**REVISED Supplementary Information for:**

# The Barrier to Enantiomerization and Dynamic Resolution of *N*-Boc-2-lithiopiperidine and the Effect of TMEDA

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*Contents:*



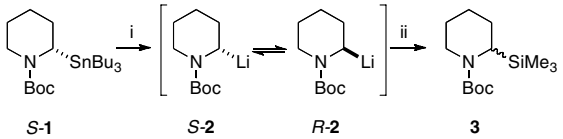
*Synthesis:*

(*S*)-*N*-Boc-2-tributylstannylpiperidine (*S*)-**1**, the alcohol corresponding to ligands **4** and **5** were prepared according to the literature.[1]

*Kinetics:*

## 1. Enantiomerization of (*S*)-*N*-Boc-2-lithiopiperidine 2 in the absence of a ligand

The stannane *S*-**1** (er 85:15) was converted to the organolithium *S*-**2** by addition of *n*-BuLi at –60 °C (Scheme 1). After 2 h, the mixture was quenched with TMSCl for about 3 h before addition of water. The enantiomer ratio (er) of the silane **3** was determined by CSP GC {β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, at 82 °C}. The retention times were confirmed by comparison with an authentic sample of racemic **3** synthesized by deprotonation and silylation of *N*-Boc-piperidine. GC traces are shown in Fig. 1.




*S*-**1** *S*-**2** *R*-**2** **3**

i, *n*-BuLi (1.1 equiv.), $Et_2O$, –60 °C, 2 h then TMSCl (5 equiv.)

***Scheme 1.*** Racemization of the organolithium **2** in the absence of a ligand.

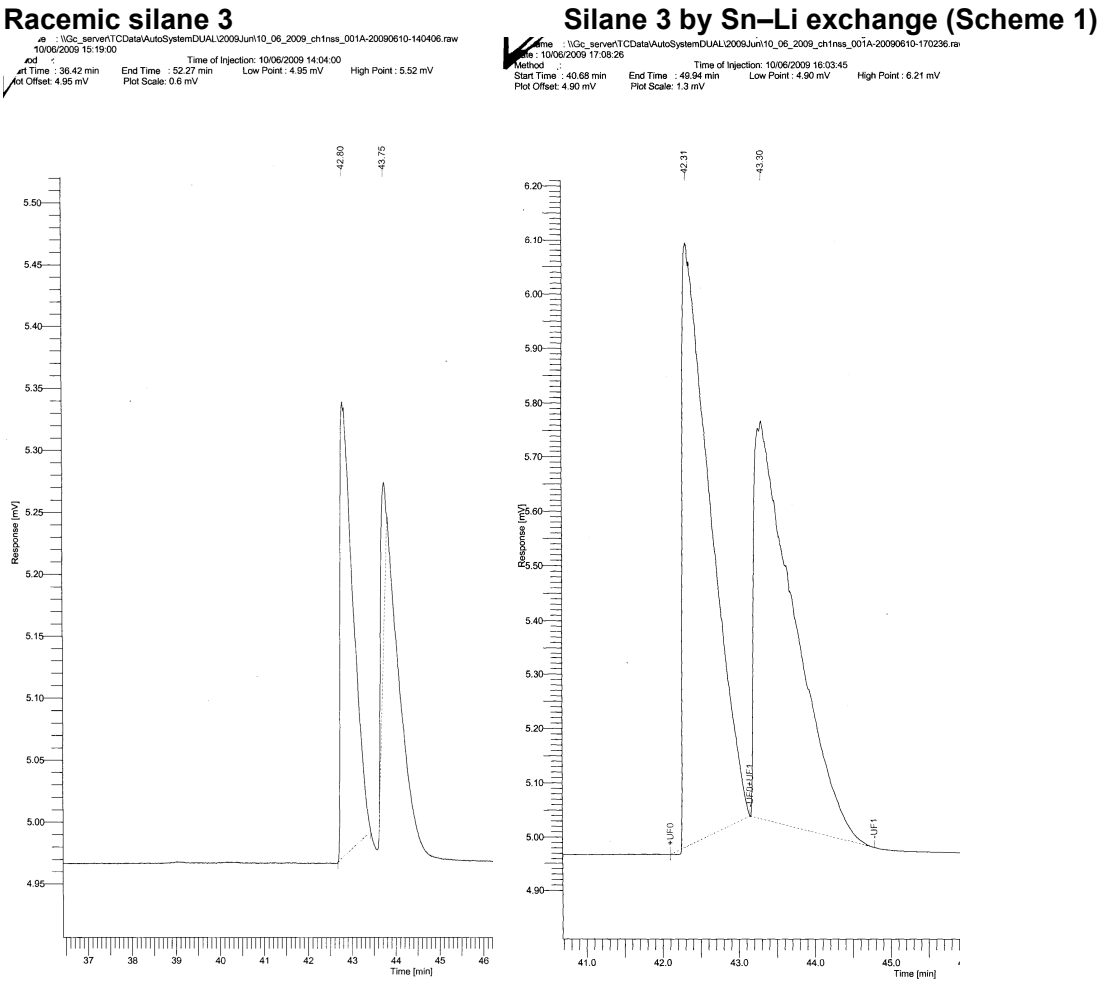



**Fig. 1:** GC traces for authentic racemic silane **3** and for silane **3** formed from (*S*)-**1** in the absence of a ligand in $Et_2O$ at –60 °C

## 2. Enantiomerization of (*S*)-*N*-Boc-2-lithiopiperidine 2 in the presence of TMEDA

This was followed by generating the organolithium **2** (er 80:20 *S*:*R*) using tin–lithium exchange in $Et_2O$ at –78 °C with *n*-BuLi and one equivalent of *N,N,N',N'*-tetramethylethylene diamine (TMEDA), followed by warming to the desired temperature for different time periods, then cooling to –78 °C and electrophilic quench with excess $Me_3SiCl$. The rate constants were determined using reported methods.[2] Typical kinetic run:

