# Effects of Lithium Salts on the Stereochemistry of Ketone Enolization by Lithium 2,2,6,6-Tetramethylpiperidide (LiTMP). A Convenient Method for Highly *E*-Selective Enolate Formation

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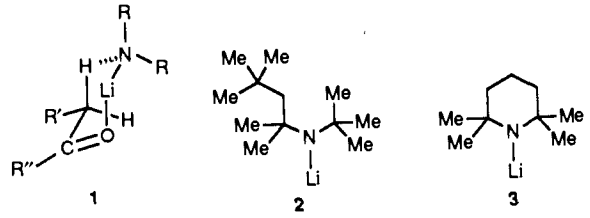
**Abstract:** Studies of the reactivity of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) with added lithium salts are described. The *E*/*Z* selectivity of 3-pentanone enolization by LiTMP displays a marked decrease as a function of added ketone (percent conversion). The enolization also shows a notable maximum of 50:1 selectivity at 0.3–0.4 equiv of added LiCl and an approximate asymptotic approach to 50–60:1 selectivity when >1.0 equiv of LiBr are added. The LiTMP–LiBr complex generated from 2,2,6,6-tetramethylpiperidinium bromide affords enolates with generally high regio- and stereoselectivity as shown by several representative enolizations. The selectivities appear to have exclusively kinetic origins and are suggested to stem from the intervention of LiTMP–LiX mixed aggregates characterized in the following paper.

## Introduction

The stereochemistry of the aldol condensation is limited in many instances by the availability of *E* and *Z* enolates.[1] In a seminal study, Ireland and co-workers reported that enolization of 3-pentanone with lithium diisopropylamide (LDA) affords predominantly the *E* enolate in THF and the *Z* enolate in THF/HMPA as shown by subsequent trapping with chlorotrialkylsilanes (Scheme I).[2] Amidst extensive mechanistic discussions it appears to be widely accepted that the *E* isomer stems from a kinetically controlled pathway, with the selectivity deriving from a chair-like transition state such as **1**.[1] Whether formation of the *Z* enolate in the presence of HMPA is a kinetic process or the result of an equilibration is less clear.

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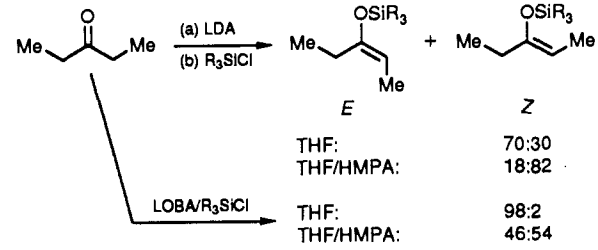
In 1984, Corey and Gross[3] reported that the *E*/*Z* selectivity for 3-pentanone enolization could be extended to 50:1 by using the severely hindered lithium 1,1,3,3-tetramethylbutyl-*tert*-butylamide (LOBA, **2**) *in the presence of chlorotrimethylsilane (TMSCl) to trap the enolate as it forms.*[4] It was suggested that the in situ trapping procedure precludes rapid isomerization of the *E* enolate during the course of the enolization. Regardless of the mechanistic interpretations, this in situ trapping protocol provides the most selective direct access to lithium enolates with *E* geometry reported to date.[5,6]

**Scheme I**




We describe studies of ketone enolizations by lithium 2,2,6,6-tetramethylpiperidide (LiTMP, **3**), paying particular attention to the consequences of added lithium salts. We will demonstrate that the addition of low concentrations of LiCl or LiBr markedly enhance—up to 60:1—the *E*/*Z* selectivity of 3-pentanone enolization. We provide a procedure for generating LiTMP–LiBr in situ from 2,2,6,6-tetramethylpiperidinium bromide (TMP·HBr) and *n*-butyllithium that does not require manipulating analytically pure LiTMP or highly hygroscopic LiBr. The resistance of TMP·HBr to hydration and air oxidation makes it an especially convenient lithium dialkylamide precursor. In the adjoining manuscript we describe structural studies that implicate mixed aggregates as the source of the selectivity changes.

## Results

Unless noted otherwise, all stereochemical studies described herein were carried out with crystalline[7] LiTMP prepared from

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(5) Less direct, yet highly selective syntheses of lithium enolates: Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441. Bertz, S. H.; Dabbagh, G.; Gibson, C. P. *Organometallics* **1988**, *7*, 563. Reich, H. J.; Holtan, R. C.; Borkowsky, S. L. *J. Org. Chem.* **1987**, *52*, 312. Reich, H. J.; Holtan, R. C.; Bolm, C. *J. Am. Chem. Soc.* **1990**, *112*, 5609 and references cited therein.

