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# Lithium Hexamethyldisilazide-Mediated Enolizations: Influence of Triethylamine on *E*/*Z* Selectivities and Enolate Reactivities

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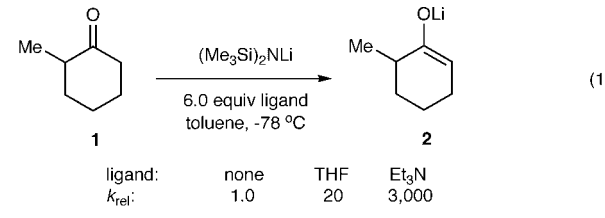
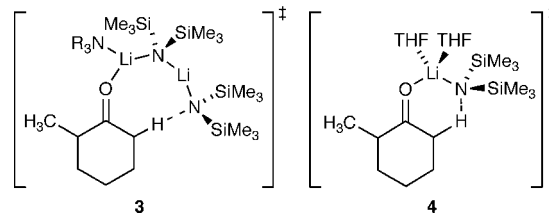
***Abstract:*** Lithium hexamethyldisilazide (LiHMDS) in triethylamine ($Et_3N$)/toluene is shown to enolize acyclic ketones and esters rapidly and with high *E*/*Z* selectivity. Mechanistic studies reveal a dimer-based mechanism consistent with previous studies of LiHMDS/$Et_3N$. *E*/*Z* equilibration occurs when <2.0 equiv of LiHMDS are used. Studies of the aldol condensation and Ireland−Claisen rearrangement of the resulting $Et_3N$-solvated enolates show higher and often complementary diastereoselectivities when compared with analogous reactions in THF. The $Et_3N$-solvated enolates also display a marked (20-fold) acceleration of the Ireland−Claisen rearrangement with evidence of autocatalysis. A possible importance of amine-solvated enolates is discussed.

## Introduction

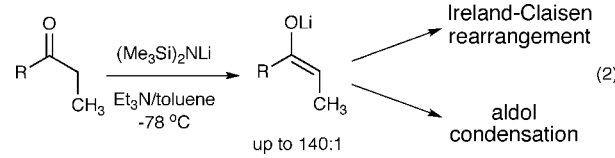
On the heels of investigations of the solvent-dependent structures of lithium hexamethyldisilazide (LiHMDS),[1,2] we began examining structure−reactivity relationships in LiHMDS-mediated ketone enolizations (eq 1).[3] We found that enolization of ketone **1** in $Et_3N$/toluene[3a] is >100 times faster than the analogous enolization in neat THF.[3b,c] This was surprising given that simple trialkylamines are particularly feeble ligands[2,3a,b,4] that have rarely been used in organolithium chemistry.[5,6] The high rates imparted by trialkylamines were traced to a dimer-based pathway exemplified by transition structure **3**. The exceptional steric demands of the trialkylamines were shown to destabilize dimeric LiHMDS reactants more than they destabilize transition structure **3**. By contrast, the LiHMDS/THF-mediated enolizations proceed via a more conventional disolvated monomer-based transition structure **4**.[3b]




(1)




We describe herein LiHMDS/$Et_3N$-mediated enolizations of acyclic ketones. The enolizations are fast, dimer-based, and, most important, highly *E* selective (eq 2). We also examine the reactivity of the $Et_3N$-solvated lithium enolates toward aldol condensations and Ireland−Claisen rearrangements and find some distinct advantages when compared with THF-solvated enolates.[7]




(2)

## Results

**Stereochemistry of Enolization.** The *E*/*Z* selectivities for LiHMDS-mediated enolizations were monitored by quenching the resulting enolate solutions with $Me_3SiCl$/$Et_3N$[8] and analyzing the products with gas chromatography (GC) using well-

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**10.1021/ja800250q CCC: $40.75** 

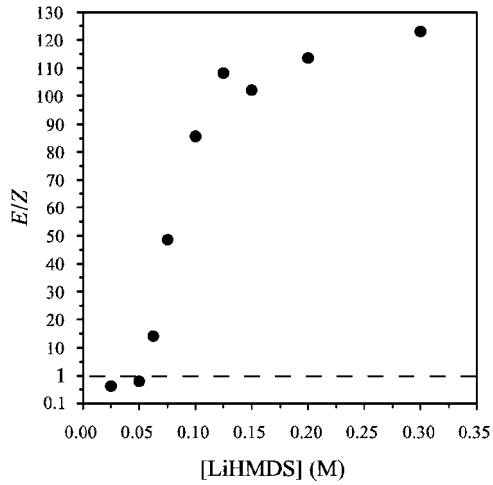
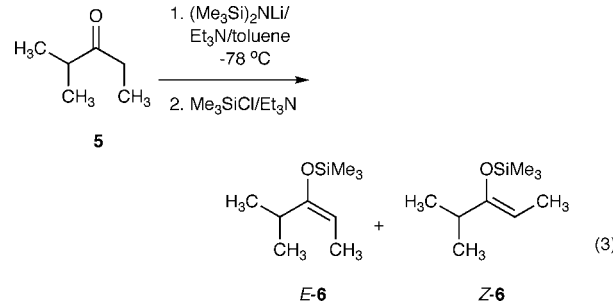



