Dynamic Resolution of Lithiated \textit{ortho}-Trifluoromethyl Styrene Oxide and the Effect of Chiral Diamines on the Barrier to Enantiomerisation

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Table of Contents

1. General Information S2
2. General Procedure for the Dynamic Thermodynamic Resolution (DTR) of 1-Li S3
3. Stereochemical Aspects of the DTR of 1-Li S3
4. Experimental Procedure Using a Sacrificial Electrophile S4
5. Eyring Plot and Free Energy Barrier for Enantiomerisation of 1-Li in Hexane/TMEDA S5
6. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(-)-Sparteine S6
7. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(+)-Sparteine Surrogate S7
8. Determination of Enantiomeric Ratios of Compounds 1, 2a–d, and 10 S8
9. Characterization and Spectral Data of Compounds 2b–d S15
10. $^1$H and $^{13}$C NMR Spectra of Compounds 2b–d S16
1. General Information

Tetrahydrofuran (THF), diethyl ether, toluene and hexane were freshly distilled under a nitrogen atmosphere: THF and diethyl ether over sodium/benzophenone ketyl, toluene and hexane over calcium hydride. For the $^1$H and $^{13}$C NMR spectra ($^1$H NMR 400 or 600 MHz; $^{13}$C NMR 100 or 150 MHz), CDCl$_3$ was used as the solvent. GC-MS spectrometry analyses were performed on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (El). Elemental analyses were performed by using a Carlo Erba CHNS-O EA1108-Elemental Analyzer. Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying with a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. sulphuric acid and heating to 473 K for some time until blue spots appear. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. Lithiation-electrophilic trapping reactions were performed in a diethyl ether/liquid N$_2$ (–120 °C), acetone/liquid N$_2$ (–90 °C) or acetone/dry ice (–78 °C) cold bath. Racemic oxirane 1 was prepared by the Corey–Chaykovsky epoxidation procedure$^1$ starting from the corresponding benzaldehyde derivative, whereas oxirane 10 was obtained according to the methodology of Durst and co-workers.$^2$

Optically active epoxides ($R$)-1 (e.r. 95:5, 15% yield) and ($R$)-10 (e.r. 98:2, 20% yield) were synthesized by means of Jacobsen’s hydrolytic kinetic resolution$^3$ starting from the corresponding racemic mixtures.

Oxiranes 1,$^4$ 2a$^4$ and 10$^5$ are known compounds and their characterization match the literature reports.

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2. General Procedure for the Dynamic Thermodynamic Resolution (DTR) of 1-Li

To a solution of oxirane 1 (1 mmol) and (–)-sparteine 3 (1.2 mmol) in 10 mL of dry hexane (or pentane), at –78 °C and under N₂, s-BuLi (1.2 mmol of a 1.4 M cyclohexane solution) was added dropwise. The resulting yellowish mixture was stirred for 30 min at the above temperature before being quenched with the electrophile (5 mmol) (neat if liquid or diluted in 2 mL of hexane if solid). After additional stirring for 30 min at –78 °C, the reaction vessel was warmed up to room temperature. Then, a solution of sat. aq. NH₄Cl (3 mL) was added and the reaction mixture was poured into 20 mL of water and extracted with Et₂O (3 × 10 mL). The combined organic layers were dried (Na₂SO₄) and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (AcOEt/petroleum ether) to afford oxiranes [D]-1, 2a-d.

3. Stereochemical Aspects of the DTR of 1-Li

Since the enantiomerisation of enantiomer-enriched (R)-1-Li occurs slowly in an apolar solvent such as hexane and in the presence of TMEDA (see Eyring plot, page S5), retention times (calculated by GC or HPLC analysis, see Section 8) of enantiomer-enriched products 2a-d (obtained upon quenching in hexane/TMEDA (R)-1-Li with the corresponding electrophiles) were compared with those of the same products prepared by DTR in hexane(pentane)/(–)-sparteine. Assuming that the reaction of (R)-1-Li with electrophiles proceeds with retention of configuration at the benzylic carbon atom (in accordance with what observed in the α-functionalisation of lithiated styrene oxide derivatives),⁶ the major enantiomer of the products 2a-d (and thus the most stable diastereomeric 1-Li/(–)-sparteine complex) was assigned the R configuration (Scheme S1). The change in the absolute configuration at the benzylic carbon in product 2b was only due to a change in the relative priority of the substituent groups (Scheme S1).

