Stereoselective Nucleophilic Additions to Trialkylsilyl-Substituted Acyclic Acetals

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Summary: Regioselective and diastereoselective Mukaiyama-type aldol reactions of silyl-substituted mixed acyclic acetals provide the aldol products with 5:1 to 14:1 selectivity.

There have been many recent reports concerning the mechanism and diastereoselectivity of nucleophilic addition reactions to cyclic acetals.[1-4] These investigations have delineated a complex mechanistic pathway which is dependent upon the structure of the cyclic acetal, the relative reactivity of the attacking nucleophile, and the Lewis acid catalyst employed. Mechanistic hypotheses ranging from the extremes of direct nucleophilic displacement (S_N2) of a Lewis acid complex to prior formation of an oxocarbenium ion (S_N1) as well as the involvement of equilibrating ion pairs have all been examined. The general conclusions which may be drawn from these studies are that cyclic acetals do not react exclusively by a single mechanism.

Acyclic acetals have not been examined in as rigorous a manner.[5] There are, however, a few reports of nucleophilic addition reactions (allyl species or hydride) to bulky acetals which occurred with a considerable degree of stereoselectivity.[6] Although the mechanisms for these nucleophilic addition reactions were not fully probed, the stereoselection may be rationalized by allylic-1,3-strain arguments.[7] In contrast to the results of nucleophilic addition to cyclic acetals,[2-4] reasonable levels of stereoselectivity for addition reactions to acyclic acetals is apparently obtained by a S_N1 pathway involving an oxocarbenium ion intermediate. Independent generation of oxocarbenium ions from enol ethers[2a] and recent computational studies of Houk and co-workers[8] lend support to this assertion. In agreement with earlier theoretical and experimental results,[9] the global conformational minima

Scheme I

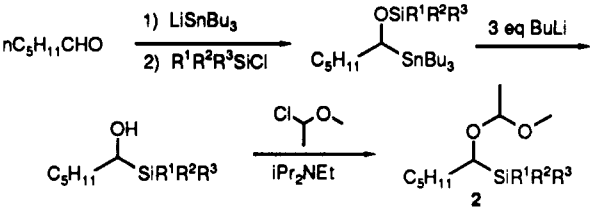
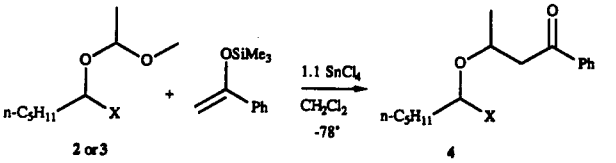


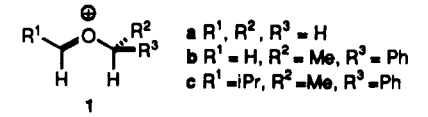
Table I. Diastereoselective Mukaiyama-Type Aldol Reactions



entry	acetal X =	selectivity[a]	yield,[b] %
1	**2a**, Me_3Si^-	5.0:1	**4a**, 71
2	**2b**, Et_3Si^-	5.5:1	**4b**, 73
3	**2c**, $tBuMe_2Si^-$	6.6:1	**4c**, 66
4	**2d**, Me_2PhSi^-	11.6:1	**4d**, 83
5	**2e**, $MePh_2Si^-$	13.0:1	**4e**, 59
6	**3**, *t*-Bu^-	1.2:1	**4f**, 92

[a] Diastereomeric ratio determined by capillary GC and/or ^1H NMR integration of the –C(H)X methane proton. [b] Isolated yield of analytically pure material. All new compounds exhibited correct spectral and analytical data.

for an oxocarbenium ion was determined to be the trans-skewed isomer 1.[8] Rotation about the CO double bond was calculated as >25 kcal/mol for **1a**, and rotation about the O–C single bond leading to an eclipsed conformer was calculated as 1.1 kcal/mol for **1b**. The computational results predict a reasonable degree of stereoselection for nucleophilic attack on oxocarbenium ion **1b**. The predictive value of this approach is illustrated by noting that a 92:8 diastereomeric ratio was realized by Imwinkelreid and Seebach[6a] in allylation of **1c**. One must note that while the relative transition-state energies control the diastereoselectivity of a reaction (Curtin–Hammett principle), it is not unreasonable to assume that factors which influence the reactant conformational energy will also influence the transition state conformational energy and therefore induce selectivity in the reaction.[10]



We wish to now report regioselective and stereoselective Mukaiyama-type aldol reactions of acyclic silyl- and stannyl-substituted mixed acetals. We believe that the

(1) For a review of chiral cyclic acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 447.