***Figure 1.*** *E*/*Z* selectivity (*E*-**6**:*Z*-**6**, eq 3) versus molarity (M) of LiHMDS in samples containing 0.10 M ketone **5** and 1.2 M excess $Et_3N$ in toluene at −78 °C.[16]

established protocols (eq 3).[9]The proportion of LiHMDS to ketone proves to be the key determinant of stereochemistry (Figure 1). At low base loadings the enolization shows a modest *Z* selectivity akin to that observed for LiHMDS/THF mixtures.[10–12]

The *E* selectivity rises markedly with increasing quantities of LiHMDS, approaching 110:1 at ≥2.0 equiv of LiHMDS per ketone.




The dependencies of the E/Z selectivities on the equivalents of LiHMDS could be construed as evidence of intervening lithium enolate/LiHMDS mixed aggregates in a kinetically controlled enolization.[9,13–15] It is mathematically impossible, however, for a 100:1 selectivity at 50% conversion (2.0 equiv of base) to be reversed to a 1:2 selectivity at full conversion (1.0 equiv of base) *without* an intervening equilibration. Indeed, when a reaction mixture resulting from a highly *E*-selective enolization of ketone **5** is subsequently treated with cyclohexyl ethyl ketone as a surrogate to consume the remaining LiHMDS (eq 4), the *E* selectivity in the enolization of **5** is lost. Under no circumstance, however, is a *regiochemical* equilibration observed.

A limited survey of hindered trialkylamines and dialkyl ethers in toluene as the cosolvent afforded the *E*/*Z* selectivities listed in Table 1. LiHMDS/$Et_3N$ affords the highest selectivities.[11] The selectivity reversal caused by decreasing the THF concentrations was noted by Xie and Wielgosh.[12]

The generality of the *E*-selective enolization by LiHMDS/$Et_3N$ was established by surveying the enolizations summarized in Table 2. Results derived from LiHMDS/THF are included for comparison. Although the selectivities were not optimized

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(16) The concentration of LiHMDS, although expressed in units of molarity, refers to the concentration of the monomer unit (normality). Concentrations of the $Et_3N$ refer to the concentrations of the free (uncomplexed) amine rather than to the total unless stated otherwise.

***Table 1.*** Solvent-Dependent *E*/*Z* Selectivities Resulting from the Enolization of Ketone **5** (eq 3)[a]

| solvent, S | *E*-**6**:*Z*-**6** |
|---|---|
| $Et_3N$ | 110:1 |
| $Me_2NEt$ | 90:1 |
| $(i\text{-Pr})_2NEt$ | 40:1 |
| $i\text{-Bu}_3N$ | 60:1 |
| THF (0.5 M) | 13:1 |
| THF (10 M) | 1:13 |
| $Me_4THF$[b] | 40:1 |
| TMEDA | 30:1 |

[a] [**5**] = 0.050 M; [LiHMDS] = 0.15 M; [S] = 1.5 M in toluene; −78 °C. [b] $Me_4THF$ = 2,2,5,5-tetramethyltetrahydrofuran (1.5 M in toluene).

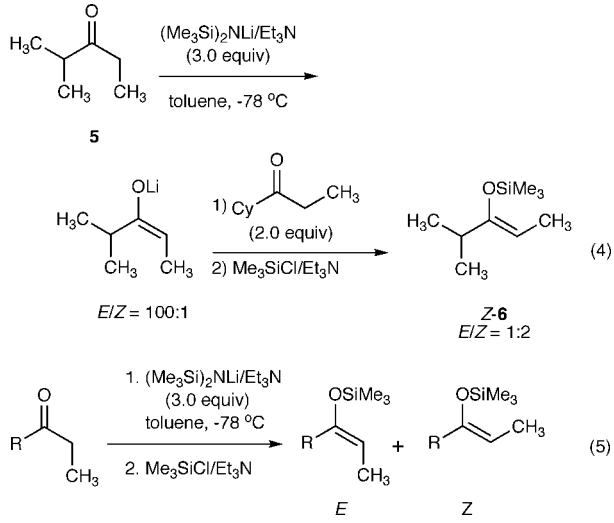



***Table 2.*** Solvent-Dependent *E*/*Z* Selectivities[11] for Enolization by LiHMDS (eq 5)[a]

| R | E/Z selectivity $Et_3N$/toluene[b] | E/Z selectivity THF[c] |
|---|---|---|
| Et | 140:1 | 1:4[11a] |
| *i*-Pr (**3**) | 100:1 | 1:14[11a] |
| Cy | 80:1 | 1:30[10] |
| Ph | 3.5:1 | 1:>100[11a] |
| $CH_3O$ | 22:1 | 1:12[11b,k] |
|  | 50:1 | 1:8[11c,d] |



[a] [ketone] = 0.05 M; [LiHMDS] = 0.15 M. [b] [$Et_3N$] = 1.5 M in toluene; −78 °C. [c] Neat THF.

