with interesting and valuable structural,^[5d] dynamic,^[5e] mechanistic,^[5f] catalytic/synthetic,^[5g] and biological^[5h] properties. The separation of atropisomers due to slow rotation about C–S bonds has however never been reported, and in this Communication we show for the first time that compounds made chiral by virtue of an atropisomeric C–S bond—in particular diaryl sulfides and sulfones—may be a) resolved and b) made in an enantioselective manner.

Heavily substituted diaryl ethers are known to be atropisomeric.^[6] NMR data suggest that bond rotations in diaryl sulfides **1** are slightly faster than in related diaryl ethers,^[7] but with four *ortho* substituents diaryl sulfides **1** and sulfones **3** are potentially atropisomeric at 25°C.^[8] In 2002, Buchwald and Kwong reported the synthesis of diaryl sulfides **1** by copper-catalyzed arylation of thiophenols.^[9] By adapting their conditions, we found that even the heavily encumbered aryl iodide **6** and thiophenol **7** (both obtained from arene **4** via bromide **5**) gave sulfide **1a** in good yield provided a stoichiometric amount of CuI was employed (Scheme 1). Sulfide **1a** was oxidized to sulfoxide **2a** or sulfone **3a** with *m*CPBA.

The stereochemical properties of sulfoxide **2a** were immediately evident from its ¹H NMR spectrum. Slow rotation about the two Ar–S bonds, combined with the resulting pseudoasymmetric center at sulfur, causes the two rings to occupy diastereomeric environments. A separate set of peaks is accordingly observed for each of the two aromatic rings and their substituents. Compounds **1a**, **2a**, and **3a** (Figure 1a) were furthermore separable into enantiomers by HPLC on a chiral stationary phase, though close to ambient



Scheme 1. Diaryl sulfides, sulfoxides, and sulfones by copper-catalyzed coupling. a) Br₂, Fe, CHCl₃, 0°C, 4 h (55%); b) 1. *t*BuLi, THF, –78°C, 5 min.; 2. I₂, –78°C, 2 h (87%); c) 1. *t*BuLi, THF, –78°C, 5 min.; 2. Me₂S₂, –78°C, 2 h (93%); d) *t*BuSNa (5 equiv), DMF, reflux, 16 h (93%); e) CuI (1 equiv); K₂CO₃ (2 equiv); ethylene glycol (2 equiv), *tert*-amyl alcohol, 120°C, 16 h (79%); f) *m*CPBA (1 equiv), CH₂Cl₂, RT, 1.5 h (80%); g) *m*CPBA (4 equiv), CH₂Cl₂, RT, 16 h (quant.).

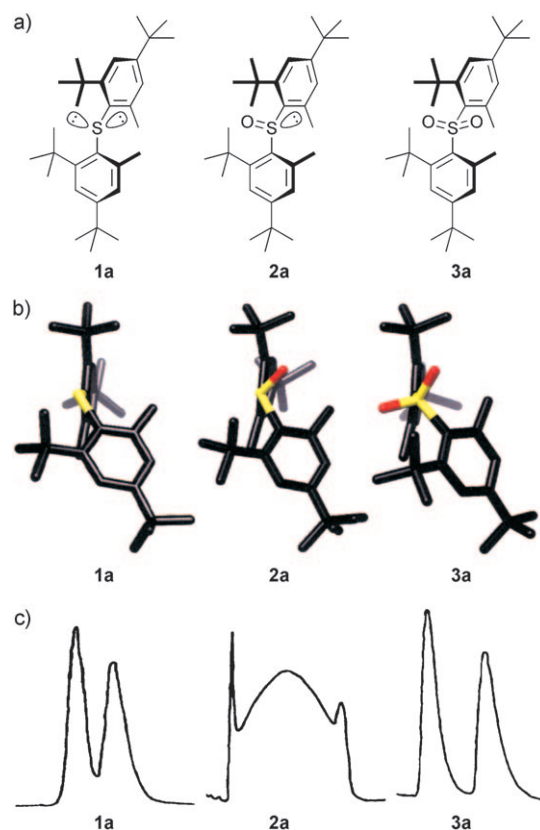


Figure 1. Structure and configuration of sulfide **1a**, sulfoxide **2a**, and sulfone **3a**. a) Structural formulae; b) X-ray crystal structures; c) HPLC traces on a chiral stationary phase (Chiralpak AD-H; **1a** and **3a**: 25°C; **2a**: 17°C).