(2) (a) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458. (c) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485. (d) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475. (e) Denmark, S. E.; Willson, T. M.; Almstead, N. G. *J. Am. Chem. Soc.* **1989**, *111*, 9258.

(3) (a) Mori, I.; Ishikara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107. (For stereoselective additions to thionium ions, see: Mori, I.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 5966). (b) Ishikara, K.; Yamamoto, H.; Heathcock, C. H. *Tetrahedron Lett.* **1989**, *30*, 1825. (c) Ishikara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074.

(4) (a) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997. (b) Sato, T.; Otera, J.; Nozaki, H. *J. Org. Chem.* **1990**, *55*, 6116. (c) Yamamoto, Y.; Abe, H.; Nishii, S.; Yamada, J. *J. C. S. Perkins 1* **1991**, 3253.

(5) Several examples of acyclic acetals are included within earlier studies cited; see, for example, refs 2a, 3a, and 4b.

(6) (a) Imwinkelreid, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 591. (b) Mukaiyama, T.; Ohshima, M.; Muyishi, N. *Chem. Lett.* **1987**, 1121. (c) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314. (d) Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **113**, 3608. The structural effects on unsymmetrical acetal cleavage have been examined in detail: (e) Willson, T. M.; Amburgey, J.; Denmark, S. E. *J. Chem. Soc., Perkins Trans. 1* **1991**, 2899.

(7) For a review of allylic-1,3-strain as a means for stereocontrol, see: Hoffman, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(8) Broecker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.

(9) (a) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435. (b) Blackburn, C.; Childs, R. F.; Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1985**, *107*, 2442. (c) Lottes, A. C.; Landgrebe, J. A.; Larsen, K. *Tetrahedron Lett.* **1989**, *30*, 4089.

(10) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science (Washington, D.C.)* **1986**, *231*, 1108.

0022-3263/92/1957-5078$03.00/0

stereoselectivity of this reaction is due to generation of an oxocarbenium ion prior to nucleophilic addition.

The (α-hydroxyalkyl)trialkylsilane precursors were prepared via the reverse Brook methodology[11] illustrated in Scheme I. Protection of the alcohol as the acetal **2** was then accomplished in good yield. Each mixed acetal was obtained as a 1:1 ratio of diastereomers as evidenced by GC and ^{1}H-NMR. The acetals were then subjected to Lewis acid catalyzed aldol reaction using the silyl enol ether of acetophenone, Table I. For comparison, the non-silyl-substituted acetal **3** bearing a *tert*-butyl group in place of the R_3Si moiety is also listed in Table I, entry 6. All of the aldol reactions (acetals **2a–e** and **3**) exhibited regioselective cleavage of the methoxy group. The observed regioselectivity can be readily explained by preferential complexation of the Lewis acid to the more accessible (methoxy) oxygen of the acetal.[12] The diastereoselectivity of the reaction (GC analysis of crude reaction mixtures) ranged from 5:1 for the Me_3Si substituent to 13:1 for the $MePh_2Si$-substituted acetal. Remarkably, the *t*-Bu acetal **3** provided aldol product **4f** as a 1.2:1 mixture of diastereomers. The nearly complete lack of stereoselection for the *t*-Bu acetal **3** relative to the Me_3Si acetal **2a** clearly implies that the diastereoselectivity of the nucleophilic addition reaction is not a purely steric phenomenon.

