

## Lithium 2,2,6,6-Tetramethylpiperidide-Mediated $\alpha$ - and $\beta$ -Lithiations of Epoxides: Solvent-Dependent Mechanisms

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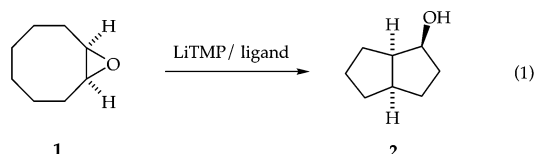
**Abstract:** Lithium 2,2,6,6-tetramethylpiperidide (LiTMP)-mediated  $\alpha$ - and  $\beta$ -lithiations of epoxides are described. LiTMP displays a markedly higher reactivity than does lithium diisopropylamide, consistent with literature reports. Detailed rate studies of LiTMP/THF and LiTMP/Me<sub>2</sub>NEt mixtures reveal similar rates but significant mechanistic differences. LiTMP-mediated  $\alpha$ -lithiation of *cis*-cyclooctene oxide with subsequent oxacarbenoid formation and transannular C–H insertion proceeds via monosolvated dimers in both THF and Me<sub>2</sub>NEt. LiTMP-mediated  $\beta$ -lithiation of 2,3-dimethyl-2-butene oxide affords the corresponding allylic alcohol via a monosolvated monomer in THF and a monosolvated dimer in Me<sub>2</sub>NEt. We discuss how the solvent-dependent aggregation of LiTMP markedly influences the rate profile. The reaction transition structures are examined with density functional computations.

### Introduction

Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) is one of the three most important lithium amides used in organic synthesis.<sup>1</sup> LiTMP is the base of choice for a number of enolizations,<sup>2</sup> ortholithiations,<sup>3,4</sup> and epoxide lithiations.<sup>5</sup> LiTMP is functionally more basic than lithium diisopropylamide (LDA)<sup>6,7</sup> yet manifests highly solvent-dependent aggregation akin to lithium hexamethyldisilazide (LiHMDS).<sup>8,9</sup> There are, however, limitations that have restricted applications of LiTMP in synthesis: (1) despite a seemingly trivial two-step synthesis, 2,2,6,6-tetramethylpiperidine is expensive; (2) the high basicity of LiTMP can lead to facile lithiation of standard ethereal solvents;<sup>6</sup>

and (3) there are few mechanistic insights into the chemistry of LiTMP.<sup>9,10</sup> The first drawback is being addressed; LiTMP will soon be commercially available on a large scale.<sup>11</sup> We have begun to address the latter two.

We describe our first efforts to understand structure–reactivity relationships in LiTMP through the  $\alpha$ - and  $\beta$ -lithiations of epoxides shown in eqs 1 and 2, which are emblematic of eliminations that have captured the imagination of synthetic chemists.<sup>12,13</sup> Whereas  $\beta$ -lithiations afford allylic alcohols,<sup>14</sup>



$\alpha$ -lithiations and the resulting oxacarbenoids<sup>14–16</sup> can lead to (1) transannular C–H bond insertions to give cyclic alkoxides,<sup>17</sup> (2) vicinal C–H insertions to give lithium enolates,<sup>18</sup> or (3) vicinal C–H insertions to form allylic alkoxides.<sup>14a,c</sup> Recent rate studies of LDA-mediated lithiations of epoxides **1** and **3** provide direct mechanistic comparisons.<sup>19</sup>

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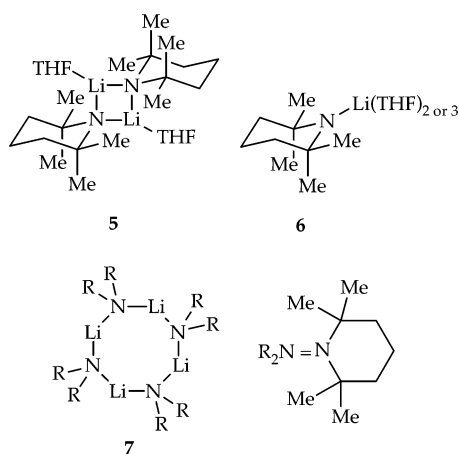
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## Results

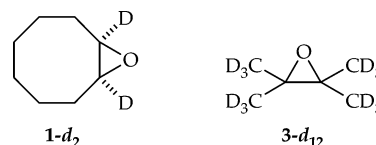
The results are presented successively as follows: (1) LiTMP solution structures establish the aggregation and solvation states of the lithium dialkylamide reactant; (2) rate studies display solvent-dependent monomer- and dimer-based lithiation; and (3) computations using density functional theory (DFT) illuminate details of the transition structures for  $\alpha$ - and  $\beta$ -lithiation.

**Structures of LiTMP.** Rate studies *must* be founded on a firm understanding of solution structures because the rate law provides the stoichiometry of the transition structure *relative to the reactants*.<sup>20</sup> LiTMP in THF/pentane exists as  $C_{2h}$  dimer **5**, whereas low concentrations of monomer **6** ( $\approx 20\%$ ) appear in neat THF.<sup>9a,21</sup> In contrast, LiTMP forms exclusively ( $>95\%$ ) *unsolvated tetramer* (**7**) in Me<sub>2</sub>NEt/hexane mixtures at all Me<sub>2</sub>NEt concentrations.<sup>9d,f</sup> All four conformers of the tetramer **7** have been characterized.<sup>9d</sup>



**Rate Studies: General.** The LiTMP used to study LiTMP/THF-mediated reactions was recrystallized<sup>22a</sup> and used as freshly prepared stock solutions.<sup>9b</sup> Due to the limited solubility of recrystallized LiTMP in Me<sub>2</sub>NEt, stable stock solutions of LiTMP/Me<sub>2</sub>NEt were prepared in situ from 2,2,6,6-tetramethylpiperidine and recrystallized *n*-BuLi.<sup>22b,c</sup> Pseudo-first-order

conditions were established with LiTMP at normal concentrations (0.04–0.40 M) by restricting the epoxide concentration to  $\leq 0.004$  M. “[LiTMP]” and “LiTMP concentration” refer to the formal molarity of the monomer unit (normality). The solvent concentration refers to the concentration of *free* (uncoordinated) donor solvent in pentane cosolvent. In all cases, the loss of the epoxide substrate follows a clean first-order decay to five half-lives. The reaction rates were monitored by following loss of the epoxides and formation of products of quenched samples by well-documented gas chromatographic analyses.<sup>23</sup> The resulting pseudo-first-order rate constants are independent of the initial substrate concentration (0.004–0.04 M). Isotope effects were determined by comparing the lithiations of epoxides **1** and **3** to deuterated analogues **1-d<sub>2</sub>**,<sup>24</sup> and **3-d<sub>12</sub>**,<sup>25</sup> respectively, and are all consistent with rate-limiting steps involving C–H(D) cleavages. Notably, we observed relatively



small isotope effects for the  $\alpha$ -lithiation of **1** and large isotope effects for the  $\beta$ -lithiation of **3**.<sup>26</sup> The results of the rate studies are summarized in Table 1. Representative rate data are depicted in Figures 1–8; additional data are included in the Supporting Information.