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temperature sulfoxide **2a** showed the broadened peak shape characteristic of a compound racemizing on the timescale of the HPLC elution (Figure 1c).^[10]

Barriers to racemization of all three compounds were determined,^[11] and are shown in Table 1. Sulfone **3a** racemizes some ten times slower than its sulfide analogue **1a**,

Table 1: Structural parameters for **1a**, **2a** and **3a**.

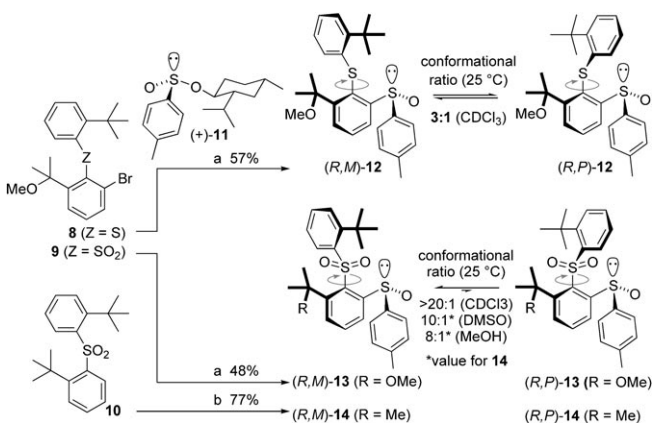
	Sulfide 1a	Sulfoxide 2a	Sulfone 3a
$\Delta G^\ddagger$ [kJ mol ⁻¹] ^[a]	100.8 (40°C)	86.3 (17°C)	106.5 (50°C)
$t_{1/2}^{\text{rac}}$ [h] ^[b]	14 h	70 s	6 days
C–S bond length [pm] ^[c]	179.4	182.0	180.8

[a] Barrier to C–S bond rotation. [b] Estimated half life for racemization (25°C), assuming $\Delta S^\ddagger = 0$. [c] Determined from crystallographic data.

though sulfoxide **2a** racemizes at least three orders of magnitude faster than either **1a** or **3a**. Crystal structures of the three compounds were obtained (Figure 1b):^[12] the enantiomeric instability of **2a** may be related to its longer C–S bond, with steric hindrance contributing to the enantiomeric stability of **3a**.

Having demonstrated for the first time atropisomerism in diaryl sulfides and sulfones, we set out to synthesize them in enantiomerically enriched form. Dynamic resolution under thermodynamic control (dynamic thermodynamic resolution)^[13] is particularly well suited to the asymmetric synthesis of atropisomers^[14] because an enantiomerically pure auxiliary substituent placed adjacent to the potentially atropisomeric axis can lead to a conformational bias in favor of one of the two diastereomeric axial conformers. The most effective controlling auxiliaries employed for this strategy have been sulfoxides.^[5b,6b,14a] In order to evaluate the effectiveness of an adjacent sulfinyl substituent in the control of a C–S axis, we made the sulfoxides **12–14** by lithiating^[15] **8–10** and quenching with (1*S*,2*R*,5*S*)-(+)-menthyl-(*R*_s)-*p*-toluenesulfinate (+)-**11** (Scheme 2).^[16]

Derivatives **12–14** are only tri-*ortho*-substituted about the C–S–C axis, and so presumably^[6,7] cannot exist as atropisomers. Sulfinyl sulfide **12** showed two conformers in a ratio of 3:1



Scheme 2. Synthesis and conformational preference of sulfinyl sulfides and sulfinyl sulfones. a) *n*BuLi, THF, –78°C, 1 min, then (+)-**11**; b) *s*BuLi, THF, –78°C, 30 min, then (+)-**11**.

in its ¹H NMR spectrum at 25°C in CDCl₃, indicating that the sulfinyl substituent exerts only weak control over the C–S axis.^[17] In sulfinyl sulfones **13** and **14** only a single conformer is evident, indicating that the interaction between the sulfinyl substituent and the C–SO₂ bond leads to population of one of the diastereomeric conformers with > 20:1 selectivity.

