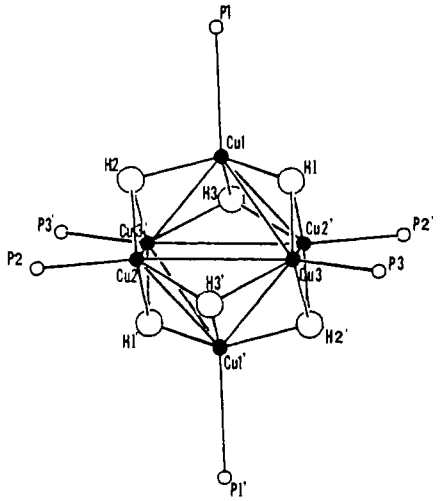

Figure 1. Molecular structure of the $H_6Cu_6P_6$ core of the $H_6Cu_6[P(p\text{-tolyl})_3]_6$ cluster. Thermal ellipsoids are at the 50% probability level.[11] Average pertinent distances: Cu-Cu(long) = 2.68 (4) Å, Cu-Cu(short) = 2.52 (3) Å, Cu-H = 1.76 (3) Å. Primed atoms are related to unprimed ones by a crystallographic inversion. The drawing shows one of the two independent clusters in the unit cell.

during data collection and refinement limited us to a low resolution analysis: (i) Data were collected at room temperature due to a destructive phase transition occurring at approximately 265 K. (ii) Because of the crystal's lack of diffracting ability beyond $2\theta = 75°$, $\lambda = 1.15930$ (12) (partially due to the relatively high data collection temperature), a comparatively small amount of data (2808 reflections) was obtained, given the size of the unit cell ($U = 6616(6)$ Å^3). (iii) Due to the limited amount of data available and the large number of independent atoms (270), rigid body refinement was employed in which the *p*-tolyl groups were held rigid, and only the rotational angles about the P–C_{ipso} bond lengths were refined.[8] (iv) In order to further reduce the number of parameters and increase the data/parameter ratio, the isotropic temperature factors for groups of atoms also were constrained equal to one other.

A view of the structure of the core of $H_6Cu_6[P(p\text{-tolyl})_3]_6$ is illustrated in Figure 1. Consistent with previous studies,[1,2,4] the geometry of the cluster is that of a distorted octahedron of copper atoms with six short [average 2.52 (3) Å] and six long [average 2.68 (4) Å] Cu–Cu edges, thus resulting in six small and two large faces. The average Cu–Cu distances compare well with those determined by X-ray diffraction:[2] Cu–Cu short = 2.54 (1) Å and Cu–Cu long = 2.66 (1) Å. Two independent clusters are present in the unit cell, and each cluster possesses crystallographic inversion symmetry. All six face-capping hydrides were located on the small faces from a single difference-Fourier map. The average Cu–H bond distance is 1.76 (3) Å, with an average out-of-plane distance of 1.0 (1) Å. These values compare well with Co–H = 1.734 (4) Å and H···Co_3 = 0.978 (3) Å in $(\mu_3\text{-H})FeCo_3(CO)_9[P(OCH_3)_3]_3$[9] and Ni–H = 1.691 (8) Å and H···Ni_3 = 0.907 (6) Å in $(\mu_3\text{-H})_3Ni_3(C_5H_5)_4$.[10] Despite the somewhat low precision of the present analysis, the main conclusions are clear and unambiguous: All six hydrides are definitively found to be face-capping, consistent with the findings of Caulton, Huffman, and co-workers[4] and speculations of Stucky and co-workers.[3]

Acknowledgment. This research was supported by NSF Grant CHE 87-03425 (R.B.) and the W.C. Hamilton Memorial Fund (R.C.S.). Work at Brookhaven National Laboratory was performed under contract DE-ACO2-76CH00016 with the U.S. Department of Energy, Office of Basic Energy Sciences. We thank D. Rathjen and J. Guthy for technical assistance.

Supplementary Material Available: Tables consisting of crystal data and data collection parameters (Table S1), atomic coordinates and thermal parameters (tables S2), and bond distances and angles (Table S3) (8 pages); table of observed and calculated structure factors (Table S4) (8 pages). Ordering information is given on any current masthead page.