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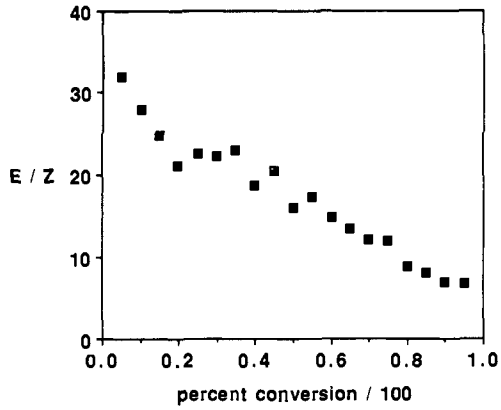



**Figure 1.** Selectivity of 3-pentanone enolization according to eq 1. $E/Z$ = [6]/[7]. Enolization was effected at −78 °C with 0.1 M LiTMP in THF.

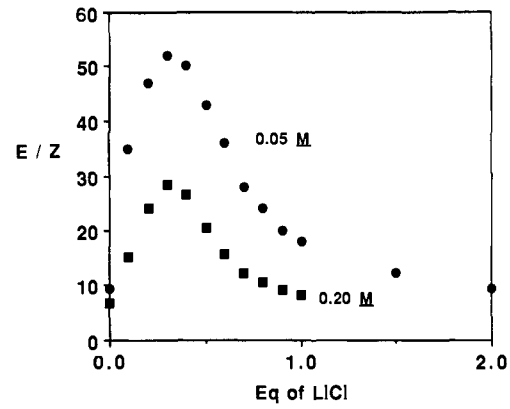
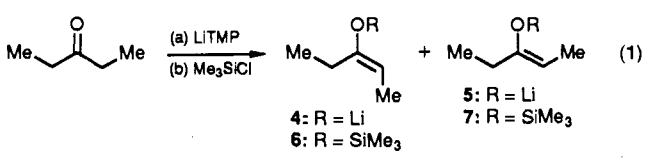



**Figure 2.** Selectivity of 3-pentanone enolization according to eq 1. $E/Z$ = [6]/[7]. Enolization was run to 77% conversion at −78 °C by LiTMP (at concentrations indicated) with varying amounts of added LiCl in THF.

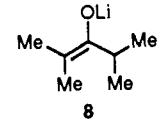
*n*-BuLi. The LiTMP stock solutions were freshly prepared and their titer checked before each experiment. The lithium halides were carefully purified and shown to contain <1% protic impurities.

**3-Pentanone Enolization Selectivity: Dependence on Percent Conversion.** The enolization of 3-pentanone by LiTMP in THF (eq 1) has been reported[8-10] to proceed in 5:1 $E/Z$ selectivity. However, during the course of any organolithium reaction the conditions can change quite drastically, resulting in a dependence of selectivity on percent conversion. Indeed, Rathke noted a substantial increase in the $E/Z$ selectivity when low concentrations of 3-pentanone (≤0.5 equiv) were added to LiTMP.[8,9] While an enolate equilibration process could be readily monitored near ambient temperatures, it would appear that the rate is far too low to account for a loss in selectivity at the reduced temperatures of the enolization.[10]




(1)

Upon reinvestigation of the enolization of 3-pentanone by LiTMP, we observe a similar loss of selectivity when increasing quantities of 3-pentanone are added to 0.1 M solutions of LiTMP in THF at −78 °C (Figure 1). Under any given set of conditions, the selectivity is not affected by the rate of ketone addition, age of the resulting enolate solution, quenching method, or presence of added tetramethylpiperidine. To determine if the reduced selectivities observed at high percent conversion arose from an equilibration, we effected a highly selective enolization at low conversion and then brought it to high conversion with a surrogate ketone. Thus, sequential addition of 10 mol % 3-pentanone, 80 mol % cyclohexanone, and excess TMSCl provides the same high $E/Z$ selectivity as an analogous procedure without the added cyclohexanone. We conclude that *the reduced selectivities observed at high percent conversions are not the result of isomerization of E enolate 4 subsequent to its formation.*[10] However, we also found that addition of 80 mol % cyclohexanone followed by 10 mol % 3-pentanone resulted in a surprisingly high 20:1 $E/Z$ selectivity. This seemed to suggest that either cyclohexanone enolate is a poor model for $E$ enolate **4** or that the sharp increase in proportion of $Z$ enolate **5** discernible in Figure 1 is mediated by the $Z$ enolate **5** (rather than **4**) in a form of an autocatalytic process. Consistent with the latter hypothesis, we find that addition of 80 mol % 2,4-dimethylpentanone (to generate enolate **8** as a