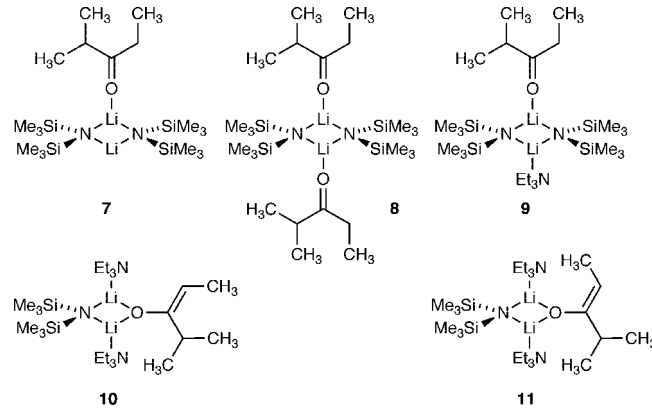
for each case, we suspect there is only limited room for improvement.

**Aggregate Structures.** Adding ketone **5** to LiHMDS in either toluene or $Et_3N$/toluene mixtures at −78 °C and monitoring with in situ IR spectroscopy reveals that **5** (1714 $cm^{-1}$) is quantitatively converted to LiHMDS-ketone complexes (1698 $cm^{-1}$).[17,18] (The less reactive 2,4,4-trideuterated ketone, **5**-$d_3$,[19] was used to monitor structures and rates in some instances.) Dimers bearing one or two complexed ketones (**7** and **8**) are readily characterized with $^6Li$ and $^{15}N$ NMR spectroscopy[1,20,21] using [$^6Li$,$^{15}N$]LiHMDS[22] (Table 3). Putative LiHMDS-ketone complex **9** was too reactive to characterize but is almost certainly isostructural to the closely related complex characterized previously.[3b] Enolization of **5** with 3.0 equiv of LiHMDS/$Et_3N$ at −78 °C affords mixed dimer **10** (Table 3). If the enolization is carried out under poorly selective conditions at 0 °C using 3.0 equiv of [$^6Li$,$^{15}N$]LiHMDS, both mixed dimer **10** and the corresponding *Z*-enolate-derived mixed dimer **11** are observed.[15b]

***Table 3.*** NMR Spectroscopic Data[a]

| compd | $\delta$ $^6Li$ (mult, $J_{LiN}$) | $\delta$ $^{15}N$ (mult, $J_{LiN}$) |
|---|---|---|
| **7** | 1.00 (*t*, 4.0) | 41.4 (*q*, 3.8) |
| | 1.48 (*t*, 3.1) | |
| **8** | 1.85 (*t*, 3.3) | 38.7 (*q*, 3.4) |
| **10** | 0.48 (*d*, 3.4) | 40.34 (*q*, 3.4) |
| **11** | 0.51 (d, 3.5) | 40.31 (m, −) |

[a] Spectra were recorded in 0.10 M [$^6Li$,$^{15}N$]LiHMDS in toluene containing $Et_3N$. Coupling constants were measured after resolution enhancement and reported in hertz. Multiplicities are denoted as follows: *d* = doublet, *t* = triplet, and *q* = quintet. The chemical shifts are reported relative to 0.30 M $^6LiCl$/MeOH at −90 °C (0.0 ppm) and neat $Me_2NEt$ at −90 °C (25.7 ppm).




**Mechanism of Enolization.** The structural similarities of ketones **1** and **5** certainly suggest a common mechanism. Indeed, rate studies using well-documented protocols[3,21] confirm the mechanistic parallels as follows. Pseudo-first-order conditions were established by maintaining low concentrations of ketone **5** (0.004−0.010 M) and high, yet adjustable, concentrations of recrystallized[22] LiHMDS (0.05−0.40 M) and $Et_3N$ (0.15−2.40 M), with toluene as the cosolvent. Monitoring the loss of LiHMDS-ketone complex **9** with in situ IR spectroscopy (1698 $cm^{-1}$) shows clean first-order decays to ≥5 half-lives. The resulting pseudo-first-order rate constants ($k_{obsd}$) are independent of ketone concentration (0.004−0.040 M). Re-establishing the IR baseline and monitoring a second aliquot of ketone reveals no significant change in the rate constant, showing that

(17) For leading references and recent examples of detectable organolithium-substrate pre-complexation, see:(a) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1. (b) Andersen, D. R.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 7553. (c) Pippel, D. J.; Weisenberger, G. A.; Faibish, N. C.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 4919. (d) Bertini-Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(18) For a general discussion of ketone-lithium complexation and related ketone-Lewis acid complexation, see: Shambayati, S.; Schreiber, S. L. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon: New York, 1991; Vol. 1, p 298.