*n*-BuLi (80 mL, 0.19 mmol, 2.37 M) was added to (*S*)-**1** (75 mg; 0.16 mmol) and freshly distilled TMEDA (24 mL, 0.16 mmol) in dry $Et_2O$ (0.63 mL) at –78 °C. After 1 h, the mixture was

warmed to –50, –45, –40, or –30 °C. After a measured time period (between 30 and 2640 s), the mixture was cooled to –78 °C and trimethylsilyl chloride (60 mL, 0.47 mmol) was added. After 2 h, MeOH (0.5 mL) was added and the mixture was allowed to warm to room temperature. The mixture was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98:2), to give the silane **3**, data as reported.[2] Analysis of the er was performed by CSP-GC on a β-cyclodextrin-permethylated 120 fused silica capillary column [30 m × 0.25 mm i.d., 20% permethylated β-cyclodextrin in SPB-35 poly(35% diphenyl/65% dimethyl)siloxane, nitrogen carrier at 14 psi, faster running enantiomer = (*S*) (at 82 °C)].

**Table 1**: Rate constants for enantiomerization of **2** (0.25 M) at 233 K with varying [TMEDA]

| Entry | Equiv. TMEDA | [TMEDA], M | $k_{obs}$ (x $10^{-4}$ $s^{-1}$) |
|---|---|---|---|
| 1 | 0.10 | 0.025 | 1.9 ± 0.2 |
| 2 | 0.50 | 0.125 | 5.9 ± 0.1 |
| 3 | 0.75 | 0.1875 | 8.35 ± 0.2 |
| 4 | 1.00 | 0.250 | 10.6 ± 0.8 |
| 5 | 2.00 | 0.50 | 3.5 ± 0.1 |

**Graphics:**

A plot of $k_{obs}$ (racemization) versus [TMEDA] is shown below (Chart 1).

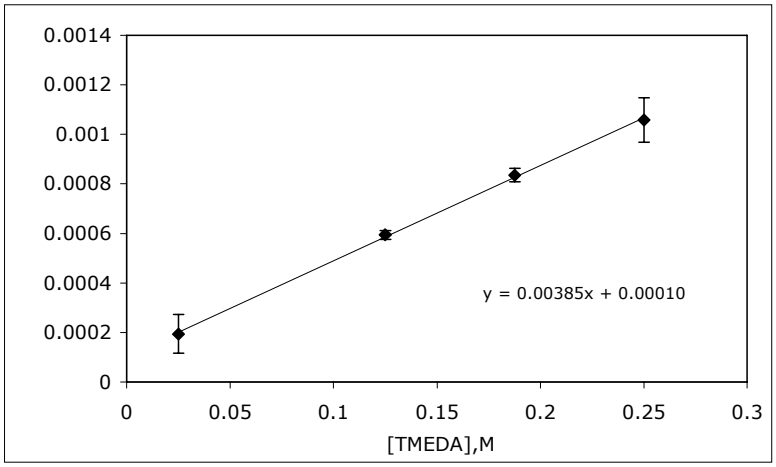



**Chart 1:** Dependence of rate of racemization of (S)-**2** on [TMEDA] from 0 to 1.0 eq TMEDA

Linearity signifies a 1st-order dependence of the rate of racemization of (*S*)-**2** on [TMEDA] up to 1.0 equiv. The non-zero intercept indicates racemization in the absence of a ligand at 233 K. The value 1.0 x $10^{-4}$ $s^{-1}$ for the intercept is not in agreement with the experimentally observed rapid

racemization on transmetalation in the absence of a ligand. We have found that, at –78 °C, TMEDA (0.1 or more equiv.) has a stabilizing effect on the configurational stability of the organolithium, but allows slow racemization at elevated temperatures.

**Table 2: Enantiomer ratios over time for racemization of 2 in the presence of TMEDA**

| Temperature (K) [°C] | Time (s) | Ratio (*S*:*R*) | ½ ln(0.25-2[*R*])[a] |
|---|---|---|---|
| 223 [–50] | 300 | 79.17:20.83 | -0.962588 |
| | 1080 | 75.20:24.80 | -1.035737 |
| | 2520 | 65.96:34.04 | -1.264116 |
| | 3660 | 64.78:35.22 | -1.302521 |
| 228 [–45] | 480 | 71.47:28.53 | -1.115830 |
| | 1620 | 62.77:37.23 | -1.375609 |
| | 2100 | 60.83:39.17 | -1.457999 |
| | 2640 | 59.73:40.27 | -1.511552 |
| 233 [–40] | 120 | 78.74:21.26 | -0.970014 |
| | 360 | 66.54:33.46 | -1.246268 |
| | 900 | 63.25:36.75 | -1.357160 |
| | 1320 | 56.57:43.43 | -1.707902 |
| | 1740 | 56.34:43.66 | -1.725719 |
| | 2400 | 52.30:47.70 | -2.232704 |
| 243 [–30] | 30 | 79.17:20.83 | -0.962588 |
| | 120 | 62.78:37.22 | -1.375218 |
| | 300 | 52.52:47.48 | -2.187029 |
| | 540 | 50.40:49.60 | -3.107304 |

[a]Total concentration ([*S*]+[*R*]) = 0.25 M

The above kinetic data were treated under reversible first-order conditions in **2** using the following equation

$$\ln\left([2]-\frac{(1+K_{eq})}{K_{eq}}[R]\right)=(k_1+k_{-1})t+c \qquad (1)$$

where the observed rate constant, $k_{obs} = (k_1 + k_{-1})$ = slope obtained from a plot of the left hand side of equation (1) against time, t. [**2**] = total concentration of compound **2**, and the concentration of the *(R)* enantiomer, [*R*], is obtained from the fraction of the *(R)* enantiomer of **2**, given by:

$$[R] = f_R \times [2] \qquad (2)$$

For racemization $K_{eq} = 1$ and $k_1 = k_{-1}$ so equation (1) simplifies to

$$0.5\ln([2] - 2[R]) = -k_1 t + c \qquad (3)$$

The results, using Eq 3, are displayed in Chart 2.