The X-ray crystal structure analysis of **13** and **14** (Figure 2a, b) indicates that the molecules adopt (*R*,*M*) conformations in the solid state,^[12] which we assume is also the favored conformation in solution. This conformation may result from an electrostatic interaction between the sulfoxide S atom and the pro-*S* sulfone O atom (leading to a near-linear O_{sulfone}–S_{sulfoxide}–O_{sulfoxide} arrangement and close O_{sulfone}–S_{sulfoxide} approach, as shown in Figure 2c). Since a similar attraction to the pro-*R* oxygen atom would incur encumbrance between the two rings (Figure 2c), a conformational preference is imposed upon the C–S bonds of both the sulfone and the sulfoxide. Consistent with this dipole-driven rationalization of the conformational preference are the lower selectivity with sulfide **12** and the fact that **14** showed lower levels of conformational selectivity in the more polar solvents DMSO or MeOH.^[18]

We expected that a fourth substituent *ortho* to the C–S–C axis would give rise to atropisomeric structures. Bromide **15**

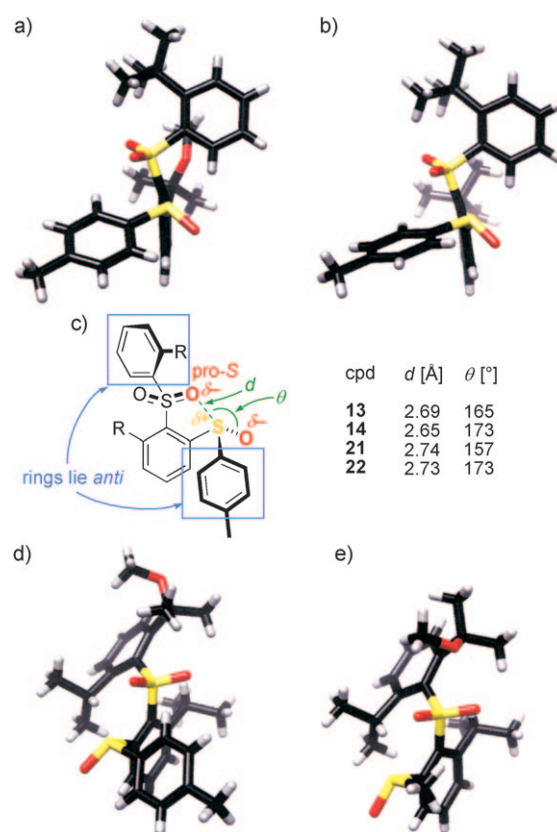
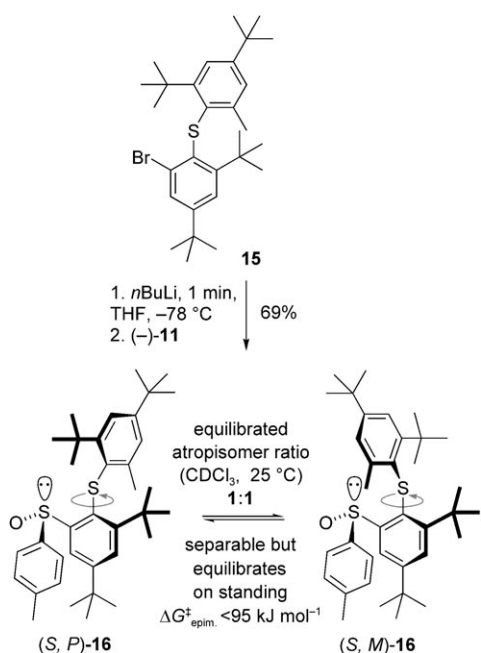
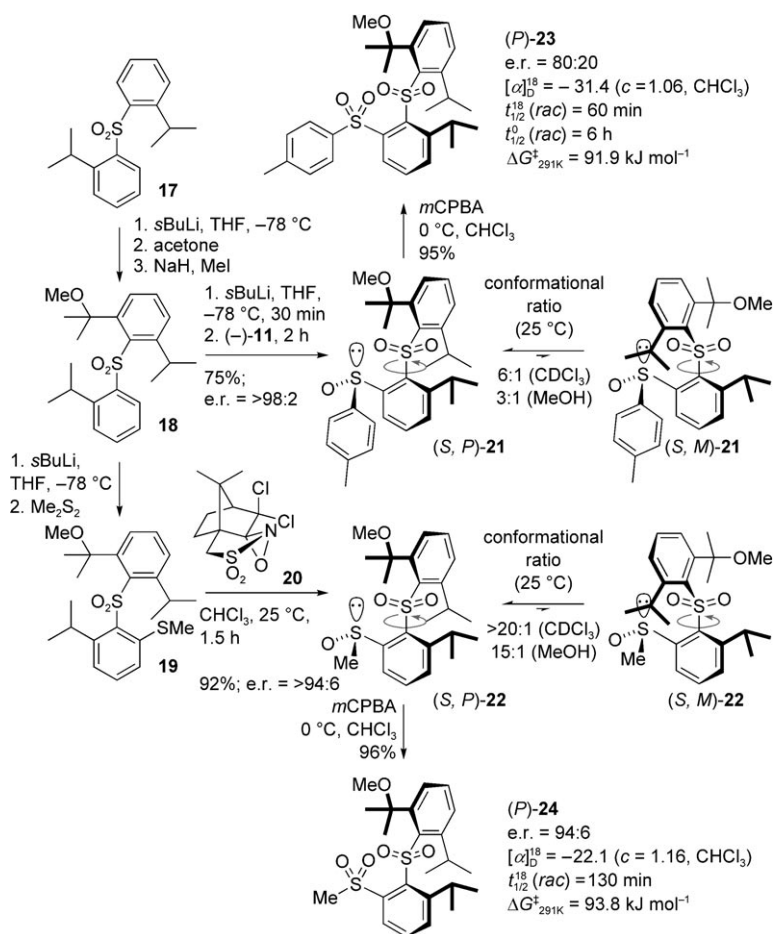


Figure 2. X-ray crystal structures of a) **13** and b) **14**, both showing the favored (*R*,*M*) conformation. c) Presumed governing SO₂–SO dipole/Ar–Ar steric interaction, with values of *d* (distance between sulfone pro-*S* O atom and sulfoxide S atom) and θ (angle formed by sulfone pro-*S* O, sulfoxide S, and sulfoxide O atoms) for **13**, **14**, **21**, and **22**. X-ray crystal structures of d) **21** and e) **22**,^[12] both showing the favored (*S*,*P*) conformation.



Scheme 3. Conformational preference in a pair of atropisomeric sulfinyl sulfides.



Scheme 4. Asymmetric synthesis of diaryl sulfones; e.r. = enantiomeric ratio.

gave the diastereomeric sulfinyl sulfides **16** (Scheme 3), and two conformers were evident by ^1H NMR spectroscopy (25 °C, CDCl_3) in a 1:1 mixture. Chromatographic separation of the atropisomeric diastereomers was possible, but equilibration in solution was complete within 16 h at ambient temperature, and two-dimensional thin-layer chromatography demonstrated interconversion within minutes. The barrier to C–S bond rotation for both diastereomers of **16** was thus estimated to be less than 95 kJ mol $^{-1}$.