Given the fact that the *t*-Bu group is more sterically demanding than the Me_3Si group,[13] the silyl moiety must also play a stereoelectronic role in the reaction. We believe that the R_3Si substituent enhances formation of an oxocarbenium ion by a stereoelectronic effect similar to the well-documented hyperconjugative stabilization of a β-carbocation.[14] Recently, Brook and co-workers[15] have invoked hyperconjugative stabilization as a means to control the stereochemistry of addition to carbocations. To achieve stabilization by hyperconjugation, a geometric constraint is placed on the molecule to provide overlap of the C–Si σ bond and the carbocation p-orbital. An analogous argument can be made for the C–Si σ bond and the developing C=O π* orbital. Presuming an (*E*)-oxocarbenium ion stereochemistry and taking into consideration the conformational bias described by Houk and coworkers,[8] the silyl-substituted oxocarbenium ion would be expected to adopt the conformation shown as **5**. Rotation about the C–O bond of **5** would be expected to have a considerably larger energy barrier than that for oxocarbenium ion **1b**. A clear facial bias for nucleophilic attack away from the bulky Me_3Si group is evident upon examination of the Newman-type projection of **5** predicting the "anti" isomer of the aldol product. The stereochemistry of aldol products **4a–e** could not be unambiguously assigned by NMR; however, acetal **6** when reacted with silyl enol ether **7** provided aldol product **8** as a 14.0:1 mixture of diastereomers (89% yield). The semicarbazone derivative of **8** provided crystals suitable for X-ray crystal structure analysis which established the relative stereochemistry (shown in **8**) as that predicted by preferential facial attack away from the silyl substituent.

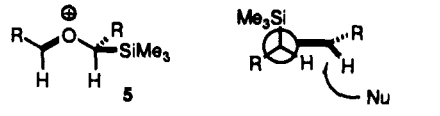
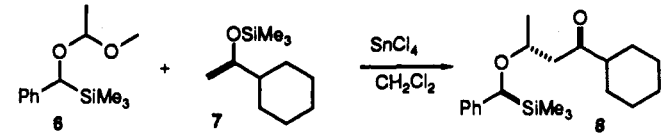


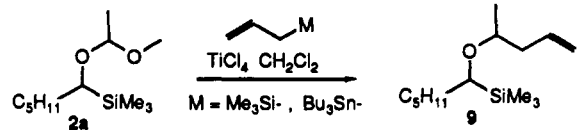
Table II. Diastereoselectivity as a Function of Lewis Acid Employed in the Conversion of 2d to 4d

entry	Lewis acid[a]	selectivity[b]	yield,[c] %
1	$SnCl_4$	11.6:1	83
2	$TiCl_4$	11.6:1	86
3	BF_3·Et_2O	11.3:1	72
4	Et_2AlCl	11.7:1	86
5	$EtAlCl_2$	11.1:1	73
6	$AlCl_3$	11.6:1	76
7	Me_3SiOTf	12.5:1	70
8	$Ti(O\text{-}i\text{-}Pr)_4$		0

[a] Reactions were carried out at −78 °C in CH_2Cl_2 (3 h) using 1.1 equiv of Lewis acid. [b] Diastereomeric ratio determined by capillary GC and/or ^{1}H NMR integration of the –C(H)X methane proton. All new compounds exhibited correct spectral and analytical data. [c] Isolated yield of analytically pure material.



This rationalization of diastereoselectivity implies that the reaction proceeds via an S_N1 pathway. The relative reactivity of the attacking nucleophile has been used as a means to assess S_N1 vs S_N2 processes.[2a,c,4b] More reactive nucleophiles provided an enhanced stereoselectivity in reactions with single isomers of cyclic acetals, indicating an S_N2 pathway. In the case of nucleophilic additions to acetal **2**, a more reactive species undergoing nucleophilic attack predominately by an S_N2 pathway should be less selective. Alkylation of **2a** to provide **9** was accomplished using both allyltrimethylsilane (65%, 5.2:1 diastereoselectivity) and allyltributylstannane (66%, 2.2:1 diastereoselectivity). The more reactive stannane[15c] did result in a less selective reaction as anticipated.