(8) Sheldrick, G. M. SHELX System of Crystallographic Programs; University of Cambridge: Cambridge, England, 1976.
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(11) Johnson, C. K. Oak Ridge National Laboratory, [Rep] ORNL (U.S.) 1976, ORNL-5138.

Chemoenzymatic Preparation of *trans*-2,6-Dialkylpiperidines and of Other Azacycle Building Blocks. Total Synthesis of (+)-Desoxoprosopinine

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The aza-Achmatowicz reaction (**1** → **2**)[4] has emerged as a practical route to indolizidines, quinolizidines, and piperidines, the latter in the form of oxazolones of the type **6**.[5] Compound **6** may be prepared in either antipodal form (>95 % ee, 10–50 g scale) by the simple chemoenzymatic method summarized in Scheme II,[6] whereas other materials of the type **2** were hitherto available solely in racemic form. Herein, we disclose extension of aza-Achmatowicz techniques to the enantioselective preparation of compounds **2**. In this connection, amidoalkylation reactions of certain derivatives of **6** were examined. Surprisingly, such reactions were found to follow a stereochemical course *opposite to that observed for monocyclic analogues of our substrates*. Consequences of our findings are presented below.[7]

The carbonyl group in **6** may be reduced with complete stereocontrol. Ethanolic $NaBH_4$ (−60 °C) produced an equatorial alcohol, conveniently characterized as the acetate. By contrast, L-selectride in THF (−78 °C) caused formation of the axial alcohol, again characterized as the acetate.[8] Complete stereoselectivity in both cases was apparent within the limits of 300 MHz ^{1}H NMR spectrometry. No unusual effect[9] interfered with the stereochemical course of these reductions. Hart–Kraus allylation of acetate (+)-**9** occurred rapidly upon treatment with allyltrimethylsilane/$TiCl_4$ (CH_2Cl_2, 25 °C),[10] providing *axially allylated* (+)-***10*** *as the exclusive product* (88% chromatographed yield, $[a]_D = +17.3°$; $c = 1.003$, EtOH). The structure of **10** is firmly established. In addition to extensive NMR studies,[11] an X-ray

(1) Recipient of a Dow Predoctoral Fellowship, 1987–1988.
(2) Author to whom correspondence regarding the X-ray data should be addressed.
(3) Recipient of a Robert A. Welch Predoctoral Fellowship, 1987–1988.
(4) Ciufolini, M. A.; Wood, C. Y. *Tetrahedron Lett.* **1986**, *27*, 5085.
(5) The structure of **6** was ascertained by X-ray crystallography. Monoclinic crystals from THF, space group $P2_1/a$; $a = 8.582$ (6) Å; $b = 10.608$ (5) Å; $c = 10.160$ (7) Å; $\beta = 114.92$ (4)°; $Z = 4$; $V = 839$ (2) Å^3. $R = 0.036$, $R_w = 0.052$ for 1515 observed reflections. An ORTEP plot of **3** is provided as Supplementary Material.
(6) Drueckhammer, D. G.; Barbas, III, C. F.; Nozaki, K.; Wong, C. H.; Wood, C. Y.; Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607.
(7) All new compounds described in this paper were thoroughly characterized. HRMS and spectral data are provided as Supplementary Material.
(8) The presence of the ketone during the planned transformations would be damaging to the stereochemical integrity of the molecule. Reduction was therefore necessary.
(9) Danishefsky, S.; Langer, M. E. *J. Org. Chem.* **1985**, *50*, 3472. See, also: Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(10) Other Lewis acids, e.g., BF_3OEt_2, were ineffective. For similar reactions, see: (a) Hart, D. J.; Tsai, Y. M. *Tetrahedron Lett.* **1981**, *22*, 1567. (b) Kraus, G. A.; Neuenschwander, K. *J. Chem. Soc., Chem. Commun.* **1982**, 134. For excellent reviews on amidoalkylations, see: (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (d) Shono, T. *Tetrahedron* **1984**, *40*, 811. (e) Zaugg, H. E. *Synthesis* **1984**, *85*, 181.

