# Diastereoselective Routes to a 1β-Methylcarbapenem Key Intermediate. Scope of Ate Complex Formation between Ester Enolates and Organoboranes and -alanes

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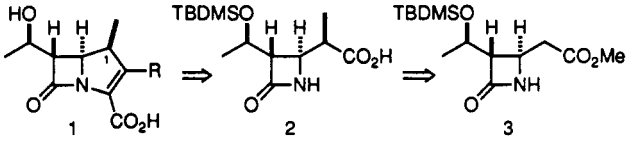
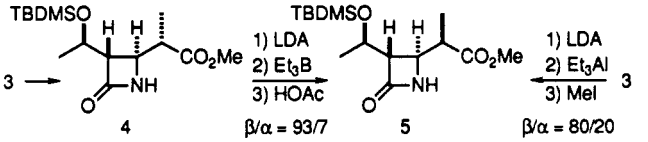
Two diastereoselective syntheses of the 1β-methylcarbapenem key intermediate **5** are described. Triethylborane-mediated epimerization of the α-methyl diastereomer **4** proceeds with high stereoselectivity to give pure **5** in good yield. Triethylaluminum-mediated methylation of the desmethyl analogue **3** gives **5** with modest stereoselectivity. Low-temperature FT-IR studies of reaction intermediates demonstrated that the epimerization proceeds via an ate complex, while the methylation does *not* involve ate complex formation. The scope of ate complex formation with trialkylboranes and trialkylalanes was thus more clearly defined, with the IR data providing a rough indication of the extent to which trialkylaluminum ate complexes are less stable than the trialkylborane analogs. The IR studies also provided useful information about enolate aggregation and the effects of cations, amines, HMPA and temperature on ate complex formation.

The 1β-methyl group of the pharmaceutically important carbapenems **1** imparts enhanced chemical and metabolic stability to the carbapenem skeleton.[2] This discovery has prompted a variety of stereoselective syntheses of **2**[3a–1,4–8] as well as later intermediates.[3m,6] Many of these syntheses proceed from 4-acetoxy-2-azetidinones.[3] Other methods for introduction of the β-methyl group include catalytic hydrogenation[3d,4] and L-Selectride (Aldrich)[5a] or borane[5b] reduction of olefinic precursors of **2**; reduction of a hexacarbonyldicobalt-stabilized propargyl cation;[6] β-lactam formation from components derived from either (*S*)- or (*R*)-methyl 3-hydroxy-2-methylpropionate;[7] and use of lactone intermediates.[8]




We report two diastereoselective routes to the methyl ester of **2** (intermediate **5**) which proceed from the readily available 2-azetidinon-4-ylacetic acid derivative **3**.[2a,9] One route proceeds from **3** via a $Et_3B$-mediated epimerization of the α-methyl diastereomer **4**.[10a] The other route involves direct, diastereoselective, $Et_3Al$-mediated methylation of **3**.[10b] Low-temperature FT-IR of imidate and ester enolate species contributed to the development and understanding of these reactions.




Our aim was to exploit the stereochemistry of the ester enolate of **4** simply by protonation from the presumably less hindered α-face.[11] Initially, lithium, zinc, and other

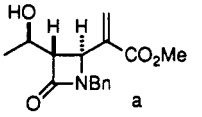
(1) Present Address: Lederle-Praxis Biologics, 4300 Oak Park, Sanford, NC 27330.

(2) (a) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29. Recent examples and leading references: (b) Meropenem (SM-7338): Sunagawa, M.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiotics* **1990**, *43*, 519. Neu, H. C.; Novelli, A.; Chin, N.-X. *Antimicrob. Agents Chemother.* **1989**, *33*, 1009. (c) LJC10,627: Ubukata, K.; Hikida, M.; Yoshida, M.; Nishiki, K.; Furukawa, Y.; Tashiro, K.; Konno, M.; Mitsuhashi, S. *Antimicrob. Agents Chemother.* **1990**, *34*, 994. (d) Kim, C. U.; Luh, B. Y.; Misco, P. F.; Hitchcock, M. J. M. *J. Med. Chem.* **1989**, *32*, 601.

(3) (a) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 4673. (b) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675. (c) Deziel, R.; Favreau, D. *Tetrahedron Lett.* **1986**, *27*, 5687. (d) Kim, C. U.; Luh, B.; Partyka, R. A. *Tetrahedron Lett.* **1987**, *28*, 507. (e) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.* **1985**, *26*, 4739. (f) Shirai, F.; Nakai, T. *J. Org. Chem.* **1987**, *52*, 5491. (g) Endo, M. *Can. J. Chem.* **1987**, *65*, 2140. (h) Ito, Y.; Terashima, S. *Tetrahedron Lett.* **1987**, *28*, 6625. Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801. (i) Martel, A.; Daris, J.-P.; Bachand, C.; Corbeil, J.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1537. (j) Sowin, T. J.; Meyers, A. I. *J. Org. Chem.* **1988**, *53*, 4154. (k) Shibata, T.; Sugimura, Y. *J. Antibiot.* **1989**, *42*, 374. (l) Uyeo, S.; Itani, H. *Tetrahedron Lett.* **1991**, *32*, 2143. (m) Deziel, R.; Endo, M. *Tetrahedron Lett.* **1988**, *29*, 61. Endo, M.; Droghini, R. *Can. J. Chem.* **1988**, *66*, 1400.

(4) (a) Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. G. *J. Org. Chem.* **1987**, *52*, 2563. (b) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. (c) Kitamura, M.; Nagai, K.; Hsiao, Y.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 549.

(5) (a) Iimore, T.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 2149. The key reaction for introduction of the β-methyl group involved L-Selectride reduction of a in *sec*-butanol/THF.




(b) Rao, A. V. R.; Gurjar, M. K.; Khare, V. B.; Ashok, B.; Deshmukh, M. N. *Tetrahedron Lett.* **1990**, *31*, 271.

(6) Prasad, J. S.; Liebeskind, L. S. *Tetrahedron Lett.* **1987**, *28*, 1857.

(7) (a) Kawabata, T.; Kimura, Y.; Ito, Y.; Terashima, S.; Sasaki, A.; Sunagawa, M. *Tetrahedron Lett.* **1986**, *27*, 6241; *Tetrahedron* **1988**, *44*, 2149. (b) Ihara, M.; Takahashi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 9; *Heterocycles* **1988**, *27*, 327; *J. Chem. Soc., Perkin Trans. I* **1989**, 2215. (c) Shirai, F.; Nakai, T. *Tetrahedron Lett.* **1988**, *29*, 6461. (d) Shirai, F.; Nakai, T. *Chem. Lett.* **1989**, 445. (e) Rao, A. V. R.; Gurjar, M. K.; Ashok, B. *Tetrahedron: Asymmetry* **1991**, *2*, 255.

(8) (a) Hatanaka, M. *Tetrahedron Lett.* **1987**, *28*, 83. (b) Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1988**, *53*, 2131; **1989**, *54*, 2103. (c) Bayles, R.; Flynn, A. P.; Galt, R. H. B.; Kirby, S.; Turner, R. W. *Tetrahedron Lett.* **1988**, *29*, 6345. (d) Kaga, H.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 113.

(9) (a) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783; **1981**, *22*, 913. (b) Melillo, D. G.; Cvetovich, R. J.; Ryan, K. M.; Sletzinger, M. *J. Org. Chem.* **1986**, *51*, 1498. (c) Loewe, M. F.; Cvetovich, R. J.; Hazen, G. G. *Tetrahedron Lett.* **1991**, *32*, 2299.

(10) Some of these results have been disclosed: (a) Bender, D. R.; Shinkai, I.; DeMarco, A. M.; McCauley, J. A. *U. S. Patent* 4,816,577, Mar 28, 1989. (b) Bender, D. R.; DeMarco, A. M.; Melillo, D. G.; Shinkai, I. *Eur. Pat. Appl.* EP364,033, 18 Apr 1990.

