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STERIC INFLUENCE OF SILYL GROUPS IN TITANIUM- AND LITHIUM-MEDIATED ALDOL CONDENSATIONS

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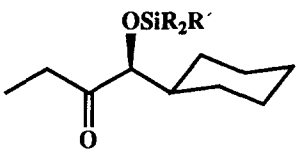
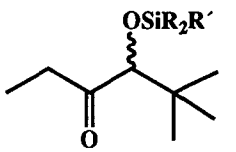
Abstract: Reactions of lithium enolates of α-silyloxyketones **1a**, **1b**, **2a**, and **2b** with benzaldehyde yield opposite diastereoselection depending upon the size of the silyl group, but all four titanium enolates lead to high diastereofacial selectivities. These results implicate a nonchelated transition structure which is insensitive to the steric size of the silyl group for the titanium-mediated aldol reactions. Ketone **1a** is shown to give high selectivities for the two opposite syn adducts (99:1 with Ti; 10:90 with Li). Because it is readily prepared in monochiral form, **1a** may offer advantages as a chiral precursor for preparation of either product stereochemistry, as desired.

The aldol condensation is one of the most important C–C bond-forming reactions. Asymmetric aldol reactions between chiral ketones and aldehydes have been found to be highly useful in organic syntheses, where the two new chiral centers formed can be controlled by the stereochemistry of the chiral ketones.[1,2] For instance, two closely related α-silyloxy ketones, **1b** and **2a**, independently introduced by the groups of Masamune[3,4,5] and Heathcock,[6,7]



1a R = R´ = Me
1b R = Me; R´ = CMe_3



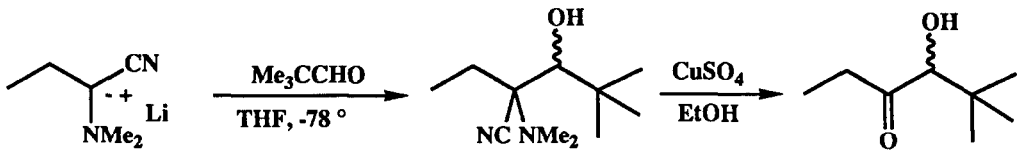
2a R = R´ = Me
2b R = Me; R´ = CMe_3

respectively, have been reported to give moderate to high diastereofacial selectivity depending upon the choice of the enolate metal ion. The boron enolate of **1b** gives a useful level of selectivity favoring the aldol product diastereomer expected from a nonchelated transition structure, but lithium gives poor stereoselectivity with this system. However, the *opposite* diastereoselectivity was observed in the aldol adducts derived from the lithium enolate of **2a** with benzaldehyde, i. e., **1b** gives 56:44[8,9] whereas **2a** gives 18:82,[10] and has recently been developed to yield < 5:95 ratios with several aldehydes.[11]

Two possible factors could be responsible for the above dichotomy between **1b** and **2a**: either the alkyl side chain, e. g., the secondary nature of the cyclohexyl vs. the tertiary *tert*-butyl , or the silyl group, i. e., trimethylsilyl vs. the bulkier *tert*-butyldimethylsilyl (or both). We envisioned that careful comparisons of these stereoselective outcomes with those of the other two α-silyloxyketones, **1a** and **2b**, would experimentally explain the dichotomy and identify the origin of the effect.

In this letter, we wish to report the first evidence of the significant effect of silyl group size on the aldol stereoselection of lithium and titanium enolates. Silyl group bulk has been shown to control stereochemical outcomes in a number of other chemical reactions.[12] However, considering that the silyloxy groups in enolates of types **1** and **2** could apparently rotate to avoid direct steric interactions, it seemed that the major difference between **1** and **2** might well lie in the secondary vs. tertiary alkyl groups. Hence, it was by no means clear that silyl group size should be the controlling factor in *aldol* transition structures.

α-Silyloxyketones **1a** and **1b** were prepared by silylation of the parent alcohol.[3–5,8,9] Compounds **2a** and **2b** were prepared in the same manner from the parent alcohol,[6,7] which was alternatively prepared as shown in eq 1.[13]



(1)

Reaction of the masked carbonyl equivalent lithium salt[14,15] with trimethylacetaldehyde provided the adduct in 90% yield, and hydrolysis with $CuSO_4$ in ethanol ultimately gave the desired precursor of **2a** and **2b** in quantitative yield.

