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

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Abstract

The kinetics of enantiomerization and dynamic thermodynamic resolution (DTR) of *N*-Boc-2-lithiopiperidine have been measured, revealing significant differences in enthalpy and entropy for these processes and a role for the achiral ligand TMEDA: the racemization and the DTR are catalytic and first order in [TMEDA], and this has implications for asymmetric synthesis with chiral organolithiums.

Substituted piperidines are key structures for the synthesis of many alkaloids and medicinal compounds. A direct method to access 2-substituted piperidines is by electrophilic quench of the corresponding 2-lithiated derivative.¹ The racemic organolithium can be prepared most conveniently by proton abstraction, and a suitable method is to use *N*-*tert*-butoxycarbonyl-piperidine (*N*-Boc-piperidine) with *sec*-BuLi and *N,N,N',N'*-tetramethylethylenediamine, TMEDA.² Unfortunately, the use of chiral ligands to effect an asymmetric deprotonation has met with limited success.³ An alternative approach is to use dynamic resolution⁴ and the first promising results for resolution of 2-lithiated piperidines have been reported recently.⁵ For high yields in this chemistry, carbanion inversion is required in the presence of the chiral ligand. Therefore it is crucial to have an understanding of the barriers to this inversion. This paper describes quantitative kinetic data for the enantiomerization of *N*-Boc-2-lithiopiperidine in the presence of TMEDA. In addition we have determined the activation parameters for dynamic thermodynamic resolution (DTR) of *N*-Boc-2-lithiopiperidine in the presence of a chiral ligand. This study has revealed a significant role for the ligand TMEDA in the rate of both enantiomerization and dynamic resolution.

In previous work, we determined the enantiomerization barrier of several lithiated pyrrolidines.⁶ The barrier to enantiomerization for *N*-Boc-2-lithiopiperidine **2** was determined in the same way, starting with the enantioenriched stannane **1** (prepared by DTR)⁵ (Scheme 1). Transmetalation at -78 °C in the presence of 1 equiv. of TMEDA, then equilibration at temperatures from -50 to -30 °C, followed by cooling to -78 °C and electrophilic quench with TMSCl gave *N*-Boc-2-trimethylsilylpiperidine **3**.³

Under these conditions, the enantiomer ratio (er) of the silane reflects the ratio of organolithium enantiomers *R*-**2** and *S*-**2**.⁷ These experiments gave rise to good first order plots for the loss of the major enantiomer over time from which an Eyring plot led to the determination of the activation parameters (Table 1 entry 1 and Supplementary Information[†]). Transmetalation of

the stannane **1** (er 80:20) in Et₂O in the absence of any ligand gave (after addition of TMSCl) a low yield of racemic silane **3** even at low temperature, which precluded kinetic measurements of racemization in the absence of any ligands.

The rate of enantiomerization with varying amounts of TMEDA was measured at -40 °C (see Supplementary Information[†]). The linear correlation of k_{enanti} vs. [TMEDA] reveals a first-order dependence on [TMEDA].

Of significance for asymmetric synthesis, we carried out kinetic studies of the resolution of organolithium **2** in the presence of the chiral ligand **4** (Scheme 2). This ligand is known to promote dynamic resolution of **2** at -40 °C, under thermodynamic control, with a preference for one diastereomeric complex (*S*-**2**·**4**:*R*-**2**·**4** = 77:23).^{5b} Interestingly, in the absence of TMEDA, DTR was not observed at this temperature. However, at higher temperatures it was possible to obtain reasonable kinetic data. Hence, DTR of **2** by **4** at -10, 2, 10 and 20 °C gave, in moderate yields, the silane *S*-**3** with increasing enantioenrichment over time, to a maximum er of 77:23. An Eyring plot (see Supplementary Information[†]) revealed activation parameters shown in Table 1 entry 2. Similar experiments with 2 equiv. of TMEDA added, conducted at -30, -20, -7, and -2 °C yielded the thermodynamic parameters listed in Table 1 entry 3.