**8**

model of $Z$ enolate **5**) followed by 10 mol % 3-pentanone affords 9:1 $E/Z$ selectivity. Spectroscopic studies described in the following paper[11] indicate that kinetic enolizations mediated by LiTMP/lithium enolate mixed aggregates may be the source of the observed selectivities.

**3-Pentanone Enolization Selectivity: Effects of Added Lithium Halides.** We suspected that the enhanced selectivities observed by Corey and Gross[3] using TMSCl as an in situ trapping reagent arose from the generation of LiCl during the course of the enolization rather than from suppression of equilibration pathways. Accordingly, the effects of lithium salts on the LiTMP enolization selectivities were investigated.

Lithium chloride has a dramatic influence on the enolization of 3-pentanone (Figure 2). A maximum $E/Z$ selectivity of 50–60:1 occurs at 0.3–0.4 equiv of LiCl. The selectivity is reduced at high LiCl content, asymptotically approaching a value only slightly higher than that observed for LiTMP in the absence of LiCl. Although the optimal *ratio* of LiTMP/LiCl is the same at all absolute concentrations studied, the *amplitude* of the selectivity maximum is decreased at high absolute concentrations and low THF concentrations (achieved using pentane as the diluent). Furthermore, addition of the LiCl after enolization affords selectivities indistinguishable from halide-free enolizations. During the course of the enolization with LiTMP/LiCl, the proportions of LiTMP, LiCl, and lithium enolate change continuously over the course of the reaction. Since both high lithium enolate/LiTMP and high LiCl/LiTMP ratios afford low $E/Z$ selectivities, we reasoned that the $E/Z$ selectivity would decrease (or at least change) as a function of percent conversion for LiTMP/LiCl mixtures as well. The enolization of 3-pentanone by the optimal LiTMP/LiCl mixture exhibits selectivities that are *independent of percent conversion.* Even after extensive spectroscopic and stereochemical studies,[11] many of these results remain mystifying.

We briefly explored temperature modulation as a means of optimizing selectivity. Surprisingly, in the absence of LiCl the $E/Z$ enolization selectivities *increase* at elevated temperatures (11:1 at −20 °C) and are percent conversion independent. In the presence of LiCl, the maximum selectivity (still at 0.3–0.4 equiv of LiCl per LiTMP) *decreases* at elevated temperature (23:1 at −20 °C). While these results are provocative, temperature effects provide little mechanistic insight given the complexity of the

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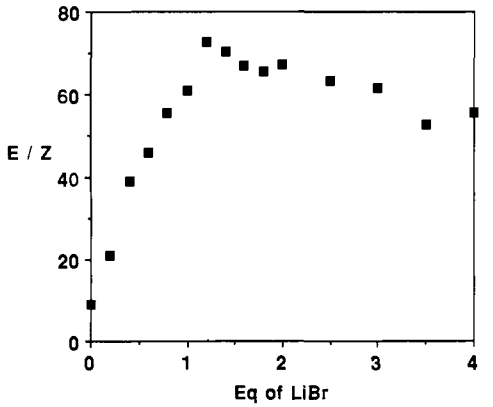



**Figure 3.** Selectivity of 3-pentanone enolization according to eq 1. $E/Z$ = [6]/[7]. Enolization was run to 77% conversion at −78 °C by 0.05 M LiTMP with varying amounts of added LiBr in THF.

aggregation equilibria involved.[11]

The enolization of 3-pentanone with LiTMP/LiBr mixtures affords $E/Z$ selectivities that can exceed those derived from LiTMP/LiCl. In contrast, to LiTMP/LiCl, only slight losses in selectivity occur at high LiBr content (Figure 3). $LiClO_4$ and $LiBPh_4$ have no measurable effects on the selectivity, while LiF and LiI are too insoluble to afford meaningful results.