Aldol reactions of lithium and titanium enolates of these ketones were carried out by previously developed procedures.[6–9] The results of our investigations are presented in Table I. Stereostructures of aldol adducts were determined by comparison of ^1H NMR spectra with previously reported data.[6–9] Stereochemical assignments of **3b** and **5b** were previously proved;[5,8] the ratio was taken by comparison of the doublet signals of the benzylic methine protons at δ 5.05 and δ 4.92, respectively. Close analogy permitted evaluation of the diastereomeric ratio of **3a** at δ 5.03 to **5a** at δ 4.95. Similarly, the stereochemistries of **4a** and **6a** have been previously assigned;[6,7] the ratios of aldol adducts derived from **2a** and **2b** were obtained from the singlet signal of the proton bearing the silyloxy group: **4a**, δ 3.88; **6a**, δ 3.77; **4b**, δ 3.95; **6b**, δ 3.81.

Ketones **1a** and **2a**, containing the less bulky silyl group (TMS), have shown high selectivity as their lithium enolates, giving syn products with two new chiral centers anti to the silyloxy moiety (S_2). Surprisingly, ketones **1b** and **2b**, containing the bulkier silyl group (TBDMS), show very low levels of diastereoselectivity. Ketone **1a** is readily available in monochiral form and gave a high stereoselectivity ratio with benzaldehyde. Such aldol adducts quantitatively provide the corresponding enantiomeric β-hydroxy-α-methylcarboxylic acids, very useful synthetic intermediates, via deprotection and sodium metaperiodate oxidation.[5]

The Zimmerman-Traxler model,[16] a six-membered transition structure having a chair conformation, best explains these results. The boron enolates of both **1b** and **2a** give the same facial selectivity, resulting in **3b** and **4a**, respectively. Since boron cannot engage in chelation with the silyloxy group when also coordinated to the aldehyde, nonchelated transition structure **A** is indicated as the source of the observed stereochemistry. This transition structure places the smallest group (H) attached at the chiral center inward, so that the silyloxy group and the alkyl group R″ are both oriented away from the metal and its ligands as well as the quasi-axial H from the aldehyde. **A** should be favored relative to the nonchelated alternative **D** since the repulsive interaction between R″ and the quasi-axial H should be larger in **D** than the corresponding silyloxy···H repulsion in **A**; moreover, a dipolar repulsion between the polar $C–O^{\delta-}Si$ bond and the $O^{\delta-}$ of the enolate, present in **D** but not in **A**, should be significant in such a solvent of low dielectric constant solvent. The source for products S_1 is therefore best interpreted as transition structure **A**.

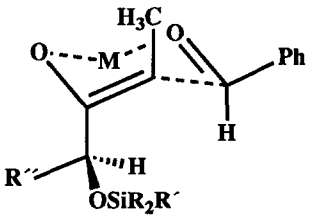
Lithium, however, is in principle capable of chelation, and it has been proposed that the lithium enolate of **2a** reacts at its less hindered face via chelated transition structure **C** to give predominantly **4a**.[6,7,10] **C** should be preferred over the chelated alternative **B**, since **B** contains a repulsive silyloxy···quasi-axial H interaction, while **C** contains only an H···H interaction instead. It is thus likely that **5a** is also obtained via transition structure **C**. The low selectivities given by the lithium enolates of **1b** and **2b** indicate that the larger steric requirement of the *tert*-butyldimethylsilyl group discriminates against transition structure **C**.

Despite the effect of the silyloxy group in the aldol reactions of the lithium enolates, the corresponding titanium enolates of all four chiral ketones gave a unique and dramatic result—they gave the syn, syn product (S_1), indicating very high nonchelation control, in every case (employing a three-fold molar excess of $ClTi(OCH(CH_3)_2)_3$, as we had discovered to be required for high stereoselectivities[8,9]).[17] These results are surprising in view of our prior demon-

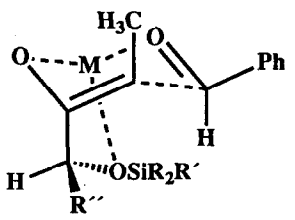
Table I. Stereoselection of Ketones **1a**, **1b**, **2a**, and **2b** with Benzaldehyde

Enolate	Ketone	Products	Diastereomeric %,[a] S_1:S_2
Lithium	**1a**	**3a:5a**	10:90
Lithium	**1b**	**3b:5b**	56:44[b]
Lithium	**2a**	**4a:6a**	18:82[c]; < 5:95[d]
Lithium	**2b**	**4b:6b**	43:57
Titanium	**1a**	**3a:5a**	99:1
Titanium	**1b**	**3b:5b**	99:1[b]
Titanium	**2a**	**4a:6a**	95:5[e]
Titanium	**2b**	**4b:6b**	93:7

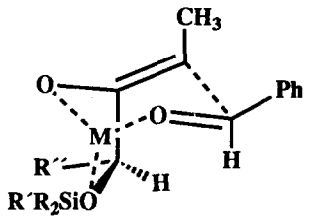
[a]Percents determined by 500 MHz ^{1}H NMR of crude mixture. [b]From[8]. [c]From[10]. [d]From[11]. [e]Cf.[17].