(11) Review of kinetic protonation of enolates: Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263. See also ref 32d.

0022-3263/92/1957-2411$03.00/0 

metal enolates were protonated with various acids. The resulting isomer ratios varied broadly, but selectivity for β-methyl isomer **5** was only modest at best.[12a] We then became aware of the highly facial selective L-Selectride reduction of an olefinic precursor of **2**.[5a] The selectivity of this reaction must result from diastereoselective protonation of the intermediate trialkylborane/enolate complex. We presumed that an analogous complex could be accessed via the lithium enolate of **4**, although the less hindered $Et_3B$ was required for this approach. A process using this chemistry was then developed and used for large-scale preparation of **5**. Also, a study of the effect of $Et_3Al$ on the epimerization of **4** led to the $Et_3Al$-mediated methylation of **3** to give **4** and **5** with modest selectivity for the β-methyl diastereomer **5**.

In the course of this work, FT-IR spectroscopy provided information which not only became the foundation for rationalizing the selectivity of these reactions but also could be used to address a number of more general issues relating to anion structure and reactivity. Specifically, it provided useful information about enolate aggregation[13] and scope of ate complex formation[14] with trialkylboranes and trialkylalanes. To address these issues as well as to describe the two syntheses of **5**, this article is organized as follows.

The initial results which led to both routes to **5** are described in section A but discussed in later sections. In section B, IR data for lithium mono- and dianions of **3**, **4**, and **5** are presented. This database provides essential reference points for discussion of structure in sections C, E, and F. In addition, examples of interpretation relating to enolate aggregation are mentioned primarily throughout this section. The $Et_3B$-mediated epimerization of **4** to **5**, including essential processing details as well as a proposed rationalization of the protonation selectivity, is described in section C. Incorporation of the $Et_3B$-mediated epimerization of **4** to **5** into a suitable large-scale process for conversion of **3** to **5** required a modified methylation process for conversion of **3** to **4**, which is described in section D. Section E contains a description and a proposed rationalization of the $Et_3Al$-mediated methylation of **3**, including additional IR data relating to this reaction as well as to the discussion of ate complex formation which takes place in section F. In section F, IR data from sections B, C, and E are tied together in a generalized discussion of ate complex formation which rationalizes a variety of published results. The resulting view also provides support for the suggestion that the $Et_3B$-mediated epimerization of **4** to **5** proceeds via an ate complex, while the $Et_3Al$-mediated methylation of **3** to **5** does *not* involve ate complex formation.

## Results and Discussion

### A. Initial Studies with Triethylborane and Triethylaluminum.

Initially we formed the dianion of **4** with LDA in THF/hexane, added $Et_3B$, aged at −75 °C, and quenched with acetic acid. Isomer ratios [**5**(β)/**4**(α)] were higher using 200 mol % $Et_3B$ (β/α ~ 76/24) instead of 100 mol % (β/α ~ 72/28), as well as when the cold $Et_3B$ age was followed by an age at −45 °C (β/α ~ 80/20 with 100 mol % $Et_3B$, ~90/10 with 200 mol %). More favorable ratios were obtained with $Et_3B$ than with *sec*-$Bu_3B$ (β/α ~ 90/10 vs 70/30, respectively, using 200 mol % $R_3B$).

Substitution of $Et_3Al$ for $Et_3B$ in the lithium enolate mediated epimerization of **4** gave the opposite selectivity (i.e., β/α ~ 10/90). This result prompted the use of $Et_3Al$ in the methylation of **3** to test for an analogous reversal of selectivity, since methylation of dianions of **3** normally gives predominantly **4**.[2a,4a] The dianion of **3** was formed with LDA in THF/hexane and aged with 200 mol % $Et_3Al$ at −75 °C. Methyl iodide was then added. After 2 h at −75 °C, ~50% conversion to give mostly β-methyl **5** (β/α = 80/20) was achieved in 33% assay yield of **4** plus **5** (not corrected for unreacted **3**). Raising the methylation temperature to force complete reaction lowered the selectivity, and use of $Me_3Al$ or *i*-$Bu_3Al$ gave less selectivity than did $Et_3Al$.

The cation associated with these complexes plays a key role. The effect of using cations other than lithium is summarized in Table I. In the epimerization of **4**, every combination of metal enolate plus $Et_3B$ or $Et_3Al$ gave mostly β-methyl **5** except, as noted above, the combination of lithium and $Et_3Al$, which gave mostly α-methyl **4**. Similarly, every combination used for the methylation of **3** gave mostly α-methyl **4** except, as noted above, lithium and $Et_3Al$, which gave mostly β-methyl **5**. These results suggested a unique structure for the Li/$Et_3Al$ complexes, while the other complexes would appear to have the dianion species in roughly similar conformations.

These early results indicated that a variety of factors were at work. The study of these factors not only allowed us to design an efficient and dependable process for synthesis of β-methyl **5** but also enabled us to unravel the intriguing complexities of these enolate reactions. Our results follow.

**Table I. Effect of Complex Composition on Epimerization and Methylation Isomer Ratios**

A. Epimerization [**4** → **4**(α) + **5**(β)]

| $R_3M$ | cation | β/α |
|---|---|---|
| $Et_3B$ | Li | 90/10 |
| | K[a,b] | 79/21 |
| $Et_3Al$ | Li | 10/90 |
| | K[a,b] | 70/30 |

B. Methylation [**3** → **4**(α) + **5**(β)]

| $R_3M$ | cation | β/α |
|---|---|---|
| $Et_3B$ | Li | 1/99 |
| | Na[c] | 11/89 |
| $Et_3Al$ | Li[d] | 80/20 |
| | Na[c] | 21/79 |
| | K[a] | 10/90 |

[a] Enolate was formed with potassium bis(trimethylsilyl)amide. [b] β-Methyl **5** was used as starting material. See Section B. [c] Enolate was formed with sodium bis(trimethylsilyl)amide. [d] Both LDA and lithium bis(trimethylsilyl)amide gave mostly **5**(β), indicating that switching between diisopropylamine and bis(trimethylsilyl)amine has no major effect on selectivity.

**B. Low-Temperature FT-IR of Enolates.** To develop and understand these reactions, we required a convenient method for direct observation of imidate and ester enolate intermediates. NMR has been used for this purpose,[15] but $^{13}C$ NMR of our substrates gave severe line

(12) (a) For example, protonation of the dilithium dianion of **4** with acetic acid, fluorene, thiophenol, and triphenyltin hydride (Hirai, H.; Sawada, K.; Aratani, M.; Hashimoto, M. *Tetrahedron Lett.* **1985**, *26*, 1739) gave **5**(β)/**4**(α) ratios of 20/80, 30/70, 40/60, and 70/30, respectively. Magnesium, tin(II), and zinc enolates were prepared at −75 °C by treating the lithium enolate with $MgBr_2$, $Sn(OTf)_2$/THF, or $ZnCl_2$/THF; protonation with acetic acid gave β/α ratios of 43/57, 55/45, and 60/40, respectively. (b) A reviewer has suggested that the difference in facial selectivity between alkylation of the lithium dianion of **3** (see ref 27) and protonation of the lithium dianion of **4** might be a result of a lithium-mediated proton delivery from one enolate face and alkylation from the other face.

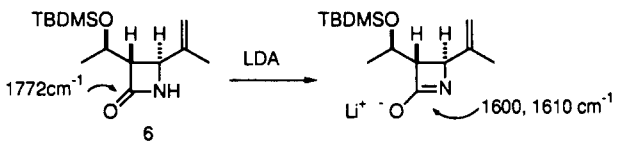
(13) (a) Leading references: Arnett, E. M.; Palmer, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 7354. Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7288. (b) Recent review: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

(14) Reviews: (a) Wittig, G. *Quart. Rev.* **1966**, *20*, 191. (b) Tochtermann, W. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 351.

broadening at the low temperatures (about −70 °C) required for direct observation. FT-IR presented an attractive alternative.[16,17a] Use of a jacketed IR cell and cooled transfer line allowed both transfer and observation at low temperature. Our minimum need was simply to know whether complete enolate formation had been achieved. In addition, the technique provided useful information about enolate aggregation, structure of ate complexes, and extent of ate complex formation.