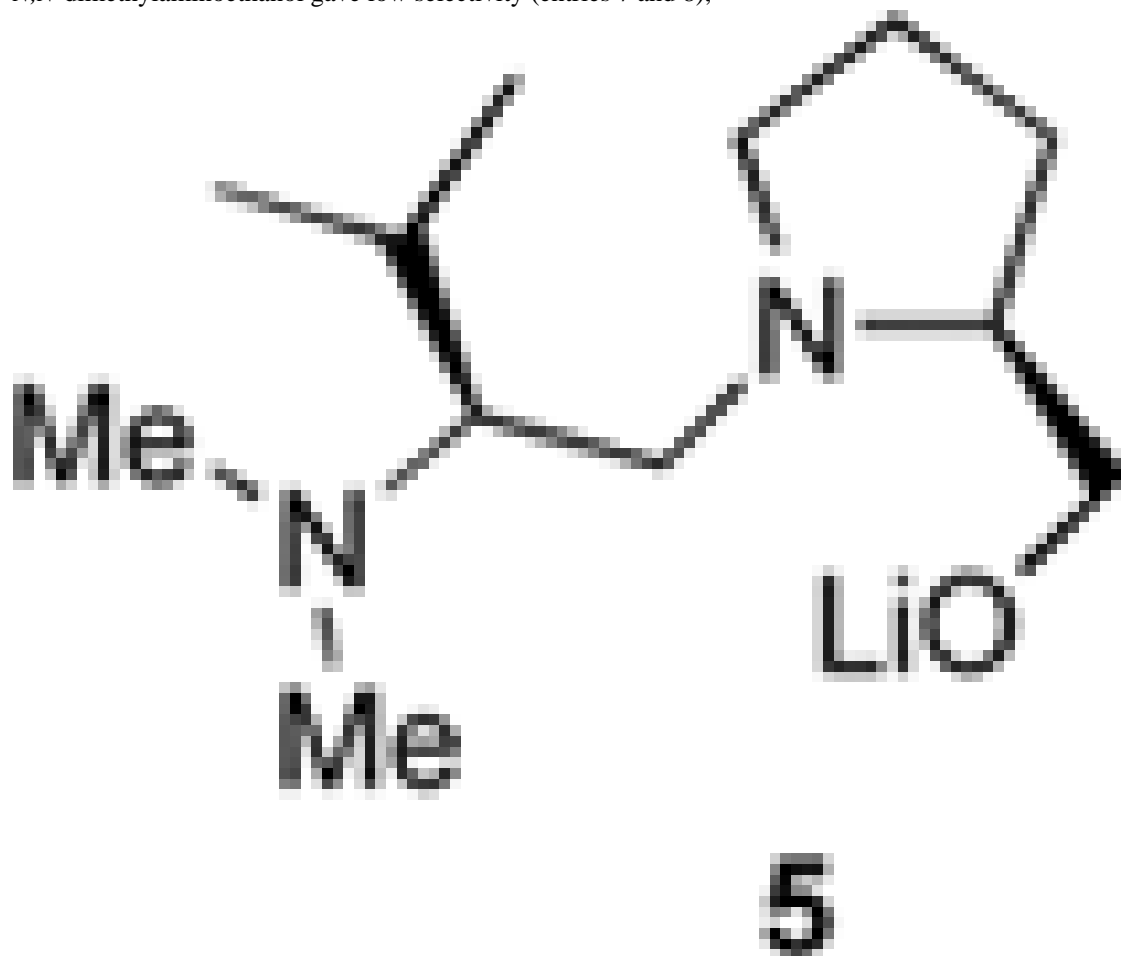
Examination of the enthalpic and entropic contributions to the free energies for inversion in the enantiomerization and resolution reveal interesting differences, indicative of different mechanisms in each case. A plot of ΔG^\ddagger vs. temperature for the three systems studied is illustrated in Fig. 1. These findings indicate a role for TMEDA in both the enantiomerization and the DTR. Particularly intriguing is the effect of TMEDA on the DTR. The large negative entropy in Table 1 entry 3 indicates significant order in the transition state of the rate-determining step (rds) for the DTR process. Note, however, that the rds need not be the carbanion inversion (see below).

