We have shown that equilibrium constants are about 0.2 M^{-1} for association of phosphate monoanions with monocations; so all these results represent partial association ranging from approximately 20% association at 1 M to 50% association at 5 M. In addition, it must be kept in mind that ion exchange is fast so the data represent time averages for all states of $H_2PO_2^-$.[1,2]

Figure 2 displays data for three tetraalkylammonium chlorides. There is a straight line correlation of ΔJ and $\Delta\delta$ for $(CH_3)_4N^+$, $(C_2H_5)_4N^+$, and $(C_4H_9)_4N^+$ solutions. In all cases decreases in chemical shifts and coupling constants are observed; the largest effects are observed with 3 M tetra-*n*-butylammonium chloride: $\Delta J = -29.4$ Hz and $\Delta\delta = -5.6$ ppm.

Since the more hydrophobic ammonium ions cause the largest decreases in $^1J_{PH}$, we propose that $^1J_{PH}$ decreases because of aggregation of the hydrophobic ions near $H_2PO_2^-$, thereby displacing water from the solvation shell and causing a large decrease in dielectric constant in the environment surrounding the $H_2PO_2^-$ ions. The low dielectric constant will cause greater electrostatic repulsion between the two oxygen atoms in $H_2PO_2^-$ leading to a widening of the O–P–O bond angle. Since a larger bond angle demands more s character at phosphorus for the P–O bonds, there must be less s character at phosphorus in the P–H bonds and this will cause the observed decreases in coupling constants. The reverse effect with small metal ions[2] is consistent with this origin of the changes in coupling constants.

^{31}P chemical shifts have been related to structure in phosphates: bond angle effects are thought to control ^{31}P chemical shifts.[6,7] Figures 1 and 2 show that there is direct correlation between decreased coupling constant and increased shielding. Some of the chemical shifts (Figure 2) are quite large. The decreased coupling constants are associated with larger O–P–O bond angles and larger bond angles are expected to cause deshielding.[6,7] Consequently, the increased shielding observed here must be due to increased electron density at phosphorus; this would be expected from increased electrostatic repulsion between the two oxygen atoms because this effect will force electrons toward the phosphorus atom. Therefore, it seems clear that there can be cases where bond angle effects are less significant than effects involving redistribution of electron density. This is also true for metal ions; those metal ions which appear to have small effects on the PO_2^- bond angle[2] cause deshielding of the ^{31}P nucleus.[1]

Possible Application to Nucleic Acid Structure. $H_2PO_2^-$ is structurally similar to the phosphate monoanion groups in nucleic acids. Previously, discussions of nucleic acid structure have focused on conformational changes.[8] Our results in this and the previous[2] paper indicate that there should be significant structural changes in nucleic acids if the phosphate monoanion groups change environment from association with metal cations[2] to a hydrophobic protein environment.[9] This could have important functional consequences for genetic expression, for enzymes which act on nucleic acids, and particularly for DNA structural changes including supercoiling and the A, B, and Z helices. These electrostatic effects can be large and could easily drive the observed structural changes.[10,11]

Acknowledgment. We thank Joyce Wilde for help with the NMR instrumentation. NSF and the Dreyfus fund contributed to purchase of the NMR instrument.

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Highly Diastereoselective Alkylation onto 4-Acetoxy-2-azetidinones Employing Tin(II) Enolates of C4-Chiral 3-Acyl-1,3-thiazolidine-2-thiones

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In the field of carbapenem syntheses, the carbon–carbon bond-formation methods at the 4-position of 2-azetidinones have been intriguing and the various fascinating reactions have been reported.[5] However, there is no report on a facile and efficient method for the chiral alkylation at the 4-position of achiral 2-azetidinones (e.g., 4-acetoxy-2-azetidinone (**3**)). We now report a new efficient methodology for the preparation of chiral 2-azetidinone intermediates applicable to the total synthesis of (+)-thienamycin and (−)-1-β-methylcarbapenem[6] based on the highly diastereoselective aldol-type reaction employing C4-chiral 3-acyl-1,3-thiazolidine-2-thiones[7,8] and 4-acetoxy-2-azetidinones.