Previous studies have also indicated that the choice of Lewis acid may affect the stereoselectivity of the addition reaction to cyclic acetals.[2-4] Table II lists the diastereoselectivity for a series of reactions of acetal **2d** to aldol product **4d**. The reactions of **2d** were surprisingly insensitive to the Lewis acid employed with selectivities ranging from 11.1:1 for $EtAlCl_2$ to 12.5:1 for Me_3SiOTf. These results provide evidence in favor of an S_N1 mechanism.[2] However, the stereoselectivity of reactions of the Me_3Si-substituted acetal **2a** did reveal a strong dependence on the Lewis acid. As illustrated in Table I, entry 1, $SnCl_4$-catalyzed conversion of **2a** to **4a** occurred with a 5.0:1 diastereoselectivity while the same reaction using Me_3SiOTf provided the aldol product in 85% yield as a 10.0:1 ratio of diastereomers. These data indicate that the Me_3Si-substituted acetal may be undergoing the aldol reaction by a blend of S_N1 (stereoselective) and S_N2 (nonstereoselective) mechanistic pathways similar to that observed for the cyclic acetals. Further support for a stereoselective polar S_N1 mechanism was obtained by

(11) Linderman, R. J.; Ghannam, A. *J. Am. Chem. Soc.* **1990**, *112*, 2392.

(12) For recent examples of regioselective acetal cleavage, see: (a) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101. (b) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7223.

(13) For a discussion of steric effects for R_3Si, see: Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599.

(14) (a) For a review, see: Lambert, J. B. *Tetrahedron*, **1990**, *46*, 2677. (b) Nguyen, K. A.; Gordon, M. S.; Wang, G.-T.; Lambert, J. B. *Organometallics* **1991**, *10*, 2798. (c) Lambert, J. B.; Wang, G. T.; Teramura, D. H. *J. Org. Chem.* **1988**, *53*, 5422.

(15) (a) Brook, M. A.; Neuy, A. *J. Org. Chem.* **1990**, *55*, 3609. (b) Dallaire, C.; Brook, M. A. *Organometallics* **1990**, *9*, 2873. The extent of stabilization is dependent on the substituents on silicon.[15b] Hagen and Mayr[15c] have also reported a similar affect in a quantitative determination of the nucleophilicity of allylmetal species: (c) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.

Scheme II

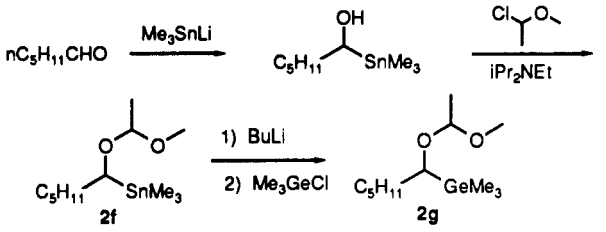


Table III. Stereoelectronic Effects on the Diastereoselectivity of the Aldol Reaction

entry	acetal X = [a]	selectivity[b]	yield,[c] %
1	**2a**, Me_3Si^-	10.0:1	**4a**, 85
2	**2g**, Me_3Ge^-	10.9:1	**4g**, 75
3	**2f**, Me_3Sn^-	15.5:1	**4h**, 80
4	**3**, *t*-Bu	1.4:1	**4f**, 90

[a] For acetal structure, see Table I. All reactions were carried out at −78 °C in CH_2Cl_2 (3 h) using 1.1 equiv of Me_3SiOTf. [b] Diastereomeric ratio determined by capillary GC and/or ^1H NMR integration of the −C(H)X methane proton. [c] Isolated yield of analytically pure material.

comparing the Me_3SiOTf-catalyzed reaction of **2a** to **4a** in hexane. While the reaction in CH_2Cl_2 as solvent gave 10.0:1 selectivity, the product **4a** obtained from the reaction carried out in hexane was isolated as only a 3.0:1 ratio.

Additional evidence in support of the stereoelectronic role of the silyl substituent has also been obtained. A competition reaction combining Me_3Si substituted acetal **2a** and the *t*-Bu-substituted acetal **3** in a reaction with the silyl enol ether of acetophenone resulted in the silyl-substituted aldol product **4a** exclusively. None of the *t*-Bu adduct **4f** was detected in the crude reaction mixture. This result clearly implies that the trimethylsilyl-substituted acetal ionizes at a faster rate than the *t*-Bu substituted acetal.