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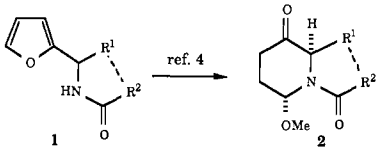
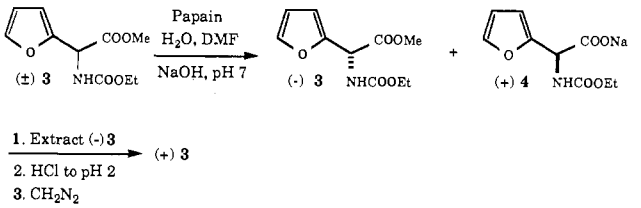
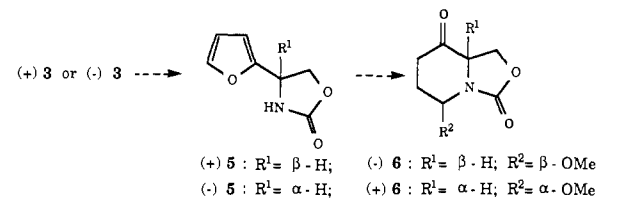
Scheme I

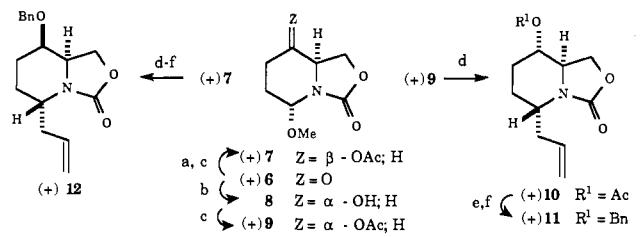


Scheme II



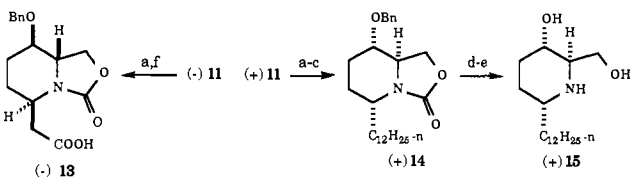


Scheme III[a]



[a] a. L-Selectride, THF, −78 °C, 88%; b. $NaBH_4$, EtOH, −60 °C, 90%; c. Ac_2O, pyridine, 98%; d. $Me_3SiCH_2CH{=}CH_2$, $TiCl_4$, CH_2Cl_2, 25 °C, 88%; e. K_2CO_3, MeOH, 98%; f. NaH, BnBr, THF, 95%.

Scheme IV[a]

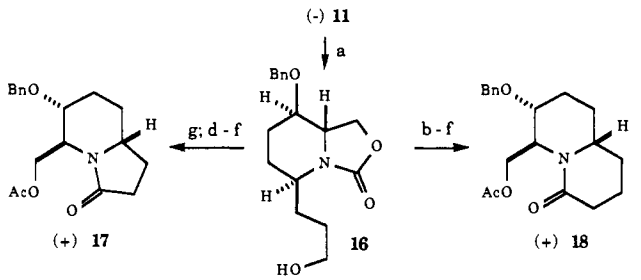


[a] a. O_3, CH_2Cl_2, MeOH, then Me_2S, 90%; b. n-$C_9H_{18}CH{=}PPh_3$, THF, reflux, 35%; c. H_2, Pd(C), 1000 psi, 100%; d. aqueous NaOH, EtOH, reflux, 97%; e. Li, liquid NH_3, 77%; f. H_2CrO_4, acetone, 93%.

structural determination was carried out using acid (−)-**13**, mp 185–187 °C, $[a]_D$ = −96.4° (*c* 0.525, EtOH),[12] easily prepared as shown below.