To tin(II) enolate **2a**,[9] prepared from 3-acetyl-4(*S*)-ethyl-1,3-thiazolidine-2-thione (**1a**) was added a THF solution of 4-acetoxy-2-azetidinone (**3**) at −40 °C. After being stirred at 0 °C for 1 h, the reaction mixture was subjected to the usual workup to afford a yellow mixture of **6a** and **7a** in a 95:5 ratio (HPLC analysis[7a]). The major product **6a** was readily isolated in 82% yield by silica gel column chromatography (Scheme I). Other similar chiral alkylations of **3** by the tin(II) enolates of **1b–d** gave, with high diastereoselectivity in the range of 90:10–98:2 ratios, the corresponding 4-alkylated 2-azetidinones **6b–d** in 75–85% yields.[10]

Absolute configurations of the major products **6a** and **6b** were confirmed by their chemical conversion to the known compound **17** [$[\alpha]^{20}_D$ + 41.4° (*c* 0.86, benzene), lit.[11] $[\alpha]^{20}_D$ + 43.2° (*c* 0.37,

(1) Institute for Chemical Research, Kyoto University.
(2) Lederle (JAPAN) Ltd.
(3) Faculty of Pharmaceutical Sciences, Kyoto University.
(4) Osaka University of Pharmaceutical Sciences.
(5) (a) Karady, S.; Amato, J. S.; Reamer, R. A.; Weinstock, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 6765. (b) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076. (c) Greengrass, C. W.; Hoople, D. W. T. *Tetrahedron Lett.* **1981**, *22*, 5335. (d) Greengrass, C. W.; Nobbs, M. S. *Tetrahedron Lett.* **1981**, *22*, 5339. (e) Reider, P. J.; Rayford, R.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 379. (f) Koller, W.; Linkies, A.; Pietsch, H.; Rehling, H.; Reuschling, D. *Tetrahedron Lett.* **1982**, *23*, 1545. (g) Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293. (h) Aratani, M.; Sawada, K.; Hashimoto, M. *Tetrahedron Lett.* **1982**, *23*, 3921. (i) Hirai, K.; Iwano, Y.; Fujimoto, K. *Tetrahedron Lett.* **1982**, *23*, 4025. (j) Fujimoto, K.; Iwano, Y.; Hirai, K. *Tetrahedron Lett.* **1985**, *26*, 89. (k) Hua, D. H.; Verma, A. *Tetrahedron Lett.* **1985**, *26*, 547. (l) Tajima, Y.; Yoshida, A.; Takeda, N.; Oida, S. *Tetrahedron Lett.* **1985**, *26*, 673. (m) Shibata, T.; Iino, K.; Tanaka, T.; Hashimoto, T.; Kameyama, Y.; Sugimura, Y. *Tetrahedron Lett.* **1985**, *26*, 4739. (n) Chiba, T.; Nagatsuma, M.; Nakai, T. *Chem. Lett.* **1985**, 1343. (o) Fliri, H.; Mak, C.-P. *J. Org. Chem.* **1985**, *50*, 3438.
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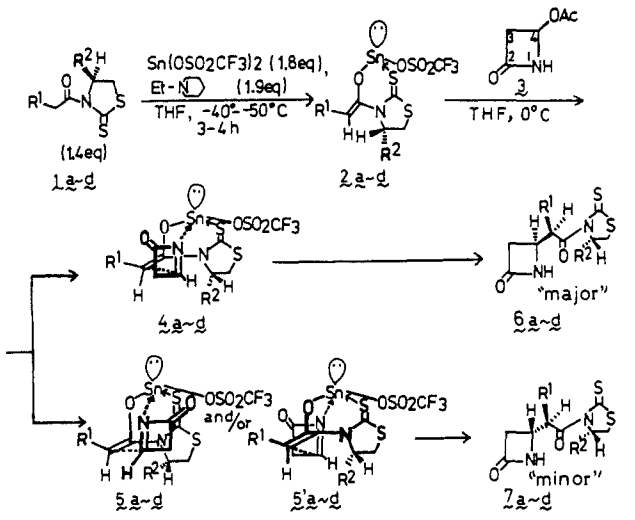
(10) Experimental details and results are available as Supplementary Material.

