Atropisomeric Ethers

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Enantioselective Synthesis of an Atropisomeric Diaryl Ether**

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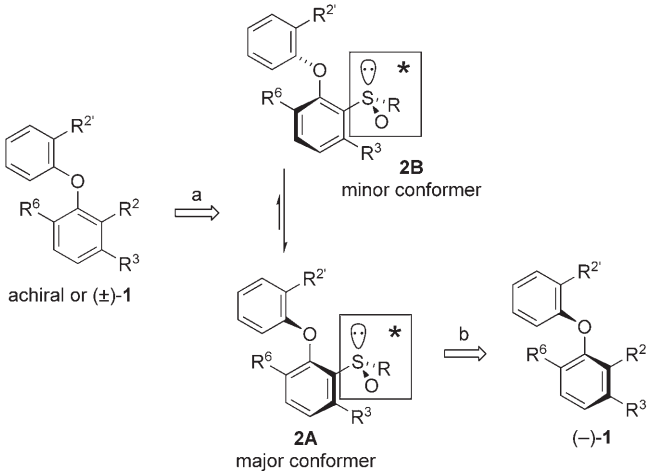
Members of the diaryl ether family of compounds have diverse functions as mammalian hormones (thyroxine),[1] powerful antibiotics (vancomycin, teicoplanin, ristocetin),[2] and ligands for transition-metal-promoted hydroformylation (bis(2-diphenylphosphinophenyl)ether; DPEphos).[3] They are present in a range of natural products including the bastadins, perottetines, riccardin B, and cyclic peptide K3.[4] Stereochemical interest in diaryl ethers is focused on their perpendicular conformation[1,5] and on their ability to exhibit atropisomerism, particularly when constrained within a macrocyclic ring, as they are in the vancomycin antibiotics.[2,6] Recently we showed that atropisomerism is a general feature of diaryl ethers **1** even outside of macrocyclic rings;[7] ethers **1** are generally resolvable, chiral compounds provided that a) they bear at least three substituents *ortho* to the ether axis and b) two of those substituents are bulky (*tert*-butyl group or similar). Atropisomeric compounds have proved to be supremely versatile, particularly as chiral ligands for metals, yet chiral biaryl ethers remain an unexplored and underexploited class of atropisomers, not least because—in stark contrast with the biaryls—no method yet exists for their asymmetric synthesis.

In this communication we report the first enantioselective route to a diaryl ether. The strategy[8] we employ makes use of thermodynamic control over the orientation of the Ar–OAr′ bond (Scheme 1). Incorporation of a chiral substituent (in this case, a sulfoxide) with the ability to govern the favored orientation of a nearby bond—a "conformational auxiliary"—allows one conformer of intermediate **2** to predominate. Subsequent transformation of the auxiliary into a bulky substituent traps the major conformer as a single atropisomer and transforms a conformational preference into an atropisomeric enantiomeric excess.[9,10] The overall transformation of (±)-**1** to (−)-**1** can be termed a dynamic thermodynamic resolution.[11]

The versatility of sulfoxide chemistry,[12] along with the powerful dipole associated with the S–O bond,[13] prompted us to choose a sulfinyl group as a means of achieving conformational control. Sulfinyl groups have previously performed well in controlling functional group orientation in aromatic amides[10,13,14] and ureas.[15] We chose to make the



Scheme 1. A strategy for the asymmetric synthesis of atropisomeric diaryl ethers under thermodynamic control. a) Incorporate auxiliary to govern bond orientation. b) Transform auxiliary into bulky R^2 group while avoiding rotation.

required ethers by the route shown in Scheme 2. Nucleophilic aromatic substitution of 3-bromo-2-chlorobenzonitrile (**3**)[7] by 2-*tert*-butylphenoxide gave ether **4**, which was converted into sulfoxides by using either diacetonylglucose (DAG) sulfinate esters **12** or isopropyl isopropylthiosulfinate (*i*PrS-S(O)*i*Pr).[16] The cyano group of **4** withstands bromine–lithium exchange at low temperature, giving sulfoxides **5a** and (S_S)-**5b**. Alternatively, the cyano group was converted by a three-step sequence into the methoxymethyl group of **7**, which also underwent clean bromine–lithium exchange and sulfinylation with (S_S)-**12a**, (R_S)-**12a**, and (S_S)-**12b** to yield sulfoxides (S_S)-**8a**, (R_S)-**8a**, and (S_S)-**8b**, respectively.