Identical allylation conditions induced conversion of (−)-**9** into (−)-**10**, $[a]_D$ = −16.8° (*c* 0.800, EtOH), and of (+)-**7** into (+)-**12**. The latter transformation demonstrated that axial selectivity in the allylation reaction is independent of the stereochemistry of the acetoxy substituent in **7**. Specific axial delivery of the allyl group is in agreement with transition state models for nucleophilic additions to immonium species,[13] yet it is in stark contrast to the

Scheme V[a]



[a] a. BH_3-SMe_2, THF, then H_2O_2, aqueous NaOH, 89%; b. MsCl, Et_3N, CH_2Cl_2, 94%; c. NaCN, DMSO, 90%; d. aqueous NaOH, reflux, then aqueous HCl (hydrochloride); e. toluene, reflux, Dean–Stark trap, 60–80%; f. Ac_2O, pyridine, 85%; g. H_2CrO_4, acetone, 98%.

reported behavior of *monocyclic* analogues of **9**, which, under identical allylation conditions,[14] furnish a 2,6-cis-disubstituted piperidine. In our case, the allylation reaction affords protected *trans*-2,6-dialkyl piperidines, subunits readily identifiable in a number of important alkaloid systems. Unlike their cis isomers, they are difficult to prepare, in spite of recent advances in the area.[15] These findings enhance considerably the usefulness of this type of amidoalkylation reaction, now proven to be subject to stereochemical control in the piperidine series. An application is presented in the form of a concise total synthesis of (+)-deoxoprosopinine, **15**,[16] an alkaloid of *Prosopis africana* Taub. Compound (+)-**11**, subject to the sequence outlined below, furnished fully synthetic (+)-**15**, mp 87.0–88.5 °C, $[a]_D$ = +13.2° (*c* 0.310, $CHCl_3$), lit.[14a] mp 85.5 °C, $[a]_D$ = +12°.

The preparation of other important azacyclic synthons was easily accomplished from the allylated compounds. For instance, (−)-**11** served as a convenient point of entry into the izidine[17] manifold, as shown by its smooth conversion into functionalized indolizidine (+)-**17**, $[\alpha]_D$ = +36.4° (*c* 1.106, EtOH) and quinolizidine (+)-**18**, $[\alpha]_D$ = +23.0° (*c* 0.934, EtOH).[18,19] The preparation of these commonly encountered structures augurs well for future applications to alkaloid synthesis.

Chemoenzymatic aza-Achmatowicz methods have thus been extended to the enantiocontrolled preparation of piperidine, indolizidine, and quinolizidine building blocks, in high optical purity, through a key amidoalkylation reaction, which permits stereospecific generation of protected trans-2,6-disubstituted piperidines. Further implications of these findings are being investigated.

Acknowledgment. Generous support for this work was provided by the National Science Foundation (Grant CHE-8708130) and

(11) Crude **10** was homogeneous (^1H, ^{13}C NMR). The coupling constants between the homoallylic methine and the neighboring ring methylene protons were nearly identical (2 Hz; 300 MHz ^1H NMR), consistent with the axial orientation of the allyl group.

(12) (a) Acid **13** is a valuable presursor to β lactams, and applications in this area will be presented in a future report. (b) Orthorombic crystals were obtained from ethyl acetate, space group $P2_12_12_1$ (no. 19); a = 7.517 (1) Å; b = 32.382 (7) Å; c = 6.304 (2) Å; β = 114.92 (4)°; Z = 4; V = 1534.6 (6) Å^3. R = 0.051, R_w = 0.066 for 1134 observed reflections. ORTEP plots are reported as Supplementary Material.

(13) (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289. (b) Deslongschamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, U.K., 1983; p 211ff. It is recognized that the allyl group enters from the *convex* face. The shape of the molecule may well buttress the stereoelectronic effect.

(14) (a) Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. (b) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.

(15) See, e.g.: (a) Mundy, B. P.; Bjorklund, M. *Tetreahedron Lett.* **1985**, *26*, 3899. (b) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973. (c) Saitoh, Y.; Moriyama, H.; Takahashi, T.; Khuong-Huu, Q. *Tetreahedron Lett.* **1980**, *21*, 75. (d) Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. *Tetreahedron Lett.* **1977**, *18*, 825. See also ref 14b,c and literature cited therein.

