# Highly Stereoselective Kinetic Enolate Formation: Steric vs Electronic Effects

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The utility of enolates has been well exemplified by their applications in the synthesis of many biologically important natural products via aldol condensation reactions.[1] Since specific biological activities of many natural products are regulated by their stereochemistry, excellent stereoselection during their synthesis is highly demanded.[2] Previous studies have shown that kinetic aldol diastereoselectivity depends to a large degree on the geometry (cis or trans) of preformed enolates.[3] One important method of forming enolates is to deprotonate a carbonyl compound with a base under either kinetic or thermodynamic conditions. The more desirable kinetic deprotonation usually results in regioselectively less substituted enolates from unsymmetric ketones. Variables that affect such regioselectivity have been previously reviewed.[4] However, factors governing *stereoselectivity* of kinetic enolate formation are less well understood. In this paper, we report the effects of the steric and eletronic nature of lithium amide bases on the stereoselectivity of kinetic enolate formation.

Among many lithium amides used in kinetic enolate formation, the most popular ones include lithium diisopropylamide (LDA), lithium tetramethylpiperidide (LTMP), and lithium hexamethyldisilazide (LHMDS). Through their elegant work with ethyl ketones, Heathcock and co-workers have reported the stereoselectivity of kinetic enolization of many ketones with these bases.[3a] Other researchers have studied related systems,[5] employing different reaction conditions that result in either thermodynamic or kinetic control. While LTMP was shown to give slightly better kinetic selectivity in favor of the *E* (or *trans*) enolate than LDA, LHMDS, a base with comparable steric hindrance to both LDA and LTMP, was reported to produce significantly more *Z* (or *cis*) enolate. Use of strong cation solvating agents such as hexamethylphosphoramide (HMPA) in enolization also led to a substantial increase in the *Z* preference.[5b,d,6] It is not clear whether such enhanced *Z* preference is a result of thermodynamic or kinetic deprotonation and, if the latter, how the stereoselectivity is controlled by the nature of active base species. This has prompted us to investigate in more detail the relative importance of steric vs electronic factors in the process of kinetic enolization. We set out to study enolate selectivity from six ketones (**1a**−**f**) in THF by four lithium amide bases: lithium *N*-isopropyl(trimethylsilyl)amide (**2**), lithium *N*-*tert*-butyl(trimethylsilyl)amide (**3**), lithium *N*-isopropylanilide (**4**), and lithium *N*-(trimethylsilyl)anilide (**5**). Our results suggest that excellent purity of *E*- or *Z*-enolate can be selectively achieved by modifying the steric and electronic nature of the bases.

## Results and Discussion

Six acyclic ketones were subject to kinetic enolization in THF with bases **2**−**5**, which were prepared by treating their corresponding amines[7] with *n*-butyllithium. The enolates formed were quenched with chlorotrimethylsilane to give trimethylsilyl enol ethers, which were then analyzed on GC and $^1$H NMR.[8] The resulting *E*/*Z* ratios are summarized in Table 1. The *E*/*Z* ratios previously reported for LDA, LTMP, and LHMDS are also included for comparisons.

We tested the temperature dependence of enolate selectivity for 3-pentanone (**1a**) by each base in order to find optimum condition for maximum stereoselectivity. It is clear from Table 1 that the *E*/*Z* ratios given by **2** and **4** show negligible variation with temperatures ranging from 23 to −78 °C, but those by **3** and **5** are highly temperature dependent. It is most interesting to note that **3** gave the best *E* selectivity at *room temperature* (entries 7−9 and 35−37), while **5** afforded outstanding *Z* selectivity at −78 °C (entries 10−12). This striking preference for the *Z*-enolate exhibited by **5** will be discussed later in more detail. Comparison of the data in Table 1 also indicates that both **2** and **4** gave similar *E*/*Z* selectivity to that of LDA for all ketones studied. This can be rationalized in view of the transition state model proposed by Ireland and others (Scheme 1).[6,9] The cyclic chairlike transition state involves a concerted proton transfer from the carbonyl compound to the base and the lithium cation coordination to the oxygen. The amount of *E*- and *Z*-enolates is determined by the energy difference between the two competing transition states $A^‡$ and $B^‡$ that lead to the *E*- and *Z*-enolates, respectively. The stability of the two transition states is, in turn, determined by both steric and electronic factors within the structures. Due to the comparable steric hindrance[10] of an isopropyl, a phenyl, and a trimethylsilyl group, the

