Published in final edited form as:
J Am Chem Soc. 2009 May 27; 131(20): 6908–6909. doi:10.1021/ja900755a.

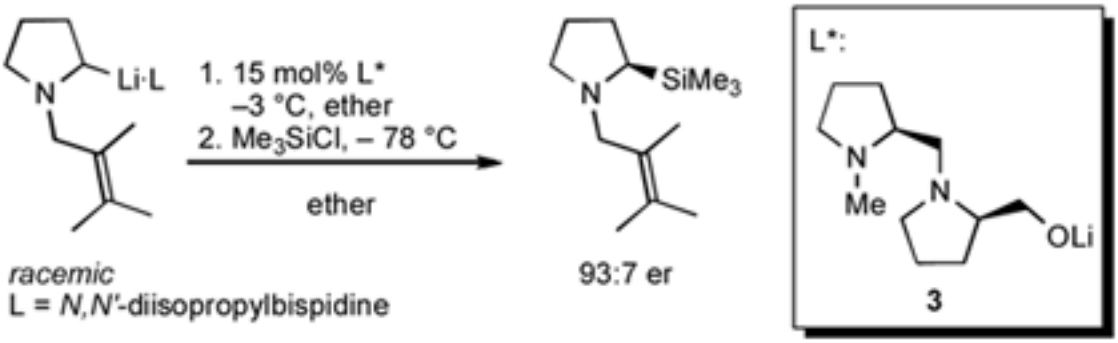
Enantiomerization Dynamics and a Catalytic Dynamic Resolution of *N*-Trimethylallyl-2-lithiopyrrolidine

Timothy K. Beng[a], **Taher I. Yousaf**[a], **Iain Coldham**[b,*], and **Robert E. Gawley**[a,*]

[a] Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR, 72701, USA

[b] Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK, S3 7HF

Abstract



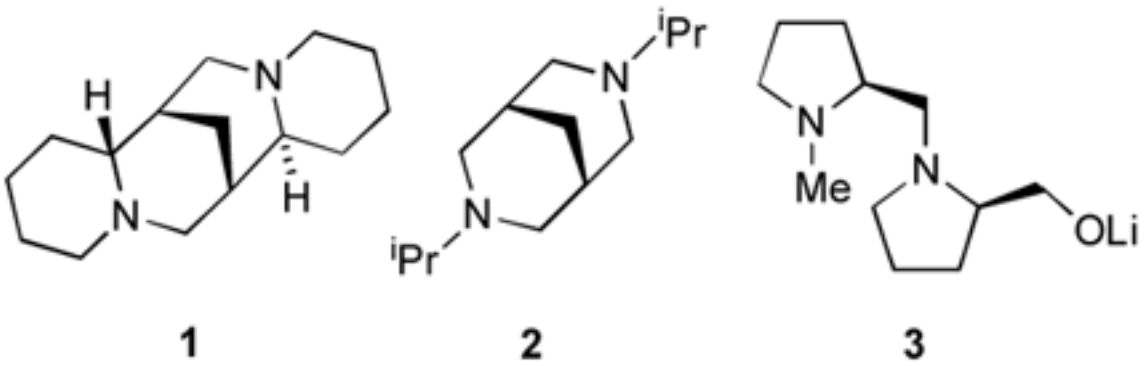
The barriers to enantiomerization of *N*-trimethylallyl-2-lithiopyrrolidine have been measured in the presence of sparteine, **1**, *N*,*N*′-diisopropylbispidine, **2**, and diaminoalkoxide **3**. We have additionally demonstrated a rare example of a catalytic dynamic resolution using either of two ligands, achieving enantiomer ratios of up to 93:7.

Lithium alkyls are ubiquitous in organic synthesis.[1] In one popular application, stoichiometric chiral ligands such as (−)-sparteine **1**, when complexed to *sec*-butyllithium, form a chiral base that is capable of enantioselective deprotonation.[2] Recently, O'Brien has shown that sub-stoichiometric amounts of **1**, in combination with bispidine **2** are also capable of asymmetric deprotonation.[3] The enantioselective deprotonation of *N*-Boc-pyrrolidine is conducted at − 78 °C, and at this temperature, *N*-Boc-2-lithiopyrrolidine is configurationally stable when coordinated to either **1** or **2**,[4] consistent with a kinetically controlled enantioselective deprotonation.

bgawley@uark.edu, i.coldham@sheffield.ac.uk.