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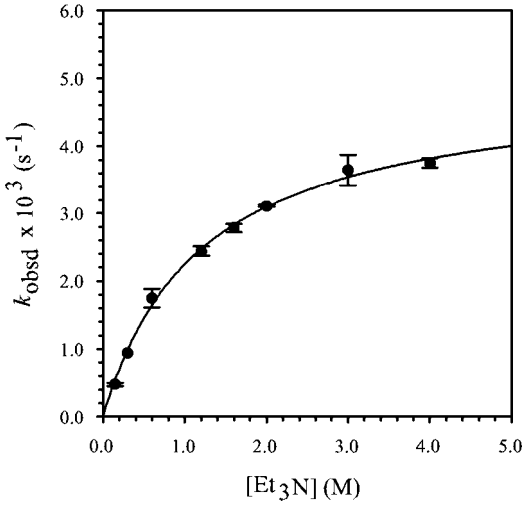



***Figure 2.*** Plot of $k_{obsd}$ versus [$Et_3N$] in toluene cosolvent for the enolization of **5**-$d_3$ (0.005 M) by LiHMDS (0.10 M) at −78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = a[Et_3N]/(1 + b[Et_3N])$, where $a = 4.0 \pm 0.1$, $b = 8.2 \pm 0.6 \times 10^{-1}$.

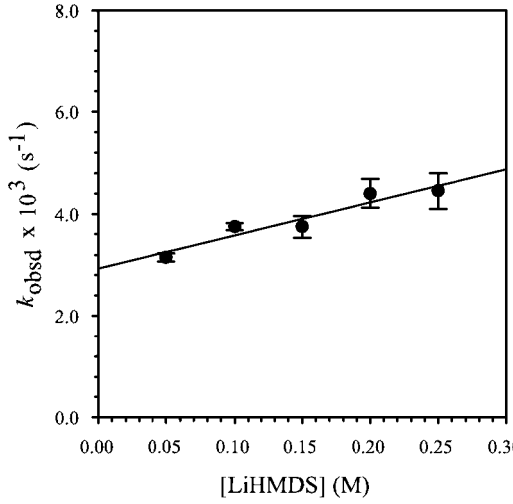



***Figure 3.*** Plot of $k_{obsd}$ versus [LiHMDS] in 4.0 M $Et_3N$/toluene solution for the enolization of **5**-$d_3$ (0.005 M) by LiHMDS at −78 °C. The curve depicts an unweighted least-squares fit to $k_{obsd} = a[\text{LiHMDS}] + b$, where $a = 5 \pm 1$, $b = 3.0 \pm 0.1$.

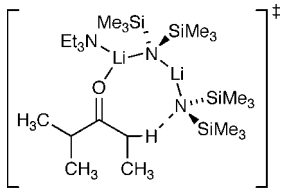
conversion-dependent autocatalysis or autoinhibition are unimportant under these conditions.[23,24] Comparison of **5** and **5**-$d_3$ provided a large kinetic isotope effect ($k_H/k_D > 10$),[25] confirming rate-limiting proton transfer.[26,27]

A plot of $k_{obsd}$ versus [$Et_3N$] shows saturation kinetics (Figure 2).[3b,24,28] At low $Et_3N$ concentrations, unsolvated complex **7** is the dominant form (see above), affording a first-order [$Et_3N$] dependence. At high concentrations of $Et_3N$, fully solvated complex **9** becomes the dominant form, and a zeroth-order $Et_3N$ dependence results. A plot of $k_{obsd}$ versus [LiHMDS] at elevated $Et_3N$ concentration reveals a zeroth-order dependence (Figure 3). (The slight upward drift results from residual saturation kinetics affording complex **9**).[3a] The idealized rate law (eq 6) is consistent with the generic mechanism described by eqs 7 and 8 and monosolvated dimer-based transition structure **12**.[29]

$$-\text{d[complex]}_{total}/\text{dt} + (k' K_{eq}[Et_3N][\text{complex}]_{total})/(1 + K_{eq}[Et_3N]) \quad \text{such that } [\text{complex}]_{total} = [7] + [9] \tag{6}$$

$$[\{(Me_3Si)_2NLi\}_2(\text{ketone})] + Et_3N \underset{(7)}{\overset{K_{eq}}{\rightleftharpoons}} \underset{(9)}{[\{Me_3Si)_2Nli\}_2(Et_3N)(\text{ketone})} \tag{7}$$

$$[\{(Me_3Si)_2NLi\}_2(Et_3N)(\text{ketone})] \underset{(9)}{\overset{k'}{\longrightarrow}} \underset{(12)}{[\{Me_3Si)_2NLi\}_2(Et_3N)(\text{ketone})]^{\ddagger}} \tag{8}$$



