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# Lithium−Sulfoxide−Lithium Exchange for the Asymmetric Synthesis of Atropisomers under Thermodynamic Control

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Thermodynamic control is well suited to the enantioselective construction of atropisomeric molecules whose precursors display some degree of rotational freedom.[1,2] Earlier examples of thermodynamic control in the asymmetric synthesis of atropisomers used (−)-ephedrine[3] and a proline-derived diamine[4] as auxiliaries to control the stereochemistry of atropisomeric amides.[5] In this communication we show that the temporary presence of an enantiomerically pure sulfoxide substituent is enough to exert complete thermodynamic control over the stereochemistry of an atropisomer. Easy introduction[6] and removal[7] by organolithium chemistry makes the sulfoxide a versatile precursor to a range of highly enantiomerically enriched atropisomeric products.

Amides **1a**−**1g**[8] were lithiated with *s*-BuLi in THF[9] to give organolithiums **2a**−**2g** which were treated with (1*R*,2*S*,5*R*,$S_S$)-(−)-menthyl *p*-toluenesulfinate. Excellent yields of sulfoxides **3a**−**3g** were obtained (Table 1) as single enantiomers[10] by substitution of menthoxide with inversion,[6] and (to the limits of NMR detection) as single atropisomeric diastereoisomers.[11]

Organometallic nucleophiles attack sulfoxides with displacement of the most stable organometallic.[7] Treatment of sulfoxides **3a**−**f** with *t*-BuLi (3 equiv) at −78 °C in THF accordingly regenerated the organolithiums **2**. After 5 min at −78 °C, an electrophile (Table 2) was added, the reaction was quickly worked up, and the products **4a**−**f**, which in many cases are known to be atropisomeric,[8] were isolated and purified by flash chromatography with cold eluents. Most of the products (Table 2) were almost enantiomerically pure.[12]

The stereochemistry of **4** and therefore (*R*)-**2** confirms for the first time that a 2-lithio substituent is capable of restricting rotation about an amide Ar−CO bond at −78 °C.[13] Sulfoxides **3** must be formed with uniform absolute stereochemistry at both the sulfoxide stereogenic center and the amide stereogenic axis, and must have anti relative stereochemistry. Since **2** is chiral and the precursor to **3**, (±)-**2**, must be racemic, some form of dynamic resolution must operate in the formation of *anti*-**3**, under either kinetic[14] or thermodynamic[15] control (Scheme 1).

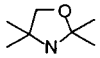
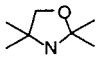
To assess the relative stability of the sulfoxides' diastereoisomers, sulfides **5a**−**d**[16] were oxidized to sulfoxides **6a**−**d** with *m*-CPBA (Scheme 2). After workup at room temperature, a single diastereoisomer of **6a**−**c** was isolated,[17] but a mixture of diastereoisomers of **6d**. These results point to a reaction under thermodynamic control, made possible by the poor barriers to bond rotation offered by second-row elements (Si,[8b] P,[2d] S[2d]). Rapid equilibration at ambient temperature gives single atropisomers of **6a**−**c**, while selectivity in **6d** is marred by a partial mismatch between the thermodynamic influences of the sulfoxide and of the Si-bearing center.[2a,d]

Further evidence that any kinetic stereoselectivity in the formation of **6** is overturned by thermodynamic factors was provided by oxidation of **5c** at −15 °C in an NMR tube. A 75:25 mixture (by $^1$H NMR) of two sulfoxides **6c** formed rapidly on addition of *m*-CPBA, but on warming to 0 °C this ratio decayed to an equilibrium value of >99:1 over a period of 2 h. We therefore deduce a remarkably short half-life for epimerisation of **6c** of about 15 and 1 min at 0 and 20 °C, respectively.

Our rationale for the enantioselective formation of (*R*)-**2** (Scheme 1) is therefore that (±)-**2** reacts with (1*R*,2*S*,5*R*,$S_S$)-(−)-menthyl *p*-toluenesulfinate to form a mixture of *syn*- and *anti*-**3**, but that on warming to room temperature, the less stable *syn*-**3** is fully and rapidly converted to *anti*-**3**.[18]

Additions of **2** to *t*-BuCHO are diastereoselective,[8c] and give principally the *syn* diastereoisomer of **7**, which epimerises to *anti*-**7** on heating. Sulfoxides **3a**, **3c**, and **3f** were treated with *t*-BuLi (3 equiv) and *t*-BuCHO to yield the alcohols **7a**, **7c**, and **7f** in high ee (Scheme 3).[19] *syn*-**7a** was also obtained with good ee by bromine−

***Table 1.*** Stereoselective Synthesis of the Sulfoxides

| entry | starting material | $NR^1_2$ | $R^2$ | $R^3$ | product | yield (%) | $[\alpha]_D$[a] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | N*i*-$Pr_2$ | | benzo[b] | **3a** | 89 | −298.5 |
| 2 | **1b** | $NEt_2$ | | benzo[b] | **3b** | 77 | −97.2 |
| 3 | **1c** |  | | benzo[b] | **3c** | 84 | −465.4 |
| 4 | **1d** | N*i*-$Pr_2$ | MeO | MeO | **3d** | 87 | −32.8 |
| 5 | **1e** | N*i*-$Pr_2$ | MeO | H | **3e** | 89 | −85.2 |
| 6 | **1f** |  | MeO | H | **3f** | 79 | −36.8 |
| 7 | **1g** | N*i*-$Pr_2$ | H | H | **3g** | 81 | −85.2 |

[a] See Supporting Information for details. [b] 1-Naphthamide.