Dedicated to the memory of Professor Al Meyers

Supporting Information Available: Full experimental details, kinetics plots and analysis. This information is available free of charge via the internet at http://pubs.acs.org



1 **2** **3**

An interesting new approach to asymmetric synthesis using chiral organolithiums employs dynamic thermodynamic resolution, or DTR.[5] In DTR, a racemic organolithium is complexed to a chiral ligand, rendering the complexes diastereomeric. If the equilibrium favors one carbanion configuration over the other (which is not always the case[6]), cooling the mixture to freeze the equilibrium can result in highly selective electrophilic substitutions. In 2006, Coldham, et al, reported that ligand **3** is effective in DTR of *N*-trimethylallyl-2-lithiopyrrolidine **5** (obtained from **4** by tin-lithium exchange), affording 96:4 er when quenched at − 78 °C with phenyl isocyanate (Scheme 1).[7]

As part of an investigation into the carbanion inversion dynamics of chiral organolithiums, we now report the parameters for **5** in the presence of ligands **1, 2** and **3**, using the methods reported previously.[4,8] It was not possible to transmetalate **4** to **5** in the absence of a ligand, but tin-lithium exchange was achieved in Et_2O at − 27 °C in the presence of **1**, **2**, or **3**. Thus, **4** was treated with n-BuLi and the ligand in ether at − 27 °C for two hours, then warmed to the various temperatures (see Supporting Information, SI). After several time intervals, the reaction flasks were cooled to − 78 °C and quenched with Me_3SiCl. Enantiomer ratios were determined by chiral stationary phase gas chromatography.

In all cases, the inversion data fit well to first order kinetic plots. Eyring analysis of the rate constants obtained at several temperatures provided the thermodynamic parameters listed in Table 1 (see SI for details). Comparing the effect of ligands **1**, **2** and **3** on the inversion barrier of **5** reveal significant differences, as revealed by the plots of $\Delta G^{\ddagger}$ *vs.* Temperature shown in Figure 1. These barriers reveal striking differences in configurational stability (Table 1).

The fraction of the major enantiomer in a DTR (*R* in this example), starting from a racemate, as a function of time (*t*), is given by:

$$(R)_t=(R)_{eq}+(0.5-(R)_{eq})\left(e^{k_{eq}t}\right)$$

where k_{eq} is the observed rate constant for equilibration. Using the thermodynamic data for DTR of **5**·**3** in Table 1, $k_{eq} = 1.61\times10^{-5}$ sec^{-1} at 263K, and the calculated er after 90 minutes would be only 53:47 er (*R:S)*. The difference between the two systems is the presence of TMEDA in the DTR of Scheme 1, and its absence in the DTR of **5**·**3** in Table 1. This indicates that TMEDA catalyzes the DTR in Scheme 1. Bispidine **2** does as well (see below and SI).

Given the differences in free energy barriers in the presence of different ligands, we decided to investigate the possibility of catalysis of the resolution by chiral ligands **1** and **3**. Catalytic dynamic resolution of racemic **5** was evaluated as illustrated in Scheme 2. In five oven-dried vials, *rac*-**4** was treated with excess BuLi and bispidine **2** at − 3 °C for 1 hour to effect tin-

lithium exchange, affording *rac*-**5**·**2**. The chiral ligand (L*, either **1** or **3**; 15 mol%) was then added; if ligand exchange occurs, diastereomeric complexes *R*-**5**·**L*** and *S*-**5**·**L*** enter the equilibrium. At various time intervals, a vial was cooled to − 78 °C and quenched with Me_3SiCl. With **1**, a 75:25 (*R:S*) er of **7** was achieved after 4 h, equaling the ratio obtained when stoichiometric **1** was employed in the DTR. With ligand **3**, a 93:7 (*R:S*) ratio of **7** was achieved after 6 h.

In the above small-scale experiments, no yield was determined, and the question arose whether **5**·**2** was decomposing faster than **5**·**L***, thereby enriching the er. Organolithiums have limited lifetimes at 0 °C. Also, silane **7** is fragile, and on one occasion we isolated significant quantities of de-allylated silane after silica gel chromatography. Therefore, the catalytic DR was repeated with ligand **3** (15 mol%) for one hour at 0 °C. In two experiments, we used bispidine **2** as an internal standard, and calculated 55% and 67% conversion of **4** to **7** (having 78:22 and 76:24 er, respectively). Under the same conditions, racemic **4** was converted to **7** in 48% yield, having an er of 72:28.[9] To test the effect of electrophile, **6** was obtained in 70:30 er after 1 h and 79:21 er after 2 h. Although there is a 65:35 kinetic preference for alkylation of *R*-**5**·**3** over *S*-**5**·**3**, this preference cannot account for the observed er (see SI).