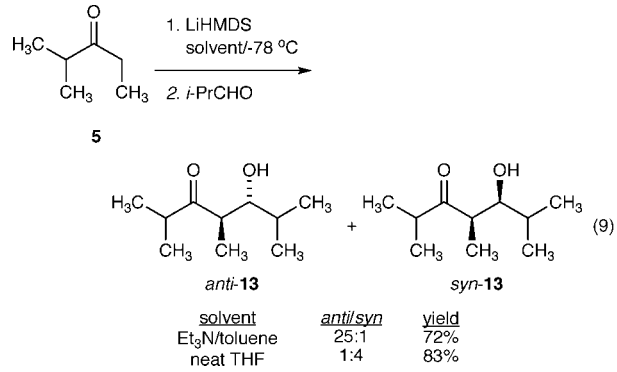

**12**

**Aldol Condensation.** We examined the reactivities and selectivities of enolates bearing poorly coordinating and sterically demanding $Et_3N$ ligands and compared them with those observed in neat THF. For example, eq 9 illustrates a sequential enolization with LiHMDS (3.0 equiv) in $Et_3N$/toluene followed by an aldol condensation with isobutyraldehyde affording primarily *anti*-**13** (anti/syn = 25:1).[30] By contrast, the analogous reaction in neat THF shows decidedly inferior stereocontrol with opposite selectivity. Several additional aldol condensations are included as Supporting Information.

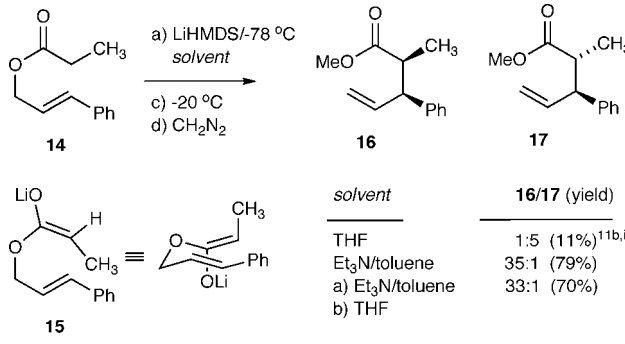
By carrying out the enolizations in different solvents, we are comparing the chemistry of enolates that differ in both stereochemistry and coordinating ligand. To isolate the influence of solvent on only the aldol condensation, we enolized **5** with LiHMDS/$Et_3N$ and subsequently added THF prior to the addition of *i*-PrCHO; the anti/syn selectivity drops to 18:1. Thus, there is no apparent advantage offered by the THF-solvated enolate. Nonetheless, we believe that such strategies can be important (vide infra).

**Ireland−Claisen Rearrangement.** We examined a lithium enolate variant of the Ireland−Claisen rearrangement[7,11b,31] to

(23) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624. (b) Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 2459. (c) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1984**, *107*, 1810. (d) Thompson, A.; Corley, E. G.; Huntington, M. F.; Grabowski, E. J. J.; Remenar, J. F.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 2028.
(24) Depue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524.
(25) The undeuterated ketone reacted so quickly at −78 °C that only a lower limit on the measured isotope effect is warranted.
(26) Isotope effects for LiHMDS-mediated ketone enolizations have been measured previously. (a) Held, G.; Xie, L. F. *Microchem. J.* **1997**, *55*, 261. (b) Xie, L. F.; Saunders, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 3123.
(27) The regioselectivity indicated in eq 1 was shown to be >20:1 by trapping with $Me_3SiCl/Et_3N$ mixtures and comparing the crude product with authentic material by GC.[26]
(28) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995; pp 86−90. Dunford, H. B. *J. Chem. Educ.* **1984**, *61*, 129.
(29) Mordini, A.; Rayana, E. B.; Margot, C.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2401. For a bibliography of lithium amide open dimers, see: Ramirez, A.; Sun, X.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 10326.
(30) (a) Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (c) Van Horn, D. E.; Masamune, S. *Tetrahedron Lett.* **1979**, 2229.
(31) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.