Previous studies[15] suggested that alkylsulfinyl groups with tertiary alkyl substituents were essential for high levels of conformational control, but we were unable to make *tert*-alkylsulfoxides directly from **4** or **7**. We therefore treated **5** and **8** with a base to deprotonate α to the sulfur center, and quenched the resulting anions with methyl iodide. α Alkylations of **8** were successful and yielded sulfoxides **9**. With **5**, however, the electron-withdrawing cyano substituent led to ortholithiation of the sulfoxide;[17] methylation and subsequent in situ lateral lithiation of the sulfoxide yielded the ethyl-substituted ethers **6**.

Diastereoisomeric conformers about the Ar–OAr′ bond of ethers **2** interconvert slowly enough on the NMR timescale for their conformational ratio to be detectable by ^{1}H NMR spectroscopy at ambient temperature,[7,18] but the selectivity for one conformer over the other in **5**, **6**, and **8** was disappointingly low (Table 1, entries 1–8). Nonetheless, taking the lead from a clear trend towards greater selectivity with more hindered substituents, we ortholithiated and

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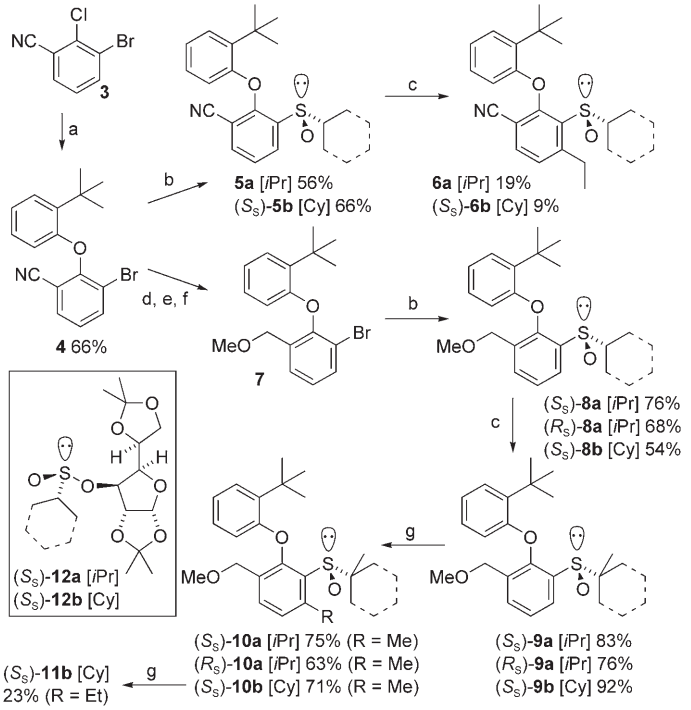


Scheme 2. Synthesis of sulfinyl ethers. Reagents and conditions: a) Potassium 2-*tert*-butylphenoxide, DMF, 150 °C, 16 h; b) 1. *n*BuLi, THF, −78 °C, 1 min; 2. *i*PrS-S(O)*i*Pr, **12a**, or **12b**, −78→+20 °C, 16 h; c) 1. LDA, −78 °C, THF, 0.5 h; 2. MeI, −78→+20 °C, 3 h; d) DIBAL-H, tol, −78→+20 °C, 16 h; e) $NaBH_4$, THF, 30 min, 20 °C; f) NaH, MeI, THF, 20 °C, 30 min; g) 1. *n*BuLi, THF, −78 °C, 1 h; 2. MeI, −78→+20 °C, 2 h. DIBAL-H = diisobutylaluminum hydride; LDA = lithium diisopropylamide.

Table 1: Conformational ratios in sulfinyl ethers **2**.