4. Experimental Procedure Using a Sacrificial Electrophile

To a solution of oxirane 1 (1 mmol) and (−)-sparteine 3 (1.2 mmol) in 10 mL of dry pentane, at −78 °C and under N₂, s-BuLi (1.2 mmol of a 1.4 M cyclohexane solution) was added dropwise and the resulting yellowish mixture was stirred for 15 min. Then, the reaction vessel was cooled to −120 °C and acetone (0.2 mmol diluted in 2 mL of pentane) was slowly added. The mixture was stirred for additional 5 min at −120 °C and, after this time, CH₃OD (5 equiv) was added all at once. Upon warming up to room temperature, the mixture was poured into 20 mL of water and extracted with Et₂O (3 × 10 mL). The organic layers were combined, dried (Na₂SO₄) and evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (AcOEt/petroleum ether 1/9) to afford oxiranes 2d (15 % yield, e.r. 52:48, R:S) and [D]-1 (75 % yield, e.r. 82:18, R:S) (see Table 1 in the main text).
5. Eyring Plot and Free Energy Barrier for Enantiomerisation of 1-Li in Hexane/TMEDA

![Eyring Plot](image)

**Figure S1.** Plot of ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on ortho-trifluoromethylstyrene oxide (R)-1 in hexane/TMEDA.

**Table S1.** Inversion barrier, racemisation half-life and enantiomerisation rate constant for lithiated ortho-trifluoromethylstyrene oxide 1-Li in hexane/TMEDA at 195 K.

<table>
<thead>
<tr>
<th>ee</th>
<th>t (sec)</th>
<th>$k_{\text{enant}}$ (s$^{-1}$)</th>
<th>$\Delta G^\neq$ (kcal/mol)</th>
<th>$t_{1/2 \text{ rac}}$ (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>52</td>
<td>180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>420</td>
<td>$3.01 \times 10^{-3}$</td>
<td>$13.5 \pm 0.1$</td>
<td>115</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(-)-Sparteine

Figure S2: Plot of Ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on ortho-trifluoromethylstyrene oxide (R)-1 in hexane/(-)-sparteine.

Table S2. Inversion barriers and enantiomerisation rate constants for lithiated ortho-trifluoromethylstyrene oxide 1-Li in hexane/(-)-sparteine at 195 K.

<table>
<thead>
<tr>
<th>ee</th>
<th>t (sec)</th>
<th>(k_{S\to R} \text{ (s}^{-1})</th>
<th>(\Delta G_{S\to R} \text{ (kcal/mol)})</th>
<th>(k_{R\to S} \text{ (s}^{-1})</th>
<th>(\Delta G_{R\to S} \text{ (kcal/mol)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>82</td>
<td>120</td>
<td></td>
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<td>70</td>
<td>300</td>
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<tr>
<td>78</td>
<td>180</td>
<td></td>
<td></td>
<td>62</td>
<td>420</td>
</tr>
<tr>
<td>70</td>
<td>300</td>
<td>6.81 \times 10^{-4}</td>
<td>14.1 ± 0.1</td>
<td>54</td>
<td>600</td>
</tr>
<tr>
<td>62</td>
<td>420</td>
<td></td>
<td></td>
<td>2.03 \times 10^{-4}</td>
<td>14.5 ± 0.1</td>
</tr>
<tr>
<td>54</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. Eyring Plot and Free Energy Barriers for Enantiomerisation of 1-Li in Hexane/(+)-Sparteine Surrogate

\[ \text{L}^*\text{-Li}_{\text{R}} \text{Li}_{\text{S}} \text{O} \xrightarrow{\text{hexane}} 195 \text{K} \text{L}^*\text{-Li}_{\text{S}} \text{Li}_{\text{R}} \text{O} \]

\( (R)-1\text{-Li/L}^* \quad (S)-1\text{-Li/L}^* \)

L* = (+)-sparteine surrogate

**Figure S3:** Plot of Ln(ee/100) vs delay time at 195 K in lithiation–deuteration exchange on ortho-trifluoromethylstyrene oxide 1 in hexane/(+)-sparteine surrogate.

**Table S3.** Inversion barriers and enantiomerisation rate constants for lithiated ortho-trifluoromethylstyrene oxide 1-Li in hexane/(+)-sparteine surrogate at 195 K.

<table>
<thead>
<tr>
<th>ee</th>
<th>t (sec)</th>
<th>( k_{\text{R} \rightarrow \text{S}} ) (s(^{-1}))</th>
<th>( \Delta G_{\text{R} \rightarrow \text{S}}^\ddagger ) (kcal/mol)</th>
<th>( k_{\text{S} \rightarrow \text{R}} ) (s(^{-1}))</th>
<th>( \Delta G_{\text{S} \rightarrow \text{R}}^\ddagger ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>62</td>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>48</td>
<td>420</td>
<td>8.37 \times 10^{-4}</td>
<td>14.0 ±0.1</td>
<td></td>
<td>3.59 \times 10^{-4}</td>
</tr>
<tr>
<td>40</td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
8. Determination of Enantiomeric Ratios of Compounds 1, 2a–d, and 10