compare selectivities *and* reactivities of THF- and $Et_3N$-solvated enolates. Enolization of **14** using LiHMDS (3.0 equiv) and $Et_3N$ (10 equiv per lithium) in toluene at −78 °C affords an estimated 20:1 preference for enolate **15** (see Table 2, R = OMe). Claisen rearrangement of **15** at −20 °C affords a 35:1 ratio of **16**[31] and **17**[31] in 79% isolated yield. Addition of 10 equiv of THF (per lithium) subsequent to enolization in $Et_3N$/toluene affords a comparable 33:1 selectivity in 70% yield (albeit much more slowly; vide infra). Curiously, the standard protocol−enolization *and* rearrangement in neat THF−proceeds in 11% yield. The low yields using LiHMDS/THF could stem from either a poor enolization or a poor rearrangement from the *Z* isomer as noted by Ireland in a similar silyl Claisen.[11i]




Qualitative rate studies of the rearrangement are quite interesting. In situ IR spectroscopy revealed the loss of the $Et_3N$-solvated ester enolate **15** (1675 and 1659 $cm^{-1}$) and formation of carboxylate absorbances (1610, 1600, 1582, and 1424 $cm^{-1}$).[32] A sigmoidal behavior (Figure 4, curve A) is indicative of autocatalysis[24,33] occurring as the enolate is replaced with carboxylates, presumably within aggregates. By contrast, addition of 10 equiv of THF (per lithium) subsequent to enolization affords a THF-solvated enolate, as evidenced by the replacement of absorbances at 1675 and 1659 $cm^{-1}$ with an absorbance at 1657 $cm^{-1}$.[34] Of special importance, rearrangement in $Et_3N$/toluene (Figure 4, curve B) proceeds approximately 20 times *faster* than with added THF. *The $Et_3N$ solvated enolate is substantially more reactive.*

## Discussion

We previously showed that LiHMDS/$Et_3N$-mediated enolizations are very fast compared to LiHMDS/THF and traced

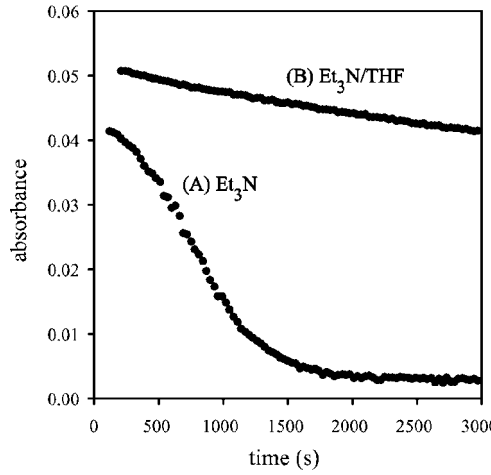



***Figure 4.*** IR absorbance of enolate **15** versus time in (A) 1.5 M $Et_3N$/toluene and (B) 1.5 M $Et_3N$/1.5 M THF/toluene.

the accelerations to a dimer-based mechanism.[3b,29] We hasten to add that the high rates are only observed using ≥2.0 equiv of LiHMDS. (Equimolar LiHMDS and ketone afford an inert bis-ketone solvated LiHMDS dimer.) Of course, such accelerations are notable, but the procedure may also be cost-effective. LiHMDS is now used routinely on large scales for complex drug synthesis.[35,36] Using $Et_3N$/hydrocarbon mixtures instead of THF could offer considerable savings.[10,37]

***E*-Selective Enolizations.** Acting on a hunch, we found LiHMDS/$Et_3N$-mediated enolizations of *acyclic* ketones are very fast *and* afford high *E*/*Z* selectivities (Tables 1 and 2). Excess (≥2.0 equiv) LiHMDS is required to maintain high rates and selectivities. Enolizations of ketone **5** with only 1.0 equiv of LiHMDS/$Et_3N$ suffer from *E*/*Z* equilibration. Overall, the procedure is more selective and more convenient than that using LiTMP/LiBr mixtures, which has afforded lithium enolates with the highest *E*-selectivity (up to 50:1) reported to date.[9]

**Mechanism of Enolization.** NMR spectroscopic studies of the enolization of ketone **5** using 3.0 equiv of LiHMDS revealed lithium enolate-LiHMDS mixed dimer **10**. The loss in stereoselectivity when <2.0 equiv LiHMDS/$Et_3N$ was used derived

(32) *Spectrometric Identification of Organic Compounds*; Silverstein, R. M., Webster, F. X. Eds.; John Wiley & Sons, Inc.: New York, 1998; p 97.

(33) (a) Nudelman, N. S.; Velurtas, S.; Grela, M. A. *J. Phys. Org. Chem.* **2003**, *16*, 669. (b) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265. (c) Alberts, A. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1990**, 453. (d) Xie, L.; Saunders, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 3123.