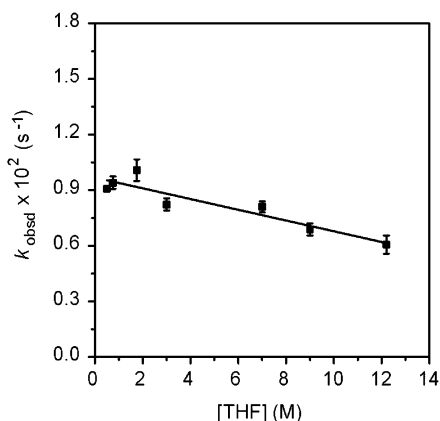
**LiTMP/THF/3.** Rate studies of the LiTMP/THF-mediated  $\beta$ -lithiation of **3** (eq 2) in pentane displayed the modest complexity anticipated for a base that undergoes limited ligand-concentration-dependent deaggregation. A plot of  $k_{\text{obsd}}$  versus THF concentration at 0.1 M LiTMP provides a zeroth-order dependence on the THF concentration with a slight inverse dependence at high THF concentration (Figure 1; Table 1). A

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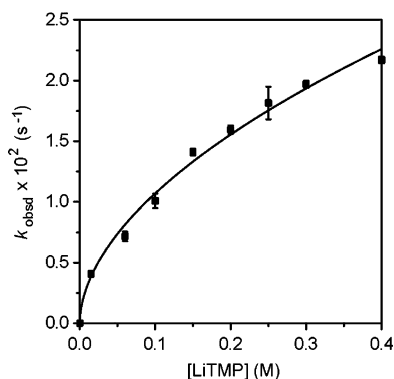
**Table 1.** Summary of Rate Studies for the LiTMP-Mediated Lithiation of **1** (eq 1) and **3** (eq 2)

entry	T (°C)	epoxide	ligand	LiTMP order	ligand order	$k_{\beta}/k_{\alpha}$
1	0	<b>3</b>	THF	$0.53 \pm 0.03^a$	0	$19 \pm 1^a$
2	0	<b>3</b>	THF	$0.70 \pm 0.03^b$	0	$17.5 \pm 0.7^b$
3	0	<b>1</b>	THF	$0.98 \pm 0.05^c$	$-1.07 \pm 0.03$	$3.4 \pm 0.4^c$
4	0	<b>3</b>	Me <sub>2</sub> NEt	$0.50 \pm 0.02^d$	$1.03 \pm 0.03$	$17 \pm 1^d$
5	0	<b>1</b>	Me <sub>2</sub> NEt	$0.51 \pm 0.02^d$	$1.04 \pm 0.06$	$3.5 \pm 0.5^d$

<sup>a</sup> [THF] = 1.75 M. <sup>b</sup> [THF] = 9.0 M. <sup>c</sup> [THF] = 5.0 M. <sup>d</sup> [Me<sub>2</sub>NEt] = 3.0 M.

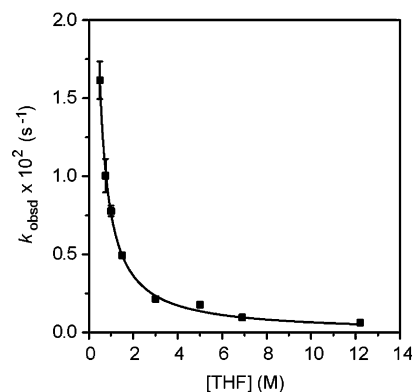
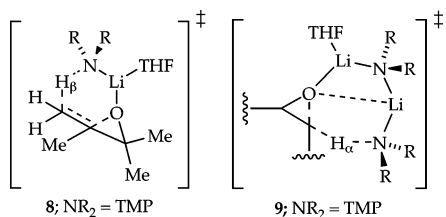


**Figure 1.** Plot of  $k_{\text{obsd}}$  vs [THF] in pentane for the  $\beta$ -lithiation of 2,3-dimethyl-2-butene oxide (**3**, 0.004 M) by LiTMP (0.10 M) at 0 °C. The line depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{THF}] + k'$  ( $k = (-2.9 \pm 0.5) \times 10^{-4}$ ,  $k' = (9.7 \pm 0.3) \times 10^{-3}$ ).



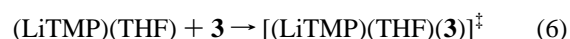
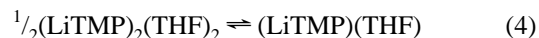
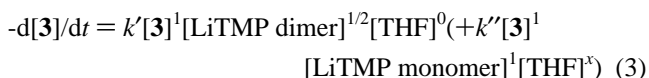
**Figure 2.** Plot of  $k_{\text{obsd}}$  vs [LiTMP] in THF (1.75 M) and pentane for the  $\beta$ -lithiation of 2,3-dimethyl-2-butene oxide (**3**, 0.004 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{LiTMP}]^n$  ( $k = (3.7 \pm 0.2) \times 10^{-2}$ ,  $n = 0.53 \pm 0.03$ ).

plot of  $k_{\text{obsd}}$  versus LiTMP concentration at 1.75 M THF in pentane provides a half-order dependence (Figure 2; Table 1), implicating a monomer-based pathway at low THF concentration. A plot of  $k_{\text{obsd}}$  versus LiTMP concentration in 9.0 M THF/pentane affords a higher fractional order (Table 1, entry 2). The increasing LiTMP order with increasing THF concentration is consistent with the measurable deaggregation. (If the monomer

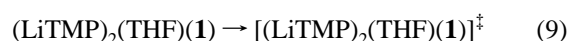


**Figure 3.** Plot of  $k_{\text{obsd}}$  vs [THF] in pentane for the  $\alpha$ -lithiation of *cis*-cyclooctene oxide (**1**, 0.004 M) by LiTMP (0.10 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{THF}]^n$  ( $k = (7.6 \pm 0.1) \times 10^{-3}$ ,  $n = -1.07 \pm 0.03$ ).

had become the sole observable form, one would observe a first-order dependence on the LiTMP concentration.) Additionally, if the fully solvated LiTMP monomer requires dissociation of a THF ligand, one would observe inhibition by THF at the high THF concentrations. Thus, the drifting LiTMP and THF orders are both compatible with low concentrations of monomer appearing at elevated THF concentrations. The idealized rate law for the  $\beta$ -lithiation of **3** (eq 3) is consistent with the generic mechanism described in eqs 4–6 and a monomer-based transition structure such as **8**.<sup>19,27,28</sup>