In this section IR data are presented for lithium mono- and dianions of **3**, **4**, and **5**. These data are later compared in sections C, E, and F with IR bands for $Et_3B$ and $Et_3Al$ complexes of the dianions. A principle conclusion, discussed in detail in section F, is that the enolate C=C and the imidate C=N absorptions shift ~20–25 $cm^{-1}$ to higher frequency upon ate complex formation with $Et_3B$ or $Et_3Al$.

Monoanions of **3**, **4**, **5**, and β-lactam **6**[18] were formed with 100 mol % LDA in THF/hexane. Complete β-lactam anion formation was confirmed by absence of the β-lactam carbonyls in the typical range of 1767–1772 $cm^{-1}$. Observation of the monoanion of **6** permitted assignment of bands at 1600 and 1610 $cm^{-1}$ to the lithium imidate. The low frequencies and close proximity of the two bands indicate that both bands arise from bonds having a high degree of C=N character, and the existence of two bands instead of one in this region suggests that the imidate may be in two environments—either within one aggregate[19] or in two different aggregates.

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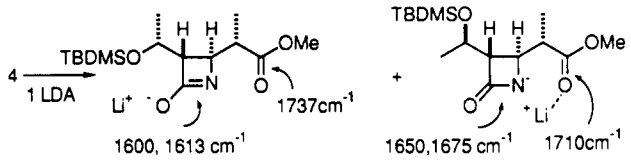
The spectrum of the monoanion of α-methyl **4** showed two ester carbonyls and two pairs of imidate bands, indicating two distinctly different species. One ester carbonyl (1737 $cm^{-1}$) was unperturbed from its position in the spectrum of the parent compound, and two imidate bands were about the same frequency as those of the monoanion of **6**. These bands were assigned to ester i, in which lithium might be chelated by the silylated oxygen. The other ester carbonyl was at lower frequency (1710 $cm^{-1}$), while the other pair of imidate bands (about 1650 and 1675 $cm^{-1}$) were at a higher frequency than those of the monoanion of **6**. The species producing these bands is postulated to be chelate ii.[20] The ratio of the two ester carbonyl intensities (i/ii ~ 2.0 at −40 °C) was invariant to concentration changes or addition of 1 equiv of HMPA, which supports the suggestion that the band multiplicity involves a chelate instead of different states of intermolecular complexation. The amount of ii increased on increasing the temperature to 22 °C (i/ii ~ 0.9). The spectrum of the monoanion of β-methyl **5** was similar to that of α-methyl **4**, but a higher ratio of free ester carbonyl to chelated ester carbonyl (~2.6 at −40 °C) indicated a reduced amount of chelated species. This can be ascribed to increased steric interaction between the β-methyl group and the lactam ring.




*i* *ii*

The spectrum of the monoanion of desmethyl **3** showed predominance of the free ester carbonyl absorption along with two broadly overlapping ester carbonyl bands at lower frequency, one at 1710 $cm^{-1}$ (chelate) and the other as a low frequency tail on the stronger free ester band. In addition, the bands between 1700 and 1600 $cm^{-1}$ were no longer resolved into distinct components. This could arise from more weakly chelated structures having less hindered rotation about the bonds between the carbonyl and the β-lactam ring or from the existence of a number of aggregated structures.

Spectra of the dilithio dianions of α-methyl **4** and β-methyl **5** at −50 °C were totally congruent, indicating, as expected, that both **4** and **5** give the same dianion species.[21] This species showed one slightly asymmetric band at 1655 $cm^{-1}$ and three slightly asymmetric and overlapping bands at ~1632 (sh), 1625 (most intense), and ~1617 (sh) $cm^{-1}$. The higher frequency band at ~1655 $cm^{-1}$ probably arises from the N-bonded "imidate" of the proposed structures iii (as seen with the monoanions). The lower frequency bands are in the vicinity expected for an O-bonded imidate and for ester enolates.[17] Dianion iii may exist as chelate iiia or as ion triplet iiib.[22] The other major species is presumably iv. The moderately sharp features of this spectrum suggested that iii and iv are in environments which are, geometrically at least, somewhat well defined. On the other hand, the spectrum of the dianion derived from desmethyl **3** with LDA exhibited a band maximum at lower frequency (about 1600 $cm^{-1}$ at −50 °C) which was broad, asymmetric (slopes extend to baseline at ~1680 and 1570 $cm^{-1}$), and featureless, indicating presence of many molecular arrangements.

**C. Triethylborane-Mediated Epimerization of 4.** Careful control of temperature and time during every step of the epimerization process was essential for maintaining optimum yield and isomer ratios. Temperatures less than −75 °C during addition of **4** to LDA were required in order to maintain the assay yield of **4** plus **5** above 80%. After an initial age of 20–30 min at −75 °C, a warmer age at −45

(15) Review: Gunther, H.; Moskau, D.; Bast, P.; Schmalz, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1212.

(16) Review of IR of enolates: Corset, J. In *Comprehensive Carbanion Chemistry, Part A*; Elsevier: 1980; Chapter 4.

(17) (a) Rathke, M. W.; Sullivan, D. F. *J. Am. Chem. Soc.* **1973**, *95*, 3050. The LDA-derived enolate of *tert*-butyl acetate shows a band at 1620 $cm^{-1}$, assigned to the carbon double bond stretch. (b) A spectrum of the monoanion of an N-substituted derivative of **4** or **5** could conceivably provide further support for our ester enolate assignments. However, monoanions of N-substituted derivatives decompose,[2a] presumably by a reverse Michael reaction to species analogous to **7**.

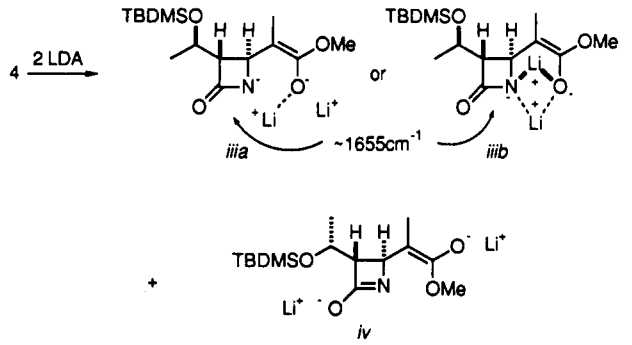
(18) Provided by F. W. Hartner of these laboratories.

(19) Maetzke, T.; Hidber, C. P.; Seebach, D. *J. Am. Chem. Soc.* **1990**, *112*, 8248.

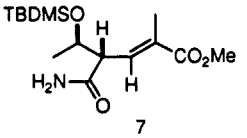
(20) Similar carbonyl frequency shifts upon complexation with $Li^+$ have been noted with amides: (a) Wuepper, J. L.; Popov, A. I. *J. Am. Chem. Soc.* **1969**, *91*, 4352. (b) Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080 and references therein.

(21) In relation to the study summarized in Table I, we attempted to form the disodium dianion of **4** with sodium bis(trimethylsilyl)amide (NHMDS) in THF, but we suspected lack of enolate formation even at −50 °C. Indeed, FT-IR indicated no disappearance of the ester carbonyl until the temperature reached −35 °C or higher, at which point ketene formation accompanied ester disappearance. β-Methyl **5** was much more reactive with NHMDS, but acetic acid quench of this reaction at various times while aging at −50 °C indicated that even with this isomer enolate formation was slow. Acetic acid quench of the reaction of potassium bis(trimethylsilyl)amide (KHMDS) with **5** (−45 °C, 1.5 h) gave the same isomer ratio (β/α ~ 25/75) as that seen after quenching the reactions of potassium diisopropylamide (BuLi/potassium *tert*-butoxide followed by diisopropylamine) with **4** *or* **5** (−50 °C, 3 h), suggesting that the conditions indicated for reaction of **5** with KHMDS gave essentially complete enolate formation. These conditions were used for the study described in Table I.