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(36) For selected examples in which LiHMDS is used on large scale, see: (a) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L., Jr.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119. (b) Boys, M. L.; Cain-Janicki, K. J.; Doubleday, W. W.; Farid, P. N.; Kar, M.; Nugent, S. T.; Behling, J. R.; Pilipauskas, D. R. *Org. Process Res. Dev.* **1997**, *1*, 233. (c) Ragan, J. A.; Murry, J. A.; Castaldi, M. J.; Conrad, A. K.; Jones, B. P.; Li, B.; Makowski, T. W.; McDermott, R.; Sitter, B. J.; White, T. D.; Young, G. R. *Org. Process Res. Dev.* **2001**, *5*, 498. (d) Rico, J. G. *Tetrahedron Lett.* **1994**, *35*, 6599. (e) DeMattei, J. A.; Leanna, M. R.; Li, W.; Nichols, P. J.; Rasmussen, M. W.; Morton, H. E. *J. Org. Chem.* **2001**, *66*, 3330.

(37) Rutherford, J. L.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 199.

from a facile equilibration and consequent formation of mixed dimers **10** and **11**. There is no affiliated regiochemical equilibration.

Rate studies of the enolization under pseudo-first-order conditions (a large excess of LiHMDS) confirmed that a dimer-based enolization—transition structure **12**—is the source of the high selectivities. Previous semiempirical computational studies of enolizations by amine-solvated lithium amides failed to predict the observed high selectivities.[38]

**Aldol Condensation.** The facile enolizations in $Et_3N$/toluene allowed us to examine the reactivity of $Et_3N$-solvated enolates and to compare them with their THF-solvated counterparts. We first examined the aldol condensation—the most prevalent application of *E*-selective enolizations—to ascertain whether the high enolization selectivities could be translated into high syn/anti selectivities. The aldol condensations are generally anti selective using the LiHMDS/$Et_3N$-based protocol (eq 9 and Supporting Information). We examined whether the selectivity might improve if THF was added before the addition of the aldehyde. This sequence is tantamount to doing the enolization in $Et_3N$ and the aldol condensation in THF. The selectivities did not improve.

**Claisen Rearrangement.** We investigated a lithium enolate variant of the Ireland-Claisen rearrangement shown in eq 10.[7] The low yields using LiHMDS/THF were previously observed by Ireland on a closely related case and were attributed to the formation of an unreactive stereoisomer. We concur with this notion. The improved selectivity toward enolate **15** expected for LDA/THF could, in principle, solve the problem, but we obtained complex mixtures that probably derived from allylic metalation of, or 1,2-addition to, the cinnamyl ether moiety.[39] By contrast, LiHMDS/$Et_3N$-mediated enolization affords **15** rapidly and selectively. Subsequent rearrangement proceeded in good yield and exceptional selectivity.

A distinct benefit of the Ireland—Claisen rearrangement is that it is slow enough to allow us to readily monitor reaction rates. We found that $Et_3N$-solvated enolates rearrange approximately 20 times faster than the analogous THF solvates, and there is evidence of autocatalysis.[33] We are likely to examine Ireland—Claisen rearrangements in more detail later.

**On the Role of Solvent Mixtures.** There are *very* few ligands—probably far fewer than most organic chemists realize—that can displace THF from lithium.[1,20] When an enolate is generated in THF, the subsequent reaction is necessarily THF dependent in most instances. By contrast, highly hindered trialkylamines are substitutionally labile, potentially allowing many ligands to coordinate and influence subsequent reactions. Although substituting THF for $Et_3N$ in a few instances described herein did not offer obvious benefits, the principle is an important one. *Organolithium intermediates generated in poorly coordinating solvents are especially well suited for subsequent ligand substitutions*. If $Et_3N$ and the electrophile are incompatible (alkyl halides, for example), highly hindered dialkylethers may suffice.[3d]

## Conclusion

LiHMDS/$Et_3N$ offers a particularly convenient, cost-effective protocol for generating lithium enolates with the highest *E* selectivity reported to date. The $Et_3N$-solvated enolates are also provocative species. As expected, the high *E* selectivities can be translated into relatively highly stereoselective aldol condensations and Ireland—Claisen rearrangements. Moreover, the potential importance of amine-solvated lithium enolates is underscored by a marked (20-fold) acceleration of the Ireland—Claisen rearrangement when compared with the rates observed using THF-solvated variant. One might ask why, if $Et_3N$ elicits such favorable reactivities, have simple (monodentate) trialkylamines played such a minor role in organolithium chemistry?[5,6] The answer may be simple. $Et_3N$ is a poorly coordinating ligand that cannot compete with ethereal solvents for coordination to lithium: $Et_3N$ *requires* hydrocarbons as cosolvents to be effective. We suggest that trialkylamine/hydrocarbon mixtures are worthy of more careful consideration in other applications within organolithium chemistry.