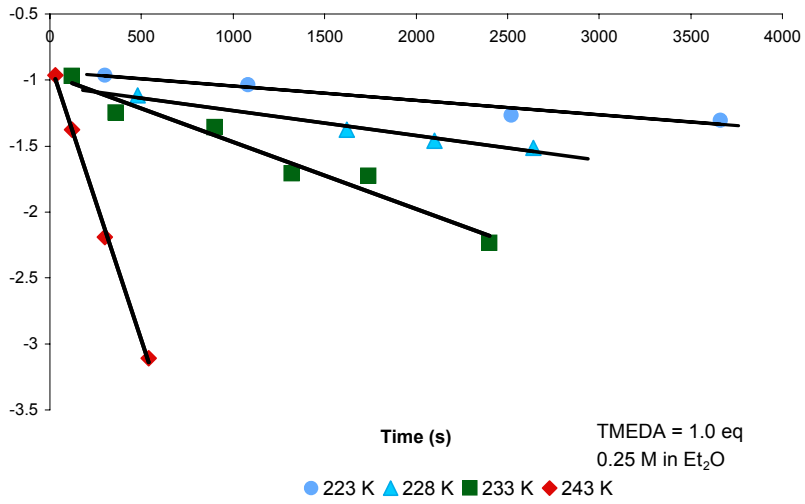



**Chart 2: Log plot for racemization of 2 (no chiral ligand) with 1 equiv. TMEDA.**
Temperatures: ○, 223 K; △, 228 K,; □, 233 K, ◇, 243 K

The values for the rate constants can be taken from the slope of the log plots shown in Chart 2. However, improved data that avoids numbers tending to ln(0) as the reaction approaches equilibrium are obtained using a nonlinear fit to the zero order plots using Equation 4 and the fact that $k_{obs} = (k_1 + k_{-1})$.

$$S_t = S_{eq} + (S_0 - S_{eq})e^{-(k_1 + k_{-1})t} \qquad (4)$$

This analysis provides the following parameters (Table 3).

**Table 3.** Parameters for enantiomerization of (*S*)-**2** with 1 equiv. TMEDA (no chiral ligand)

| | **Temperature (K)** | | | |
|---|---|---|---|---|
| **Parameters** | **223 (–50 °C)** | **228 (–45 °C)** | **233 (–40 °C)** | **243 (–30 °C)** |
| $k_{obs}$ **($10^{-4}s^{-1}$)** | 2.1 ± 0.2 | 4.9 ± 0.4 | 10.6 ± 0.8 | 66.3 ± 2.5 |
| $k_1$ **($s^{-1}$)**[a] | 0.000104 | 0.000247 | 0.000529 | 0.003314 |
| **ln($k_1$/T)** | -14.57816 | -13.73348 | -12.99575 | -11.20268 |
| **1/T ($K^{-1}$)** | 0.0044843 | 0.00438596 | 0.0042918 | 0.0041152 |
| $t_{1/2}$ **(s)**[b] | 6664 | 2801 | 1310 | 209 |
| **(min)** | 111 | 47 | 22 | 3.5 |

[a] $k_{obs} = k_1 + k_{-1}$; for racemization, $k_1 = k_{-1}$, so the rate constant for enantiomerization, $k_1 = k_{obs}/2$;

[b] $t_{1/2}$ for enantiomerization

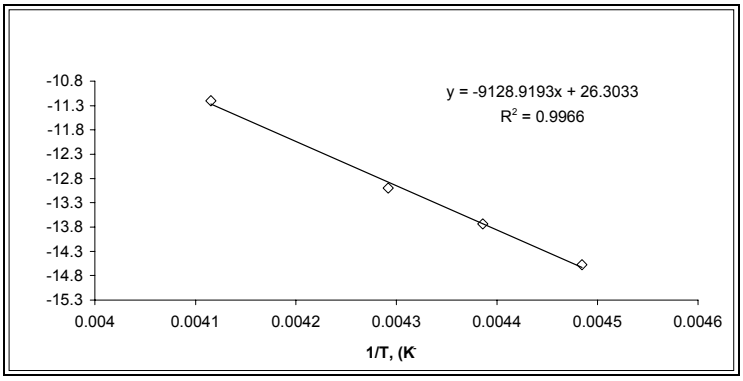



**Chart 3: Eyring plot for enantiomerization of (*S*)-2.**

Slope = –9128.92; $\Delta H^{\ddagger} = -\text{slope} \times R$

Intercept = 26.30; $\Delta S^{\ddagger} = R \times [\text{intercept} - \ln(k_B/h)]$

**Table 4**. Activation parameters for enantiomerization of **2** with 1 equiv. TMEDA

| | | |
|---|---|---|
| **$\Delta H^{\ddagger}$ (kcal/mol)** | 18.1 ± 0.7 | |
| **$\Delta S^{\ddagger}$ (cal/mol·K)** | 5.0 ± 3.2 | |
| **$\Delta G^{\ddagger}$ (kcal/mol)** | **223 K (–50 °C)** | 17.0 ± 1.0 |
| | **228 K (–45 °C)** | 17.0 ± 1.1 |
| | **233 K (–40 °C)** | 16.9 ± 1.1 |
| | **243 K (–30 °C)** | 16.9 ± 1.1 |
| | **273 K (0 °C)** | 16.7 ± 1.2 |