To further probe this role, the DTR of **2** by **4** was studied with varying amounts of TMEDA at -10 °C. Fig. 2 shows first order rate constants for DTR using 1 equivalent of **4**, plotted against [TMEDA] from zero to one equivalent of TMEDA. The linear correlation suggests that *the DTR of 2 by 4 is first order in the achiral ligand TMEDA*. The intercept of $3.8(\pm 0.8) \times 10^{-5} \text{ sec}^{-1}$ indicates a competing DTR having a zero-order dependence on TMEDA (*i.e.*, DTR not catalyzed by TMEDA), and is in agreement with the experimental value of $3.3(\pm 0.2) \times 10^{-5} \text{ sec}^{-1}$ at -10 °C (see Supplementary Information[†]). The rate constant of the DTR in Et₂O at -10 °C in the presence of 1.0 equiv. TMEDA, $k = 3.2(\pm 0.2) \times 10^{-4} \text{ s}^{-1}$, is approximately ten times that in the absence of TMEDA.

Scheme 3 illustrates equilibria that could exist in the dynamic resolution, including a catalytic role for TMEDA in the DTR which is consistent with the kinetics. Parallel pathways of dynamic resolution are implicated, one of which is catalyzed by TMEDA. This could occur through mixed aggregates such as **2**·**4**·TMEDA or through the simple **2**·TMEDA complex. We know that k_2 , the rate constant for the uncatalyzed dynamic resolution (Scheme 3), is slow relative to the catalyzed process, but the rds of the latter is not known. Structural details of the components of this reaction are unknown at present. Each species is drawn as a monomer for simplicity. TMEDA is normally bidentate,⁸ and lithiated β -aminoalkoxides are chelated and form dimeric or tetrameric mixed aggregates with simple alkylolithiums.⁹ However, the degree of chelation and aggregation of diaminoalkoxides such as **4** is unknown, so we have not speculated on possible structural details of mixed aggregates at this time.

[†]Electronic Supplementary Information (ESI) available: kinetic data for racemization and dynamic resolution. See DOI: 10.1039/b000000x/

As TMEDA has a significant role in the DTR, we tested ligands other than TMEDA for this process. Racemic **2** was generated by tin–lithium exchange in the presence of the chiral ligand **5** and the additional ligand. After 90 min at $-40\text{ }^{\circ}\text{C}$ the mixture was cooled to $-78\text{ }^{\circ}\text{C}$ prior to addition of TMSCl. With one equivalent of TMEDA, chiral ligand **5** promotes DTR to give silane **3**, er 80:20 (Table 2, entry 1).^{5a} Entries 2 and 3 indicate that dynamic resolution is operative using various amounts of TMEDA. However, without TMEDA at this temperature a low yield of racemic silane **3** was produced (entry 4). Et₃N and (–)-sparteine **1** gave racemic silane **3** (entries 5–6). Pentamethyldiethylenetriamine (PMDTA) and the lithium alkoxide of *N,N*-dimethylaminoethanol gave low selectivity (entries 7 and 8),



suggesting only slow turnover in the catalytic cycle. More closely related to TMEDA is the ligand tetraethylethylenediamine (TEEDA), which gave a low yield of the silane **3** with slightly enhanced er (entry 9). From Table 2 it is clear that, of the ligands studied, TMEDA has the most beneficial influence on overall yield and selectivity.