(16) (a) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 425. Previous syntheses: (b) Saitoh, Y.; Moriyama, Y.; Hirota, H.; Takahashi, T.; Khuong-Huu, Q. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 488 [(−) form, unnatural]. (c) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37 [(±) form]. Ours appears to be the first synthesis of the natural enantiomer of **15**.

(17) The term "izidine" refers to any type of 1-azabicyclo [*m*,*n*,0] ring system.

(18) Izidines **17** and **18** were obtained as thick oils which could not be induced to crystallize. Their rotations, recorded using chromatographed materials, were somewhat variable.

(19) ^1H and ^{13}C NMR spectra (300 MHz) of the MTPA derivatives of optically active **17** and **18** indicated the latter to be optically pure (no diastereomers detected), upon comparison with the spectra of MTPA derivatives of racemic **17** and **18**.

by the Robert A. Welch Foundation (Grant C-1007). We thank Professor Andrew Holmes, University of Cambridge, England, for kindly sharing with us the spectra of natural deoxoprosopinine and Dr. Terry D. Marriott, of this department, for performing all the high-resolution mass spectral measurements.

Supplementary Material Available: ORTEP plots of compounds **6** and **13** and HRMS and spectral data (mp, ^{1}H NMR, $[\alpha]_D$, and ^{13}C NMR) for compounds **7** and **9–18** (8 pages). Ordering information is given on any current masthead page.

Mechanistic and Stereochemical Divergence in the Allylsilane–Acetal Addition Reaction

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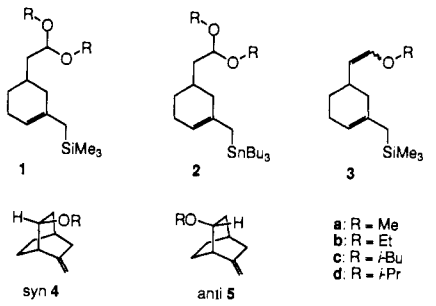
The reaction between acetals and allylic silanes is a mild and general method for formation of homoallylic ethers, Scheme I.[1] Although as first described the reaction required stoichiometric amounts of a Lewis acid, subsequent studies have shown that the reaction can be run *catalytically* using TMSOTf,[2a] TMSI,[1c] or $Ph_3C^+ClO_4^-$.[2b] The stereochemical aspects of the reaction have been slow to develop compared to the related condensations of aldehydes.[3] In the only systematic study on internal asymmetric induction with (*E*)- and (*Z*)-crotylsilanes, Sakurai reported a divergence in behavior between aliphatic and aromatic dimethyl acetals.[1d] Internal stereocontrol in additions of crotylsilanes to glycal acetates has also been studied.[4] In view of the growing interest in selective addition of silicon nucleophiles to chiral acetals[5] we have investigated the mechanism and stereochemical course of the reactions. The questions which have been the focus of our studies are as follows: (1) does the reaction proceed by an S_N1- or S_N2-like mechanism, (2) what factors (acetal structure, allylmetal, Lewis acid) affect the mechanism of the reaction, and (3) is there a mechanistically derived stereochemical preference?

We have addressed these questions by examination of the model systems **1a–d**,[6] **2a–d**,[6] and **3a,b**, and **d**.[6] These systems are related to the analogous models for allylmetal–aldehyde reactions which have been reported previously.[7] In this case, however, cyclization of **1–3** under various conditions will afford the bicyclic ethers **4**[6] and **5**.[6]



The first series of experiments addressed the Lewis acid dependence of cyclization stereochemistry with allylsilane **1a**, Table I. The wide range of selectivities from highly syn selective (TMSOTf) to unselective ($TiCl_4$) strongly suggests the involvement of the Lewis acid in the stereochemistry-determining event and argues against a common oxocarbenium ion intermediate. This idea finds additional support in the comparison of $SnCl_4$ stoichiometries (entries 8 and 9). The divergent selectivities with 1.0 and 0.5 equiv are indicative of direct Lewis acid involvement during bond formation.[8] A parallel series of experiments with the allylstannane **2a** showed similar behavior, Table II. Thus, the nature of the metal had little effect on the outcome of this reaction.[9]

We next examined the effect of acetal structure on the stereochemical course of reaction with the substrates **1a–d** and **2a,b** and **d**. To examine this feature we employed TMSOTf as the Lewis acid (Table III), and the results were surprising. For both **1** and **2** the methyl, ethyl, and isobutyl (**1** only) series were generally syn selective. However, the isopropyl cases were strikingly different showing a slight anti preference. We interpret the dramatic difference in selectivity as representing a change in mechanism rather than a steric effect related to the branching of the isopropyl group.