***Table 2.*** Asymmetric Synthesis of Atropisomeric Amides

| entry | SM[a] | $E^+$ | product | yield (%) | ee (%) | $[\alpha]_D$[b] | $t_{1/2}$[c] |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | Me | **4a** (E = Me) | 91 | 98 | +65.2 | 36 h[d] |
| 2 | **3a** | Et | **4a** (E = Et) | 97 | 96 | +62.4 | 43 h[d] |
| 3 | **3a** | $Ph_2CO$ | **4a** (E = $C(OH)Ph_2$) | 94 | >99 | +36.9 | − |
| 4 | **3a** | $(CH_2)_3CO$ | **4a** (E = $COH(CH_2)_3$) | 94 | 92 | +77.4 | − |
| 5 | **3a** | $C_2H_4Br_2$[e] | **4a** (E = Br) | 91 | >99 | +41.2 | 200 d[f] |
| 6 | **3a** | $C_2H_4I_2$[e] | **4a** (E = I) | 92 | 99 | +39.2 | 110 h[g] |
| 7 | **3b** | various[h] | **4b** | 50−65 | 12−22 | − | − |
| 8 | **3c** | EtI | **4c** (E = Et) | 94 | >99 | +44.6 | − |
| 9 | **3d** | $C_2H_4Br_2$[e] | **4d** (E = Br) | 91 | 88 | +14.4 | − |
| 10 | **3e** | $C_2H_4Br_2$[e] | **4e** (E = Br) | 92 | 84 | +50.8 | 33 d[g] |
| 11 | **3f** | $C_2H_4Br_2$[e] | **4f** (E = Br) | 94 | 26 | +18.1 | − |

[a] Starting material. [b] See Supporting Information for details. [c] Estimated half-life for racemisation at 25 °C (assuming invariance of $\Delta G_{rac}^{\ddagger}$ with temperature) calculated by repeated sampling of ee over a period of time. [d] From ref 8b. [e] 1,2-Dihaloethane. [f] By polarimetry at 40 °C. [g] By repeated HPLC of a sample incubated at 40 °C. [h] MeI or $C_2H_4Br_2$ or $Ph_2CO$.

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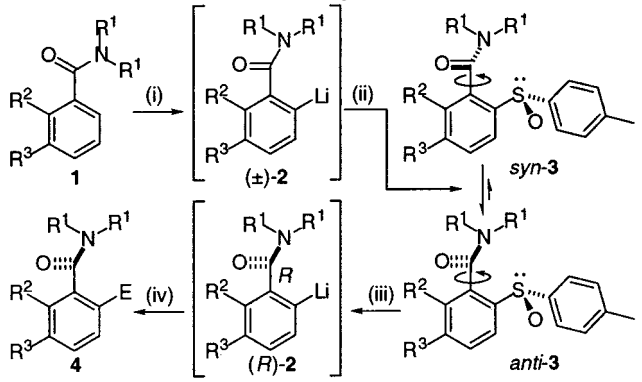
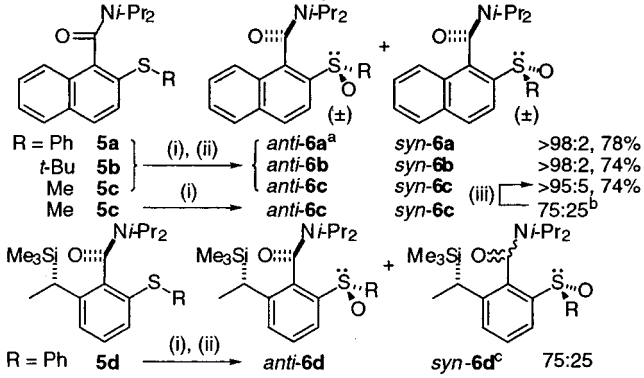
***Scheme 1.*** Asymmetric Synthesis of Atropisomeric Amides by Lithium−Sulfoxide−Lithium Exchange[a]



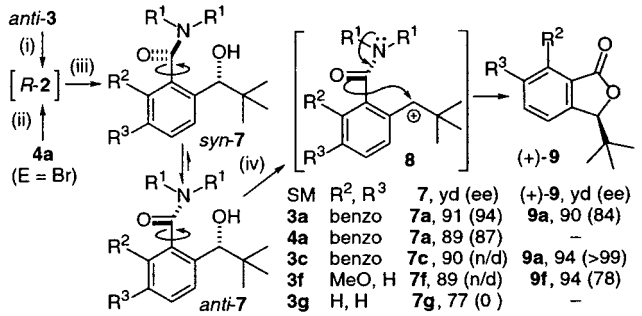

[a] Reagents: (i) s-BuLi, THF, −78 °C; (ii) (1*R*,2*S*,5*R*,$S_S$)-(−)-menthyl *p*-toluenesulfinate, −78 to 0 °C then $NH_4Cl$, 20 °C; (iii) *t*-BuLi (3 equiv), THF, −78 °C, 5 min.; (iv) $E^+$ (Table 2).