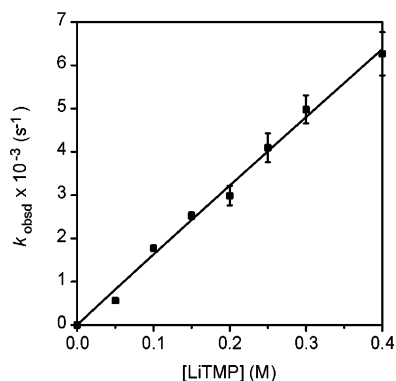
**LiTMP/THF/1.** Rate studies of the LiTMP/THF-mediated  $\alpha$ -lithiation of **1** in pentane solutions (eq 1) revealed an *inverse*-first-order dependence on the THF concentration (Figure 3) and a first-order dependence on the LiTMP concentration (Figure 4). (The potential impact of the monomer on the rate constants is obscured by the inverse THF dependence.) The idealized rate law in eq 7 is consistent with the generalized mechanism in eqs 8 and 9 and an open-dimer-based transition structure such as **9**.<sup>29</sup> The transannular O–Li contact in **9** is depicted in view of computational studies reported below (*vide infra*).<sup>30</sup>



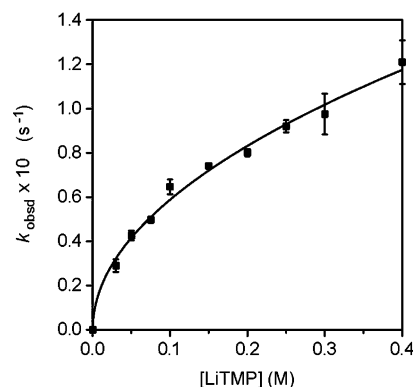
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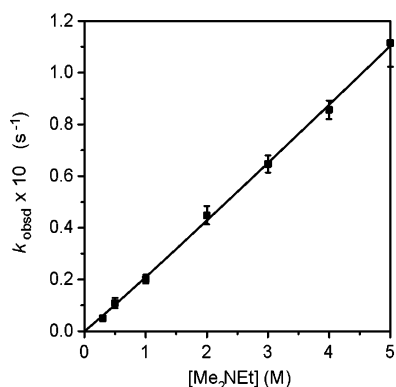
(29) Open dimers were first proposed for the isomerization of oxiranes to allylic alcohols by mixed metal bases: Mordini, A.; Rayana, E. B.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401. For a bibliography of lithium amide open dimers, see refs 9f and 22b.



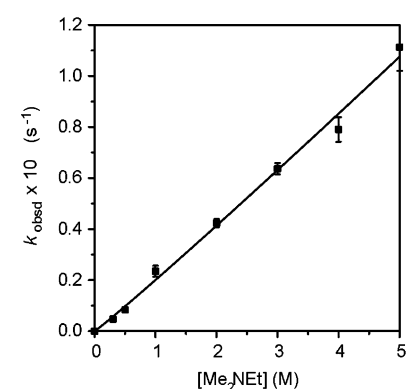
**Figure 4.** Plot of  $k_{\text{obsd}}$  vs [LiTMP] in THF (5.0 M) and pentane for the  $\alpha$ -lithiation of *cis*-cyclooctene oxide (**1**, 0.004 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{LiTMP}]^n$  ( $k = (1.6 \pm 0.1) \times 10^{-2}$ ,  $n = 0.98 \pm 0.05$ ).



**Figure 6.** Plot of  $k_{\text{obsd}}$  vs [LiTMP] in  $\text{Me}_2\text{NEt}$  (3.0 M) and pentane for the  $\beta$ -lithiation of 2,3-dimethyl-2-butene oxide (**3**, 0.004 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{LiTMP}]^n$  ( $k = 0.18 \pm 0.01$ ,  $n = 0.50 \pm 0.02$ ).



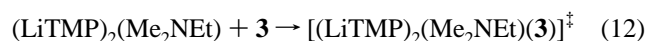
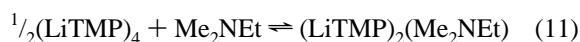
**Figure 5.** Plot of  $k_{\text{obsd}}$  vs  $[\text{Me}_2\text{NEt}]$  in pentane for the  $\beta$ -lithiation of 2,3-dimethyl-2-butene oxide (**3**, 0.004 M) by LiTMP (0.10 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{Me}_2\text{NEt}]^n$  ( $k = (2.1 \pm 0.1) \times 10^{-2}$ ,  $n = 1.03 \pm 0.03$ ).



**Figure 7.** Plot of  $k_{\text{obsd}}$  vs  $[\text{Me}_2\text{NEt}]$  in pentane for the  $\alpha$ -lithiation of *cis*-cyclooctene oxide (**1**, 0.004 M) by LiTMP (0.10 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{Me}_2\text{NEt}]^n$  ( $k = (2.0 \pm 0.2) \times 10^{-2}$ ,  $n = 1.04 \pm 0.06$ ).

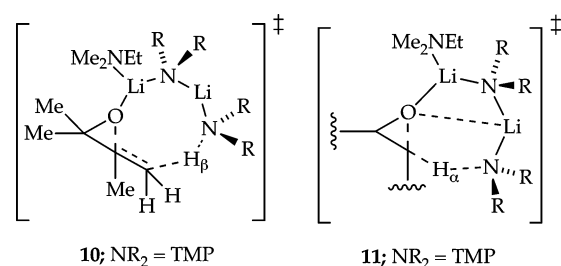
**LiTMP/Me<sub>2</sub>NEt/3.** Rate studies for the lithiation of **3** using LiTMP/Me<sub>2</sub>NEt mixtures revealed rates that are comparable to LiTMP/THF mixtures but through a very different mechanism (Table 1, entry 4). Plots of  $k_{\text{obsd}}$  versus Me<sub>2</sub>NEt concentration (Figure 5) and  $k_{\text{obsd}}$  versus LiTMP concentration (Figure 6) display first-order and half-order dependencies, respectively. Although half-order dependencies are usually emblematic of dimer–monomer preequilibria, LiTMP in Me<sub>2</sub>NEt is an *unsolvated tetramer*. Therefore, the idealized rate law (eq 10) is consistent with the dimer-based pathway depicted in eqs 11 and 12 and transition structure **10**.

$$-\text{d}[\mathbf{3}]/\text{d}t = k'[\mathbf{3}]^1[\text{LiTMP}]^{1/2}[\text{Me}_2\text{NEt}]^1 \quad (10)$$



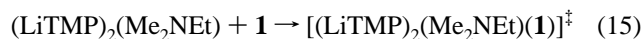
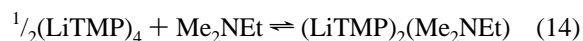
**LiTMP/Me<sub>2</sub>NEt/1.** Rate studies of the LiTMP/Me<sub>2</sub>NEt-mediated  $\alpha$ -lithiation of **1** revealed a first-order dependence on the Me<sub>2</sub>NEt concentration (Figure 7) and a half-order dependence on the LiTMP concentration (Figure 8). The idealized rate law (eq 13) is consistent with an  $\alpha$ -lithiation via exclusively monosolvated dimers (eqs 14 and 15) and transition structure **11**. It is interesting that, despite drastic differences between the

dence on the LiTMP concentration (Figure 8). The idealized rate law (eq 13) is consistent with an  $\alpha$ -lithiation via exclusively monosolvated dimers (eqs 14 and 15) and transition structure **11**. It is interesting that, despite drastic differences between the