(22) Streitwieser, A. *Acc. Chem. Res.* **1984**, *17*, 353.




to −50 °C for ~45 min was needed to achieve complete enolate formation within an acceptable period of time. $Et_3B$ addition below −75 °C was required—again to maintain the assay yield above 80%. As noted in section A and further discussed below, a warmer complex age prior to quench (about −50 °C, 1 h) was needed to achieve high isomer ratios. However, for this step a compromise had to be reached between optimizing yield and optimizing isomer ratio since formation of the elimination product 7[23] was competitive. Quenching above −70 °C slightly reduced the assay yield. While adherence to this protocol was needed for optimum results, modest departures generally resulted in yield or isomer ratio penalties of less than 5%.[24] At a scale of 100 g, this process gave an assay yield (4 + 5) of 82% and a 5(β)/4(α) isomer ratio of 93/7. β-Methyl 5 was isolated in 66% overall yield from 4 and 98+% de by aqueous hydrogen peroxide/isopropyl acetate workup, solvent exchange to heptane, and a single crystallization from heptane. At pilot plant scale, maintaining the temperature/time protocol during the epimerization was challenging, but the process nonetheless proved workable.

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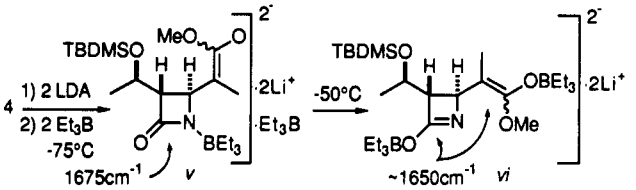
FT-IR observation of the $Et_3B$ complex formation stage of the process suggested an explanation of the need for a "warm" (−50 °C) age. After addition of $Et_3B$ at −75 °C, disappearance of the lithium enolate and imidate bands (most intense bands at 1655 and 1625 $cm^{-1}$, see section B) indicated complete complex formation within one hour. Two, new, higher frequency bands were attributed to an *N-bonded* "imidate" ate complex (1675 $cm^{-1}$) and an ester enolate complex (1638 $cm^{-1}$, possibly an ate complex) approximated by structure v. Upon warming a single broad band (~1650 $cm^{-1}$) appeared at the expense of the other two bands. This band presumably contains contributions from an *O-bonded* imidate ate complex along with an ester enolate ate complex as depicted in structure vi. Recooling did not change the spectrum.[25] It is reasonable to expect that the bulk of the $Et_3B$ group would force the ester enolate of the N-bonded complex v to adopt a conformation in which the latent ester group is oriented at least somewhat away from the nitrogen of the β-lactam ring as shown for v, thus leading to reduced selectivity for β-methyl 5 on protonation. On the other hand, protonation of the more stable O-bonded imidate ate complex vi could reasonably be expected to take place predominantly from the less hindered "back" face of the enolate to give high selectivity for 5. Justification for postulating ate complex formation is presented in section F.




The reversal of protonation selectivity brought about by ate complex formation with $Et_3B$ could stem from a combination of effects which could have wide-ranging implications for enolate reactions in general. The suggested intermediates iii and iv, present in roughly equal amounts, are undoubtedly aggregated in different types of structures. With iii, one might expect preferred formation of β-methyl 5 regardless of proton source and aggregation state. But with iv, enolate position relative to the β-lactam ring could easily depend on aggregate structure, which in turn could be influenced by steric and electronic factors associated with the proton source. Face accessibility would then be influenced by the resulting conformation of iv, aggregate structure, and the size of the proton source. This could explain the wide range of isomer ratios seen on protonation of the dilithium dianion of 4.[12] On the other hand, the proposed ate complex vi could be a monomeric ion pair[26] at each of its ends, allowing the bulky $Et_3B$ groups to accentuate a predictable steric preference for "back-side" protonation.

**D. Large-Scale Process for Conversion of 3 to 5.** Our early large-scale preparations of β-methyl 5 involved methylation of the lithium enolate of 3 at −75 °C [5(β)/4(α) ~ 45/55][27] and epimerization of 4 at −75 °C via its zinc enolate (β/α ~ 60/40).[12a] Diastereomer separation was conveniently achieved at multikilogram scale to give *both* 4 and 5 in high diastereomeric purity by employing a cyclic, selective dissolution process.[28] Availability of the highly selective, $Et_3B$-mediated epimerization of 4 required a methylation process which simply maximized efficient production of methylated material. As described below, the effect of enolate solubility on throughput (i.e., allowable batch concentration) was a key factor in our evaluation of methylation conditions.

(23) Elimination product 7 was formed as the major product when the lithium enolate of 4 was treated with $ZnCl_2$[12a] at −40 °C. It was identified by observation of characteristic resonances in the $^1H$ NMR spectrum of the crude mixture. Its presence under other reaction conditions was monitored by HPLC.

(24) Triethylborane quality must be high for the epimerization process to work well. Exposure of $Et_3B$ to air results in rapid conversion by oxygen to $Et_2BOOEt$.[a] Reaction of this peroxy compound with $Et_3B$ itself or with nucleophiles (e.g., an enolate anion or water from air) will lead to other oxygenated boron compounds at widely ranging rates.[a] We have shown that the oxygenated boron compound $(MeO)_3B$ gives both a low yield and a low isomer ratio in the epimerization reaction.[b] We have also used FT-IR to correlate amount of oxygenated boron compounds in $Et_3B$ samples with reductions in epimerization yield and β/α ratio.[b] (a) Abraham, M. H.; Davies, A. G. *J. Chem. Soc.* **1959**, 429. (b) Unpublished results, these laboratories.

(25) The IR spectrum of the Li/$Et_3B$ complex derived from desmethyl 3 was much less dependent on temperature. Treatment of the dilithio dianion of 3 (IR broad band maximum at 1600 $cm^{-1}$, see section B) with 200 mol % $Et_3B$ led to higher frequency IR bands at 1665, 1644, and 1623 $cm^{-1}$, with the latter two bands overlapping. Warming to −50 °C slightly increased the intensity of the band at 1665 $cm^{-1}$ at the expense of the other two bands, the shapes of which were changed only slightly. Recooling had essentially no effect. Consistent with these slight changes and with the indication of ate complex formation at both the imidate and ester enolate, methylation of the complex before or after warming gave >90% α-methyl 4 (β/α = 6/94 after complex formation at −70 °C; 1/99 after warming to −50 °C).

(26) Negishi, E.-i.; Idacavage, M. J.; Chiu, K.-W.; Yoshida, T.; Abramovitch, A.; Goettel, M. E.; Silveira, A.; Bretherick, H. D. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1225.

(27) Methylation of the lithium enolate of 3 with methyl iodide in THF/HMPA at −75 °C gave β/α ~ 20/80.[2a] Methylation in THF alone improved the ratio to 33/67 at −55 °C and 45/55 at −75 °C.

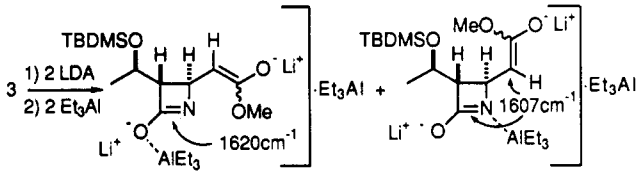
(28) Bender, D. R.; DeMarco, A. M.; McCauley, J. A. To be published.