***Scheme 2.*** Oxidation of 2-Sulfenyl-Substituted Amides[d]




[a] Relative stereochemistry confirmed by X-ray crystallography. [b] Experiment carried out in NMR tube. [c] Axial stereochemistry unknown. [d] Reagents: (i) *m*-CPBA, $CH_2Cl_2$, −15 °C; (ii) aqueous workup, 20 °C; (iii) 0 °C, 2 h.

***Scheme 3*** "Fixing" the Amide Stereochemistry[a]




[a] Reagents: (i) *t*-BuLi (3 equiv), THF, −78 °C, 10 min; (ii) *t*-BuLi (1 equiv), THF, −78 °C, 10 min; (iii) *t*-BuCHO; (iv) $MeSO_3H$, MeOH, Δ, 5−10 min.

lithium exchange of (*R*)-**4a** (E = Br).[20] Lactonisation of **7a**, **7c**, and **7f** gave benzofuranones **9a** and **9f** in good ee, presumably by stereospecific capture of a forming benzylic cation **8**.[21] The conversion of enantiomerically pure amides to amide-free targets illustrates the potential for sulfoxides as a source of chiral memory.[22]

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**Supporting Information Available:** X-ray crystallographic data for **3f**, **3g**, and **6a** (CIF); experimental procedures and full characterization for sulfoxides **3** and **6**, enantiomerically pure amides **4** and **7**, sulfides **5** and lactones **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Although ee's were not determined at this stage, the enantiomeric purity of compounds later in the sequence proved this to be the case.

(11) Typically, tertiary benzamides bearing a chiral 2-substituent exist as a pair of slowly interconverting ($t_{1/2} \approx 0.1$ s) diastereoisomeric conformers discernible by $^1H$ NMR. Similarly, tertiary 1-naphthamides and tertiary 2,6-disubstituted benzamides **3** bearing a chiral 2-substituent typically exist as two diastereoisomeric atropisomers (interconversion $t_{1/2} \gg 1$ min) (see refs 2 and 8). *Anti* relative stereochemistry is assigned to **3** on the basis of X-ray crystal structures of **3f** and **3g**.

(12) Enantiomeric excess was determined by HPLC on the (*S,S*)-Whelk-O1 chiral stationary phase. The major enantiomers of **4a** (E = alkyl) eluted faster than the minor, indicating (*R*) stereochemistry: see Pirkle, W. H.; Welch, C. J.; Zych, A. J. *J. Chrom. (A)* **1993**, *648*, 101.

(13) Enantiomeric excess was decreased if the organolithium was maintained at −78 °C for longer periods or if <3 equiv of *t*-BuLi were used in the substitution step. From the dependence of the ee of **4a** (E = Me) and **4e** (E = Br) on the time before electrophilic quench, we crudely estimate half-lives for racemisation of organolithiums **2a** and **2e** at −78 °C of 20 h and 6 min, respectively. Low ees in entries 7 and 11 suggest that the less encumbered organolithiums **2b** and **2f** racemize within minutes at −78 °C. Detailed solution structures of organolithiums **2** have not been determined, but crystalline racemic **2a** forms heterochiral dimers: see Clayden, J.; Davies, R. P.; Hendy, M. A.; Snaith, R.; Wheatley, A. E. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1238.

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(16) **5a**−**c** were made in 65−70% yield from **1a** by ortholithiation−quench with $R_2S_2$ (ref 9). **5d** was made by the method of ref 2d.

(17) X-ray crystallography confirmed the stereochemistry of *anti*-**6a**.

(18) An indication of why *anti*-**3** is more stable than *syn*-**3** is given by the crystal structures of **3f**, **3g**, and **6a**, which show the sulfoxide lone pair eclipsing the Ar−CO bond, placing small, electron-rich O on one face of the ring and large, nonpolar Ar on the other. The amide then prefers to align $NR_2$ *anti* to bulky Ar and the C=O dipole *anti* to S−O. For comparable discussions, see refs 2−4.

(19) Unsurprisingly, the same reaction with **3g** gave racemic material.

(20) The bromine−lithium exchange method retains ee with only 1 equiv of *t*-BuLi, making it suitable for use with more valuable electrophiles.

(21) The absolute stereochemistry of **9**, and hence the stereochemical sense of the cyclisation, is provisional. However, all simple known 2-alkylbenzofuranones are dextrorotatory if 3-*S* and levorotatory if 3-*R*.

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