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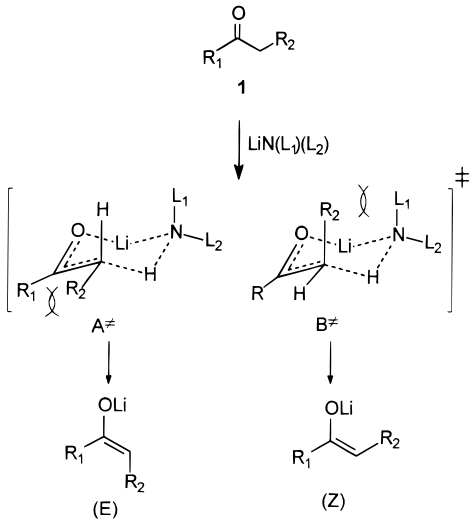
**Table 1. Stereoselectivity of Kinetic Enolate Formation: Effects of Steric and Electronic Nature of Lithium Amide Bases[a]**

| entry | ketones | condns | *E*/*Z* | entry | ketones | condns | *E*/*Z* |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | LDA, −70 °C | 70:30[b] | 21 | **1b** | **5**, −78 °C | 5:95[c] |
| | | | | 22 | **1c** | LDA | <2:98[b] |
| 2 | **1a** | LTMP, −70 °C | 80:20[b] | 23 | **1c** | LTMP | <2:98[b] |
| | | | | 24 | **1c** | LHMDS, −70 °C | <2:98[b] |
| 3 | **1a** | LHMDS, −70 °C | 34:66[b] | | | | |
| | | | | 25 | **1c** | **3**, 23 °C | 11:89 |
| 4 | **1a** | **2**, −78 °C | 81:19 | 26 | **1c** | **4**, 0 °C | 2:98 |
| 5 | **1a** | **2**, 0 °C | 86:14 | 27 | **1c** | **5**, −78 °C | 0:100 |
| 6 | **1a** | **2**, 23 °C | 82:18 | 28 | **1d** | LDA, −70 °C | <2:98[b] |
| 7 | **1a** | **3**, −78 °C | 77:23 | | | | |
| 8 | **1a** | **3**, 0 °C | 92:8 | 29 | **1d** | LHMDS, −78 °C | <2:98[b] |
| 9 | **1a** | **3**, 23 °C | 94:6 | | | | |
| 10 | **1a** | **4,** −78 °C | 66:34 | 30 | **1d** | **2**, −78 °C | 2:98 |
| 11 | **1a** | **4,** 0 °C | 68:32 | 31 | **1d** | **3**, 23 °C | 48:52 |
| 12 | **1a** | **4,** 23 °C | 68:32 | 32 | **1d** | **5**, −78 °C | 0:100 |
| 13 | **1a** | **5,** −78 °C | 7:93 | 33 | **1e** | LDA, −60 °C | 87:13[d] |
| 14 | **1a** | **5,** 0 °C | 19:81 | | | | |
| 15 | **1a** | **5**, 23 °C | 23:77 | 34 | **1e** | **2**, −78 °C | 89:11[e] |
| 16 | **1b** | LDA, −70 °C | 40:60[b] | 35 | **1e** | **3**, −78 °C | 77:23[e] |
| | | | | 36 | **1e** | **3**, 0 °C | 90:10[e] |
| 17 | **1b** | LTMP, −70 °C | 68:32[b] | 37 | **1e** | **3**, 23 °C | 93:7[e] |
| | | | | 38 | **1e** | **4**, 0 °C | 80:20[e] |
| 18 | **1b** | LHMDS, −70 °C | 2:98[b] | 39 | **1e** | **5,** −78 °C | 10:90[e] |
| | | | | 40 | **1f** | **3**, 23 °C | 91:9 |
| 19 | **1b** | **3**, 23 °C | 94:6[c] | 41 | **1f** | **5**, −78 °C | 2:98 |
| 20 | **1b** | **4**, 0 °C | 42:58[c] | | | | |

[a] All results were obtained with a base-to-ketone ratio of 1.1:1. Increasing the ratio to 2:1 gave identical *E*/*Z* ratios within experimental error. [b] Reference 3a. [c] Less than 1% of the more substituted regioisomeric enolate was also obtained. [d] Reference 5b. [e] The combined yield of the *E*- and *Z*-enolates from methylene deprotonation is less than 16%. The major product derived from enolization at the methyl carbon accounts for 84−91% of the total enolates, as would be expected from a kinetic deprotonation.