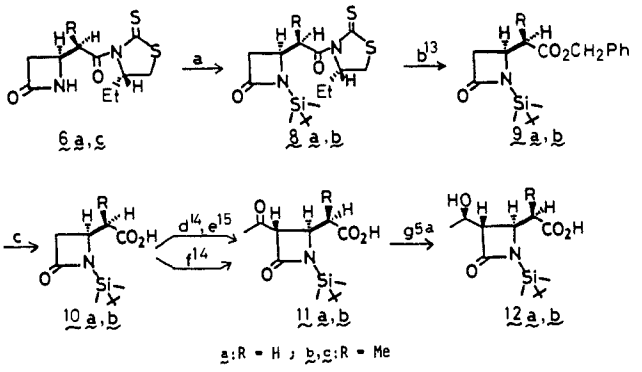
0002-7863/86/1508-4673$01.50/0

Scheme I



a: R^1 = H, R^2 = Et; **b**: R^1 = H, R^2 = *i*-Pr; **c**; R^1 = Me, R^2 = Et; **d**: R^1 = Me, R^2 = *i*-Pr

Scheme II[a]



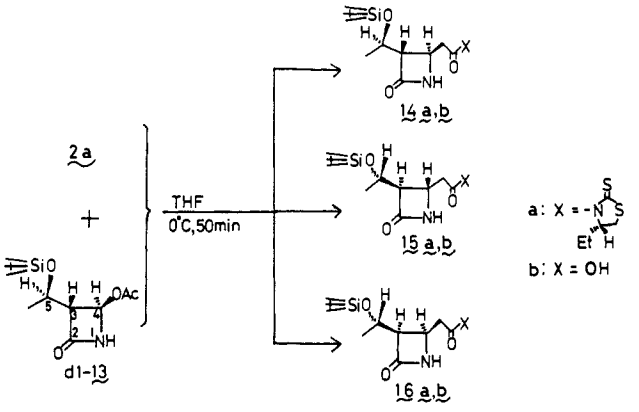
[a](a) TBDMS-Cl, Et_3N, DMF, 0 °C; **8a** 98%, **8b** 99%. (b) $PhCH_2ONa$, toluene, 0 °C (1 h) → room temperature (30 min); **9a** 44%, **9b** 40%. (c) H_2–5% Pd-C, MeOH; **10a** 87%, **10b** 99%. (d) LDA (2 equiv), CH_3CHO, THF, −78 °C. (e) $K_2Cr_2O_7$–H_2SO_4, Et_2O–H_2O, −20 °C; **11a** 35% from **10a**. (f) LDA (2 equiv), THF, −40 °C; *N*-acetylimidazole, THF, −78 °C → room temperature. (g) $(i\text{-Pr})_2NH$-BH_3, $(CF_3CO_2)_2Mg$, Et_2O, −78 °C; **12a** 60%, **12b** 60% from **10b** via f.

benzene)]. Stereochemistry of **6c** and **6d** was established by X-ray analysis[12] of the carboxylic acid **10b** [mp 128–129 °C ($CHCl_3$–hexane), $[\alpha]^{26}_D$ −66.7° (*c* 0.6, $CHCl_3$)] which was derived from **6c** (or **6d**) by a sequential reaction shown in Scheme II.

This excellent *re* face selective alkylation into a presumed cyclic acyl imine derived in situ from **3** can be rationalized in terms of the most likely transition state **4**. The contribution of the transition state **5** and/or **5′** for *si* face selection of the imine group should be very minor due to steric repulsion between the C3-α proton of the cyclic imine miety and the C4-β and C5-β protons of the thiazolidine-2-thione moiety (**5** in Scheme I) and/or steric repulsion between the imine moiety and the C4-α R^2 group of the thiazolidine-2-thione moiety (**5′** in Scheme I).