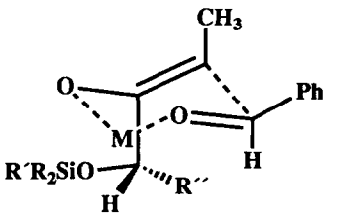
A



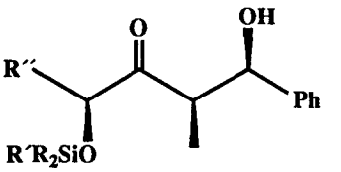
B



C

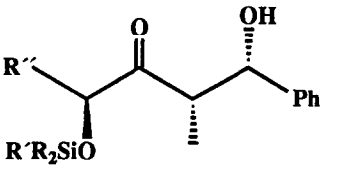


D



S_1

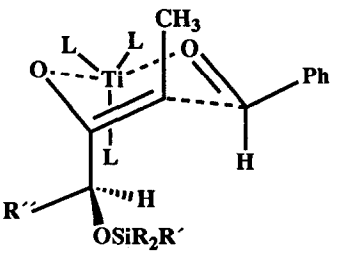
3a R = R´ = Me; R´´ = cyclohexyl
3b R = Me; R´ = CMe_3; R´´ = cyclohexyl
4a R = R´ = Me; R´´ = CMe_3
4b R = Me; R´ = CMe_3; R´´ = CMe_3



S_2

5a R = R´ = Me; R´´ = cyclohexyl
5b R = Me; R´ = CMe_3; R´´ = cyclohexyl
6a R = R´ = Me; R´´ = CMe_3
6b R = Me; R´ = CMe_3; R´´ = CMe_3

stration of chelation control in the aldol reaction of a titanium enolate derived from an acyloxazolidinone.[18] They are, however, in excellent agreement with our previously proposed transition structure similar to A,[8,9] as shown in E. To minimize steric repulsions, the bulky alkyl side chain is preferentially oriented away from the pseudo-axial aldehydic proton, and the *tert*-butyldimethylsilyloxy group is simultaneously oriented away from the titanium ligands. Even though the smaller OTMS group suffices to permit strong chelation control with lithium, and in spite of the fact that chelation control is known to exist with another titanium enolate,[18] the indication is that the OTMS and the titanium isopropoxy ligands conspire to yield a net steric repulsion which overcomes the potential favorablility of chelation.



E

Two main conclusions can be drawn from this work. (1) We have shown that the hexahydromandeloyl system **1a**, which can be readily prepared from commercially available, monochiral mandelic acid,[3–5,8,9] has interesting possible potential for preparation of S_1 (at 99:1, via its titanium enolate) *or* S_2 (at 10:90, via its lithium enolate). Thus, *either* syn product would be available from the *single*, readily available precursor **1a**. (2) Mechanistically, we have shown that the bulk of the silyloxy group (OTMS vs. OTBDMS) is the stereocontrolling factor in reactions of the lithium enolates of substrate types **1** and **2** with benzaldehyde, and that, in the case of titanium enolates, the titanium ligands apparently preclude otherwise favorable chelation of the OTMS group.

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References

(1) Heathcock, C. H. In *Asymmetric synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, **1984**; Vol. 3, pp 111–212.

(2) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.

(3) Masamune, S.; Choy, W. *Aldrichim. Acta* **1982**, *15*, 47–63.

(4) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 557–558.

(5) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566–1568.

(6) Heathcock, C. H.; Pirrung, M. C.; Lampe, J.; Buse, C. T.; Young, S. D. *J. Org. Chem.* **1981**, *46*, 2290–2300.

(7) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 7077–7079.

(8) Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722–5728, and references therein.

(9) Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 457–460.

(10) Heathcock, C. H.; Arseniyadis, S. *Tetrahedron Lett.* **1985**, *26*, 6009–6012. See also: *Ibid.* **1986**, *27*, 770.

(11) Heathcock, C. H. ACS Award for Creative Work in Synthetic Organic Chemistry: award address; *Abstracts of Papers*, 199th National Meeting of the American Chemical Society, Boston, MA; American Chemical Society: Washington, DC, 1990; ORGN 193, and Private Communication of results (in press).

(12) Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599–1615.

(13) A convenient preparation of monochiral **2a** has been developed (Ref. 11).

(14) Reutrakul, V.; Nimgirawath, S.; Panichanun, S.; Ratananukul, P. *Chem. Lett.* **1979**, 399–400.

(15) Albright, J. D.; McEvoy, F. J.; Moran, D. B. *J. Heterocycl. Chem.* **1978**, *15*, 881–892.

(16) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

(17) The *E*-titanium enolate of **2a** has also been shown to undergo aldol reactions in precisely the same sense as the *Z*-titanium enolates of **1a** and **2a** as shown in Table I (Ref. 11).

(18) Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897–900.

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