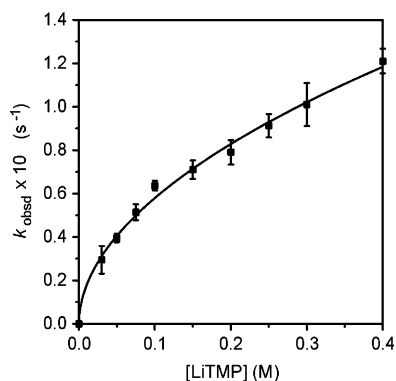
solvation and the aggregation states of LiTMP/THF and LiTMP/Me<sub>2</sub>NEt mixtures, putative transition structures **9** and **11** are isostructural.

$$-\text{d}[\mathbf{1}]/\text{d}t = k'[\mathbf{1}]^1[\text{LiTMP}]^{1/2}[\text{Me}_2\text{NEt}]^1 \quad (13)$$



**Solvent-Dependent Relative Rates.** The relative rate constants for the LiTMP-mediated  $\alpha$ - and  $\beta$ -lithiations of epoxides **1** and **3** (0.50 M coordinating ligand; 0.10 M LiTMP) are summarized in Table 2. (These rates are *not* supported by

(30) Computational evidence for transannular contacts: Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339. Nakamura, M.; Nakamura, E. *J. Chem. Soc., Faraday Trans.* **1994**, 1789. Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 11016. Haefner, F.; Sun, C.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 12542. Schleyer, P. v. R.; Kaufmann, E. *J. Am. Chem. Soc.* **1985**, *107*, 5560. Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523.



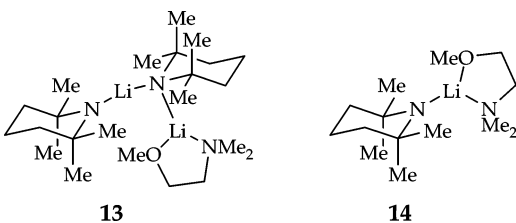
**Figure 8.** Plot of  $k_{\text{obsd}}$  vs  $[\text{LiTMP}]$  in  $\text{Me}_2\text{NEt}$  (3.0 M) and pentane for the  $\alpha$ -lithiation of *cis*-cyclooctene oxide (**1**, 0.004 M) at 0 °C. The curve depicts an unweighted least-squares fit to  $k_{\text{obsd}} = k[\text{LiTMP}]^n$  ( $k = (1.9 \pm 0.1) \times 10^{-1}$ ,  $n = 0.51 \pm 0.02$ ).

**Table 2.** Relative Rate Constants for the LiTMP-Mediated Lithiation of Epoxides **1** and **3**<sup>a</sup>

ligand	$k_{\text{rel}}^b$	
	<b>1</b>	<b>3</b>
THF	40	20
$\text{Me}_2\text{NEt}$	20	25
2,2- $\text{Me}_2\text{THF}$	20	8
<i>n</i> -BuOMe	20	12
<i>t</i> -BuOMe	6	4
$\text{Et}_3\text{N}$	4	2
<i>i</i> -Pr <sub>3</sub> N	2	1
$\text{MeOCH}_2\text{CH}_2\text{NMe}_2$	20	45

<sup>a</sup>  $[\text{Ligand}] = 0.5 \text{ M}$ ,  $[\text{LiTMP}] = 0.1 \text{ M}$ , 0 °C. <sup>b</sup> All values are scaled to the  $k_{\text{obsd}}$  for LiTMP/*i*-Pr<sub>3</sub>N-mediated lithiation of **3**.

detailed structural and rate studies in most cases.) Although no reaction is observed in the absence of an ether or a trialkylamine, the rates are remarkably insensitive to the choice of solvent. The low rates for sterically demanding trialkylamines are consistent with an anticipated reluctance to coordinate lithium in a congested transition structure.<sup>9d,f,22a</sup>  $\text{MeOCH}_2\text{CH}_2\text{NMe}_2$  (**12**) has been used to elicit considerable accelerations for LDA-mediated lithiations of epoxides<sup>19</sup> but offers no special advantage for LiTMP. In contrast to LDA/**12** mixtures, in which accelerations occur because the reactants are  $\eta^1$ -solvated dimers,<sup>23a,31</sup> LiTMP/**12** exists as a mixture of chelated open dimer **13** and monomer **14**.<sup>9f</sup> Accelerations by hindered ligands are not



observed because the steric demands of LiTMP preclude binding as noted.<sup>9d</sup> Similar steric effects have been observed for reactions of LDA<sup>32</sup> and LiHMDS.<sup>33</sup>

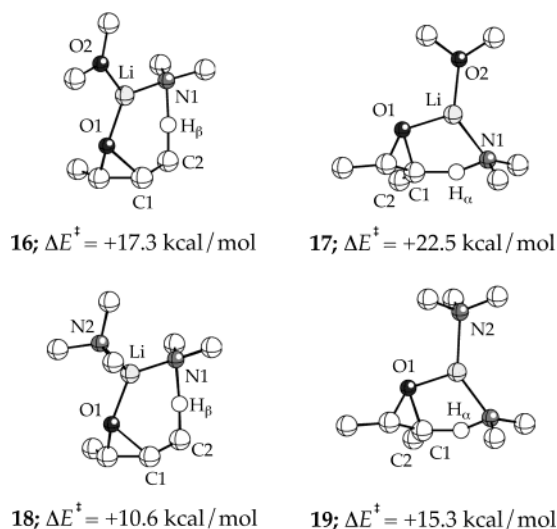
**Thermal Stability of LiTMP Solutions.** Solutions of LiTMP in etheral solvents are prone to base-mediated solvent decomposition.<sup>6</sup> Indeed, the LiTMP/THF solutions required special

(31) Remenar, J. F.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1997**, *119*, 5567.

(32) Bernstein, M. P.; Collum, D. B. *J. Am. Chem. Soc.* **1993**, *115*, 8008.

(33) Zhao, P.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 4008.

**Chart 1**



handling, otherwise byproducts began to appear in the GC chromatogram. Aging LiTMP/THF solutions for 24 h at 0 °C resulted in a marked (25%) loss in reactivity toward epoxide lithiation. In contrast, LiTMP/ $\text{Me}_2\text{NEt}$  in pentane appeared to be almost indefinitely stable at 0 °C. Aging samples for 24 h at 30 °C showed only minimal (<8%) loss in reactivity.

**DFT Computational Studies.** We explored the transition structures using DFT calculations at the B3LYP/6-31G\* level.<sup>34</sup> (*Z*)-2-Butene oxide (**15**) was used as a model for epoxides **1** and **3**. LiTMP, THF, and  $\text{Me}_2\text{NEt}$  were modeled by  $\text{Me}_2\text{NLi}$ ,  $\text{Me}_2\text{O}$ , and  $\text{Me}_3\text{N}$ , respectively. All calculations were executed using the Gaussian 98 program.<sup>35</sup> A range of initial geometries was sampled for both reactants and transition structures. Saddle points were confirmed by the existence of a single imaginary frequency. Transition structures **16**–**27** are represented in Charts 1 and 3. Selected geometric characteristics of **16**–**27** are summarized in Tables 3 and 4.