To evaluate the effect of varying amounts of **3**, catalytic DRs were conducted using 5, 15, and 50 mol% catalyst (and 100 mol% as a control). After 1 h at 0 °C, enantiomer ratios for **7** of 54:46, 71:29, 90:10, and 95:5 were observed.[10]

From the thermodynamic values in Table 1, we can estimate that there should be less than 1% inversion of **5**·**2** at 0 °C in the course of an hour. To test the configurational stability of *R*-**5**·**2** under the catalytic conditions, *R*-**4**[11] was converted to *R*-**5**·**2** by tin-lithium exchange and subjected to the catalytic conditions in Scheme 2. In duplicate experiments, the er was monitored and no loss of enantiopurity was observed over the course of 90 min, indicating that the conversion of *R*-**5**·**2** to *S*-**5**·**2** does not occur under these conditions. Furthermore, kinetic measurements reveal that **2** accelerates the catalytic DR of **5** by both **1** and **3** (see Supporting Information).

To our knowledge, there is only one previous report of a DTR using substoichiometric quantities of chiral ligand.[12] The authors showed that the driving force for the resolution was formation of homochiral dimers or oligomers.[12b] Since the *N*-methyl analog of **5** is a homochiral dimer[13] and the *N*-ethyl analog is a mixture of aggregates,[14] a similar effect may be operative here (although we observe no precipitation). A catalytic cycle involving ligand exchange, as indicated in Scheme 2, must also be operative. Another driving factor may be the excess of **2** over **1** or **3**, thereby assisting the conversion of *R*-**5**·**L*** to *R*-**5**·**2**.

In summary, determination of the thermodynamic activation parameters for enantiomerization of **5** in the presence of both chiral and achiral diamine ligands revealed significant differences in thermodynamic parameters for carbanion inversion, and a catalytic role for both TMEDA and bispidine **2** in the DTR. We further report a rare example of a catalytic dynamic resolution. Experiments to explore ligand exchange dynamics in this and related systems, and the scope and limitations of catalytic dynamic resolutions are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Science Foundation (CHE 0616352). Core facilities were funded by the NIH (R15569) and the Arkansas Biosciences Institute. We are grateful to Dr Nick Williams (Sheffield) for helpful discussions, Dr Nadeem Sheikh (Sheffield) for technical assistance, and a reviewer for insightful comments.

References

1. (a) Clayden, J. Organolithiums: Selectivity for Synthesis. Pergamon: 2002. (b) Hodgson, DM., editor. Organolithiums in Enantioselective Synthesis. Vol. 5. Springer-Verlag; Berlin Heidelberg: 2003. (c) Rappoport, Z.; Marek, I., editors. The Chemistry of Organolithium Compounds. Wiley; New York: 2004. (d) Majewski, M.; Snieckus, V., editors. Organometallics: Compounds of Group 1 (Li … Cs). Thieme; Stuttgart: 2006. p. 8a
2. (a) Hoppe D, Hense T. Angew Chem Int Ed 1997;36:2283–2316.(b) Hoppe, D.; Christoph, G. The chemistry of organolithium compounds. Rappoport, Z.; Marek, I., editors. John Wiley and Sons, Ltd; Oxford: 2004. p. 1055-1164. (c) Beak P, Johnson TA, Kim DD, Lim SH. Top Organomet Chem 2003;5:139–176.
3. McGrath MJ, O'Brien PJ. Am Chem Soc 2005;127:16378–16379.
4. Yousaf TI, Williams RL, Coldham I, Gawley RE. Chem Commun 2008:97–98.
5. (a) Beak P, Anderson DR, Curtis MD, Laumer JM, Pippel DJ, Weisenburger GA. Acc Chem Res 2000;33:715–727. [PubMed: 11041836] (b) Lee WK, Park YS, Beak P. Acc Chem Res 2009;42:224–234. [PubMed: 19152329]
6. Coldham I, Patel JJ, Sanchez-Jiminez G. Chem Commun 2005:3083–3085.
7. Coldham I, Dufour S, Haxell TFN, Patel JJ, Sanchez-Jimenez GJ. Am Chem Soc 2006;128:10943–10951.
8. Ashweek NJ, Brandt P, Coldham I, Dufour S, Gawley RE, Haffner F, Klein R, Sanchez-Jimenez GJ. Am Chem Soc 2005;127:449–457.
9. If the 15% of 5·3 were resolved to 96:4, and the remaining 85% of 5·2 was racemic, the er would be 57:43.
10. If 5·2 was racemic and 5·3 was resolved to 96:4 er, the observed er would be 52:48, 57:43, 73:27 for the substoichiometric reactions.
11. Prepared in 41% yield and 95:5 er by dynamic resolution as outlined in Scheme 1.
12. (a) Nakamura S, Hirata N, Kita T, Yamada R, Nakane D, Shibata N, Toru T. Angew Chem Int Ed 2007;46:7648–7650. (b) Nakamura S, Hirata N, Yamada R, Kita T, Shibata N, Toru T. Chem Eur J 2008;14:5519–5527.
13. Low E, Gawley REJ. Am Chem Soc 2000;122:9562–9563.
14. Gawley RE, Klein R, Ashweek NJ, Coldham I. Tetrahedron 2005;61:3271–3280.