**Scheme 1. Kinetic Enolate Formation: Ireland's Transition State Model**




**1a**: $R_1$=$CH_2CH_3$, $R_2$=$CH_3$
**1b**: $R_1$=$CH(CH_3)_2$, $R_2$=$CH_3$
**1c**: $R_1$=$C(CH_3)_3$, $R_2$=$CH_3$
**1d**: $R_1$=Ph, $R_2$=$CH_3$
**1e**: $R_1$=$CH_3$, $R_2$=$CH_2CH_3$
**1f**: $R_1$=$CH_2CH(CH_3)_2$, $R_2$=$CH(CH_3)_2$

competing steric interactions ($R_1 \leftrightarrow R_2$ and $R_2 \leftrightarrow L_1$) should be more or less the same for **2** ($L_1$ = *i*-Pr, $L_2$ = TMS), **4** ($L_1$ = *i*-Pr, $L_2$ = Ph), and LDA ($L_1 = L_2$ = *i*-Pr). As a result, comparable *E*/*Z* ratios are observed for all three bases. It is important to note that electronic nature (and basicity) of the nitrogen has changed as one *i*-Pr group in LDA is replaced by the electron-withdrawing TMS and Ph groups in **2** and **4,** respectively. Nevertheless, the steric effect remains predominant over the electronic effect.

From the transition state model in Scheme 1, one would expect a sterically more demanding $R_2 \leftrightarrow L_1$ interaction to destabilize the TS B‡ and lead to an increased *E* preference. This has indeed been generally supported by literature data. For example, the highly hindered amide base[11] lithium *tert*-butyl-*tert*-octylamide, has been reported to give predominantly the *E*-enolate. However, the preparation of this amide base and other bulky bases such as lithium di-*tert*-butylamide is rather difficult. On the other hand, **3** is a highly hindered base and can be readily prepared from commercially available *N*-*tert*-butyl(trimethylsilyl)amine. It is remarkable to note that the best *E*/*Z* selectivity can be achieved with **3** at *room temperature* (see entries 7−9 and 35−37). This finding is of great synthetic significance because most reported enolate forming reactions had to be carried out at 0 °C or lower to achieve better selectivity. Compared to the popular bases LDA and LTMP, **3** yields significantly enhanced *E* selectivity for all ketones studied. For example, it gave better than 90% (and as high as 94%) of *E*-enolate from ketones **1a**, **1b**, **1e**, and **1f** in THF at 23 °C. Even with a larger $R_1$ group, as in 1-phenyl-1-propanone (**1d**) and 2,2-dimethyl-3-pentanone (**1c**), **3** still afforded 48% and 11% of *E*-enolate, respectively, (entries 31 and 25) as compared to less than 2% *E*-enolate given by the other bases. The enhanced *E* selectivity is conceivably due to the severe $R_2 \leftrightarrow L_1$ interaction imposed by **3** in the transition state B‡, which compensates for the $R_1 \leftrightarrow R_2$ interaction in A‡. It is worthwhile noting that **3** was previously reported to give only slightly better *regioselectivity* than LDA when employed in the enolization of unsymmetric ketones.[12]

We now return to the remarkable reversed *Z* selectivity given by **5**. We undertook the study of this base to gain a better understanding of why *Z*-enolate is favored by lithium disilylamides (such as LHMDS) more than lithium dialkylamides (such as LDA). For all ketones studied, outstanding *Z* selectivity (greater than 90% in all cases, entries 13, 21, 27, 32, 39, and 41) was observed with **5**. The high *Z* selectivity displayed by **5** is of particular synthetic interest since previous *Z* selectivity was most commonly achieved through the use of a considerable amount of HMPA,[5b,d,6] a toxic and carcinogenic solvent additive.[13] Our experimental evidence strongly suggests that this *Z* preference afforded by **5** is a result of kinetic deprotonation rather than thermodynamic enolate equilibration. First, enolates were formed in quantitative yields and no ketones in excess could be detected in our reactions. Second, the less substituted enolates accounted for 84% of the total enolates produced from **1e** and 99% of the total enolates from **1b**, as expected from a kinetically controlled enolization. Third, we allowed the enolates from **1a** to equilibrate in the presence of excess ketone (**1a**) and found the thermodynamic *Z* selectivity (*E*/*Z* = 12:88)[14] to be *lower* than the kinetic *Z* selectivity given by **5**. If the deprotonation of

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(14) The equilibrium constant for **1a** enolates was measured in the presence of 20% excess ketone **1a**. The ratio is independent of the nature of bases used.