Enantiomeric ratios were determined as follows. In the case of compounds 1, 2a–c and 10, by GC analysis employing a Chirasil-DEX CB column (250-0.25 mm, column head pressure 18 psi, He flow rate 2 mL min⁻¹): oven temperature 75 °C for [D]-1 [(R): t<sub>R</sub><sub>major</sub> = 21.9 min; (S): t<sub>R</sub><sub>minor</sub> = 22.7 min]; oven temperature 75 °C for 2a [(R): t<sub>R</sub><sub>major</sub> = 17.3 min; (S): t<sub>R</sub><sub>minor</sub> = 17.8 min]; oven temperature 70 °C for 2b [(S): t<sub>R</sub><sub>major</sub> = 81.9 min; (R): t<sub>R</sub><sub>minor</sub> = 85.3 min]; oven temperature 100 °C for 2c [(R): t<sub>R</sub><sub>minor</sub> = 58.5 min; (S): t<sub>R</sub><sub>major</sub> = 60.5 min]; oven temperature 70 °C for 10 [(R): t<sub>R</sub><sub>major</sub> = 14.8 min; (S): t<sub>R</sub><sub>minor</sub> = 15.4 min]. In the case of compound 2d, by HPLC analysis employing a Daicel Chiralcel OD-H column: 250-4.6 mm, n-hexane/i-PrOH 90:10, flow rate 0.5 mL min⁻¹, λ = 260 nm; (R): t<sub>R</sub><sub>minor</sub> = 9.7 min; (S): t<sub>R</sub><sub>major</sub> = 10.2 min.
9. Characterization and Spectral Data of Compounds 2b-d

Trimethyl[1-(2-trifluoromethylphenyl)epoxyethyl]silane (2b): 70%, yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): 0.03 (s, 9 H), 3.05 (d, $J = 5.1$ Hz, 1 H), 3.12 (d, $J = 5.1$ Hz, 1 H), 7.33–7.59 (m, 4 H). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ: -3.6, 52.8, 54.8, 124.5 (q, $^1J_{CF} = 274.0$ Hz), 126.2, 127.0, 129.9, 131.5, 140.0. GC-MS (70 eV) m/z (%): 260 (9, M$^+$), 191 (74), 149 (90), 129 (98), 77 (100). FT-IR (film) cm$^{-1}$: 843, 1035, 1124, 1316, 2924, 2960. **Elemental analysis** calcd (%) for C$_{12}$H$_{15}$F$_3$OSi: C, 55.36; H, 5.81; found: C, 55.52; H, 5.93.

1,1-Diphenyl-2-(2-trifluoromethylphenyl)-2,3-epoxy-1-propanol (2c): (75%), waxy solid. $^1$H NMR (DMSO-d$_6$, 600 MHz) δ: 2.52 (d, $J = 4.2$ Hz, 1 H), 2.69(d, $J = 4.2$ Hz, 1 H), 6.20 (bs, 1 H), 7.10–7.70 (m, 14 H). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ: 51.9, 64.2, 78.7, 124.6 (q, $^1J_{CF} = 274.0$ Hz), 126.8, 127.3, 127.5, 127.6, 127.9, 128.4, 129.8 (q, $^2J_{CF} = 30.7$ Hz), 130.7, 131.7, 135.2, 141.9, 142.8. GC-MS (70 eV) m/z (%): 352 (20, M$^-$-H$_2$O), 183 (100), 165 (57), 105 (75), 77 (3). FT-IR (film) cm$^{-1}$: 701, 770, 1036, 1108, 1315, 1448, 3468. **Elemental analysis** calcd (%) for C$_{22}$H$_{17}$F$_3$O$_2$: C, 71.34; H, 4.63; found: C, 71.52; H, 4.70.

2-Methyl-3-(2-trifluoromethylphenyl)-3,4-epoxy-2-butanol (2d): (90%), yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz) δ: 1.25 (s, 3 H), 1.27 (s, 3 H), 2.02 (bs, 1 H), 3.04 (d, $J = 4.6$ Hz, 1 H), 3.50 (d, $J = 4.6$ Hz, 1 H), 7.46–7.75 (m, 4 H). $^{13}$C NMR (CDCl$_3$, 600 MHz) δ: 25.4, 26.9, 53.3, 64.1, 71.3, 124.5 (q, $^1J_{CF} = 274.0$ Hz), 128.6 (q, $^2J_{CF} = 30.0$ Hz), 128.5, 131.1, 131.9, 135.6. GC-MS (70 eV) m/z (%): 188 (20), 168 (100), 140 (43), 129 (98), 59 (55). FT-IR (film) cm$^{-1}$: 770, 1036, 1119, 1175, 1315, 2984, 3468. **Elemental analysis** calcd (%) for C$_{12}$H$_{13}$F$_3$O$_2$: C, 58.54; H, 5.32; found: C, 58.71; H, 5.66.
10. $^1$H and $^{13}$C NMR Spectra of Compounds 2b-d

$^1$H NMR, CDCl$_3$, 400 MHz

$^{13}$C NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 600 MHz
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**1H NMR, CDCl₃, 600 MHz**

![1H NMR spectrum of compound 2d](image)

**13C NMR, CDCl₃, 150 MHz**

![13C NMR spectrum of compound 2d](image)