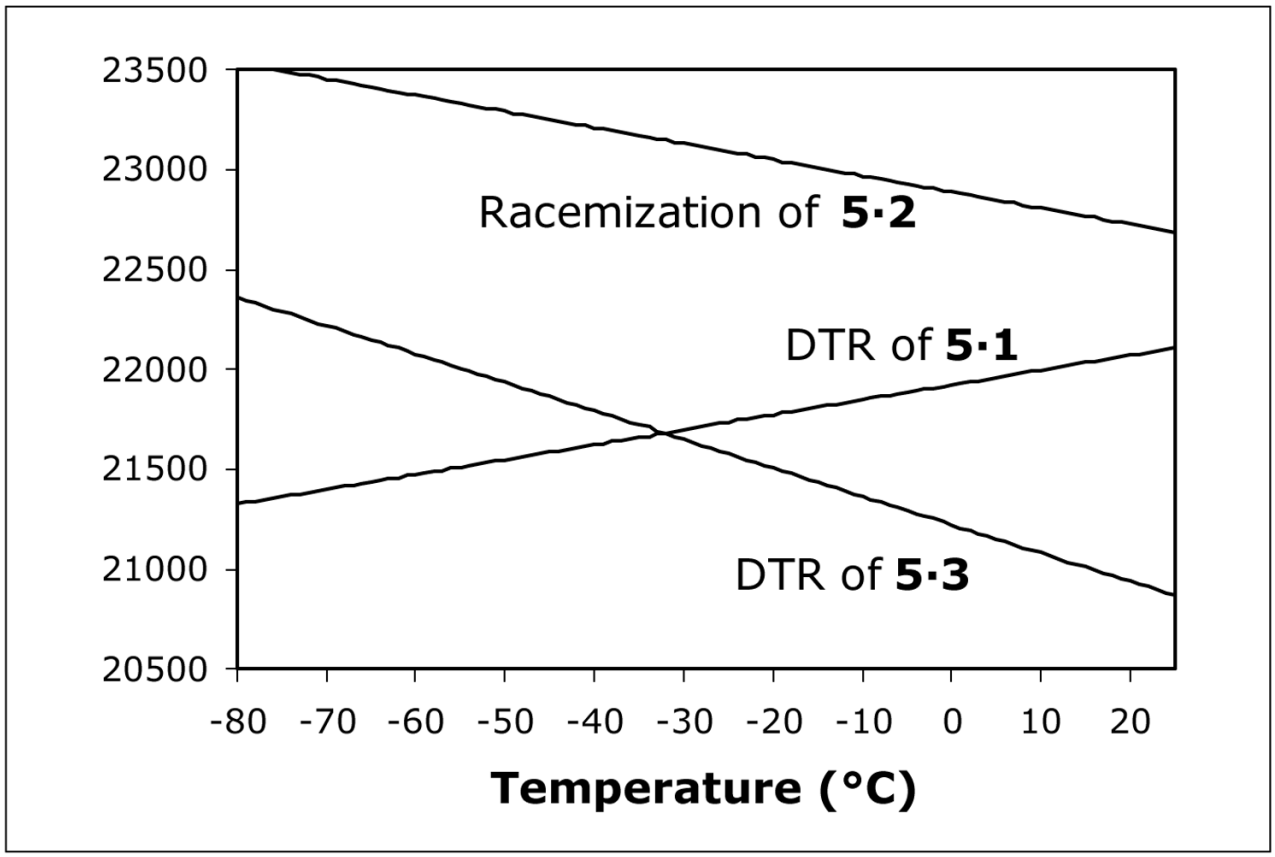
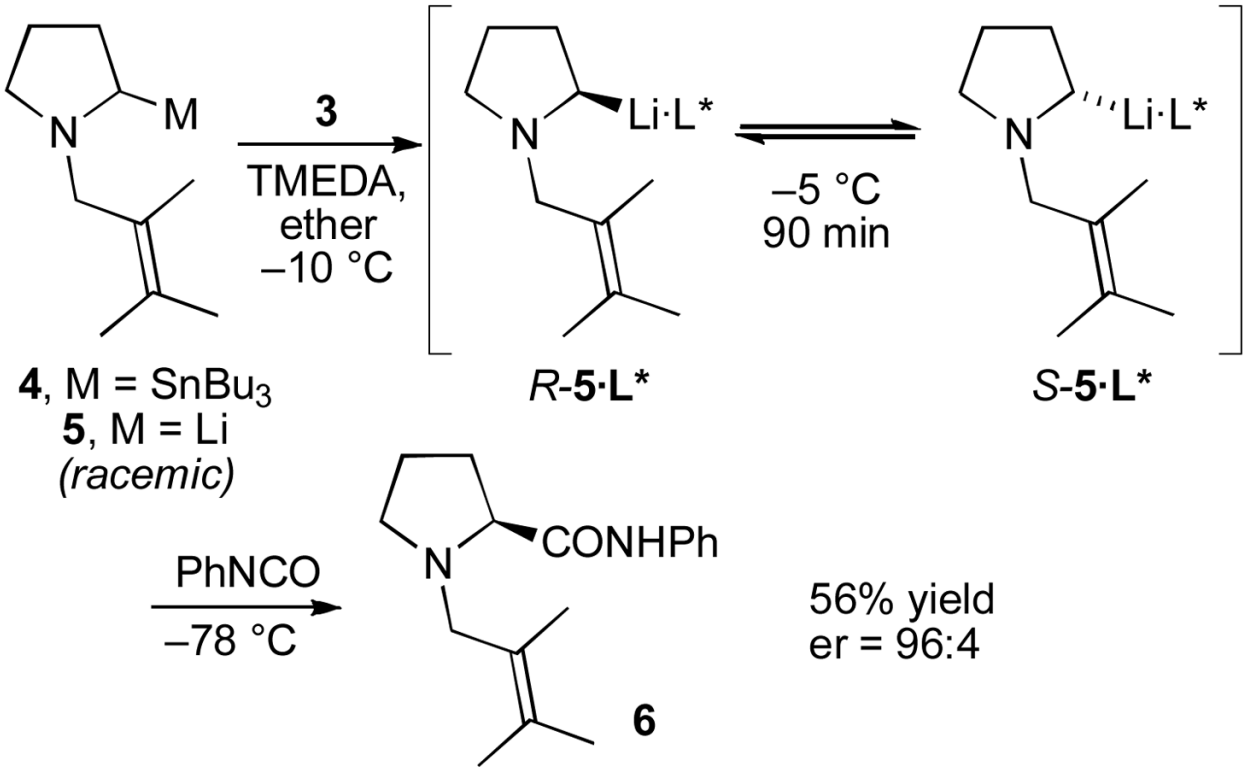
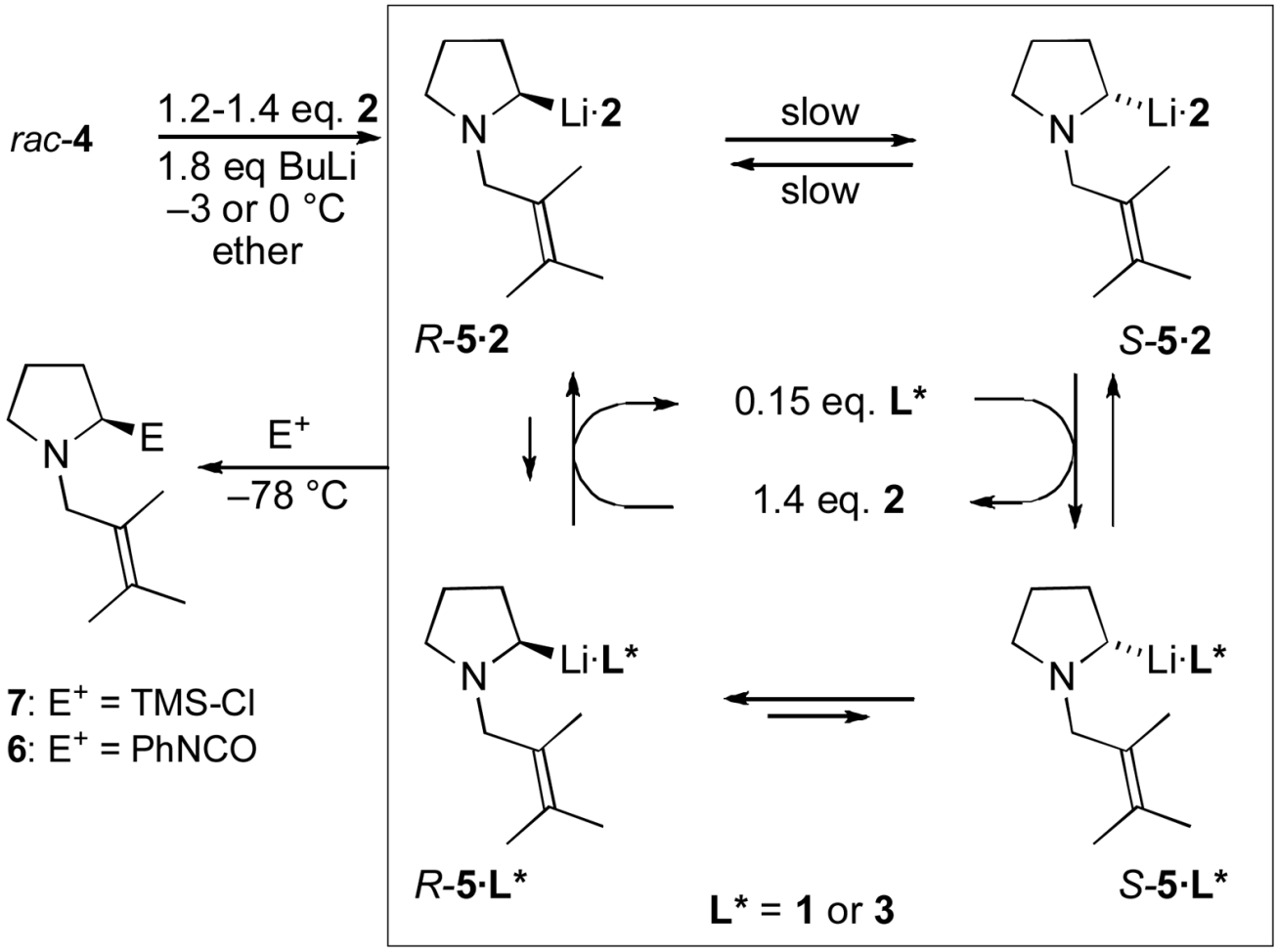


Figure 1.
The relationship of inversion barrier to temperature for racemization of **5** in the presence of **2**, and DTR (*S*→*R*) in the presence of **1** or **3**.



Scheme 1.
DTR of *N*-trimethylallyl-2-lithiopyrrolidines.[7]



Scheme 2.
Catalytic dynamic resolution of *rac*-**5**. All species are drawn as monomers for simplicity. L* = **1** or **3**.

Table 1

Thermodynamic parameters for inversion of **5**.

RLi·L	$\Delta H^{\ddagger}$ (*S*→*R*) (kcal/mol)	$\Delta S^{\ddagger}$ (*S*→*R*) (cal/mol·K)	$t_{1/2}$ for equilibration at 0° C
5·**1**[a]	19.9±2.2	−7.4±7.7	6.15 hrs
5·**2**	25.1±1.4	8.1±5.0	36.6 hrs
5·**3**[b]	25.1±1.7	14.2±6.1	1.7 hrs

[a] Calculated using K = 4.26 (81:19 er); see SI for details.

[b] Calculated using K = 24 (96:4 er); see SI for details