In summary, the thermodynamic parameters for racemization of *N*-Boc-2-lithiopiperidine (**2**·TMEDA) and resolution of *N*-Boc-2-lithiopiperidine (**2**·**4** and **2**·**4**·TMEDA) are significantly different. Indeed, the resolution of **2**·**4**·TMEDA is mostly entropy controlled. We have found parallel pathways for the DTR, the slower of which is zero order in TMEDA, whereas the faster one has a first order dependence in TMEDA. Other ligands are less effective for the asymmetric substitution of *N*-Boc-2-lithiopiperidine. The results reported here have implications for dynamic resolution chemistry and it will be important to determine how widespread is the requirement for added achiral ligands in such processes.

Supplementary Material

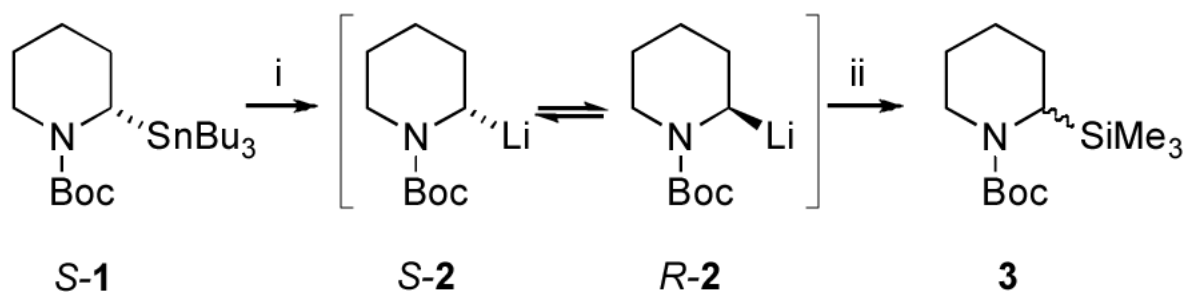
Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

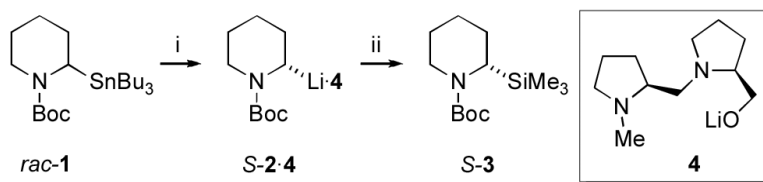
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**Scheme 1.**

i, *n*-BuLi (1.1 equiv.), Et₂O, TMEDA (1 equiv.), -78 °C, 1 h then warm to -50, -40 or -30 ° C for various times; ii, -78 °C, TMSCl.

**Scheme 2.**

i, *n*-BuLi (1.2 equiv.), Et₂O, alone or with 2 equiv. TMEDA, -78 °C, 1 h then **4** (1 equiv.) then warm to temperatures listed in text and Supporting Information for various times; ii, cool to -78 °C, TMSCl.

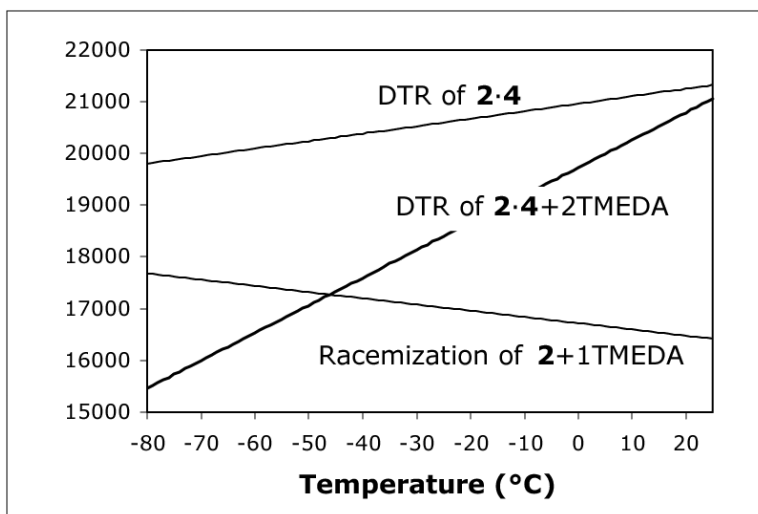


Fig. 1. The relationship between ΔG^\ddagger and temperature for the three systems studied (Table 1). For the DTRs, the barriers are for $R\text{-}2 \rightarrow S\text{-}2$.