There are two possible limiting mechanisms for reaction, S_N2 via a complex and S_N1 via an oxocarbenium ion. The results from variations in Lewis acid and acetal structure suggested that there may be a stereochemical manifestation of the changes in mechanism. We sought to test this hypothesis by establishing the stereochemical outcome of cyclizations with the putative oxocarbenium ion, i, formed by protonation of the enol ethers, **3**, Scheme II. If the reactions of **1a–d** with TMSOTf involve prior formation of i, then the same stereochemical outcome should obtain if i is generated by TfOH protonation of the enol ethers **3**. Contrariwise, if the enol ethers cyclize to give different results, then the TMSOTf reactions cannot proceed through i.[10]

Cyclization of the enol ethers was promoted with 0.95 equiv of TfOH, and the results are found in Table IV. Initially, we anticipated a difference between the *E* and *Z* isomers,[10] but the results are nearly identical in each case. The dramatic difference of the results from the methyl enol ethers (**3a**) and corresponding acetal **1a** (Table III) strongly suggests the operation of two different mechanisms of cyclization. An analogous divergence can be seen for the ethyl enol ether (**3b**) and corresponding acetal (**1b**). On the other hand, the similarity in stereochemical outcome for the isopropyl cases (**3d** vs **1d**, Table III) may be taken as a reflection of reaction via a common intermediate.[11]

We conclude that the stereochemistry of cyclization of models **1** and **2** was dependent on the mechanism of activation. Thus with

(1) (a) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941. (b) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (c) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745. (d) Hosomi, A.; Ando, M.; Sakurai, H. *Chem. Lett.* **1986**, 365.

(2) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71. (b) Mukaiyama, T.; Nagaoka, H.; Murakami, M.; Ohshima, M. *Chem. Lett.* **1985**, 977.

(3) Aspects of anomeric stereocontrol in the context of C-glycoside synthesis have been studied: (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *37*, 3803. (c) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. (d) Keck, G. E.; Enholm, E. J.; Kachensky, D. F. *Ibid.* **1984**, *25*, 1867.

(4) Danishefsky, S. J.; Lartey, P.; DeNinno, S. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

(5) (a) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (b) Andrew, R. G.; Conrow, R. E.; Elliott, J. D.; Johnson, W. S.; Ramezani, S. *Tetrahedron Lett.* **1987**, *28*, 6535. (c) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755. (d) Seebach, D.; Imwinkelried, R.; Stucky, G. *Helv. Chim. Acta* **1987**, *70*, 448.

(6) All new compounds have been fully characterized by ^{1}H and ^{13}C NMR, IR, MS, and microanalysis (±0.3%).

(7) (a) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655. (b) Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970. (c) Denmark, S. E.; Henke, B. R.; Weber, E. J. *Ibid.* **1987**, *109*, 2512. (d) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053.

(8) Low-temperature, ^{1}H NMR spectroscopic examination of solutions containing **1a** with 1.0 and 0.5 equiv of $SnCl_4$ showed the exclusive existence 1:1 and 2:1 complexes, respectively.

(9) In the intermolecular additions to steroidal acetals, Yamamoto found a metal-dependent stereoselectivity and invoked a metal-based change in mechanism to explain this. Yamamoto, Y.; Nishii, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116.

(10) This hypothesis presupposes that the oxocarbenium ion formed from the different precursors is of the same configuration, assumed to be *E*. Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.

(11) The interesting trend toward anti selectivity with increasing steric bulk of R in **3** will be discussed in a full account of this work.

0002-7863/89/1511-3475$01.50/0