### 3. Resolution of *N*-Boc-2-lithiopiperidine 2 with the chiral ligand 4

#### A. Resolution of *N*-Boc-2-lithiopiperidine 2 in the absence of TMEDA

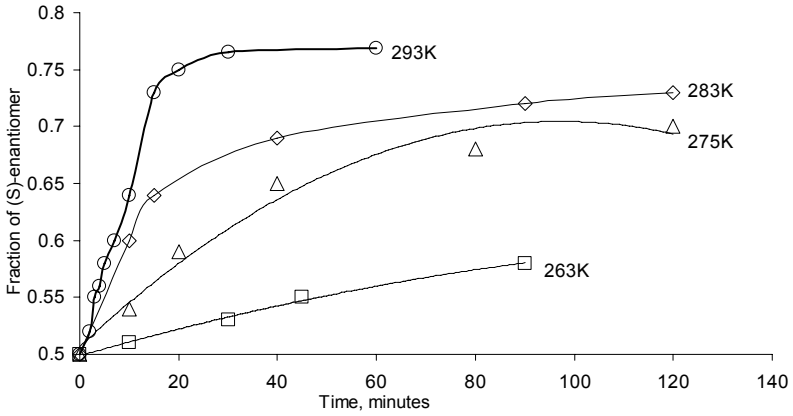



**Chart 4.** Zero-order plots for DTR of **2** in the presence of 1.0 of **4**. Temperatures: ○, 293 K; ◇, 283 K; △, 275 K; □, 263 K.

In this case, the increasing enantiomer is *S,* so equation 1 becomes:

$$\ln\left([2]-\frac{(1+K_{eq})}{K_{eq}}[S]\right)=(k_1+k_{-1})t+c \qquad (5)$$

The data are plotted in Chart 5.

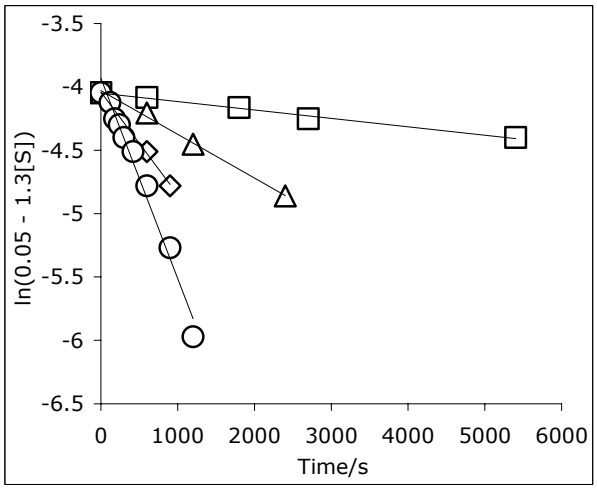



**Chart 5.** Log plots for resolution of **2** in the presence of 1.0 eq **4**. Temperatures: ○, 293 K; ◇, 283 K; △, 275 K; □, 263 K.

The values for the rate constants can be taken from the slope of the log plots shown in Chart 5. However, improved data that avoids numbers tending to ln(0) as the reaction approaches equilibrium are obtained using a nonlinear fit to the zero order plots using Equation 4 and the fact that $k_{obs} = (k_1 + k_{-1})$:

$$S_t = 0.77 + (0.50 - 0.77)e^{-k_{obs}t} \quad (6)$$

Note: Although all the rate constants are obtained from nonlinear fits of the zero order plots (Eq 6), their respective errors were obtained by linearizing the plots and using regression analysis (Eq 5) at a 95% confidence level.

**Table 5.** Eyring plot parameters for resolution of **2** in the presence of 1.0 equiv. **4**

| Temp (K) | 1/T ($K^{-1}$) | $k_{obs}$ (x $10^{-4}$ $s^{-1}$) | -ln($k_{obs}$/T) | -ln($k_1$/T) | -ln($k_{-1}$/T) |
|---|---|---|---|---|---|
| 293 | 0.003413 | 14.2 ± 1.92 | 12.2379 | 12.4992 | 13.7079 |
| 283 | 0.003534 | 6.07 ± 0.31 | 13.0517 | 13.3129 | 14.5216 |
| 275 | 0.003636 | 2.59 ± 0.14 | 13.8745 | 14.1358 | 15.3444 |
| 263 | 0.003802 | 0.675 ± 0.03 | 15.1751 | 15.4364 | 16.6450 |

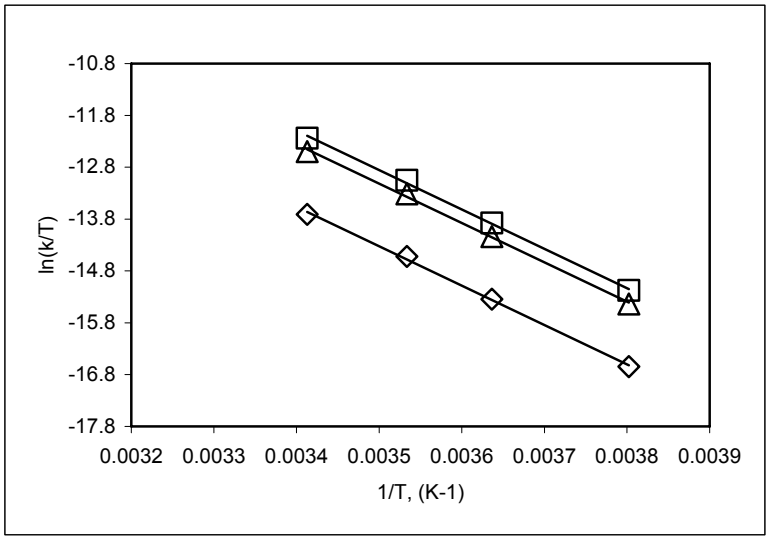



**Chart 6.** Eyring plots for resolution of **2** in the presence of 1.0 eq **4**. KEY: □, $k_{obs}$; $k_{R\rightarrow S}$, △; ◇, $k_{S\rightarrow R}$.