The major products **6a** and **6c** were successfully converted into the new useful compounds **12a** [mp 75–77 °C (Et_2O–hexane), $[\alpha]^{25}_D$ −65.0° (*c* 0.4, $CHCl_3$)] and **12b** [mp 130–132 °C (Et_2O–hexane), $[\alpha]^{26}_D$ −54.6° (*c* 0.5, $CHCl_3$)] as depicted in Scheme II.[5a,13–15] During the synthetic course, direct conversion of **8a,b** into **10a,b** by hydrolysis of the former in aqueous THF and MeOH

Scheme III



was attempted using weak bases such as K_2CO_3 and $NaHCO_3$. The reaction proceeded but the yields of the desired carboxylic acids **10a** and **10b** were less than 20%.

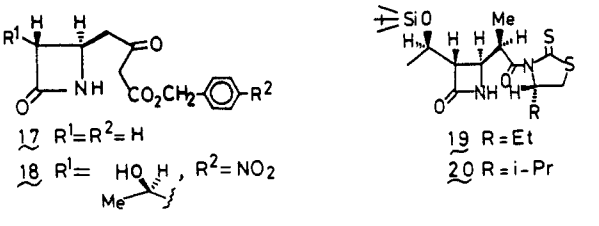
Subsequently, we investigated the reactions of racemic 3-substituted 4-acetoxy-2-azetidinones **13** with chiral tin(II) enolate **2a** derived from 3-acetyl-4(*S*)-ETT (**1a**).

To a solution of enolate **2a** prepared in situ from the reaction of **1a** (3.4 mmol) and *N*-ethylpiperidine (4.6 mmol) in THF (12 mL) at −50 to −40 °C for ca. 3–4 h, a solution of *dl*-2-azetidinone **13** (2.4 mmol) in THF (5 mL) was added at −40 °C. The mixture was stirred at 0 °C for 50 min and then treated as usual. Chromatographic separation of the yellow oily crude product afforded **15a** (20% yield), **14a** (42% yield), and **16a** (9% yield) (Scheme III).[10] Hydrolyses of active amides **14a–16a** were carefully carried out in an aqueous THF solution containing 1 N NaOH for 10–30 min to give the each corresponding carboxylic acids **14b–16b** in various yields (**14b**, 71%; **15b**, 48%; **16b**, 58%) (Scheme III).[10,16]

The absolute configuration of **14b** was confirmed by chemical correlation with the reported compound **18** [mp 126–127 °C (THF–Et_2O), $[\alpha]^{25}_D$ +21.3° (*c* 0.24, $CHCl_3$); lit.[17] mp 123–124 °C, $[\alpha]^{25}_D$ + 21.0° (*c* 0.19, $CHCl_3$)]. Compound **15b** was confirmed to be the antipodal compound of **14b** by the specific rotation and spectroscopic evidence. The stereochemistry of **16b** was tentatively assigned on the basis of its ^1H NMR spectra [δ C4-H 3.97 ($CDCl_3$), J = 5–6 Hz (multiplet)] and the mechanistic consideration.[18]

The observed outcome of diastereofacial selectivity in the reactions of the chiral tin(II) enolate **2a** with *dl*-3-substituted 4-acetoxy-2-azetidinones **13** can be also rationalized, inspecting the similar transition state models like **4**, **5**, and **5′**.[18]

Finally, optically active **13** was allowed to react with chiral tin(II) enolates **2c** and **2d** in THF at 0 °C for 1 h to afford the desired chiral azetidinones, **19** [80% yield, mp 85.5–86.5 °C (hexane–EtOAc), $[\alpha]^{25}_D$ + 233.9° (*c* 0.8, $CHCl_3$)], in a 90:10 (**19**/other isomers) ratio, and **20** [74% yield, mp 131.5–132.5 °C (hexane–EtOAc), $[\alpha]^{25}$ + 295.7° (*c* 0.9, $CHCl_3$)] in a 91:9 (**20**/other isomers) ratio, respectively.



Thus, we succeeded in the first aldol-type chiral alkylation of cyclic acyl imines by tin(II) enolates of C4-chiral 3-acyl-1,3-

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(12) Crystallographic structure of compound **10b** and its data are available as Supplementary Material.
(13) Nagao, Y.; Seno, K.; Kawabata, K.; Miyasaka, T.; Takao, S.; Fujita, E. *Chem. Pharm. Bull.* **1984**, *32*, 2687.
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(15) Beckmann, E. *Ann. Chem.* **1889**, *250*, 325.