Entry	Struct.	R	$R^{2'}$	R^3	R^6	Ratio[a] **2A:2B**
1	**5a**	*i*Pr	*t*Bu	H	CN	57:43
2	**5b**	Cy	*t*Bu	H	CN	60:40
3	**6a**	*i*Pr	*t*Bu	Et	CN	66:34
4	**6b**	Cy	*t*Bu	Et	CN	66:34
5	**8a**	*i*Pr	*t*Bu	H	CH_2OMe	66:34
6	**8b**	Cy	*t*Bu	H	CH_2OMe	57:43
7	**9a**	*t*Bu	*t*Bu	H	CH_2OMe	86:14
8	**9b**	C(Me)$(CH_2)_5$	*t*Bu	H	CH_2OMe	80:20
9	**10a**	*t*Bu	*t*Bu	Me	CH_2OMe	95:5
10	**10b**	C(Me)$(CH_2)_5$	*t*Bu	Me	CH_2OMe	94:6
11	**11b**	C(Me)$(CH_2)_5$	*t*Bu	Et	CH_2OMe	93:7
12	**13a**	CMe_2Et	*t*Bu	H	CH_2OMe	80:20
13	**13b**	CMe_2Et	*t*Bu	Me	CH_2OMe	91:9
14	**14a**	*i*Pr	*i*Pr	H	CH_2OMe	83:17
15	**14b**	*t*Bu	*i*Pr	H	CH_2OMe	98:2
16	**15**	Cy	*i*Pr[c]	H	CN	60:40
17	**15**	Me	*i*Pr[c]	H	$C(Me)_2OMe$	78:22

[a] Substituents refer to structure **2**. [b] Measured by ^1H NMR spectroscopy in $CDCl_3$. [c] With a Me group in the 6-position of the phenyl ring. Cy = cyclohexyl.

gave crystals suitable for X-ray crystallography analysis,[19] and for reasons described below we presume that their major Ar–O–Ar′ conformer in solution corresponds to that in the solid state. The X-ray crystal structures of (S_S)-**10a** and (S_S)-**10b** are shown in Figure 1, and the presumed Ar–O–Ar′ conformation of **10** and **11** is indicated in Figure 2.

We propose that a combination of steric and electronic effects underlie the conformational preference of **10** and **11**. Dipole repulsion between the S–O bond and the proximal Ar–O bond of the ether, in combination with steric repulsion between the aryl and alkyl substituents of the sulfoxide group, favors conformations in which a lone pair of electrons of the sulfoxide group eclipses, or lies gauche to, the proximal Ar–O bond (Figure 2). Steric repulsion between the ether substituents (the upper ring) and the alkyl substituent on the sulfoxide group then favor Ar–O–Ar′ conformer **A** over conformer **B**. Such a rationale is in accord with the observed increased selectivity afforded by bulkier substituents α and *ortho* to the sulfoxide group.

We made some attempts to increase the level of conformational control achievable in **2** by synthesizing **13**, **14**, and **15** using routes analogous to those used previously (Scheme 2). Despite their

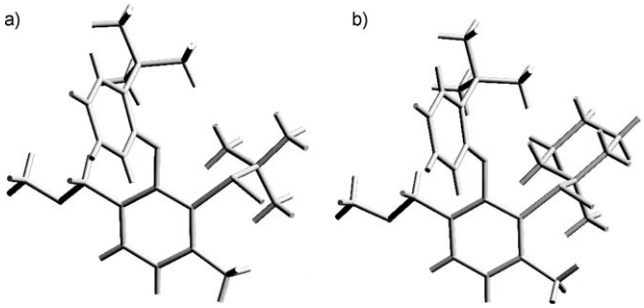


Figure 1. a) X-ray crystal structure of (S_S)-**10a**; b) X-ray crystal structure of (S_S)-**10b**.