**Table 6.** Activation parameters for resolution of **2** in the presence of 1.0 eq **4**.

| $\Delta H^{\ddagger}$ (R→S) (kcal/mol) | $\Delta S^{\ddagger}$ (R→S) (cal/mol.K) | $\Delta H^{\ddagger}$ (S→R) (kcal/mol) | $\Delta S^{\ddagger}$ (S→R) (cal/mol.K) |
|---|---|---|---|
| 15.1 ± 0.4 | -20.4 ± 1.4 | 15.1 ± 0.4 | -22.8 ± 1.4 |

B. **Resolution of *N*-Boc-2-lithiopiperidine 2 with varying amounts of TMEDA**

This was followed by generating the organolithium **2** (er 50:50) using tin–lithium exchange in $Et_2O$ at –78 °C with *n*-BuLi and 0.1, 0.5, 0.75, 1.0, 2.0 equiv of tetramethylethylene diamine (TMEDA), followed by warming to the desired temperature for different time periods then cooling to –78 °C and electrophilic quench with excess $Me_3SiCl$. The rate constants were determined using reported graphical methods.[2]

Typical kinetic run:

Standard solutions (0.25 M) of *rac*-**1** (592 mg, 1.25 mmol in 5.0 mL $Et_2O$), TMEDA (145 mg, 1.25 mmol, in 5 mL $Et_2O$), and the alcohol corresponding to **4** (250 mg, 1.25 mmol in 5 mL $Et_2O$) were prepared. To each tube, the following standard solutions were added: 0.20 mL of **1**, 0.2 mL conjugate acid of **4**, and the corresponding amount of TMEDA were added. A small amount of freshly distilled $Et_2O$ was added to maintain a total volume of 1.0 mL. Hence the total concentration of the organolithium, was 0.05 M. Transmetallation to the N-Boc 2-lithiopiperidine was effected by addition of *n*-BuLi (1.2 eq) at -78 $^{o}$C for 1h in the presence of TMEDA. Ligand **4** was generated from the corresponding alcohol in a separate tube by addition of *sec*-BuLi.(1.0 eq) at –78 °C for an hour. The two solutions were mixed at –78 °C and the tubes were quickly transferred from the –78 °C bath to the –10 °C cooling unit. After a measured time period (between 0 and 120 min), the mixture was cooled to –78 °C and trimethylsilyl chloride (60 mL, 0.47 mmol) was added. After 240 min, 10 % $H_3PO_4$ (2 mL) was added and the mixture was extracted with $Et_2O$. The mixture was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98:2), to give the silane **3**, data as reported.[1] The silanes were subsequently purified and analyzed by CSP-SFC at a wavelength of 210 nm. The chiral ligand was recovered by acidification (with 2 M HCl), then basification (with 2 M NaOH) followed by extraction with $Et_2O$.

**Table 7.** Enantiomer ratios over time for resolution of **2** in the presence of 1.0 eq **4** at 263 K and 0.1 eq TMEDA

| Entry | Time(min) | Ratio (S:R) | ln(0.05-1.3[S]) |
|---|---|---|---|
| 1 | 0 | 50:50 | -4.046 |
| 2 | 10 | 52:48 | -4.122 |
| 3 | 30 | 57:43 | -4.346 |
| 4 | 45 | 59:41 | -4.452 |
| 5 | 90 | 65:35 | -4.86 |

**Table 8.** Enantiomer ratios over time for resolution of **2** in the presence of 1.0 eq **4** at 263 K and 0.5 eq TMEDA

| Entry | Time(min) | Ratio (S:R) | ln(0.05-1.3[S]) |
|---|---|---|---|
| 1 | 0 | 50:50 | -4.046 |
| 2 | 10 | 53:47 | -4.164 |
| 3 | 30 | 60:40 | -4.51 |
| 4 | 45 | 66:34 | -4.948 |
| 5 | 60 | 69:31 | -5.268 |

**Table 9.** Enantiomer ratios over time for resolution of **2** in the presence of 1.0 eq **4** at 263 K and 0.75 eq TMEDA

| Entry | Time(min) | Ratio (S:R) | ln(0.05-1.3[S]) |
|---|---|---|---|
| 1 | 0 | 50:50 | -4.046 |
| 2 | 10 | 54:46 | -4.206 |
| 3 | 20 | 57:43 | -4.346 |
| 4 | 30 | 63:37 | -4.704 |
| 5 | 40 | 67:33 | -5.044 |
| 6 | 55 | 70:30 | -5.404 |
| 7 | 70 | 73:27 | -5.972 |
| 8 | 80 | 74:26 | -6.266 |

**Table 10.** Enantiomer ratios over time for resolution of **2** in the presence of 1.0 eq **4** at 263 K and 1.0 eq TMEDA

| Entry | Time(min) | Ratio (S:R) | ln(0.05-1.3[S]) |
|---|---|---|---|
| 1 | 5 | 54:46 | -4.206 |
| 2 | 10 | 55:45 | -4.25 |
| 3 | 15 | 57:43 | -4.346 |
| 4 | 25 | 62:38 | -4.636 |
| 5 | 30 | 65:35 | -4.86 |
| 6 | 50 | 71:29 | -5.56 |
| 7 | 60 | 74:26 | -6.266 |
| 8 | 90 | 76:24 | -7.418 |

**Table 11.** Enantiomer ratios over time for resolution of **2** in the presence of 1.0 eq **4** at 263 K and 2.0 eq TMEDA

| Entry | Time(min) | Ratio (S:R) | ln(0.05-1.3[S]) |
|---|---|---|---|
| 1 | 0 | 50:50 | -4.046 |
| 2 | 5 | 55:45 | -4.25 |
| 3 | 8 | 59:41 | -4.452 |
| 4 | 10 | 61:39 | -4.57 |
| 5 | 20 | 73:27 | -5.972 |
| 6 | 40 | 76:24 | -7.418 |
| 7 | 60 | 77:23 | N/A[a] |
| 8 | 90 | 77:23 | N/A |

**a**.ln(0.05 – (1.3 x 0.77 x 0.05)) = infinity; at equilibrium the log function vanishes.

Chart 7 plots these data using Eq 5.