The lithium, sodium, and potassium dianions of **3** were formed in THF with LDA and sodium and potassium bis(trimethylsilyl)amide, respectively. Treatment of these dianions with methyl iodide gave assay yields (**4** + **5**) of 82, 91, and 93% and **5**(β)/**4**(α) ratios of 45/55, 7/93 and 4/96, respectively, for lithium, sodium, and potassium. The increasing trends in assay yield and also in both chemical and diastereomeric purity gave increasing overall isolated yields (**4** + **5**) of 63, 82, and 86%. These trends clearly pointed to methylation of the potassium enolate as the method of choice. However, when the dianions of **3** "precipitate", they all produce honey-like or gelatinous mixtures which cannot be efficiently stirred. Complete enolate solution was thus required. The potassium dianion of **3** was roughly three times less soluble than the lithium and sodium dianions, and the resulting 3-fold reduction in maximum throughput outweighed the small yield advantage provided by potassium relative to sodium. The cosolvents *N,N'*-dimethylpropyleneurea or 1-ethyl-2-pyrrolidinone made the potassium dianion sufficiently soluble, but they also permitted unacceptable levels of N-methylation. We thus developed methylation of the sodium enolate of **3** for large-scale use. This process for conversion of **3** to **4**, which is fully described in the Experimental Section, provided high quality α-methyl **4** for use in the $Et_3B$-mediated conversion of **4** to **5**. β-Methyl **5** is readily hydrolyzed to **2** with equimolar LiOH (aqueous) in THF with essentially no epimerization.[29]

**E. Triethylaluminum-Mediated Methylation of 3.** Alkylation of open-chain ester enolates substituted at the β-carbon (C-3 of the ester) with acylamino,[30] hydroxy,[31] silicon,[32] or tin[33] generally gives predominantly a configuration analogous to that of α-methyl **4**, although the dominant cause of this selectivity is probably not the same for each of these groups. The $Et_3Al$-mediated methylation of **3** to give mostly β-methyl **5** provides the opposite selectivity. However, this direct conversion of **3** to **5** has two drawbacks: only modest selectivity and slow conversion. As described below, selectivity was improved somewhat by preparing the complex in a stepwise fashion. The conversion problem was explained but not solved, thus requiring a period of reaction at higher temperature with less selectivity to bring about >90% conversion. FT-IR was extensively employed during our attempts to understand and improve the reaction. The resulting data suggested an explanation of the selectivity and provided the basis for a general discussion of enolate ate complex formation (next section).

FT-IR of the complex resulting from adding 200 mol % $Et_3Al$ to the dilithio dianion of **3** in THF/hexanes at −70 °C showed a reversible temperature dependence which paralleled changes in methylation selectivity. The reversibility of these changes contrasts with the irreversible, temperature-dependent changes seen with the $Et_3B$ complex derived from α-methyl **4**. The $Et_3Al$ complex of **3** showed three bands: a strong, sharp band at 1607 $cm^{-1}$, a weak shoulder at 1620 $cm^{-1}$, and another weak band at 1656 $cm^{-1}$. The frequency of the strong band is not much different from the frequency for the broad band maximum of the dilithio dianion of **3** (1600 $cm^{-1}$, see section B), but the strong band of the $Et_3Al$ complex has a much narrower band width. The small change in frequency suggests that the electron distribution of the major species has not been significantly changed by the addition of $Et_3Al$ (i.e., no ate complex),[34] and the band sharpening suggests that $Et_3Al$ has introduced order into a previously chaotic environment. On warming to −55 °C, the intensity of both weak bands increased. On cooling, the spectrum returned to its initial appearance. Addition of HMPA also increased the intensity of the weak bands. In parallel with these spectral changes and as noted in Section A, raising the temperature reduced methylation selectivity; and, if the $Et_3Al$ complex was warmed to −55 °C and then recooled before adding methyl iodide, selectivity was unchanged. Thus, one or both of the weak bands was associated with reduced selectivity for β-methyl **5**.

Changes in the IR spectrum and chemical behavior brought about by forming the Li/$Et_3Al$ complex in a stepwise fashion suggested that the weak shoulder at 1620 $cm^{-1}$ was the key indicator of reduced selectivity for β-methyl **5**. The "stepwise" complex was formed by sequentially adding **3** to 100 mol % LDA in THF/hexanes, 100 mol % $Et_3Al$ to the resulting imidate anion, 100 mol % LDA to the imidate/$Et_3Al$ complex, and then 100 mol % $Et_3Al$ to the ester enolate, with all steps monitored by FT-IR. The resulting IR spectrum at −70 °C showed the weak band at 1656 $cm^{-1}$ and the main band at 1607 $cm^{-1}$; but the weak shoulder at 1620 $cm^{-1}$ was negligible and the band at 1656 $cm^{-1}$ was more intense than in the spectrum of the previously described "2 + 2" complex (i.e., **3** added to 200 mol % LDA, followed by addition of 200 mol % $Et_3Al$). On warming the stepwise complex to −45 °C, the shoulder at 1620 $cm^{-1}$ appeared but the intensity of this band at −45 °C was no more than its intensity in the spectrum of the 2 + 2 complex at −70 °C. On recooling the stepwise complex, the spectrum returned to its initial appearance, thus showing reversible behavior analogous to the 2 + 2 complex. In parallel with these spectral changes, reaction of the stepwise complex with methyl iodide at −50 °C gave a **5**(β)/**4**(α) ratio of 73/27, while reaction of the 2 + 2 complex at the same temperature gave a lower isomer ratio (β/α ~ 62/38) and a somewhat higher yield of **4** plus **5**. These results suggested that presence of the 1620 $cm^{-1}$ shoulder presages reduced selectivity for β-methyl **5** and that the band at 1656 $cm^{-1}$ does not correlate with selectivity, but apparently does correlate with yield.




*vii* *viii*

(29) Fuentes, L. M.; Roberts, F. E. Unpublished results, these laboratories. Hydrolysis according to the published procedure[2a] gives ~10% of the α-methyl diastereomer **4**.

(30) Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103 and references cited therein.

(31) Fráter, G.; Muller, U.; Gunther, W. *Tetrahedron* **1984**, *40*, 1269 and references cited therein as well as footnote 18 in ref 30.

(32) (a) Bernhard, W.; Fleming, I.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1984**, 28. (b) Fleming, I.; Lewis, J. J. *J. Chem. Soc., Chem. Commun.* **1985**, 149. (c) Fleming, I.; Hill, J. H. M.; Parker, D.; Waterson, D. *J. Chem. Soc., Chem. Commun.* **1985**, 318. (d) Fleming, I. *Pure Appl. Chem.* **1990**, *62*, 1879.

(33) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.

(34) In contrast with the spectrum of the *lithium*/$Et_3Al$ complexes derived from **3**, the IR spectrum resulting from adding 200 mol % $Et_3Al$ to the *dipotassium* dianion of **3** showed IR bands at 1675, 1630, and 1595 $cm^{-1}$ with relative intensities of about 0.8, 2.0, and 1.0, respectively. The higher frequency bands occur in about the same region as the bands for the lithium/$Et_3B$ complex derived from **3** (1665, 1644, 1623 $cm^{-1}$, see ref 25), and thus are probably due to ate complexes, while the band at 1595 $cm^{-1}$ is undoubtedly due to the potassium imidate and/or ester enolate. In this case, our data were insufficient to say whether $Et_3Al$ formed an ate complex only with the imidate, or only with the ester enolate, or to some extent with both.