**Monomer-Based Lithiations.** Transition structures **16** and **17** were located for the  $\text{Me}_2\text{O}$ -solvated monomer-based  $\beta$ - and  $\alpha$ -lithiations, respectively (Chart 1). Calculated activation energies ( $\Delta E^\ddagger$ ) indicate that the six-centered  $\beta$ -lithiation is 5.2 kcal/mol more stable than the five-centered  $\alpha$ -lithiation. Whereas transition structure **17** displays considerable deviation from the optimum 180° collinear proton transfer ( $\text{N}-\text{H}_\alpha-\text{C}1 = 159.5^\circ$ ), the  $\text{N}-\text{H}-\text{C}$  bond angle of transition structure **16** is almost collinear ( $\text{N}-\text{H}_\beta-\text{C}2 = 176.6^\circ$ ).<sup>36</sup> Transition structure **16** also displays a nearly planar six-membered ring and distinct Li–O

(34) (a) Ab initio calculations on the base-induced rearrangement of epoxides: Gronert, S.; Lee, J. M. *J. Org. Chem.* **1995**, *60*, 448. Morgan, K. M.; Gronert, S. *J. Org. Chem.* **2000**, *65*, 1461. (b) Computational studies on lithiated oxazolinoyloxiranes: Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049.

(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Gill, A.; Nanayakkara, C.; Gonzalez, M.; Challacombe, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(36) Narula, A. S. *Tetrahedron Lett.* **1981**, *27*, 4119.

**Table 3.** Selected Bond Lengths (Å) and Angles (deg) for Calculated Monomer-Based Transition Structures **16–19**

	16	17	18	19
Li–O(1)	1.85	1.87	1.85	1.88
Li–O(2)	1.94	1.91		
Li–N(1)	1.92	1.97	1.92	1.97
Li–N(2)			2.10	2.08
H <sub>β</sub> –N(1)	1.55		1.54	
H <sub>α</sub> –N(1)		1.25		1.25
H <sub>β</sub> –C(2)	1.26		1.26	
H <sub>α</sub> –C(1)		1.51		1.51
C(1)–C(2)	1.44	1.51	1.44	1.51
C(1)–O(1)	1.81	1.59	1.80	1.59
N(1)–H <sub>β</sub> –C(2)	176.6		176.0	
N(1)–H <sub>α</sub> –C(1)		159.5		159.1
N(1)–Li–O(1)	124.3	110.3	122.1	109.4

**Table 4.** Selected Bond Lengths (Å) and Angles (deg) for Calculated Dimer-Based Transition Structures **20–27**

	20	21	22	23	24	25	26	27
Li(1)–O(1)	1.86	1.89	1.84	1.82	1.89	1.90	1.92	1.71
Li(1)–O(2)	1.94	1.93			1.93			
Li(1)–N(1)	1.97	1.94	1.93	1.99	1.91	1.94	1.95	1.95
Li(1)–N(3)						2.09	2.12	
N(1)–Li(2)	1.92	1.99	1.97	1.91	2.01	1.98	1.94	2.05
Li(2)–N(3)								2.15
Li(2)–N(2)	1.93	1.96	2.01	2.07	1.91	1.97	1.88	2.05
H <sub>β</sub> –N(2)				1.43	1.67		1.60	1.43
H <sub>α</sub> –N(2)	1.22	1.31	1.29			1.31		
H <sub>β</sub> –C(2)				1.32	1.20		1.30	1.32
H <sub>α</sub> –C(1)	1.55	1.42	1.48			1.42		
C(1)–C(2)	1.51	1.51	1.51	1.42	1.46	1.51	1.49	1.38
C(1)–O(1)	1.57	1.59	1.56	1.90	1.72	1.59	1.49	2.25
Li(2)–O(1)	3.22	2.11	4.32	4.24	2.16	2.10	3.61	3.81
Li(1)–N(2)	4.14	4.26	2.88	2.25	4.39	4.27	3.81	3.51
N(2)–H <sub>β</sub> –C(1)				172.0	176.2		169.9	168.3
N(2)–H <sub>α</sub> –C(1)	175.1	160.9	176.3			160.8		
N(1)–Li(1)–O(1)	127.6	104.6	103.4	142.1	104.6	102.1	126.7	153.1
N(1)–Li(2)–N(2)	165.5	159.3	119.1	111.4	151.8	159.3	150.7	121.2

contacts independent of starting geometries (Table 3). The lengthening of the C2–H (1.26 Å) and C1–O (1.81 Å) bonds in **16** and the shortening of the C1–C2 bond (from 1.51 to 1.44 Å), compared to the reactant, are consistent with an E2 mechanism with partial E1 character.<sup>34,37a</sup>

The calculated energies of the transition structures corresponding to monomer-based  $\alpha$ - and  $\beta$ -lithiations solvated by Me<sub>3</sub>N confirm the higher stability of the six-membered ring isomer. Thus, transition structure **18** is 4.7 kcal/mol more stable than transition structure **19**. Structure **18** has an N–H<sub>β</sub>–C2 angle of 176.0°, while in **19** the N–H<sub>α</sub>–C1 angle is 159.1°. Additionally, transition structures **18** and **19** display similar C–H and C–O bond distances and bond angles compared to Me<sub>2</sub>NLi/Me<sub>2</sub>O analogues **16** and **17**, indicating negligible structural differences between ethereal and amine-solvated monomer-based transition structures. In comparison with the activation energies calculated for Me<sub>2</sub>O, the lower values calculated for Me<sub>3</sub>N-solvated monomeric structures do not correlate with the absence of an LiTMP/Me<sub>2</sub>NEt-monomer-based pathway. The difference may derive from simplified computational models.<sup>37b</sup>

(37) (a) Ab initio calculations have shown highly polarized C–O bonds for the nucleophilic attack of LiH to ethylene oxide: Harder, S.; van Lenthe, J. H.; van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1994**, *116*, 2508. (b) The Me<sub>2</sub>NLi grossly overestimates the stabilization caused by solvation of the LiTMP fragment with a hindered trialkylamine. Similarly, we do not observe complexation of the epoxides to LiTMP even in the absence of strong ligands as evidenced by the rate law. In contrast, epoxide–Me<sub>2</sub>NLi complexes are stable minima computationally. These complexes display no explicit N–H or Li–H (agostic) interactions foreshadowing lithiation.