**3-Pentanone Enolization Selectivity: *t*-$Bu_2NLi$ and *t*-$Bu_2NLi$/Lithium Halide.** We were interested in whether the selectivities derive from the steric demands of the LiTMP base or some influence imparted by the chair structure of LiTMP. We explored the enolization selectivity using lithium di-*tert*-butylamide (*t*-$Bu_2NLi$)[3,7] noting that a simple steric model predicts an enhanced $E/Z$ enolization selectivity in comparison with LiTMP,[12] while a conformational model predicts a loss in selectivity. In the presence of >2.0 equiv of LiBr, the $E/Z$ selectivity exceeds 70:1, consistent with a purely steric model.

***E*-Selective Enolization: In Situ Protocol.** Although the enolization selectivities described above are of a synthetically useful magnitude, the very sharp dependence of the selectivity on absolute concentrations and LiTMP/LiX ratios renders the results difficult to reproduce following the standard techniques available in a synthetic chemistry laboratory. Furthermore, the tremendous hygroscopicity of anhydrous LiCl and LiBr causes the procedure to be tedious even if the LiTMP is generated in situ from the amine and *n*-BuLi. We describe below a procedure based on the metalation of crystalline 2,2,6,6-tetramethylpiperidinium bromide (TMP·HBr) that involves generation of both the LiTMP and the LiBr under fully anhydrous conditions. The resistance of TMP·HBr to air oxidize or hydrate makes it an especially convenient lithium dialkylamide precursor even relative to the free amine in some respects.

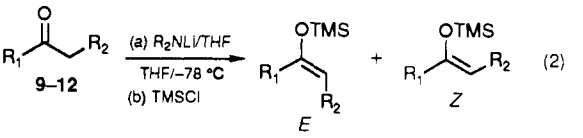
TMP·HBr is precipitated in 94% yield from a solution of 48% aqueous HBr (1.1 equiv) in THF (1:20 (v/v)) by addition of 2,2,6,6-tetramethylpiperidine[13] (TMP, Aldrich). Recrystallization from ethanol affords analytically pure material free of water, hydrazine, and 2,2,6,6-tetramethyl-4-piperidinone sometimes found in commercially available TMP. Furthermore, TMP·HBr shows no evidence of hydration even when stored for 24 h at 100% humidity. A solution of LiTMP–LiBr (1:1.2) is generated from a suspension of TMP·HBr in THF at 0 °C by addition of 1.85 equiv of *n*-BuLi/hexane with stirring until the mixture becomes homogeneous.[14] Inclusion of traces of phenanthroline indicator provides for an internal titration of the *n*-BuLi due to the persistence of an intense color upon formation of low concentrations of LiTMP.

**Table I.** $E/Z$ Enolization Selectivities for Selected Lithium Dialkylamides in THF at −78 °C (Equation 1)[a]

| ketone | $R_1$, $R_2$ | LDA[2,9] | LOBA/TMSCl[3] | LiTMP[2,8-10] | LiTMP–LiBr[c] |
|---|---|---|---|---|---|
| **9** | Et, Me | 3.3:1 | 50:1[b] | 5:1 | 50:1 |
| **10** | *i*-Pr, Me | 1.7:1 | | 2:1 | 21:1 |
| **11** | *t*-Bu, Me | 1:>50 | | 1:>20 | 1:>20 |
| **12** | Me, Ph | 13:1 | | 12:1 | 32:1[d] |

[a] The selectivities for LDA, LOBA/TMSCl, and LiTMP are literature reports as noted. [b] In situ trapping protocol. [c] A 10% molar excess of LiTMP–LiBr was used. Stereo- and regiochemical analyses were carried out according to literature methods.[2,3,9] [d] Significant erosion of the $E/Z$ selectivity occurs during a standard aqueous workup.

Enolizations of several representative ketones by the in situ generated LiTMP–LiBr are illustrated in Table I along with literature results for comparison. In general, the $E/Z$ selectivities using LiTMP–LiBr compare favorably to those derived from existing protocols (although the sterically very demanding ketone **11** affords only the $Z$ silyl enol ether after workup). Also of note, enolizations of **10** and **12** with LiTMP–LiBr exhibit 130:1 and 3:1 regioselectivities (respectively, major isomer as indicated in eq 2), comparing favorably with 17:1 and 1.4:1 regioselectivities with halide-free LiTMP.