A potential source of the 1620 $cm^{-1}$ shoulder may be an imidate/$Et_3Al$ complex having lithium *and* $Et_3Al$ associated with oxygen as depicted in structure vii (the monoanion/$Et_3Al$ complex of **3** has its most intense imidate band at about this frequency). This species could be expected to give mostly $\alpha$-methyl **4**. It is then tempting to suggest that the species responsible for giving $\beta$-methyl **5** is approximated by structure viii, in which lithium is associated with the imidate oxygen anion and $Et_3Al$ is complexed with nitrogen in typical Lewis acid fashion, thus forcing the ester enolate into a configuration suitable for giving $\beta$-methyl **5**. Methylation via viii would thus represent an example of the use of a bulky, aluminum-based Lewis acid to reverse stereoselectivity.[35] The conformation of this suggested intermediate is similar to the "low-temperature" complex v in the $Et_3B$-mediated epimerization of **4**, but viii is *not* an ate complex. Additional support for postulating that ate complexes are not involved in the methylation reaction is presented in the next section.

The inability to bring about complete methylation of the Li/$Et_3Al$ complex of **3** at −75 °C prompted a closer examination (by HPLC assay of starting material and products) of the kinetics of the reaction. Methylation under pseudo-first-order conditions ([MeI] ~ 10 × [enolate]) did not follow pseudo-first-order kinetics. A plot of log [**3**] versus time curved in a manner which suggested contribution from two rate constants with a slower reacting species gradually dominating over time. Closer examination of the methylation of the simple lithium enolate of **3** revealed the same picture. That is, methylation of the lithium enolate reached 50% conversion in less than 4 min at −75 °C, yet about 1 h at −75 °C followed by another hour at −45 °C was required to bring this reaction to >95% conversion. Similarly, the much less reactive $Et_3Al$ complex reached ~50% conversion in 1 h/−75 °C, but many hours at −45 °C were required to even approach 80–90% conversion.

An attractive explanation of these rate data is to postulate formation of a slow-reacting mixed aggregate[36] of starting material dianion and product monoanion. Indeed, when $\beta$-methyl **5** (as monoanion with 200 mol % $Et_3Al$) was added to **3** (as dianion with 200 mol % $Et_3Al$) in a 1:1 mole ratio, the methylation rate was much slower than in a normal reaction and the log [**3**] versus time plot closely approached a straight line. Similarly, when LiI was added in 1:1 mole ratio (much of it did not dissolve), the reaction was also slower, but to a much smaller extent than with added product monoanion.

A number of changes in solvent, base, and $R_3Al$ did not improve the methylation conversion or selectivity, but some of the changes provided useful structural information. Ester enolate formation using LDA in *tert*-butyl methyl ether was not possible even at −40 °C. $Et_3Al$/enolate complexes could be formed in diethyl ether, DME, and 1,3-dioxolane; but with the former there was no reaction with methyl iodide even at −45 °C, and with the latter the reaction was slower and the $\beta/\alpha$ ratio was lower (~50/50 at −55 °C). In DME, reaction rate was unchanged, but the $\beta/\alpha$ ratio was lower (~50/50 at −75 °C). Ate complex formation was not indicated by FT-IR in any of these solvents. Use of *n*-$Pr_3Al$ increased the initial rate, but the rate then reached a plateau at ~50% conversion. Use of $Me_3Al$ had no effect on rate and, as noted in section A, gave slightly reduced selectivity ($\beta/\alpha$ ~70/30 at −75 °C).

Variation of enolate-forming base (i.e., variation of the resulting amine) sometimes had substantial negative effects on reaction rate. As described below, these results were correlated with IR data which showed that amines can have a significant effect on ate complex formation. With trityllithium (no amine) and lithium diethylamide in THF, no methylation of the $Et_3Al$ complexes occurred at −75 °C. On the other hand, the lithium bases of bis(trimethylsilyl)amine, dicyclohexylamine, and 2,2,6,6-tetramethylpiperidine in THF all permitted methylation of the $Et_3Al$ complexes. The IR spectra of the $Et_3Al$ complexes varied significantly depending on the base used to make the lithium enolate. The complex made with $LiNEt_2$ showed bands at 1678 and 1620 $cm^{-1}$ with a relative intensity of ~1:2. The complex made with $LiCPh_3$ showed bands at 1678, 1648, 1620, and 1605 $cm^{-1}$ with the latter two bands being the most intense. However, the higher frequency bands at 1678 and 1648 $cm^{-1}$ were of roughly comparable intensity and somewhat more intense than the 1656 $cm^{-1}$ band of the LDA-derived complex. The bands at 1678 and 1648 $cm^{-1}$ may be associated with imidate and/or ester enolate ate complexes. On the other hand, the complex made with the lithium base of 2,2,6,6-tetramethylpiperidine showed bands similar to those of the LDA-derived complex (major band at 1607 and minor band at 1620 $cm^{-1}$).

**F. Scope of Ate Complex Formation.** Ate complex formation with trialkylboranes depends on solvent,[37] cation,[38,39] $pK_a$ of and extent of charge delocalization on the anion,[26] and steric hindrance associated with both the trialkylborane[38,39] and the anion.[39] The scope of these effects[40] is reasonably well defined except for ester enolates. The data presented in this article and further discussed in this section fill this gap. The scope of ate complex formation with trialkylalanes is much less clearly defined. Such complexes are often postulated, but supporting data are rarely offered. Our own data and circumstantial evidence from the literature will be discussed in an effort to provide some clarification.

Ate complex characterization has been focused primarily on the B–C–H portion of trialkylboranes and derived ate complexes.[41] IR (C–H stretch) and $^1H$, $^{13}C$, and $^{11}B$ NMR have been used to demonstrate characteristic frequency changes. Our initial interest in simply observing enolate formation by IR led us to focus on changes in IR frequencies for enolates and imidates. We suggest that these changes can be useful indicators of ate complex formation for these classes of substrates.

A central issue for our examples is the extent to which charge is transferred from the enolate to $Et_3B$ or $Et_3Al$. It is accepted that a shift to lower frequency of the IR band for C=C bonds conjugated with an anion is an indication of greater charge delocalization in the anion.[42] Conversely, charge localization on boron or aluminum which would occur with ate complex formation should produce a shift to higher frequency for the C=C bond of an enolate or the

(35) For more examples and a general review on organoaluminums in organic synthesis see: Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001.

(36) Leading references on mixed aggregates: (a) DePue, J. S.; Collum, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 5524. (b) Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053. (c) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 8602. (d) Jackman, L. M.; Rakiewicz, E. F.; Benesi, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 4101.

(37) Brown, H. C.; Racheria, U. S. *Organometallics* **1986**, *5*, 391.

(38) Negishi, E.-i.; Idacavage, M. J. *Tetrahedron Lett.* **1979**, 845.

(39) Idacavage, M. J.; Negishi, E.-i.; Brown, C. A. *J. Organomet. Chem.* **1980**, *186*, C55.

(40) See also: (a) Odom, J. D. In *Comprehensive Organometallic Chemistry*; Pergamon: New York, 1982; Vol. 1, Chapter 5.1. (b) Suzuki, A. *Top. Curr. Chem.* **1983**, *112*, 67.

(41) See refs 26, 37–40 and 43 and references cited therein.

(42) Menon, B. C.; Shurvell, H. F.; Colpa, J. P.; Buncel, E. *J. Mol. Struct.* **1982**, *78*, 29.