More-hindered tetra-ortho-substituted sulfinyl sulfones **21** and **22** were made by sequential double ortholithiation^[15] of bis(2-isopropylphenyl)sulfone (**17**). A sulfinyl substituent was introduced by two alternative strategies: addition to (–)-**11**^[16] gave (S)-**21** in 75 % yield, while addition to dimethyldisulfide and asymmetric oxidation of the resulting sulfide **19** with oxaziridine **20**^[19] gave S-**22** with an e.r. greater than 94:6.

The equilibrated (unchanged on heating for 48 h at 50 °C in CDCl_3) conformational ratio of toluenesulfinyl sulfone **21** was 6:1. The methylsulfinyl sulfone **22** was however essentially conformationally pure (NMR: > 20:1 conformational selectivity in CDCl_3). X-ray crystal structure analysis of **21** and (±)-**22**^[12] (Figure 2d, e) suggested that a dipole interaction (Figure 2c) similar to that in **13** and **14** was at the origin of the conformational preference. The greater selectivity with the methylsulfinyl group may be due to stronger dipole attraction (Figure 2c) in a less hindered system.

The stereogenic centers of the two sulfinyl sulfones **21** and **22** were removed by the oxidation to bissulfones (P)-**23** and (P)-**24**^[20], respectively, in CHCl_3 to maximize the conformational ratio, and at 0 °C to minimize racemization of the products. Bissulfones **23** and **24** were obtained with enantiomeric ratios which reflected the product of conformational and enantiomeric ratios of the starting sulfinyl sulfones (Scheme 4). Half-lives for racemization and barriers to C–S bond rotation are given in Scheme 4.^[11]

In conclusion, we have demonstrated that hindered diaryl sulfides and diaryl sulfones may exist as resolvable atropisomeric compounds. A dipole interaction between the sulfone and an adjacent sulfinyl group may be exploited to impose a preferred conformation on a C–SO $_2$ bond. Conversion of the sulfinyl group by oxidation to a second sulfone substituent constitutes the first asymmetric synthesis of an atropisomeric compound whose axial chirality derives from a rotationally restricted C–S bond. We are currently seeking to extend this methodology to compounds with higher barriers to provide a new class of ligands suitable for use in asymmetric catalysis.

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- [11] Rates of racemization of **1a**, **3a**, **23**, and **24** were determined by observation of first-order decay to a racemic mixture (after chromatographic resolution in the case of **1a** and **3a**) at an appropriate temperature, monitored by HPLC. The rate of racemization of **2a** was determined by application of the method of Schurig and Trapp (Ref. [10b]) to the elution profile shown in Figure 1c. Further details of kinetic parameters relating to the mechanism of racemization of these compounds will be reported in a future publication.
- [12] CCDC 724152 (**1a**), 724152, 724153 (**2a**), 724154 (**3a**), 724155(**13**), 724156 (**14**), 724158 (**21**), and 724159 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Details of the analysis are provided in the supporting information. Crystals of sulfoxides **13**, **14**, and **21** were enantiomerically pure and the absolute structure parameters confirmed their absolute configurations. We were unable to obtain good-quality crystals of enantiomerically pure **22**, and Figure 2e shows a molecule of (*S,P*)-**22** extracted from the crystal structure of ($\pm$)-**22**.
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- [20] The absolute configuration of **23** was assigned on the basis of the absolute C–S axial configuration displayed in the crystal structure of **21**. The absolute configuration of **24** is based on the relative conformational preference shown in the crystal structure of ($\pm$)-**22** coupled with the expected enantioselectivity of the oxidation of **19** (ref. [19]). Consistent with (though of course not proving) these assignments, both products are (*P*)-(–), and related atropisomeric sulfonyl ethers (ref. [6b]) are also likewise (*P*)-(–). For a conformational study of 1,2-bisulfones, see: J. Lacour, D. Monchaud, J. Mareda, F. Favarger, G. Bernardinelli, *Helv. Chim. Acta* **2003**, *86*, 65.