(2)

## Discussion

The enolization of 3-pentanone by LiTMP in THF is markedly influenced by the presence of lithium enolate. At 5% conversion, we observe a 30:1 $E/Z$ selectivity. However, when taken to full (>80%) conversion—percent conversions found in most lithium amide applications—the selectivity drops to <10:1. This phenomenon was first noted by Rathke and co-workers. Several control experiments suggest that the enolizations are under exclusively kinetic control, echoing recent conclusions of Saunders[10] and Ireland.[15] In fact, the enolate equilibration process that is often cited as a source of selectivity changes appears to be orders of magnitude slower than enolization.[8]

We also investigated the effects that lithium halides have on the stereochemistry of enolization. An optimal $E/Z$ selectivity of 50:1 was observed at 0.3–0.4 equiv of LiCl. Ironically, at ≥1.0 equiv of LiCl (the most logical quantity of an additive) the $E/Z$ selectivity is virtually indistinguishable from that obtained under halide-free conditions. In contrast, LiBr causes the 3-pentanone $E/Z$ selectivity to asymptotically approach 60:1 selectivity with slightly greater than 1.0 equiv of added salt. Other more ionizable lithium salts have little influence on enolization selectivity. As a result of the observed lithium halide dependencies we developed an especially convenient procedure for generating LiTMP/LiBr mixtures. Treatment of 2,2,6,6-tetramethylpiperidinium bromide (TMP·HBr) with *n*-BuLi affords LiTMP–LiBr mixtures that effect enolizations with an $E$ selectivity competitive with that of the best literature procedures. The LiTMP/LiBr ratio is readily controlled by the number of equivalents of *n*-BuLi while the stability of TMP·HBr toward oxidation and hydration eliminates tedious manipulations of hygroscopic LiBr and free amine.

It seems likely that the lithium salt dependent selectivities stem from the intervention of mixed aggregates in the product determining transition state(s).[11] Take as a quite complicated example the enhanced $E/Z$ enolization selectivities observed by Corey and Gross[3] using the in situ TMSCl trapped protocol (Scheme 1). The

(11) Hall, P. L.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.*, following paper in this issue.
(12) Fjeldberg, T.; Lappert, M. F.; Smith, S. J. *J. Mol. Struct.* **1986**, *140*, 209. Siam, K.; Ewbank, J. D.; Schäfer, L.; Van Alsenoy, C. *J. Mol. Struct.* **1987**, *153*, 165. Schäfer, L.; Van Alsenoy, C.; Scarsdale, J. N. *J. Mol. Struct.* **1982**, *86*, 349. Wollrab, J. E.; Laurie, V. W. *J. Chem. Phys.* **1968**, *48*, 5058.
(13) Franchimont, A. P. N.; Friedmann, H. *Recl. Trav. Chim. Pays-Bas* **1905**, *24*, 404.
(14) Snaith and co-workers clearly articulated the merits of $NH_4X$ salts as precursors to anhydrous LiX salts: Barr, D.; Snaith, R.; Wright, D. S.; Mulvey, R. E.; Wade, K. *J. Am. Chem. Soc.* **1987**, *109*, 7891.
(15) Ireland recently concluded that lithium amide-mediated ester enolate formation is under kinetic control: Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650.

requisite hindrance of the LOBA base (**2**) could serve to slow the enolization sufficiently to allow the trapping to occur competitively. The large excess of TMSCl found by the authors to provide optimal selectivities would further increase the rate of enolate trapping. Both factors would enhance a LiCl-dependent autocatalytic process by enhancing the rate of LiCl generation relative to enolization. One should bear in mind, however, that the comparison of LiTMP and LOBA is tenuous in the absence of additional data. More importantly, during the course of the enolizations the reaction conditions are changing continuously as a function of percent conversion.

In the following paper we will describe NMR spectroscopic studies of LiTMP–lithium enolate and LiTMP–lithium halide mixed aggregate equilibria that implicate an enormous mechanistic complexity of ketone enolizations.