(16) It is noteworthy that in the cases of compounds **14a–16a**, 4(*S*)-ethylthiazolidine-2-thione could be removed by direct hydrolysis, yet similar ones in the cases of **8a** and **8b** could not be directly hydrolyzed.
(17) Kametani, T.; Nagahara, T.; Honda, T. *J. Org. Chem.* **1985**, *50*, 2327.
(18) Rational mechanistic details should be reported elsewhere.

thiazolidine-2-thiones. This chiral induction proved to be strikingly effective for asymmetric syntheses of various C1-β-substituted carbapenems.

Supplementary Material Available: Tables of crystal data of compound **10b**, atomic parameters for non-hydrogen atoms, fractional coordinates for hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, bond length and valance angles, torsion angles, and observed and calculated structure factors in compounds **10b**, the perspective view for the crystallographic structure of **10b**, and experimental details and results in the reaction of **2** with **3** (or *dl*-**13**) (10 pages). Ordering information is given on any current masthead page.

Lewis Acid Mediated Condensation of Chiral Imide Enolates. A General Approach to the Synthesis of Chiral Carbapenem Precursors

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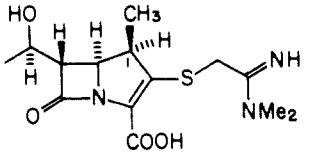
The search for carbapenem antibiotics possessing enhanced chemical and metabolic stability has generated considerable synthetic activity directed toward the synthesis of 1-β-methylcarbapenem carboxylic acids, such as (−)-(1*R*,5*S*,6*S*)-1-methyl-2-[[2-(dimethylamino)-2-iminoethyl]thio]-6-[(1*R*)-1-hydroxyethyl]-1-carbapenem (**1**).[1] The control of the stereo-

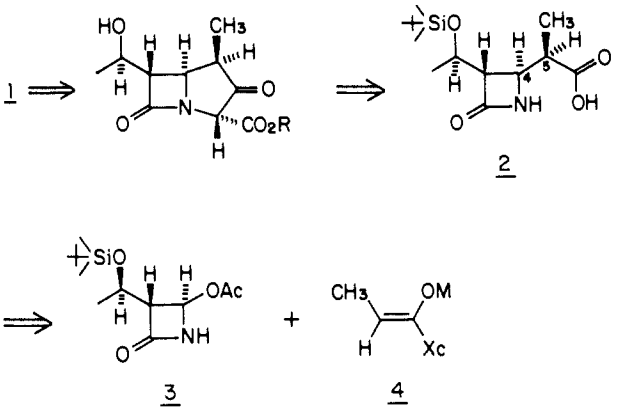


1

chemistry at the 1-position is a critical problem in the synthesis of this new generation of β-lactam antibiotics.[1a]

In this paper we wish to report the results of a highly successful double-asymmetric synthesis leading to the 1-β-methyl carbapenem antibiotic precursor **2** in ≥98% enantiomeric excess from readily available optically active azetidinone **3**.[2] The key feature in the strategy is the utilization of chiral oxazolidone enolates[3] in Lewis acid mediated carbon–carbon bond-forming reactions for the introduction of chirality at C-5 (**2**).

The structural analysis of the C-4 → C-5 bond connection of **2** reveals that the coupling of two optically pure fragments **3** and **4** could be incorporated as a logical step in their synthesis.[4] Recent investigations[3] have demonstrated the utility of propionyloxazolidone carboximides in achieving high levels of diastereofacial selection. In direct analogy with prior report,[3b] the illustrated