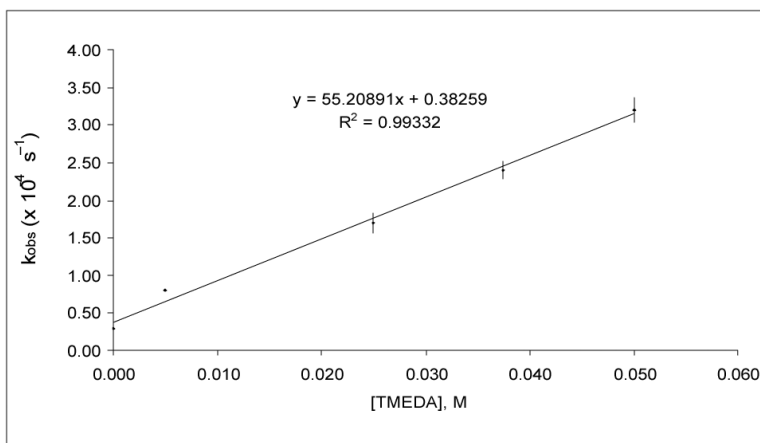
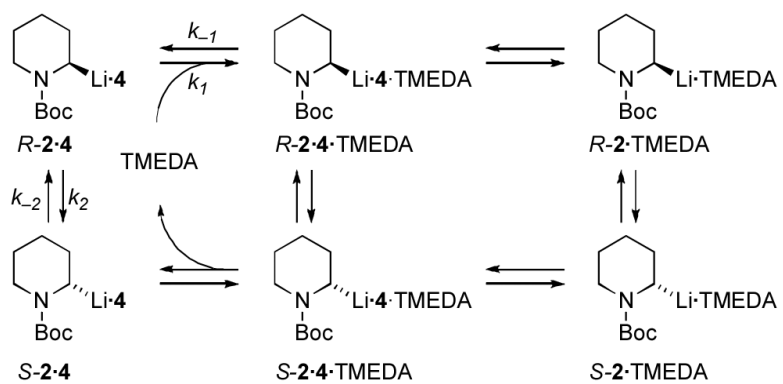


Fig. 2. Observed rate constants for DTR of **2** by **4** at -10°C vs $[\text{TMEDA}]$.



Scheme 3.
Possible equilibria and catalytic cycle for the DTR.

Table 1Thermodynamic parameters for inversion of **2**

Entry	Description	ΔH^\ddagger (kcal/mol)	ΔS^\ddagger (cal/mol·K)
1	Enantiomerization of 2 with 1 equiv. TMEDA	20.0 ± 1.7	12.0 ± 7.1
2	DTR of 2 with 1 equiv. 4	17.0 ± 0.9	-14.5 ± 3.2
3	DTR of 2 with 4 and 2 equiv. TMEDA	5.2 ± 0.8	-53.2 ± 2.9

Table 2

Dynamic resolution of 2·5 at -40 °C for 90 min

Entry	Additional ligand	Yield (%) 3	er (S:R)
1	TMEDA	73	80:20
2	TMEDA (0.1 equiv.)	68	80:20
3	TMEDA (2 equiv.)	59	77:23
4	none	<10	50:50
5	Et ₃ N	11	50:50
6	(-)-sparteine 1	27	50:50
7	PMDTA	56	59:41
8	Me ₂ NCH ₂ CH ₂ OLi	31	53:47
9	TEEDA	8	83:17