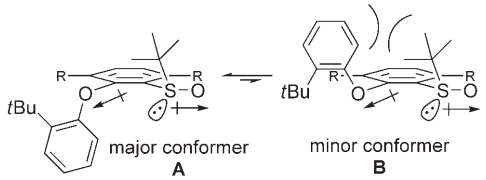
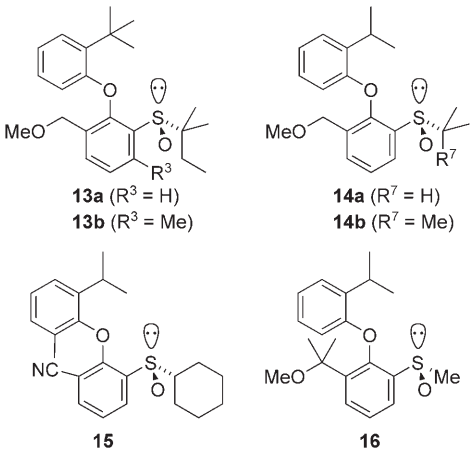


Figure 2. Conformational preference in (S_S)-sulfinyl ethers **10** and **11**.

alkylated sulfoxides **9** to yield (S_S)-**10a**, (R_S)-**10a**, and (S_S)-**10b. 10b** was furthermore laterally lithiated and methylated to yield ethyl-substituted (S_S)-**11b**.

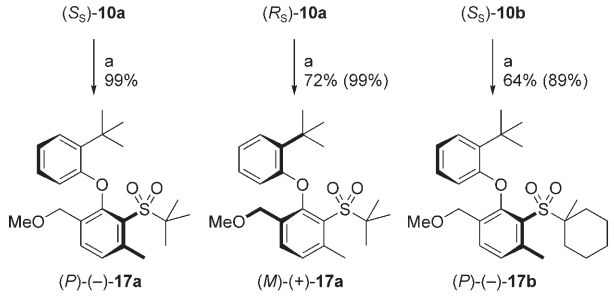
Remarkably, these alkylations increased the ratio of the conformers to 15–20:1 in favor of **2 A**. (S_S)-**10a** and (S_S)-**10b** greater steric hindrance, **13a** and **13b** and **15** exhibited conformational ratios inferior to the *tert*-butyl-substituted **9a**, **10a** and **5b**. The same relationship between slightly decreased steric hindrance and increased selectivity also held for **14**, with an *i*Pr group at the 2′-position: **14b** showed outstanding conformational selectivity, possibly because of decreased



unfavorable interactions between the 2′ substituents and the sulfinyl group (note the proximity of the two *tert*-butyl groups in Figure 1). Combining this change with a more bulky substituent at the 6 position or a 2′,6′-disubstituted distal ring (necessary to maintain a rotational barrier sufficient to retain atropisomerism) gave promising selectivity in the methylsulfoxide **16**,[20] but at the cost of greatly reduced reactivity.

The final step in the sequence employing the sulfinyl substituents as chiral auxiliaries must be the transformation of the sulfoxide into an achiral substituent of sufficient steric bulk to prevent free rotation about the Ar–O–Ar′ axis and to preserve any atropisomeric enantioselectivity achieved. We elected to use a sulfonyl group to perform this function since it could be introduced straightforwardly by oxidation of the sulfoxide groups to sulfone groups.[21]

Accordingly, the three sulfoxides (S_S)-**10a**, (R_S)-**10a**, and (S_S)-**10b** were treated with *m*CPBA in CH_2Cl_2 at 0 °C to yield atropisomeric ethers (*P*)-**17a**, (*M*)-**17a**, and (*P*)-**17b** (Scheme 3). HPLC on a chiral stationary phase indicated that the products were enantiomerically enriched (Table 2). The X-ray crystal structure of (*P*)-**17b**[19] confirmed its absolute stereochemistry and hence also our assignment of the major sulfoxide conformer in solution (Figure 3). Atropisomeric ethers **17** were stable to racemization at room temperature, but showed a first-order decay in their enantiomeric purity at 40 °C in 95:5 hexane/CH_2Cl_2 (half-lives shown in Table 2). Extrapolation of these rates to 25 °C suggests enantiomeric stability in solution over a timescale of weeks.



Scheme 3. Synthesis of atropisomeric ethers. Reagents and conditions: a) *m*CPBA, CH_2Cl_2, 0 °C. The yield in the parentheses is based on recovered starting material.