## Experimental Section

**Reagents and Solvents.** Coordinating ligands and toluene were distilled by vacuum transfer from blue or purple solutions containing sodium benzophenone ketyl. The toluene still contained 1% tetraglyme to dissolve the ketyl. $^6$Li metal (95.5% enriched) was obtained from Oak Ridge National Laboratory (Oak Ridge, TN). LiHMDS,[40] [$^6$Li]LiHMDS, and [$^6$Li,$^{15}$N]LiHMDS were prepared and purified as described previously.[22] Ketone **5**-$d_3$ was prepared as described previously.[19] Air- and moisture-sensitive materials were manipulated under argon or nitrogen using standard glovebox, vacuum line, and syringe techniques.

**NMR Spectroscopic Analyses.** Samples were prepared, and the $^6$Li and $^{15}$N NMR spectra were recorded as described elsewhere.[2]

**IR Spectroscopic Analyses.** Spectra were recorded with an in situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe optimized for sensitivity. The spectra were acquired in 16 scans (30-s intervals) at a gain of 1 and a resolution of 4 or 8. The probe was inserted through a nylon adapter and O-ring seal into an oven-dried, cylindrical flask fitted with a magnetic stir bar and T-joint. The T-joint was capped with a septum for injections and an argon line. After evacuation under full vacuum and flushing with argon, the flask was charged with the reagents via syringe.

**Representative Enolization.** A 5 mL serum vial was charged with a solution of LiHMDS (50 mg, 0.30 mmol) in $Et_3N$ (420 $\mu$L, 3.0 mmol) and toluene (1.53 mL) and cooled to −78 °C. Ketone **5** (12 $\mu$L, 0.10 mmol) in toluene (38 $\mu$L) was added with stirring. After 20 min, the reaction was quenched with 180 $\mu$L of a 4:1 solution of $Me_3SiCl/Et_3N$ (centrifuged free of solid $Et_3N$-HCl) in toluene (3.0 mL). After warming to RT, dilution with pentane, and quenching with cold aqueous $NaHCO_3$, the solution was subjected to a standard aqueous workup. The crude enol silyl ethers *E*-**6** and *Z*-**6** were analyzed by GC as described previously.[9]

**Representative Aldol Condensation.** The enolate solution prepared as described above was quenched with isobutyraldehyde (27 $\mu$L, 0.30 mmol). After an additional 10 min at −78 °C and quenching with aqueous $NH_4Cl$, a standard aqueous workup afforded a crude mixture of adducts *anti*-**13** and *syn*-**13** in 25:1 ratio as shown by GC. Flash chromatography afforded pure *anti*-**13** in 72% yield as shown by comparison with previously reported spectroscopic data.[30]

**Ireland—Claisen Rearrangement.** A solution of enolate in $Et_3N$ (1.5 M)/toluene was prepared at −78 °C as described above.[41] The sample was slowly warmed to RT to allow the rearrangement to proceed. After 10 min at RT, the reaction mixture was poured into 10 mL of 5% aqueous NaOH and washed with ether. The aqueous layer was cooled to 0 °C and acidified with concentrated HCl, and

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(40) LiHMDS dimers solvated by hindered ethers were shown to enolize ketone **1** via a dimer-based mechanism analogous to **3**.[3d]
(41) LiHMDS/$Et_3N$ mixtures were used inadvertently by Murai and coworkers when they carried out LiHMDS/toluene-mediated enolizations with a $Et_3N/Me_2SiCl_2$ in situ trap.[6]

the carboxylic acid was extracted with ether. The carboxylic acid was converted to its methyl ester by adding distilled $CH_2N_2$[42] at 0 °C until a yellow color persisted. The resulting methyl esters were analyzed using GC to show a 35:1 mixture of **16**[31] and **17**.[31] Flash chromatography afforded a 79% combined yield.

**Kinetics.** Rate constants were determined using a standard protocol exemplified as follows: The IR cell described above was charged with a solution of LiHMDS (167 mg, 1.00 mmol) in $Et_3N$ (2.09 mL, 1.5 M) and toluene (7.74 mL) and cooled to −78 °C. After recording a background spectrum, ketone **5** (50 $\mu$L, 0.050 mmol, 0.005 M final concentration) was added neat with stirring. IR spectra were recorded over 5 half-lives. To account for mixing and temperature equilibration, spectra recorded in the first 1.0 min were discarded. The rate constant was determined using an unweighted, nonlinear least-squares fit to the function $f(x) = a\,e^{bx}$.

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**Supporting Information Available:** NMR spectra and rate data. This material is available free of charge via the Internet at http://pubs.acs.org.

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