C=N bond of an imidate anion. Thus, the IR data for the $Et_3B$-mediated epimerization (section C) are used to rationalize structures v and vi as follows. The N-bonded "imidate" frequency increases ~20 $cm^{-1}$ from 1655 $cm^{-1}$ for iii to 1675 $cm^{-1}$ for v, and the ester enolate frequencies of iii and iv as well as the O-bonded imidate frequency of iv increase ~25 $cm^{-1}$ from ~1625 to ~1650 $cm^{-1}$ for vi. These shifts to higher frequency could reflect ate complex formation. Comparable shifts to higher frequency were noted in ref 25 for the Li/$Et_3B$ complexes derived from **3**. On the other hand and as noted in section E, addition of $Et_3Al$ hardly changes the IR spectrum for the dilithio dianion of **3**, except to sharpen the spectrum and to introduce a minor, higher frequency band at 1656 $cm^{-1}$. Thus, the major $Et_3Al$ complex viii is regarded as not containing an ate complex, while the minor band at 1656 $cm^{-1}$ indicates that one of the minor species is probably an ate complex at one or both of the anions. By the same argument, one can conclude that ate complex formation with $Et_3Al$ occurs to a greater extent with the dipotassium dianion of **3**[34] than with the dilithio dianion, which is consistent with published conclusions concerning cation effects on ate complex formation with trialkylboranes.[38,39]

The ate complex literature provides substantial support for the IR assignments. Charge-delocalized organolithiums derived from carbon acids whose p$K_a$'s are lower than ~20 do not form ate complexes with (*n*-alkyl)$_3$B in THF.[26] Thus, the lithium enolate of cyclohexanone forms an ate complex with $Et_3B$ to an extent of no more than 5%.[43] Esters, however, have a p$K_a$ about five units higher. One could therefore expect that lithium ester enolates could undergo complete ate complex formation with $Et_3B$, and the IR frequency shifts which occur on treatment of the lithium dianion of **4** with $Et_3B$ are consistent with this expectation. However, when we used the more hindered *sec*-$Bu_3B$ for the epimerization, the **5**(β)/**4**(α) ratio was only 70/30. This ratio is significantly less than the ratio of 88/12 seen in the L-Selectride reduction of the olefinic precursor of **2**.[5a] We suggest that under our equilibrium conditions for ate complex formation, the hindered *sec*-$Bu_3B$ gives incomplete ate complex formation with lithium ester enolates. On the other hand, the L-Selectride reduction was done with in situ protonation,[5a] suggesting the possibility of an initially formed ate complex being protonated before equilibrium could be established. This view is consistent with the observation that L-Selectride reduction of α,β-unsaturated esters, followed by treatment with alkylating agents, gives a product distribution characteristic of alkylation of lithium enolates.[44] In this example, the lithium enolate component of an equilibrium mixture would be much more reactive than the companion ate complex, which would in turn be funnelled to the lithium enolate as reaction proceeds.

Ate complex formation between organoalanes and ionic substances commonly occurs;[45] but ate complexes with enolates have merely been suggested, not demonstrated. It is reasonable to expect that the same trends for ate complex formation which have been documented for trialkylboranes would also apply to trialkylalanes provided that one accounts for the expected lower stability of aluminum ate complexes.[46] As indicated below, our data on ester enolates confirm the lower stability and provide a qualitative indication of the "border" defining whether or not ate complexes will form with trialkylalanes.

Studies of cation effects on ate complex formation between ketone enolates and (*n*-alkyl)$_3$B in THF indicate that sodium and potassium *ketone* enolates form ate complexes with (*n*-alkyl)$_3$B,[38,39] while, as noted earlier in this section, *lithium* ketone enolates form ate complexes to only a small extent.[43] Analogously, our IR data for the potassium[34] and lithium/$Et_3Al$ complexes of **3** (section E) suggest that potassium imidates and/or *ester* enolates form ate complexes with $Et_3Al$ in THF to a significant extent, while, as noted earlier in this section and in section E, *lithium* imidates and/or ester enolates form ate complexes to only a small extent. Thus, we suggest that the p$K_a$ difference between ketones and esters approximately reflects the *minimum* amount by which the "border" for ate complex formation must be shifted when comparing aluminum with boron.

Two literature reports suggesting ate complex formation between lithium enolates and $Et_3Al$[47,48] appear at first sight to contradict the view developed in this article. However, these examples used reaction conditions substantially different from our "standard" conditions; and, in particular, they used HMPA as cosolvent to increase the reactivity of the enolate. The HMPA effect is generally thought to occur via increased solvation of the cation. The accompanying effect on anion "structure" is not often studied. With several organolithium examples, HMPA induces ion triplet formation.[49] Our data suggest that with lithium imidates and/or ester enolates in the presence of $Et_3Al$, HMPA increases ate complex formation. As illustrated below, recognition of this as well as other effects mentioned in this article resolves the apparent contradiction.

In what is probably the first use of trialkylalanes to increase selectivity for monoalkylation of enolates, lithium ketone enolates are proposed to form ate complexes with $Et_3Al$.[47] We *do not doubt* this suggestion. Three aspects of this method can be regarded as favoring ate complex formation. The lithium enolates were formed from TMS enol ethers or with trityl lithium; i.e., no secondary amine was present; HMPA was used as cosolvent; and the alkylations were run at 0 °C to room temperature. In our examples, each of these conditions—no secondary amine, addition of HMPA, or increasing the temperature above −70 °C—led to increased ate complex formation. A later application of this approach used comparable alkylation conditions and also applied them to esters, although the presumed ate complex was prepared by a different route (addition of MeLi to a diisobutylaluminum enolate).[48]

In another notable example, the use of HMPA reverses aldol selectivity for lithium enolates of iron acyls in the presence of $Et_3Al$.[50] One of probably several possible explanations could be that HMPA induces ate complex formation.

We wish to emphasize a key point. Lewis acids are often used to influence reactivity and selectivity of reactions involving enolates and other anionic species. As illustrated in this article, use of an enolate, an enolate ate complex, or an enolate/Lewis acid complex which is *not* an ate

(43) Negishi, E.-i.; John, R. A. *J. Org. Chem.* **1983**, *48*, 4098.
(44) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846; *J. Org. Chem.* **1976**, *41*, 2194.
(45) Eisch, J. J. *Comprehensive Organometallic Chemistry*; Pergamon: 1983; Vol. 1, Chapter 6.
(46) Negishi, E.-i. *Organometallics in Organic Synthesis*; Wiley: New York, 1980; Vol. 1, Chapter 5.3.1.
(47) Tardella, P. A. *Tetrahedron Lett.* **1969**, 1117.
(48) Tsuda, T. T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439.
(49) (a) Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524. (b) Jackman, L. M.; Scarmoutzos, L. M.; Smith, B. D.; Williard, P. G. *J. Am. Chem. Soc.* **1988**, *110*, 6058. (c) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751.
(50) Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.

complex can give widely divergent results, and any change in reaction conditions can influence whether an ate complex will form between an enolate (or, presumably, any anionic species) and a Lewis acid. Spectroscopic characterization of these species under actual reaction conditions could greatly simplify interpretations.

## Experimental Section

**General.** The silylated derivative **3** was prepared from (3*S*,4*R*)-3-[(1*S*)-1-hydroxyethyl]-4-[(methoxycarbonyl)methyl]-azetidin-2-one (**8**) as described.[2a,51] Compound **8** was prepared as described in ref 9a,b. The following materials were obtained from commercial suppliers. Reagent-grade solvents were used as received, except that all reaction solvents were dried, if necessary, with 4A sieves to <50 μg water/mL as determined by Karl Fischer titration. LHMDS and the sodium analogue were obtained and used as THF solutions (1.0 M); the potassium analogue was obtained as a 0.65 M toluene solution (for methylation of the potassium enolate of **3** (section D), the solvent was exchanged to THF). LDA and all other lithiated amines were prepared from the amines and BuLi (1.6 or 2.5 M solution in hexanes) after drying the amines as described above and titrating the BuLi with 2,5-dimethoxybenzyl alcohol. Tritylllithium was prepared from triphenylmethane and BuLi. Boron and aluminum reagents were obtained and used as follows: $Et_3B$ (1.0 M, hexanes or heptanes), *sec*-$Bu_3B$ (1.0 M, THF), $(MeO)_3B$ (neat), $Et_3Al$ (1.0 M, hexanes), $Me_3Al$ (2.0 M, hexanes), *n*-$Pr_3Al$ (neat), *i*-$Bu_3Al$ (1.0 M, toluene). Reagent grade $ZnCl_2$/THF solutions (~1.25 M) were dried with 4A sieves to <200 μg water/mL. LiI (99%) and MeI (99%) were used as received.