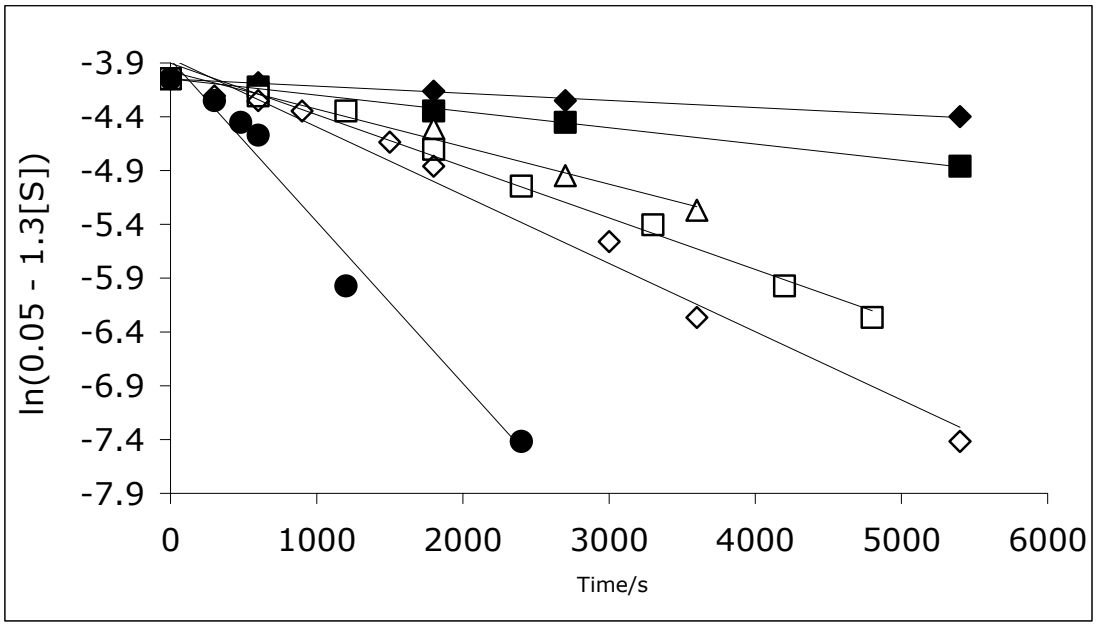



**Chart 7.** Log plot for resolution of **2** with 1 equiv. **4** and varying amounts of TMEDA at 263K (–10 °C). Equivalents of TMEDA: ◆, 0; ■, 0.1; △, 0.5; □, 0.75; ◇, 1.0; ●, 2.0.

Nonlinear fits to zero order plots (Eq 6) yielded the rate constants in Table 12. Errors were obtained by regression analysis using Eq 5.

**Table 12**. Rate constants for DTR of **2** by **4** at 263 K, with varying amounts of TMEDA. [**2**] = 0.05M (obtained from non linear fits)

| Entry | Equiv. TMEDA | [TMEDA], M | $k_{obs}$ (x $10^{-4}$ $s^{-1}$) |
|---|---|---|---|
| 1 | 0.0 | 0.000 | 0.675 ± 0.03 |
| 2 | 0.10 | 0.005 | 1.523 ± 0.04 |
| 3 | 0.50 | 0.025 | 3.05 ± 0.25 |
| 4 | 0.75 | 0.038 | 3.84 ± 0.21 |
| 5 | 1.0 | 0.050 | 4.55 ± 0.33 |
| 6 | 2.0 | 0.100 | 10.51 ± 1.12 |

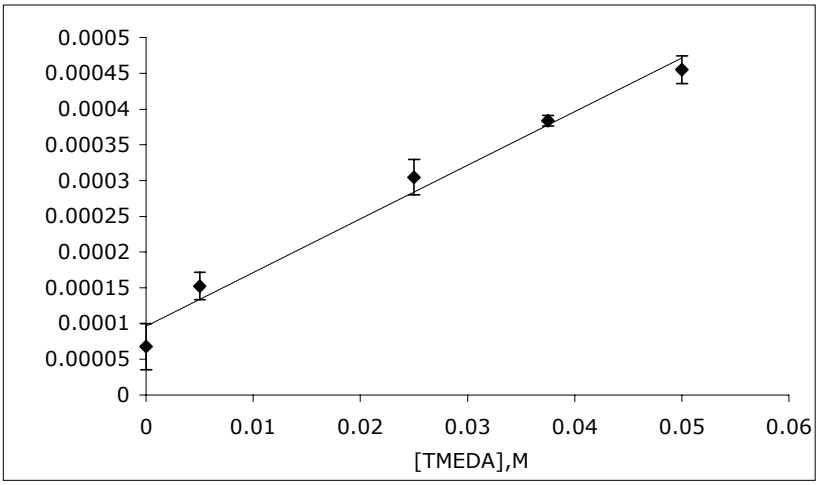



**Chart 8.** Dependence of rate constant on [TMEDA] for **2**, from 0 to 1.0 eq **4**.

CHART 8 shows the DTR rate constants plotted against [TMEDA] from 0.00 to 1.0 equivalent. A fit of the equation $k_{obs} = k' + k''[\text{TMEDA}]^n$ (specific order, n = 1.05; intercept = 9.99 ± 0.2 x $10^{-5}$ $s^{-1}$, $k''$ = 8.78 ± 0.6 x $10^{-3}$ $M^{-1}s^{-1}$) reveals a first-order dependence of rate on [TMEDA]. The $k'$ term indicates DTR uncatalyzed by TMEDA and is in reasonable agreement with the experimentally observed value of 6.75 ± 0.34 x $10^{-5}$ $s^{-1}$ for DTR in the absence of TMEDA.

