JOC*Note*

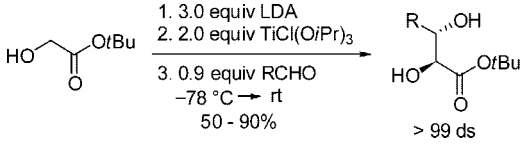
Highly Diastereoselective *anti*-Aldol Reactions of Glycolate Titanium Enolates

Dnyaneshwar Gawas and Uli Kazmaier*

Institut für Organische Chemie, Universität des Saarlandes, 66123 Saarbrücken, Germany

u.kazmaier@mx.uni-saarland.de

Received November 19, 2008



Diastereoselective aldol reactions of enolates of α-hydroxy ester with different aldehydes are metal tunable, providing either *anti*- or *syn*- products. The highest *anti*-selectivities were obtained with $TiCl(OiPr)_3$, while $Ti(OiPr)_4$ provides the opposite *syn*-products.

The aldol reaction is probably one of the most popular C−C-coupling reactions in organic chemistry and, therefore, it found a wide range of applications in total synthesis of complex natural product and related molecules.[1] Its mechanistic features and parameters influencing the stereochemical outcome of the reaction were investigated in great detail in the early 80s by Ireland,[2] Heathcock,[3] Evans,[4] and many others.[5] The relative configuration of the aldol product depends strongly on the configuration of the enolate reacting with the aldehyde. Therefore, control of the enolate geometry is important for a diastereoselective course of the aldol reaction. The configuration of the double bond in a lithium ester enolate is related to the polarity of the medium.[6] However, aldol reactions of these lithium enolates in general show no significant stereoselectivity.[7]

From a synthetic point of view, enolate formation of esters containing α-heteroatom substituents is of great importance; in many cases these enolates can be formed chelation- or nonchelation-controlled.[8]

A wide range of important compounds in organic chemistry comprise α,β-dihydroxy carbonyl functionalities. This unit occurs in carbohydrates as well as in many natural products. Not surprising, α-alkoxy- or α-silyloxy-substitued esters have been used frequently to built up partially protected polyhydroxylated esters. In all examples reported so far the *syn*-aldol product is formed preferentially.[9] On the other hand, in many natural products such as rapamycin (immune suppressant agent),[10] AI-77B (antiulcerogenic, antihistaminergic activity),[11] and tartrolon B (antibiotic),[12] the stereochemistry of diols is *anti*. These structures cannot be obtained so easily.

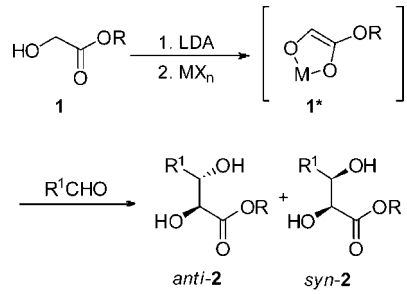
Pearson et al. reported an *anti*-selective route to optically pure α,β-dihydroxy carbonyl compounds based on the aldol condensation of chiral glycolate enolates,[13] and Andrus et al. described the formation of *anti*-diols from boron enolates of pyrone.[14] In both of these cases, chiral auxiliaries were used, which were then removed after the enolate reactions.

Mahrwald et al. reported the synthesis of *anti*-configured aldol adducts of mandelic acid esters by using (−)-*N*-methylephedrine as a chiral base.[15] Very recently, Denmark et al. described the enantioselective addition of glycolate-derived silyl ketene acetals to aldehydes using their "Lewis base activation of Lewis acids" approach.[16] They observed that TBDMS ketene acetals derived from bulky esters of α-methoxyacetic acid provide enantiomerically enriched α,β-dihydroxyesters with high *anti*-diastereoselectivity.