**Dimer-Based Lithiations.** A preliminary assessment of the  $\alpha$ - and  $\beta$ -lithiation of (*Z*)-2-butene oxide via monosolvated dimers considered two criteria: (1) the selective coordination of the ligand (S) to the lithium bearing the epoxide (Li1) or the lithium flanked by two nitrogens (Li2) and (2) the role of transannular heteroatom–Li contacts (R<sub>2</sub>N–Li or C–O–Li) that would define the mono- or bicyclic structures. The combination of these elements affords twelve limiting transition structures **I–XII** shown in Chart 2.<sup>38</sup>

Only transition structures **20**, **21**, and **22** were located for the Me<sub>2</sub>NLi/Me<sub>2</sub>O-mediated  $\alpha$ -lithiation corresponding to cases **I**, **IX**, and a hybrid of **II** and **VI**, respectively. The most stable transition structure, **21**, displays a transannular O1–Li2 contact (2.11 Å) and is solvated on the external Li (Chart 3, Table 4). Structure **21** is distinguished from **20** and **22** by the bicyclic ring, an epoxide bearing two coordinated lithiums,<sup>39,40</sup> and long C–H and C–O bonds (C1–H<sub>α</sub> = 1.42 Å, C1–O1 = 1.59 Å). Structures **20** and **22** display comparable N2–H<sub>α</sub>–C1 angles (175.1° and 176.3°, respectively), while **21** exhibits a 160.9° angle. Transition structure **22** corresponds to a formal  $\alpha$ -lithiation (C1–Li1 = 2.30 Å) displaying a small C–O bond scission (C1–O1 = 1.56 Å) and an H<sub>α</sub>–Li1 agostic interaction (2.19 Å).<sup>41</sup> The least stable structure, **20**, embodies geometric characteristics comparable to those reported for open dimers observable in the solid state.<sup>42</sup>

Among the limiting dimeric structures for Me<sub>2</sub>NLi/Me<sub>2</sub>O-mediated  $\beta$ -lithiations, only **23** and **24** (corresponding to types **VIII** and **XI**) could be located. Structure **23** contains a cyclic dimer-like dialkylamide component with a transannular N2–Li1 contact (2.25 Å), an elongated epoxide (C1–O1 = 1.90 Å), and a shortened C1–C2 bond (1.42 Å). In contrast, transition structure **24** possesses an epoxide oxygen coordinating two lithiums and displays shorter C1–O1 (1.72 Å) and C–H bonds, suggesting limited proton transfer. Despite major structural differences, **23** and **24** display identical energies. A comparison between structures **24** and **21** indicates that  $\alpha$ -lithiation benefits from the double coordination of the epoxide to Li.

A search for transition structures corresponding to Me<sub>2</sub>NLi/Me<sub>3</sub>N-mediated dimer-based lithiations afforded only structure **25** for  $\alpha$ -lithiation (type **IX**, Chart 2) and structures **26** and **27** for  $\beta$ -lithiation (types **III** and **IV**, Chart 2). Transition structure **25** is analogous to Me<sub>2</sub>O-solvated **21**, which, in turn, proves to be the most stable form of open-dimer-based  $\alpha$ -lithiation in Me<sub>2</sub>O. Transition structures **26** and **27** are fundamentally different from those obtained for Me<sub>2</sub>NLi/Me<sub>2</sub>O. Whereas Me<sub>2</sub>O-solvated analogues (**23** and **24**, respectively) contain transannular N–Li and O–Li contacts, **26** and **27** display monocyclic eight-membered open dimers. Structure **27**, solvated at the internal Li2, is 2.7 kcal/mol more stable than the externally solvated **26**. Transition structure **27** features an advanced proton

(38) For an analogous computational survey on open-dimer-based transition structures, see: Ramírez, A.; Sun, X.; Collum, D. B. Unpublished.

(39) Crystal structures showing a bridging ether to two lithiums: Ephritikhine, M.; Maury, O.; Villiers, C.; Lance, M.; Nierlich, M. *J. Chem. Soc., Dalton Trans.* **1998**, 3021. Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Duisenberg, A. J. M.; van Lenthe, J. H. *Organometallics* **1990**, *9*, 511.

(40) The cooperative activation of B and Li atoms on the epoxide oxygen has been shown by DFT calculations on the S<sub>N</sub>2 reaction of epoxides with lithium organocuprates: Mori, S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294.

(41) For a discussion on Li–H agostic interactions, see: Saá, J. M.; Martorell, G.; Frontera, A. *J. Org. Chem.* **1996**, *61*, 5194. Nakamoto, M.; Fukawa, T.; Lee, V. Y.; Sekiguchi, A. *J. Am. Chem. Soc.* **2002**, *124*, 15160 and references therein.

(42) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380.

Chart 2

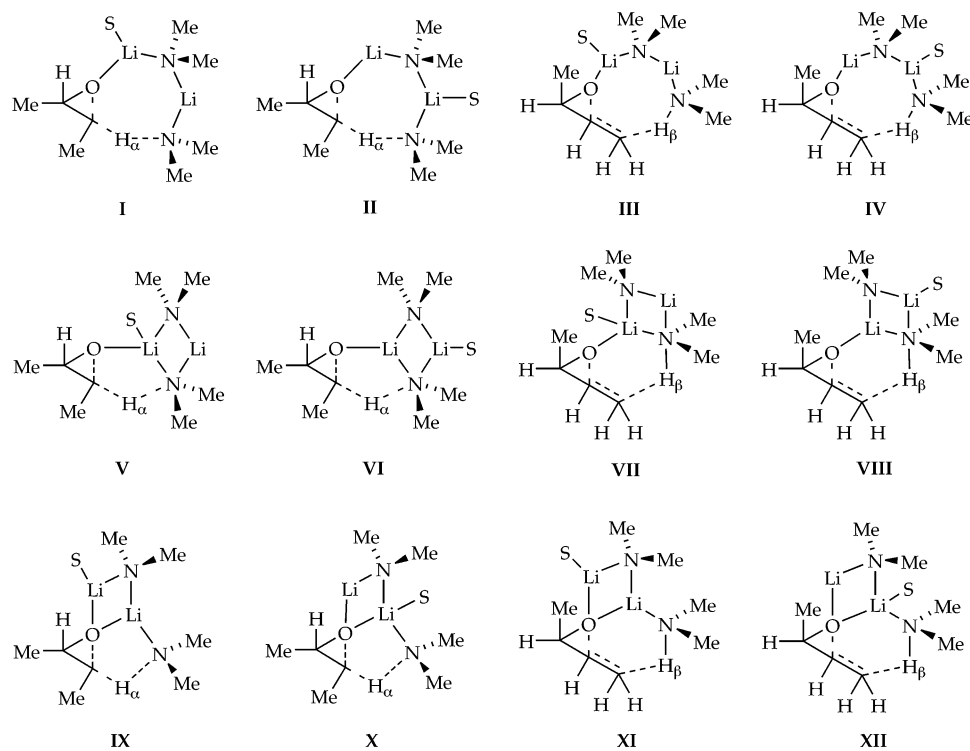
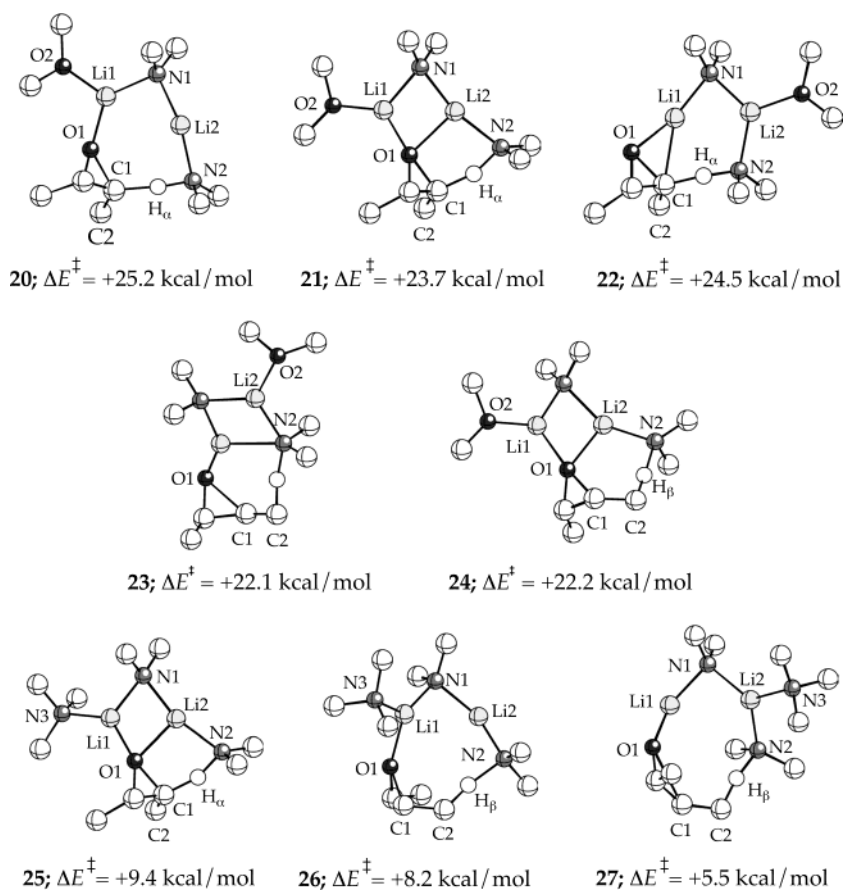