## Experimental Section

**Reagents and Solvents.** Tetrahydrofuran (THF) hydrocarbon solvents were distilled from blue or purple solutions containing sodium benzophenone ketyl under vacuum. The hydrocarbon stills contained 1% tetraglyme to dissolve the ketyl. 2,2,6,6-Tetramethylpiperidine was obtained from Aldrich and purified by fractional distillation from lithium aluminum hydride. Lithium 2,4-dimethyl-3-pentanone enolate and lithium cyclohexenolate were prepared using LiTMP[7] in hexane as described elsewhere.[16] Lithium halides were prepared and purified by modified literature procedures[17] and shown to contain <1% protic impurities with use of a titration procedure based on diphenylacetic acid.[18] The diphenylacetic acid used to determine the solution titers was recrystallized from methanol and sublimed at 120 °C under full vacuum. Cyclohexanone and 3-pentanone were obtained from Aldrich, purified by careful fractional distillation, and shown to be >98% pure by gas chromatography. *tert*-Butyl ethyl ketone was prepared by addition of *t*-BuLi to propionaldehyde (pentane, −78 °C) followed by oxidation with pyridinium chlorochromate. 2-Methyl-3-pentanone was prepared by addition of *i*-PrMgBr to propionaldehyde ($Et_2O$, −20 °C) followed by oxidation with pyridinium chlorochromate. Di-*tert*-butylamine was prepared by a literature procedure and distilled from $LiAlH_4$.[19] Air- and moisture-sensitive materials were manipulated under argon or nitrogen following standard glovebox, vacuum line, and syringe techniques.

**Lithium Di-*tert*-butylamide (*t*-$Bu_2$NLi).**[3,7] Lithium di-*tert*-butylamide was prepared from di-*tert*-butylamine[19] as follows. To a sample of freshly prepared, twice-sublimed ethyllithium (500 mg, 14.5 mmol) in a 100-mL round-bottom flask fitted with a Teflon-coated stir bar and attached to an Ar/vacuum double manifold vacuum line was vacuum transferred benzene (ca. 50 mL). After the ethyllithium dissolved at room temperature, to the pale yellow solution was added neat di-*tert*-butylamine (2.21 g, 17.1 mmol) by gas-tight syringe. The resulting yellow, homogeneous solution became turbid within 10 min. The mixture was heated to 60–70 °C for 1.0 h at 8-h intervals for a total of 90 h. The solids were collected by filtration, sequentially rinsed with benzene and hot hexane, and dried in vacuo to afford lithium di-*tert*-butylamide (1.76 g, 62% yield) as a white powder containing approximately 1 equiv of occluded benzene as shown by NMR spectroscopic analysis and titration. $^1$H NMR (THF-$d_8$, −30 °C) δ 7.15 (benzene), 1.07 (s) ppm. $^{13}$C{$^1$H} NMR (THF-$d_8$, −30 °C) δ 128.0 (benzene), 54.7 (C quat), 37.2 ($CH_3$). $^6$Li{$^1$H} NMR (3:1 THF/pentane, −115 °C) δ 1.35, 1.17 ppm. These are tentatively assigned as dimer and monomer, respectively, based on dilution studies and chemical shift analogy with LiTMP.[11] The sample is not contaminated with the *t*-$Bu_2$NLi–EtLi mixed aggregate (showing a $^6$Li resonance at 1.96 ppm). Three minor resonances constituted a total of ≤10% of the total integration.

**2,2,6,6-Tetramethylpiperidinium Bromide (TMP·HBr).**[13] To a rapidly stirred solution of 15.0 mL of 48% aqueous HBr (133 mmol) in 300 mL of THF was added 20.0 mL (16.7 g, 119 mmol) of 2,2,6,6-tetramethylpiperidine at room temperature, resulting in immediate formation of a white precipitate. After 15 min the mixture was cooled to 0 °C and the solids were collected by filtration. Vacuum desiccation over KOH pellets gave 24.8 g (94%) of TMP·HBr of suitable purity for preparative purposes. Analytically pure TMP·HBr was isolated in 75% overall yield by recrystallization from absolute ethanol. $^1$H NMR ($D_2O$, shifts relative to external TMS standard) δ 0.82 (m, 2 H), 0.72 (m, 4 H), 0.47 (s, 12 H); $^{13}$C NMR ($D_2O$, shifts relative to external standard) δ 57.0 (s, C2), 34.6 (t, C3), 26.8 (q, $CH_3$), 15.7 (t, C4).