(1) Nielsen, A. T.; Houlihan, W. J. *Organic Reactions*; Wiley: New York, 1968; Vol. 16.
(2) (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.
(3) (a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc.* **1979**, *101*, 7076–7077. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 2.
(4) (a) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *J. Pure Appl. Chem.* **1981**, *53*, 1109–1127. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1–115.
(5) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem.* **1985**, *97*, 1–30; *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1−30. (b) Braun, M. In *Advance in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: Greenwich, 1992; Vol. 1.
(6) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975–3978.
(7) Heathcock, C. H.; Buse, C. T.; Kleschik, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.
(8) Mekelburger, H. B.; Wilcox C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon Press: New York, 1991; Vol. 2, p 101ff.
(9) (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526. (b) Ku, T. W.; Kondrad, K. H.; Gelason, J. G. *J. Org. Chem.* **1989**, *54*, 3487–3491. (c) Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10420–10421. (d) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111–12112. (e) Rudge, A. J.; Collins, I.; Holmes, A. B.; Baker, R. *Angew. Chem.* **1994**, *106*, 2416–2418; *Angew Chem., Int. Ed. Engl. 1994*, *33*, 2320−2322. (f) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229–3246. (g) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549. (h) Nakamura, Y.; Hirata, M.; Kuwano, E.; Taniguchi, E. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1550–1554. (i) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (j) Haight, D.; Birrell, H. C.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Hindley, R. M.; Ramaswany, A.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1353–1367. *anti*-Aldol reactions: (k) Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173–181. *anti*-Glycolate: (l) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031. (m) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961–1963. (n) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761. (o) Saika, H.; Fruh, T.; Iwasaki, G.; Koizumi, S.; Mori, I.; Hayakawa, K. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2129–2134. (p) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III. *J. Am. Chem. Soc.* **2000**, *122*, 386–387. Diastereoselective Ti glycolate: (q) Annunziata, R.; Cinquini, M.; Cozzi, F.; Borgia, A. L. *J. Org. Chem.* **1992**, *57*, 6339–6342.
(10) (a) Vezina, C.; Kudelski, A.; Sehgal, S. N. *J. Antibiot.* **1975**, *28*, 721–726. (b) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.
(11) (a) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron Lett.* **1982**, *23*, 5435–5438. (b) Shimojima, Y.; Hayashi, H. *J. Med. Chem.* **1983**, *26*, 1370. (c) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron* **1984**, *40*, 2519–2527.
(12) Mulzer, J.; Berger, M. *Tetrahedron Lett.* **1998**, *39*, 803–806.
(13) Pearson, W. H.; Cheng, M. C. *J. Org. Chem.* **1987**, *52*, 3176–3178.
(14) Andrus, M. B.; Somasekhar, B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035–3037.
(15) Scholtis, S.; Ide, A.; Mahrwald, R. *Org. Lett.* **2006**, *8*, 5353–5355.
(16) Denmark, S. E.; Chung, W.-J. *J. Org. Chem.* **2008**, *73*, 4582–4595.

10.1021/jo8025466 CCC: $40.75
Published on Web 01/07/2009

SCHEME 1. Chelated Enolates of Glycolates and Their Aldol Reactions



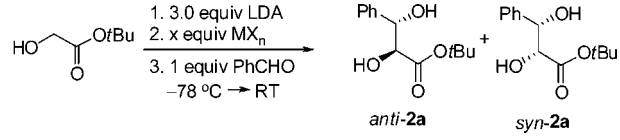
To the best of our knowledge, reactions of free glycolate esters have not been reported so far, neither in a selective *syn*-fashion nor an *anti*-fashion. While the *syn*-products can easily be obtained from the protected derivatives, an *anti*-selective aldol reaction of glycolates would be a significant improvement of this methodology.

Our group is mainly involved in amino acid synthesis, and has developed aldol reactions of chelated enolates of *N*-protected amino acid esters which proceed with high *anti*-selectivity.[17] Metal chelated enolates show higher stability than their nonchelated analogues and, due to the fixed geometry, in general, their reactions proceed more selectively.[18] Therefore, aldol reactions of chelated enolates of α-hydroxy ester with aldehyde, in principle, would be one of the most effective ways for constructing 1,2-diols in an *anti*-fashion. Furthermore, oxygen has a great tendency to form complexes with different metals, such as Ti, Zn, Cu, Sn, and Mg. Also, to the best of our knowledge, there is no report on chelated enolates of α-hydroxy ester.

This prompted us to investigate reactions of such chelated enolates of glycolates with aldehyde to obtain the required α,*β*-dihydroxy carbonyl compounds (Scheme 1). Herein we report our preliminary results of these studies. The deprotonation of an α-hydroxy ester (**1**) with LDA at −78 °C in the presence of a metal salt (MX_n) presumably results in the formation of a chelated metal enolate **1***, whose aldol reaction with aldehydes should lead to diastereomeric *anti*- and *syn*-aldol products **2** with noticeable selectivity due to the fixed enolate geometry.