Chart 3



transfer as evidenced by a long C–H bond ( $C2-H_\beta = 1.32$  Å), a short N–H bond, ( $N2-H_\beta = 1.43$  Å), an elongated C1–

O1 bond ( $2.25$  Å), a reduced O1–Li1 contact ( $1.71$  Å), and a shortened C1–C2 bond ( $1.38$  Å). Conversely, transition struc-

ture **26** displays a geometry typical of an early transition state (Table 4).<sup>43</sup>

**$\alpha$ - versus  $\beta$ -Lithiation.** The DFT computations of Me<sub>2</sub>NLi/Me<sub>2</sub>O indicate that the most favored lithiation corresponds to the monomer-based  $\beta$ -lithiation via **16**, followed by (1) dimer-based  $\beta$ -lithiation via **23** ( $\Delta E^\ddagger_{(23)} - \Delta E^\ddagger_{(16)} = 4.8$  kcal/mol), (2) monomer-based  $\alpha$ -lithiation via **17** ( $\Delta E^\ddagger_{(17)} - \Delta E^\ddagger_{(16)} = 5.2$  kcal/mol), and (3) dimer-based  $\alpha$ -lithiation via **21** ( $\Delta E^\ddagger_{(21)} - \Delta E^\ddagger_{(16)} = 6.4$  kcal/mol). These results are in qualitative agreement with experiment and are consistent with the well-known sensitivity of  $\alpha$ - and  $\beta$ -lithiations to the structure of the epoxide.<sup>13</sup> Apparent discrepancies, such as the experimentally observed dimer-based  $\alpha$ -lithiation of **1**, may derive from the simplified substituents of the computational model.<sup>44</sup> In addition, these calculations indicate the existence of a delicate balance between open-dimer-based  $\alpha$ - and  $\beta$ -lithiations.

In agreement with experiment, the most favored Me<sub>2</sub>NLi/Me<sub>3</sub>N-mediated lithiation is the dimer-based  $\beta$ -lithiation via **27**, which is followed by (1) dimer-based  $\alpha$ -lithiation via **25** ( $\Delta E^\ddagger_{(25)} - \Delta E^\ddagger_{(27)} = 3.9$  kcal/mol), (2) monomer-based  $\beta$ -lithiation via **18** ( $\Delta E^\ddagger_{(18)} - \Delta E^\ddagger_{(27)} = 5.1$  kcal/mol), and (3) monomer-based  $\alpha$ -lithiation via **19** ( $\Delta E^\ddagger_{(19)} - \Delta E^\ddagger_{(27)} = 9.8$  kcal/mol). The capacity of DFT computations to imitate the tendency of trialkylamines to promote dimer-based  $\beta$ - and  $\alpha$ -lithiations is impressive.

## Discussion

We investigated how solvation and aggregation influence the reactivity of LiTMP using  $\alpha$ - and  $\beta$ -lithiation of epoxides **1** and **3**, respectively. Although  $\alpha$ - and  $\beta$ -lithiation of epoxide **1** are possible,<sup>14c,19</sup> we observe exclusively the product derived from  $\alpha$ -lithiation with subsequent oxacarbenoid generation and transannular C–H insertion; 2-cycloocten-1-ol evidencing a vicinal ( $\beta$ ) proton abstraction is not detected. Epoxide **3**, although not as synthetically provocative, offers the distinct advantage of mandatorily undergoing  $\beta$ -lithiation en route to allylic alcohol **4**. We have examined the role of solvation and aggregation in the  $\alpha$ - and  $\beta$ -lithiations in detail using the strongly coordinating THF<sup>9a,31,45</sup> and the weakly coordinating Me<sub>2</sub>NEt.<sup>9f,33,46</sup>

LiTMP is considerably more reactive than LDA when solvated by the analogous monodentate ligands, consistent with numerous literature reports.<sup>1,6,42a</sup> By example, comparing LiTMP/THF with LDA/THF reveals an approximately 200-fold greater reactivity toward **1** and a 60-fold greater reactivity toward **3** (in 0.5 M THF).

A limited survey of ligands reveals a surprisingly narrow range of solvent-dependent rates (Table 2) as well as surprisingly similar rates for the  $\alpha$ - and  $\beta$ -lithiations of **1** and **3**, respectively. Interestingly, there is no evidence of an inverse correlation of reactivity with solvent binding constants or the accelerations deriving from hemilabile bifunctional amino ethers that have been observed in proton abstractions by LDA and LiHMDS.<sup>32,33</sup> We also find it curious that the isotope effects for  $\beta$ -lithiation

of **3** are quite large, whereas those for the  $\alpha$ -lithiation of **1** are somewhat small (Table 1).<sup>26</sup> These may correlate with DFT computations, which indicate that the proton transfer in  $\alpha$ -lithiations is more advanced than in  $\beta$ -lithiations.