**Enolization Selectivities. Method A.** A typical series of enolization selectivities using preformed LiTMP was run as follows. In an inert atmosphere glovebox, three volumetric flasks containing stir fleas were charged separately with LiTMP (680 mg, 4.62 mmol), LiCl (127 mg, 3.00 mmol), and sublimed diphenylacetic acid (265 mg, 1.25 mmol) and fitted with serum stoppers. Similarly, a 100-mL serum vial under septum was charged with 3-pentanone (320 μL, 0.260 g, 3.02 mmol). The reagents, along with fourteen additional 5-mL serum vials fitted with serum stoppers and stir fleas, were removed from the glovebox and placed under positive nitrogen pressure by standard needle inlets. Solutions of the LiCl (0.300 M) and diphenylacetic acid (0.125 M) were prepared by adjusting the volumes to 10.0-mL (accounting for the stir flea) with freshly dried THF via gas-tight syringes. The 3-pentanone sample was brought to 0.577 M by addition of 4.92 mL of dry THF. The volumetric flask containing the LiTMP was cooled in a dry ice–acetone bath and brought to volume by slow addition of THF down the glass walls with constant agitation to minimize localized heating. The LiTMP was dissolved by careful warming to −20 °C. An aliquot of the LiTMP stock solution was added to 2.3 mL of THF at −20 °C and titrated with the diphenylacetic acid solution to the yellow-to-colorless endpoint to determine the precise titer of the LiTMP solution. (The titer was routinely found to be about 95% of the calculated value.) The remaining thirteen empty serum vials were cooled to −78 °C under nitrogen and charged with 0.30 mmol (690 μL in this case) each of the LiTMP stock solution. The appropriate aliquots of LiCl stock solutions were added by gas-tight syringe to the series of serum vials and then the total volumes were corrected to 3.00 mL with dry THF with stirring for an additional 15 min. Each sample was treated with an aliquot of the 3-pentanone/THF solution (400 μL, 0.231 mmol) by motor driven syringe over 2.0 min, stirred for 10 min, and then treated with a homogeneous TMSCl/$NEt_3$ solution(3.9:1; 62 μL, 0.39 mmol of TMSCl). The ratios were determined with correction for molar absorptivities as determined by careful NMR integrations (±5%) of an authentic mixture. Yields calibrated against *n*-octane internal standard were shown to be essentially invariant (85–90%).

**Enolization Selectivities. Method B.** To a rapidly stirred suspension of TMP·HBr (504 mg, 2.27 mmol) in 25 mL of THF at 0 °C under Ar was added a 1.61 M solution of *n*-BuLi/hexanes (2.60 mL, 4.19 mmol) dropwise over a 3-min period. After being stirred for an additional 3 min, the resulting pale yellow solution was cooled to −78 °C and 3-pentanone (149 mg, 1.73 mmol) was added as a 10% solution in THF. After 15 min, 0.55 mL of a clear 4:1 (v/v) mixture of TMSCl/$NEt_3$ (3.5 mmol of TMSCl) was added in one portion. GC analysis revealed a mixture of enol ethers **6** and **7** in 50:1 ratio. By addition of 0.5 mol % phenanthroline, the TMP·HBr can be used to titrate the solution of *n*-BuLi; a deep red color persists as the first traces of LiTMP persist. One should be careful to allow sufficient time for HBr salt to dissolve. The reaction can be effected in a 5-fold decreased volume of THF with some loss in *E*/*Z* selectivity (27:1).

**Acknowledgment.** We thank W. T. Saunders (University of Rochester), L. M. Jackman (Penn State), P. v. R. Schleyer (Erlangen), and R. Snaith (Cambridge) for providing pertinent manuscripts prior to publication. We acknowledge the National Science Foundation Instrumentation Program (CHE 7904825 and PCM 8018643), the National Institutes of Health (RR02002), and IBM for support of the Cornell Nuclear Magnetic Resonance Facility. We also thank the National Institutes of Health for direct support of this work.

**Registry No. 3**, 38227-87-1; **6**, 51425-53-7; **7**, 51425-54-8; **9**, 96-22-0; **10**, 565-69-5; **11**, 564-04-5; **12**, 103-79-7; TMP·HBr, 935-21-7; LiCl, 7447-41-8; LiBr, 7550-35-8; $LiClO_4$, 7791-03-9; $LiBPh_4$, 14485-20-2; (*E*)-$Me_3SiOC(i\text{-}Pr)$=$CHCH_3$, 19980-42-8; (*Z*)-$Me_3SiOC(i\text{-}Pr)$=$CHCH_3$, 19980-41-7; (*E*)-$Me_3SiOC(t\text{-}Bu)$=$CHCH_3$, 72658-12-9; (*Z*)-$Me_3SiOC(t\text{-}Bu)$=$CHCH_3$, 61878-68-0; (*E*)-$Me_3SiOC(Me)$=CHPh, 19980-25-7; (*Z*)-$Me_3SiOC(Me)$=CHPh, 19980-24-6.

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