The influence of various metal salts on the diastereoselectivity was investigated in reactions of *tert*-butyl glycolates with benzaldehyde (Table 1). The *tert*-butyl ester was chosen because these esters in general give the best results in the reactions of amino acid ester enolates,[19] and we were interested in seeing if we can transfer reactions developed for amino acids also to α-hydroxy acids. As expected, the reactions of the lithium enolate proceeded with very low diastereoselectivity (entry 1).

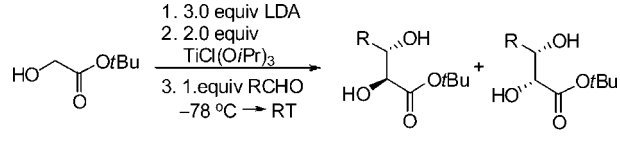
TABLE 1. Aldol Reactions of Glycolate Enolates with Benzaldehyde



entry	MXn	equiv	yield (%)	*anti*:*syn*[a]
1			82	24:76
2	$ZnCl_2$	1.1	85	34:66
3	$ZnCl_2$	2.0	81	25:74
4	$Ti(OiPr)_4$	1.1	47	20:80
5	$Ti(OiPr)_4$	2.0	68	32:68
6	$TiCl(OiPr)_3$	1.1	61	69:31
7	$TiCl(OiPr)_3$	2.0	94	>99:1
8	$TiCl(OiPr)_3$	2.5	92	>99:1

[a] Determined by GC.

TABLE 2. Addition of Ti-Chelated Glycolate Enolates with Aldehydes



entry	RCHO	product	yield (%)	ds (*anti*)[a,b]
1	benzaldehyde	**2a**	94	>99[a]
2	4-bromobenzaldehyde	**2b**	84	>99[a]
3	2-nitrobenzaldehyde	**2c**	62	>99[b]
4	4-methoxybenzaldehyde	**2d**	55	>99[b]
5	furaldehyde	**2e**	75	>95[a]
6	*n*-butanal	**2f**	67	>99[a]
7	isobutyraldehyde	**2g**	59	>99[a]
8	pivalaldehyde	**2h**	52	>99[a]

[a] Determined by GC. [b] Determined by NMR.

Addition of $ZnCl_2$ also gave the desired product **2a** in good yield; however, there was no significant effect on the diastereoselectivity (entries 2 and 3).[20] With 1.1 equiv of $Ti(OiPr)_4$, a comparable diastereoselectivity was observed for the *syn*-product, but the yield unfortunately dropped (entry 4). Increasing the amount of metal salts resulted in the increase of the yield, but at the same time in a decrease of diastereoselectivity (entry 5). On the other hand, with $TiCl(OiPr)_3$ as a metal salt, both the diastereoselectivity and the yield increased remarkably, especially when 2 equiv of $TiCl(OiPr)_3$ were used (entries 7 and 8). In this case, the desired *anti*-product was formed exclusively.[21] A larger excess of the metal salt brought no further improvements (entry 8).

To prove the generality of this aldol reaction, we subjected several other aldehydes to our titanium enolates. The results obtained are shown in Table 2. Introduction of substituents on the aromatic ring had some effect on the yield, but not on the selectivity (entries 1−4). In all examples the *anti*-product was formed exclusively, also with the heterocyclic furaldehyde (entry 5). In case of aliphatic aldehydes we observed that the yield dropped slightly, probably due to steric reasons; nevertheless there was no big influence on the diastereoselectivity (entries 6−8). In these cases, the *anti*-configuration of the products

(17) (a) Kazmaier, U.; Grandel, R. *Synlett* **1995**, 945–946. (b) Grandel, R.; Kazmaier, U.; Nuber, B. *Liebigs Ann.* **1996**, 1143–1150. (c) Grandel, R.; Kazmaier, U. *Tetrahedron Lett.* **1997**, *38*, 8009–8012. (d) Grandel, R.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, 409–417. (e) Grandel, R.; Kazmaier, U. *J. Org. Chem.* **1998**, *63*, 4524–4528. (f) Kazmaier, U.; Grandel, R. *Eur. J. Org. Chem.* **1998**, 1833–1840. (g) Kummeter, M.; Kazmaier, U. *Eur. J. Org. Chem.* **2003**, 3325–3329. (h) Kummeter, M.; Kazmaier, U. *Eur. J. Org. Chem.* **2003**, 3330–3334.