Table 2: Stereochemical data for ethers **17**.

Entry	Ether	e.r.[a]	$[\alpha]_D^{23}$[b]	$t_{1/2\,rac}$ (40 °C)[c] [h]	$\Delta G_{rac}^{\ddagger}$[d] [kJ mol^{-1}]	$t_{1/2\,rac}$ (25 °C)[e] [days]
1	*P*-(−)-**17a**	90:10	−110.9	134	113.6	100
2	*M*-(+)-**17a**	95:5	+106.2	–	–	–
3	*P*-(−)-**17b**	91:9	−172.9	260	111.8	50

[a] Determined by HPLC methods with a chiral stationary phase (Chiralcel OT(+)). [b] $c = 1.0$, acetone. [c] Determined in 95:5 hexane/CH_2Cl_2. [d] Determined at 40 °C. [e] Estimated half-life for racemization at room temperature assuming $\Delta S^{\ddagger} \approx 0$.

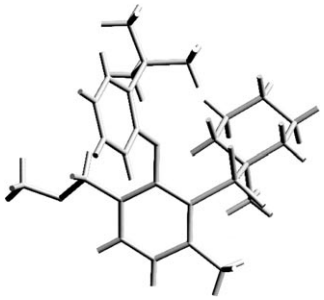


Figure 3. X-ray crystal structure of (*P*)-(−)-**17b**.

The preparation of ethers **17** represents the first enantioselective synthesis of an atropisomeric diaryl ether devoid of stereogenic features other than the ether axis itself. It was achieved by dynamic resolution under thermodynamic control, a strategy particularly suited to the synthesis of atropisomers.

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[16] Diastereoisomerically pure DAG-sulfinate esters (S_S)-**12a** and (S_S)-**12b** were made by the methods of Fernandez et al. (I. Fernandez, N. Khiar, J. M. Llera, F. Alcudia, *J. Org. Chem.* **1992**, *57*, 6789) and of Alayrac et al. (C. Alayrac, S. Nowaczyk, M. Lemarié, P. Metzner, *Synthesis* **1999**, 669). Both react with aryllithium sunstrates with inversion of configuration and a change in priority at the stereogenic sulfur atom thus yielding (S_S)-sulfoxides. (R_S)-**12a** was also available as a 96:4 diastereoisomeric mixture by the method of Fernandez et al., and was used to make (R_S)-sulfoxides. Ellman's *tert*-butyl *tert*-butylthiosulfinate (D. J. Weix, J. A. Ellman, *Org. Lett.* **2003**, *5*, 1317) is a convenient precursor to *tert*-butylsulfoxides, but it failed to react with organometallic derivatives of **4**, preventing direct synthesis of **9a** and its derivatives.

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[18] In some cases the diastereoisomeric conformers exist as separable atropisomers. For example, **8a** showed two spots on TLC; a second elution along a perpendicular axis showed cross-spots indicating interconversion on the plate over a period of minutes. Flash chromatography of **8a** allowed us to obtain mixed samples enriched in either diastereoisomer which both equilibrated to the same mixture within 12 hours at room temperature. All ratios reported in Table 1 were measured after ensuring complete equilibration between diastereoisomers.

[19] CCDC 669805 ((S_S)-**10a**), 669806 ((S_S)-**10b**) and 669807 ((*P*)-(−)-**17b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

[20] Other methylsulfoxide have shown very low levels of conformational control (see reference [15]).

[21] In general, the success of the method relies on the fact that this step of the sequence proceeds faster than the rate of interconversion of the conformers or that the rate of oxidation of the two diastereoisomeric conformers are comparable. The observation of slow diastereoisomeric interconversion in **8a** suggests the former holds true. Under these ideal conditions the e.r. of **17** is the product of the e.r. of the starting sulfoxide **10** and its conformational purity. For a discussion of the application of the Winstein–Holness equation in comparable situations, see J. I. Seeman, *Chem. Rev.* **1983**, *83*, 83; N. S. Zefirov, *Tetrahedron* **1977**, *33*, 2719.