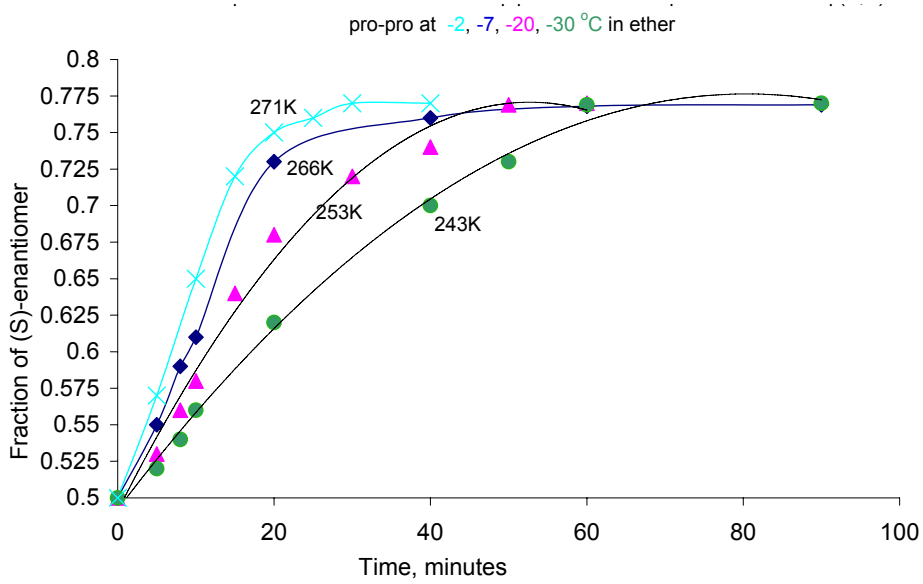



**Chart 9.** Zero-order plots for resolution of **2** in the presence of 1.0 eq **4** and 2.0 eq TMEDA. Temperatures: △, 243 K; □, 253 K; ○, 266 K; ◇, 271 K.

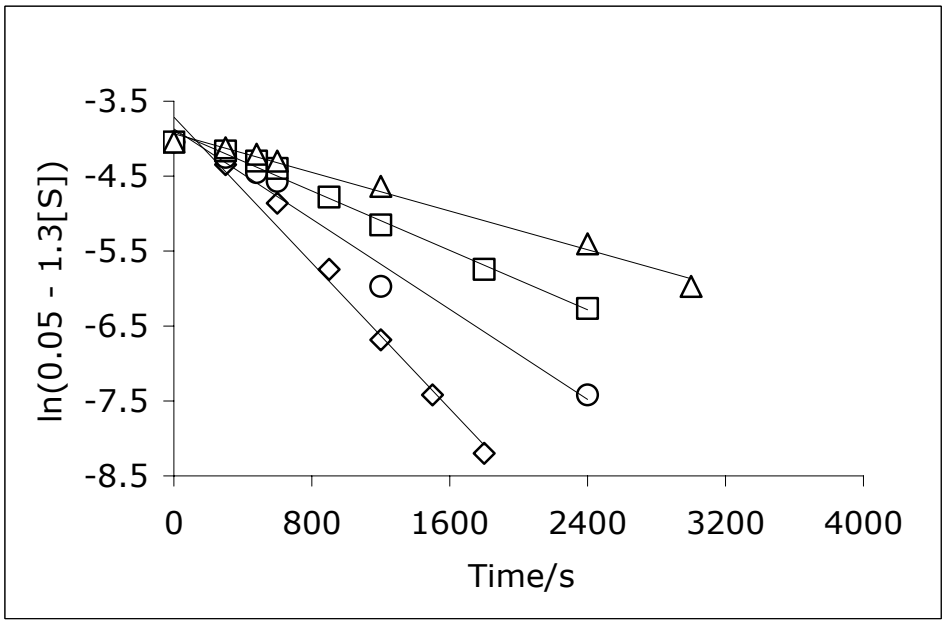



**Chart 10.** Log plots for resolution of **2** in the presence of 1.0 eq **4** and 2.0 eq TMEDA. Temperatures: △, 243 K; □, 253 K; ○, 266 K; ◇, 271 K.

The rate constants are obtained from nonlinear fits of the zero order plots (Eq 6), their respective errors were obtained by linearizing the plots and using regression analysis (Eq 5) at a 95% confidence level.

**Table 13.** Eyring plot parameters for resolution of **2** in the presence of 1.0 eq **4** and 2.0 eq TMEDA

| Temp (K) | 1/T ($K^{-1}$) | $k_{obs}$ (x $10^{-4}$ $s^{-1}$)[a] | -ln($k_{obs}$/T) | -ln($k_1$/T) | -ln($k_{-1}$/T) |
|---|---|---|---|---|---|
| 271 | 0.00369 | 15.97 ± 1.44 | 12.0420 | 12.30328 | 13.51194 |
| 263 | 0.00380 | 10.51 ±1.12 | 12.4311 | 12.69240 | 13.90107 |
| 253 | 0.003952 | 7.98 ± 0.41 | 12.6673 | 12.92858 | 14.13724 |
| 243 | 0.004115 | 5.49 ± 0.30 | 12.9997 | 13.26103 | 14.46969 |