the ketones by **5** is under kinetic control, then a prominent question is, why did the change from LDA to base **5** (by replacing the *i*-Pr's with Ph and TMS groups) increase the *Z* selectivity so dramatically? From our earlier discussion, it is clear that the change from LDA to **2** (by replacing *one i*-Pr with a TMS group) or **4** (by replacing *one i*-Pr with a Ph group) caused only a small to negligible change in *E*/*Z* ratios. The intrinsic steric hindrance is thus nearly the same for bases **2**, **4,** and LDA. If a replacement of an *i*-Pr by a TMS or a Ph group caused negligible change in steric hindrance, then the intrinsic steric hindrance of base **5** is expected to be similar to **2**, **4**, and LDA. However, we believe that the replacement of both isopropyl groups in LDA with electron-withdrawing TMS or phenyl groups significantly reduced the electron density (and the basicity) on the nitrogen in **5**. As a result, the electrostatic interaction between the less basic nitrogen and the lithium ion and the proton in the transition state is much weaker, leading to a loose (or late) transition state. Consequently, the $R_2 \leftrightarrow L_1$ interaction is significantly weakened and the transition state $B^{\ddagger}$ leading to the *Z*-enolate is favored. The change in the electronic nature of the bases has thus become a dominant factor in the enolization by base **5**. Similarly, the previously reported *Z* selectivity given by lithium disilylamides such as LHMDS and lithium bis(diphenylmethyl)silylamide can be rationalized. It is interesting that the latter, with intrinsically more hindered diphenylmethyl groups, gave much better *Z* selectivity[5c] than LHMDS. This is consistent with the above rationale that electronic stabilization due to phenyl groups on the silicon further loosened the transition state in favor of $B^{\ddagger}$. Further experimental study of such electronic effect is now under progress.

In conclusion, we have reported highly stereoselective kinetic enolate formation employing lithium amide bases with different steric and electronic characteristics. Excellent *E or Z* stereoselectivity can be achieved with sterically hindered **3** or electronically dominated **5**. We conclude that enhanced *Z* selectivity is observed only when *both* alkyl groups in LDA are changed to electron-withdrawing groups (such as TMS or Ph). Both excellent *E* selectivity by lithium *N*-*tert*-butyl(trimethylsilyl)amide (**3**) at room temperature and *Z* selectivity by lithium *N*-(trimethylsilyl)anilide are of particular synthetic importance.

## Experimental Section

**General.** Glassware and syringe needles were dried at 140 °C overnight in an oven. Gastight syringes were dried in a desiccator under vacuum (≤0.1 Torr) for at least 1 h before use. The enolization experiments were carried out in Schlenk flasks under a nitrogen atmosphere. $^1$H NMR was obtained on a JEOL-GSX 270 MHz spectrometer with a superconducting magnet. The quantitative analysis of trimethylsilyl enol ethers was carried out on an HP-5890 series GC-MS with a 5791 mass detector and on the NMR.

**Solvent.** Aldrich 99.5% tetrahydrofuran was dried over Na/benzophenone under $N_2$ until a purple color persists and distilled immediately prior to use.

***n*-Butyllithium.** Aldrich 1.6 M *n*-butyllithium in hexane was titrated with reagent grade diphenylacetic acid for its exact concentration. In most cases the *n*-butyllithium concentration was found to be within 10% of what was labeled on the bottle.

**Ketones.** 3-Pentanone, 2-methyl-3-pentanone, and 2-pentanone (Aldrich) were distilled on a B/R Model 8T micro spinning band distillation system and dried over 3 Å molecular sieves. Aldrich propiophenone and 2,6-dimethyl-4-heptanone were dried over 3 Å molecular sieves and used without further purification. 2,2-Dimethyl-3-pentanone from Wiley Organics was dried over 3 Å molecular sieves before use. The identity and purity of all ketones were confirmed by $^1$H NMR to indicate no detectable amount of impurity or water.

***N*-*tert*-Butyl(trimethylsilyl)amine.** Aldrich 98% *N*-*tert*-butyl(trimethylsilyl)amine was dried over $CaH_2$ and distilled immediately prior to use.

***N*-Isopropylaniline.** TCI America 99+% *N*-isopropylaniline was dried over 3 Å molecular sieves in a nitrogen atmosphere and used without further purification. Its purity was checked with $^1$H NMR and GC−MS.

***N*-(Trimethylsilyl)aniline.** Pfaltz & Bauer 97% *N*-(trimethylsilyl)aniline from was dried over 3 Å molecular sieves in a nitrogen atmosphere and used without further purification. The purity was confirmed by both $^1$H NMR and GC−MS.