We preface our discussion of the detailed rate studies with a truism of kinetics: *the rate law provides the stoichiometry of the transition structures relative to the reactants.*<sup>20</sup> As a corollary, the solvation and aggregation number of the transition structure can only be inferred from rate law if the solvation and aggregation numbers of the reactants are known. Once the stoichiometry of the transition structure is established, however, computational chemistry can be used to fill in experimentally elusive structural details.

In this particular study sound structural assignments are acutely important: LiTMP exists as disolvated dimer **5** (accompanied by low concentrations of monomer **6**) in THF/pentane mixtures and unsolvated tetramer **7** (and three conformational isomers)<sup>9d</sup> in Me<sub>2</sub>NEt/pentane mixtures. The most immediate consequence of the solvent-dependent aggregation number is best illustrated by example as follows. If a given reaction proceeds via isostructural monosolvated dimer-based transition structures irrespective of solvent, then the LiTMP/THF-mediated reaction will be *inhibited* by THF and display a *first-order* dependence on LiTMP (see eqs 7–9). In contrast, the LiTMP/Me<sub>2</sub>NEt-mediated reaction via an isostructural monosolvated-dimer-based transition structure will be *promoted* by high Me<sub>2</sub>NEt concentrations and display a *fractional-order* dependence on LiTMP (see eqs 13–15). We will return to the issue of how reactant structure influences the rate profile after summarizing the results of the rate studies.

As foreshadowed above, the  $\alpha$ -lithiation of epoxide **1** with subsequent oxacarbenoid formation and transannular C–H insertion proceeds cleanly via monosolvated-dimer-based transition structures irrespective of the solvent. The transition structures are depicted generically as **9** and **11**. DFT computations suggest that the most stable dimer-based transition structures, **21** and **25**, contain distinct transannular Li–O contacts.

Conversely, the mechanism for the  $\beta$ -lithiation of epoxide **3** is solvent dependent. Lithiations using LiTMP/THF proceed via monosolvated monomers depicted generically as **8**. Although we do not have a direct comparison with LDA/THF, LDA/*n*-BuOMe-mediated lithiations of **3** proceed via monosolvated monomers as well.<sup>19</sup> In contrast, the reaction of **3** with LiTMP/Me<sub>2</sub>NEt proceeds via a dimer-based transition structure depicted generically as **10**. Transition structure **10** is analogous to calculated transition structure **26**. However, transition structure **27**, which bears an unusual<sup>29</sup> solvation of the lithium flanked by the two amido groups, is found to be more stable in a simplified computational model.

Overall, THF appears to suppress the dimer-based pathway (or promote the monomer-based pathway, depending on one's frame of reference). In a previous paper on the LDA-mediated lithiation of **3**, we parenthetically noted evidence of a dimer-based  $\beta$ -lithiation, but it was too minor to document. Once again, DFT computations are instructive. In contrast to the  $\alpha$ -lithiation proceeding via a seven-membered ring displaying transannular Li–O contacts, the  $\beta$ -lithiation does not appear to benefit from such contacts. The difference may partially explain why the vicinal eliminations by LDA are primarily monomer derived.<sup>19</sup>

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(44) A dimer-based  $\beta$ -lithiation has been detected in the vicinal lithiation of cyclohexene oxide mediated by LDA/*n*-BuOMe mixtures: Ramirez, A.; Collum, D. B. Unpublished results. For the  $\beta$ -lithiation of cyclohexene oxide promoted by a dimeric norephedrine-derived chiral lithium amide, see: Pettersen, D.; Amedjkouh, M.; Lill, S. O. N.; Dahlén, K.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1654.

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(46) Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1996**, *118*, 2217.



The seven-membered ring also seems to provide the closest approach to the putatively optimal  $180^\circ$  N–H–C alignment in the proton transfer.

It is pedagogically useful to consider whether there is a relationship between the solvent-dependent structures of the reactants and transition structures. For example, to the extent that  $\text{Me}_2\text{NEt}$  completely resists solvation of the LiTMP reactant, it is not surprising that the LiTMP/ $\text{Me}_2\text{NEt}$ -mediated reactions proceed via dimer-based transition structures with low solvation numbers, 0.5 solvents per lithium. A monosolvated monomer-based pathway would require a greater per lithium solvation number *and* a greater per subunit deaggregation. Similarly, to the extent that THF tenaciously binds lithium, it is not surprising that  $\beta$ -lithiation of **3** via a monosolvated monomer-based pathway with one THF per lithium is facile compared to a lesser-solvated dimer-based pathway. It is probably most surprising that the dimer-based  $\alpha$ -lithiation of **1** requiring dissociation of a THF ligand is the preferred pathway. We suspect that the dissociation is facilitated by the severe steric congestion in LiTMP.

### Experimental Section

**Reagents and Solvents.** *cis*-Cyclooctene oxide (**1**) and all ethereal and amine ligands are commercially available. *cis*-Cyclooctene oxide- $d_2$  (**1- $d_2$** )<sup>24</sup> and amino ether  $\text{MeOCH}_2\text{CH}_2\text{NMe}_2$  (**12**)<sup>31</sup> were prepared according to literature procedures. 2,3-Dimethyl-2-butene oxide- $d_{12}$  (**3- $d_{12}$** ) was synthesized from 2,3-dimethyl-2-butene- $d_{12}$ <sup>25b</sup> following the procedure for the undeuterated analogue.<sup>25a</sup> All solvents were distilled by vacuum transfer from sodium benzophenone ketyl. The pentane still contained 1% tetraglyme to dissolve the ketyl. The LiTMP used in THF/pentane solutions was prepared from recrystallized *n*-BuLi<sup>22b,c</sup> and purified by recrystallization as described previously.<sup>22a</sup> The LiTMP used in  $\text{Me}_2\text{NEt}$  was generated in situ from recrystallized *n*-BuLi and titrated. The diphenylacetic acid used to check solution titers was recrystallized

from methanol and sublimed at  $120^\circ\text{C}$  under full vacuum.<sup>47</sup> Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

**Kinetics.** The kinetics were carried out as described previously.<sup>19</sup>

### Conclusions

The high reactivity and selectivity of LiTMP toward epoxides derives largely (but not exclusively) from dimer-based chemistry. Although the rates are surprisingly insensitive to the choice of coordinating solvent, the rate laws and affiliated rate profiles can be strikingly different due to the solvent-dependent aggregation of LiTMP in THF and  $\text{Me}_2\text{NEt}$ . Moreover, LiTMP/THF and LiTMP/ $\text{Me}_2\text{NEt}$  are not equivalent as synthetic reagents. LiTMP displays a limited solubility in  $\text{Me}_2\text{NEt}$ /pentane mixtures because  $\text{Me}_2\text{NEt}$  does *not* coordinate to the observable tetramers. Nonetheless, LiTMP/ $\text{Me}_2\text{NEt}$ /pentane mixtures show a marked resistance to thermal decomposition when compared with LiTMP/THF/pentane mixtures. It seems likely that both solvents will have a niche in synthesis.

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**Supporting Information Available:** Rate and computational data (12 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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