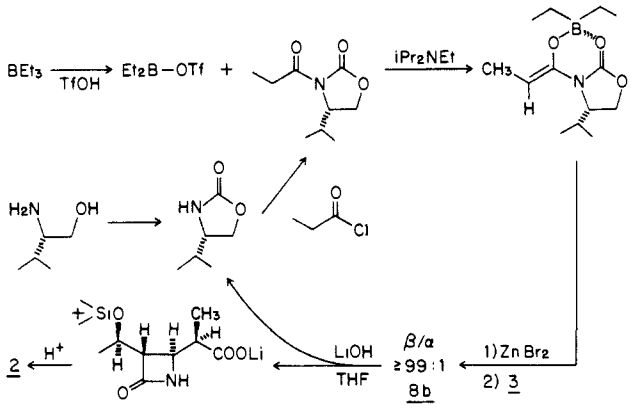


2

3 4

carboximides **6** and **7** were transformed into their respective *Z* silyl enol ethers[5] **8** and **9** (1.05 equiv of LDA, 1.10 equiv of Me_3SiCl, THF, −78 °C → room temperature). Reaction of 1.5 equiv of the enol ether **8** and **9** with the azetidinone **3** in CH_2Cl_2 (0.3 M in CH_2Cl_2 at room temperature) in the presence of a catalytic amount of ZnI_2 afforded the β-lactam carboximides **10**α and **10**β as illustrated in Scheme I. Although the chemical yields were generally quite high (78–93%), the diastereoselectivity of the process was only moderate (40–60%).[6]

Evans has extensively demonstrated the high level of efficiency of dialkylboryl enolates of carboximides in aldol condensations.[3] We have found that the dialkylboryl enolates of carboximides react smoothly with the azetidinone **3** with a high degree of diastereoselectivity under Lewis acid conditions. The Lewis acid used determined the optimum stoichiometry of enol to azetidinone and the degree of diastereoselection. The diethylboryl enolates were selectively generated by treatment of the propionamide with Et_2BOTf[7] and *i*-Pr_2NEt (0.3 M in CH_2Cl_2, −78 °C or room temperature)[8] and to this solution was added the Lewis acid followed by the azetidinone **3** at room temperature. A ≥95% mass recovery of products was obtained and the diastereomer analysis was determined by HPLC on the unpurified reaction products.[9] Treatment of the crude product **10** with 1.0 M LiOH in THF at room temperature affords **2** in 73% isolated yield (β/α ≥ 99) based on **3**.[10,11]



(1) (a) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *1*, 29. (b) Leanza, W. J.; Ratcliffe, R. W.; DiNinno, F.; Patel, G.; Wildonger, D.; Muthard, D.; Wilkening, R. R.; Christensen, B. G. Abstract 332, *23rd Interscience Conference Antimicrobial Agent and Chemotherapy* Las Vegas, 1983. (c) Shih, D. H.; Fayter, J. A.; Baker, F.; Cama, L.; Christensen, B. G. *Ibid.* Abstr. 333. (d) Kropp, H.; Sundelof, J. G.; Kahan, J. S.; Huber, J.; Bohn, D.; Gerckens, L.; Kahan, F. M.; Birnbaum, J. *Ibid.* Abstr. 334.

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(3) (a) For a recent review, see: Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

(4) R. Ratcliffe found in preliminary studies that (*Z*)-1-methoxy-1-[(trimethylsilyl)oxy]-1-propene (**4**) gave a 80:20 α/β mixture **8** (Xc = OCH_3) in the presence of different Lewis acids (unpublished work).

(5) Silyl enol ether *Z*/*E* mixtures have been prepared by using TMSOTf/Et_3N/CCl_4/room temperature. The stereochemistry of the silyl enol ether was confirmed by NMR. This is the subject of a separate report to be published.

(6) Independent generation of the zinc enolate via exchange of the lithium enolate with $ZnBr_2$ affords the β-lactam carboximides in a **10**β:**10**α ratio of 80:20.

(7) (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) The reagent of choice is the Et_2BOTf due to the high purity of commercially available Et_3B (Texas Alkyls, Inc.) and its convenient *in situ* generation. Nonreproducible results were obtained with *n*-Bu_2BOTf in CH_2Cl_2 or Et_2O which is commercially available from Aldrich.

(8) The generation and the stereochemistry of the Si, Sn, and B enolates of the chiral carboximides is the subject of a separate report to be published.

(9) **HPLC assay**: Altex Ultrasphere-Octyl, 5 μm, 25 cm × 416 mm i.d.; acetonitrile/water/H_3PO_4, 70:30:0.1, v/v; 1.1 mL/min; retention times (min) **8**β 12.0, **8**α 16.4.

(10) The oxazolidinone is recovered ≥90% yield.