The ability of trialkylstannanes to stabilize β-carbocations to a greater extent than trialkylsilanes is well-documented.[14] Therefore, the analogy to hyperconjugation implies that the stannyl-substituted acetal should be more stereoselective than the analogous silyl acetal. The Me_3Sn acetal **2f** was readily prepared by condensation of Me_3SnLi[16] and hexanal, followed by protection of the alcohol with chloroethyl methyl ether (Scheme II). The Me_3Ge acetal **2g** was prepared by alkylation of the α-alkoxylithio anion[16,17] generated from **2f** with Me_3GeCl. The results of the conversion of acetals **2a**, **2f**, and **2g** to aldol products **4a**, **4g**, and **4h** as well as **3** to **4f** using Me_3SiOTf as the Lewis acid are given in Table III. As anticipated, the selectivity of the aldol reaction for the trimethylstannyl-substituted acetal **2f** (15.5:1) was greater than that for any of the R_3Si acetals examined (compare Table I and III). Once again, the *t*-Bu acetal **3** did not undergo a stereoselective reaction.

This study indicates that acyclic acetals may undergo stereoselective nucleophilic addition reactions by prior formation of an oxocarbenium ion. The unique role of trialkylsilyl and stannyl substituents in controlling the diastereoselectivity may be due to stereoelectronic and steric factors. Given the synthetic utility of aldol products such as **4** in the synthesis of oxacyclic compounds via the electrophilic carbonyl ylide synthon methodology we recently described,[19] this novel acyclic diastereoselective reaction may have considerable potential. We are continuing to explore the salient features of the working hypothesis developed by these preliminary results to achieve further improvement in the stereoselectivity of the reaction.[20]

Acknowledgment. T.V.A. gratefully acknowledges a fellowship from the Burroughs Wellcome Fund.

Supplementary Material Available: Spectral and analytical data for acetals **2a–g**, **3**, **6**, aldol products **4a–h**, **8**, and allyl addition product **9** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980** *102*, 1201.
(17) Linderman, R. J.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491.
(18) For a recent example of a diastereoselective addition of an allylsilane involving an S_N1 mechanism, see: Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594.
(19) (a) Linderman, R. J.; Viviani, F. G.; Kwochka, W. R. *Tetrahedron Lett.* **1992**, *33*, 3571. (b) Linderman, R. J.; Graves, D. M.; Kwochka, W. R.; Ghannam, A. F.; Anklekar, T. V. *J. Am. Chem. Soc.* **1990**, *112*, 7438. For other recent examples of the synthetic utility of α-alkoxyorganostannanes, see inter alia: (c) Fuchs, P. L.; Hutchinson, D. K. *J. Am. Chem. Soc.* **1987**, *109*, 4930. (d) Chong, J. M.; Chan, P. C. M. *Tetrahedron Lett.* **1990**, *31*, 1985. (e) Prandi, J.; Audin, C.; Beau, J. M. *Tetrahedron Lett.* **1991**, *32*, 769.
(20) **General Experimental Procedure.** The silyl enol ether (0.63 mmol) and the (α-alkoxyalkyl)silane (0.54 mmol) were combined in 5.4 mL of dry CH_2Cl_2 and cooled to −78 °C (CO_2/acetone). The Lewis acid (0.63 mmol) was then added dropwise (neat) and the reaction mixture stirred at −78 °C for 2 h. The reaction mixture was quenched at −78 °C by the addition of 2 mL of water. After being warmed to room temperature, the mixture was diluted with 15 mL of ether and washed with water (2 × 15 mL). The combined aqueous phases were then washed with ether (2 × 5 mL). The organic phases were combined and dried over $MgSO_4$ and the solvent then removed at reduced pressure. The crude aldol product was assayed for % de (capillary GC) and then purified by chromatography (flash or radial preparative, SiO_2) using 5–10% ether–hexane as eluent.