***N*-Isopropyl(trimethylsilyl)amine.** This compound was synthesized following a modified literature procedure.[7] A 1 L round-bottom flask was filled with 250 mL of dry diethyl ether and 120 g of isopropylamine (2.0 mol). The content was stirred by a mechanical stirrer and cooled to 0 °C. Then 82 g (0.76 mol) of chlorotrimethylsilane was added dropwise to the flask via a dropping funnel, and white precipitates of isopropylammonium chloride started to form. After the addition of chlorotrimethylsilane, the mixture was stirred for additional 20 min before being allowed to warm to room temperature and was subsequently refluxed for 1 h.

The reaction mixture was allowed to cool to room temperature after refluxing, and the ammonium salt was filtered away by suction filtration with a frit. The flask and the salt were washed twice with 100 mL of dry ether, and the ethereal solution was combined with the mother liquor. The ether solvent and isopropylamine were removed by fractional distillation, and 55 g of the product, *N*-isopropyl(trimethylsilyl)amine, was collected (55%). The product was further purified by distillation via a micro spinning band distillation system. bp 100−101 °C (lit.[7,15] bp 98 and 101 °C). $^1$H NMR ($CDCl_3$): $\delta$ (ppm from TMS) 0.05 (s, 9H), 0.13 (s, 1H, NH), 1.03 (d, 6H), 2.92−3.08 (m, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ (ppm from TMS) 0.4, 27.8, 43.0. The amine was dried over calcium hydride and distilled immediately before use.

The above nonaqueous workup is essential to preventing *N*-isopropyl(trimethylsilyl)amine from hydrolyzing. Over a time period of several weeks, it was found that *N*-isopropyl(trimethylsilyl)amine had hydrolyzed to give 3−5% of hexamethyldisiloxane, which was difficult to separate due to its boiling point being identical with that of the amine. Control experiments, however, have shown that the presence of 3−5% hexamethyldisiloxane in the amine has no effect on the enolate stereoselectivity.

**Trimethylsilyl Enol Ethers.** Two previously reported procedures[8] were used in the synthesis of authentic samples of trimethylsilyl enol ethers from our ketones. Lithium diisopropylamide in THF at 0 °C was used for preparing kinetically controlled trimethylsilyl enol ethers, while triethylamine in refluxing DMF was used for preparing the enol ethers under thermodynamic control. The product enol ethers were separated and collected on a preparative GC. Their $^1$H NMR spectra were compared to those reported in the literature and their structures assigned on the basis of the methods developed by other authors. The structure assignment was further validated using mass spectrometry on a GC−MS.

**General Procedure of Enolization. 2**−**5** were prepared by adding 1.1 mmol of *n*-butyllithium to a stirring solution of 1.2 mmol of the corresponding amines in 5 mL of dry THF at 0 °C under nitrogen. The solution was allowed to stir for 15 min. The solution was then kept at 0 °C and raised to room temperature or lowered to −78 °C, depending on the conditions desired. Ketone (1 mmol) was then slowly added by a gastight syringe, and the reaction was stirred for an additional 15 min before quenching the enolates with 1.2 mmol of freshly distilled chlorotrimethylsilane (over $CaH_2$). After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and poured into 10 mL of pentane in a small separatory funnel. The

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mixture was washed twice with 5 mL each of saturated sodium bicarbonate solution and once with brine solution, and the organic layer was dried over anhydrous magnesium sulfate. The solution was filtered and the product ratios determined by GC−MS. At least two individual experiments (normally three or four experiments) for each entry in Table 1 were run to ensure reproducible results. Usually two or three GC injections were made for each experimental run. To ensure kinetically controlled conditions, we also carried out the above reactions using a base/ketone molar ratio of 2:1. The *E*/*Z* ratios showed no difference from those obtained with a base/ketone ratio of 1.1:1.

**Control Experiments.** Two individual experiments were carried out for the enolization of 3-pentanone by LDA and LHMDS in THF at −78 °C, and the *E*/*Z* ratios obtained were shown to be identical with the literature results within experimental error. Another control experiment was carried out to investigate the effect of 3−5% of hexamethyldisiloxane on the product enolate ratio when lithium *N*-isopropyl(trimethylsilyl)-amide was used as the base. Thus lithium *N*-isopropyl(trimethylsilyl)amide was prepared in THF as described above. The solvent and hexamethyldisiloxane were then removed by applying a high vacuum. A white solid presumably due to lithium *N*-isopropyl(trimethylsilyl)amide was obtained. The desired amount of dry THF (5 mL in all experiments) was then added to dissolve the solid, and thereafter the procedure described in **General Procedure of Enolization** was followed. The product ratio was found to be, within experimental error, identical with that given by the same base when 3−5% of hexamethyldisiloxane was present. We conclude that the effect due to the presence of 3−5% of hexamethyldisiloxane is negligible.

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