**a.** $k_{obs} = k_1 + k_{-1}$; for resolution $K_{eq} = \frac{k_1}{k_{-1}} = \frac{[S]_{eq}}{[R]_{eq}} = \frac{77}{23} = 3.3$

$k_1 = \frac{k_{obs}K_{eq}}{1+K_{eq}}$ and $k_{-1} = \left(1 - \frac{K_{eq}}{1+K_{eq}}\right)k_{obs}$

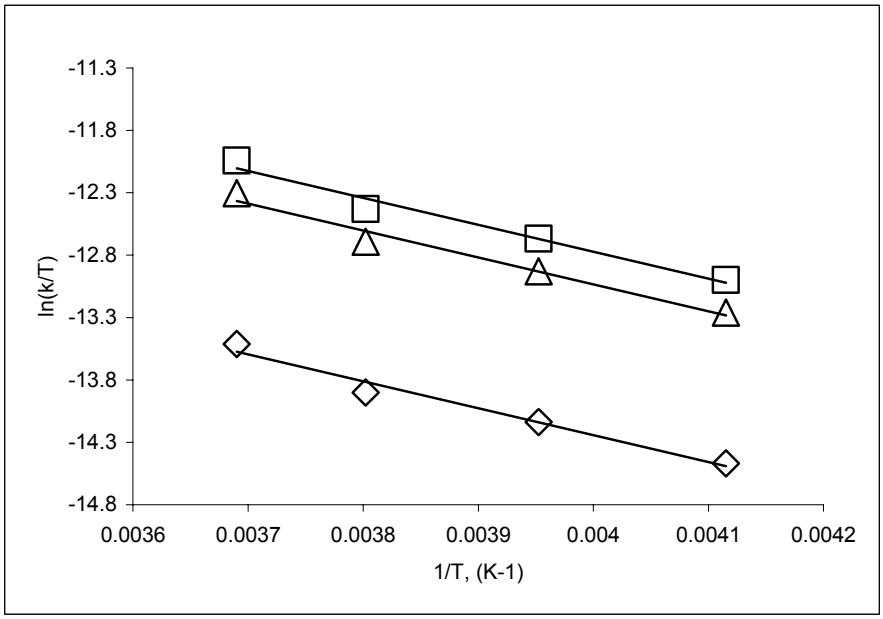



**Chart 11.** Eyring plots for resolution of **2** in the presence of 1.0 eq **4** and 2.0 eq TMEDA. KEY: □, $k_{obs}$ △, $k_{R\rightarrow S}$. ◇, $k_{S\rightarrow R}$

**Table 14.** Activation parameters for resolution of **2** in the presence of 1.0 eq **4** and 2.0 eq TMEDA.

| $\Delta H^{\ddagger}$ (R→S) (kcal/mol) | $\Delta S^{\ddagger}$ (R→S) (cal/mol.K) | $\Delta H^{\ddagger}$ (S→R) (kcal/mol) | $\Delta S^{\ddagger}$ (S→R) (cal/mol.K) |
|---|---|---|---|
| 4.3 ± 0.5 | –55.9 ± 1.8 | 4.3 ± 0.5 | –58.3 ± 1.8 |

The R→S parameters are calculated from forward rate constants, $k_{R\rightarrow S}$ and the S→R parameters are calculated from reverse rate constants, $k_{S\rightarrow R}$.

The errors in $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ are calculated using error propagation rules for addition/subtraction and multiplication/division. From an Eyring plot,

$\Delta H^{\ddagger} = -\text{slope}\cdot R$

$$\frac{Err(\Delta H)}{\Delta H} = \sqrt{\left(\frac{err(slope)}{slope}\right)^2 + \left(\frac{err(R)}{R}\right)^2} = \sqrt{\left(\frac{err(slope)}{slope}\right)^2} \text{ since err(R) = 0}$$

Similarly,

$\Delta S^{\ddagger} = \text{Intercept}\cdot R - R\ln(k_B/h)$

$$\frac{Err(\Delta S)}{\Delta S} = \sqrt{\left(\frac{\text{err(intercept)}}{\text{intercept}}\right)^2 + \left(\frac{\text{err(R)}}{R}\right)^2} = \sqrt{\left(\frac{\text{err(intercept)}}{\text{intercept}}\right)^2}$$

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

$$\frac{Err(T\Delta S)}{T\Delta S} = \sqrt{\left(\frac{err(T)}{T}\right)^2 + \left(\frac{err(\Delta S)}{\Delta S}\right)^2}$$

$$Err(\Delta G) = \sqrt{(err(\Delta H))^2 + (err(T\Delta S))^2}$$

**4. Resolution of *N*-Boc-2-lithiopiperidine 2 with the chiral ligand 5 and achiral ligands**

To test a variety of achiral ligands to assist the resolution of the organolithium **2**, the following procedure was used:

*n*-BuLi (0.22 mL, 0.53 mmol, 2.5 M) was added to *rac*-**1** (240 mg; 0.505 mmol) and freshly distilled achiral amine ligand (0.53 mmol) in dry $Et_2O$ (2.2 mL) at –78 °C. After 1 h, the chiral ligand **5** [prepared by adding *sec*-BuLi (0.50 mL, 0.656 mmol, 1.3 M in hexanes) to the corresponding alcohol (140 mg, 0.606 mmol) in $Et_2O$ (2.2 mL) at –78 °C] was added. The mixture was warmed to –40 °C. After 90 min the mixture was cooled to –78 °C and the electrophile TMSCl (0.2 mL, 1.515 mmol) was added. The mixture was allowed to warm slowly (over 18 h) to room temperature and MeOH (2 mL) was added. The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with light petroleum (b.p. 40–60 °C)–EtOAc (98:2), to give the piperidine **3**, data as reported.[1] The enantiomer ratio was determined by GC as described above.

**5. References**

1. Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E. *Chem. Commun.* **2008**, 4174.
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