Reactions were run under $N_2$ and mechanically stirred. Smaller scale (~1 mmol) reactions were often magnetically stirred. Examples described below are representative. Solvent evaporations were carried out in vacuo. HPLC was run with an Altex Ultrasphere: octyl (5 μM) column (25 cm × 4.6 mm); eluant = $CH_3CN$/water (0.1% $H_3PO_4$) (55/45); UV detection at 210 nm; sample concentration ~0.5–1 mg/mL; $t_R$ (min) at 1.1 mL/min ~10.0 (**3**), 10.0 (**7**), 11.7 (**5**) and 12.9 (**4**). Worked up extracts and crystallized products were assayed by HPLC comparison with external standards of highly purified **4** and **5** (highly enriched samples resulting from silica gel chromatography of mixtures were recrystallized several times from hexanes to give **4** (mp 135–136 °C (lit.[2a] mp 133–134 °C), contained ~0.4 area% of **5** by HPLC) and **5** (mp 121–122 °C (lit.[2a] mp 120–121 °C), free of **4** by HPLC)). Assays of reactions in progress were carried out by transfer of aliquots via cooled cannula to a cooled solution of HOAc/THF, followed by workup as described below and HPLC assay.

IR spectra were obtained by quick transfer of the reaction solutions via cannula to a "circle" cell (Spectra Tech) fitted with a GE internal reflectance element and variable temperature jacket which was mounted in the sample chamber of a Nicolet 7199 spectrometer. The cannula and transfer tubing were wrapped with dry ice. The cell temperature was maintained at the indicated temperatures with methanol circulated and chilled using a Neslab "Cryocool 100" immersion cooler. Styrofoam was taped wherever possible to the mounted cell to provide insulation.

**α-Methyl 4 from 3 via the Sodium Enolate.** Sodium bis(trimethylsilyl)amide in THF (1.0 M, 764 mL) was diluted with THF (300 mL) and cooled to −78 °C. A solution of **3** (100.1 g, 332 mmol) in THF (500 mL) was added to the suspension over 1 h at −80 °C. The resulting solution was held at −80 °C for 0.5 h, warmed to −50 °C, aged at this temperature for 1.5 h, and then recooled to −80 °C. Methyl iodide (37.2 mL, 598 mmol) was added over 10 min while the batch was maintained at −80 °C. The solution was held at −80 °C for 1.0 h, warmed to −50 °C over 10 min, and held at this temperature for 0.5 h and then recooled to −75 °C. Glacial acetic acid (100 mL, 1.75 mmol) in THF (200 mL) was added over 10 min with the batch temperature at −70 ± 5 °C. The resulting thick mixture was warmed to −20 °C, and then water (1 L) and isopropyl acetate (1 L) were sequentially added without cooling. The separated organic layer was washed sequentially with aqueous 5% $NaHSO_3$ (0.8 L), aqueous 5% $NaHCO_3$ (0.8 L), and water (0.8 L). The resulting extract contained (HPLC assay) unreacted **3** (1.8 g, <2%), β-methyl **5** (7.0 g, 6.7%), and α-methyl **4** (88.2 g, 84.3%). The solvent was exchanged to heptanes by sequentially concentrating the extract to a thick slurry (~200 mL), adding isopropyl acetate (200 mL), and again concentrating to 200 mL and then adding heptanes (200 mL) and again concentrating to 200 mL. Additional heptanes (450 mL) were added, the mixture was heated to 75 °C to dissolve all solids, and then the solution was cooled (with seeding at 68 °C with ~0.15 g of **4**) over 1 h to 25 °C. The mixture was aged at 20–25 °C/1 h, cooled to 5–10 °C, and aged another 0.5 h and then filtered. The solids were washed with heptanes (3 × 100 mL at 5–10 °C). The product was suction air dried to provide 85.4 g (82%) of **4** having an isomer ratio (**4**/**5**) of 98/2 and a wt % (**4** + **5**) purity of 99.5%.

**Triethylborane-Mediated Epimerization of 4 to 5.** To a solution of THF (500 mL) and diisopropylamine (102 mL, 728 mmol) was added a solution of BuLi in hexanes (1.45 M, 466 mL, 676 mmol) while the batch temperature was kept below −40 °C. The resulting solution was cooled to −80 °C. A solution of **4** (101 g, 320 mmol) in THF (480 mL), followed by a 20 mL of THF rinse, was added while keeping the batch at −80 to −75 °C. The solution was aged at −75 °C for 20 min and then at −47 °C for 40 min, and then it was recooled to −75 °C. $Et_3B$ in heptanes (15.4%, 407 g of solution, 640 mmol) was then added while the temperature was maintained at −75 to −70 °C. The batch was aged at −75 °C for 40 min, warmed to and aged at −48 °C for 40 min, and then recooled to −75 °C. Glacial acetic acid (140 mL) in THF (280 mL) was added while the temperature was maintained at −75 to −70 °C during the first half of the addition. During the remainder of the addition the temperature was allowed to rise to −20 °C. Water (800 mL) was then added while the temperature was allowed to rise to 0 °C. Hydrogen peroxide (30%, 220 mL, 2.16 mmol) was added while the temperature was kept at 0–5 °C, and then the mixture was warmed to and aged at 10–15 °C for 20 min. Isopropyl acetate (600 mL) was added. The separated organic layer was washed sequentially with aqueous 5% $NaHCO_3$ (2 L) and water (2 × 2 L, or an amount sufficient to reduce the peroxide level in the organic layer to <5 ppm as indicated by Peroxide Test paper [E. M. Quant]). The resulting extract contained (HPLC assay) β-methyl **5** (78.3 g, 78%) and α-methyl **4** (5.9 g, 6%). The solvent was exchanged to heptanes as described for the preparation of **4** to yield a heptane slurry (200 mL) to which additional heptanes (100 mL) were added. The mixture was heated to 70 °C to dissolve all solids, and then it was cooled and the solids were isolated as described for the isolation of **4** (seeding at 61–64 °C; cold heptane washes = 3 × 50 mL) to yield 64.3 g of **5** having a wt % and isomeric purity of 99+% (yield = 67% after correction for extract aliquots removed).

**Triethylaluminum-Mediated Methylation of 3.** To a solution of THF (2.0 mL) and diisopropylamine (0.32 mL, 2.3 mmol) was added BuLi in hexanes (2.4 M, 0.84 mL, 2.0 mmol) while the batch temperature was kept below −40 °C. The resulting solution was cooled to −78 °C. A solution of **3** (303 mg, 1.0 mmol) in THF (1.5 mL), followed by a 0.5 mL THF rinse, was added while the batch was kept at −76 to −73 °C. The solution was aged at −76 °C for 1.5 h. $Et_3Al$ in hexanes (1.0 M, 2.0 mL) was added while the temperature was kept at −76 to −73 °C. The resulting solution was aged at −76 °C for 45 min. Methyl iodide (~0.5 mL, ~8 mmol) was added over 1 min with batch temperature at −77 to −75 °C. The resulting solution was aged at −78 to −74 °C for 3 h, by which time solids had precipitated. Glacial acetic acid (0.5 mL) in THF (3 mL) was added over 5 min while the temperature was maintained between −75 and −65 °C. The mixture was warmed to −20 °C, and then an aqueous solution of L-tartaric acid (1 M, 2.0 mL) followed by water (10 mL) and ethyl acetate (10 mL) were added without cooling. The separated organic layer contained (HPLC assay) starting material **3** (89.9 mg, 30%), β-methyl **5** (110.5 mg, 35%), and α-methyl **4** (32.7 mg, 10%). The elimination product derived from **3** (analogous to **7**) was a major byproduct. A portion of the extract was evaporated and examined by $^1H$ NMR. Comparison with spectra of authentic material corraborated the identities and relative amounts of **3**, **4**, and **5**.

(51) The inversion and silylation were carried out as described by Roberts, F. E.; Abramson, N. L. These laboratories. This process is given in ref 2a.