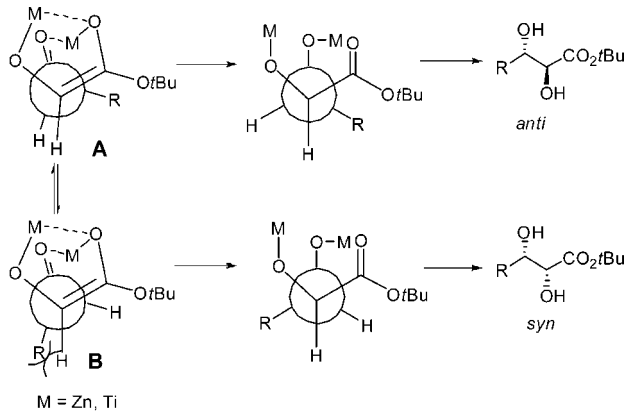
(18) (a) Kazmaier, U. *Amino Acids* **1996**, *11*, 283–299. (b) Kazmaier, U. *Recent Res. Dev. Org. Chem.* **1998**, *2*, 351–358. (c) Kazmaier, U. *Bioorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 1999; pp 201−206.

(19) (a) Kazmaier, U.; Schau*β*, D.; Raddatz, S.; Pohlman, M. *Chem. Eur. J.* **2001**, *7*, 456–464. (b) Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, 4067–4076. (c) Pohlman, M.; Kazmaier, U. *Org. Lett.* **2003**, *5*, 2631–2633. (d) Mendler, B.; Kazmaier, U. *Org. Lett.* **2005**, *7*, 1715–1718. (e) Mendler, B.; Kazmaier, U.; Huch, V.; Veith, M. *Org. Lett.* **2005**, *7*, 2643–2646. (f) Kazmaier, U.; Krämer, K. *J. Org. Chem.* **2006**, *71*, 8950–8953.

(20) In comparison, zinc enolates give by far the best results in reactions of amino acid esters (see ref 18).

(21) No second stereo isomer could be detected by GC.

SCHEME 2. Proposed Mechanism for the Aldol Reaction



formed could be confirmed by X-ray structure analysis (see the Supporting Information.

Considering all possible transition state models that are discussed for the aldol reaction,[22] the formation of *anti*-isomers in the reaction of glycolate enolates with aldehyde may be explained by the assumption that the reaction proceeds via the transition states **A** and **B** depicted in Scheme 2. Dubois[23] and Heathcock et al.[3b] proposed a skewing of the idealized 60° dihedral angle about the formed carbon−carbon bond in the chair-like transition structure toward 90°. According to their suggestions,[24] we propose transition states **A** and **B** to explain the *anti*-selective aldol reactions of our chelated glycolates. While one metal atom is involved in the formation of this chelated enolate, the other one is able to coordinate and to activate the aldehyde. The transition state **A** is favored over **B** because of the interactions between R and H in transition state **B**. The interactions of R with the ester moiety COO*t*Bu, which might be present in transition state **A**, seem to be not as important as interactions between R and H in transition state **B**.

In conclusion we have shown that aldol reactions of titanium enolates of α-hydroxy esters proceed in a highly diastereoselective fashion. Applications toward the synthesis of more complex molecules as well as further studies to confirm the proposed mechanism and aldol reactions with chiral aldehydes are currently under investigation.

Experimental Section

General Procedure for the Reaction of Ti-Enolates of *tert*-Butyl Glycolate with Aldehydes. Diisopropylamine (181 mg, 1.8 mmol) was dissolved in THF (1 mL) in a Schlenk flask under nitrogen. After the solution had been cooled to −78 °C, *n*BuLi (1.6 M, 1.12 mL, 1.8 mmol) was added slowly.

The reaction mixture was stirred for 20 min at this temperature, and then the cooling bath was removed and stirring was continued for an additional 10 min. In a second Schlenk flask *tert*-butyl glycolate (79 mg, 0.6 mmol) and $TiCl(OiPr)_3$ (1.2 mL, 1.2 mmol) were dissolved in THF (3 mL). The solution was cooled to −78 °C, before the freshly prepared LDA solution was added dropwise, whereby the solution turns dark red immediately.The stirring was continued for 30 min. At the same temperature, a solution of 0.54 mmol of aldehyde in THF (1 mL) was added and the reaction was allowed to warm to room temperature overnight. The solution was diluted with ether before 1 N HCl was added. After the separation of the layers, the aqueous layer was extracted three times with ether, and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography.

Acknowledgement. Financial support by Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged. We also want to thank Dr. V. Huch for X-ray structure analyses.

Supporting Information Available: General information, characterization data for all compounds, X-ray crystal data, NMR spectra, and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8025466

(22) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177–2194.
(23) Fellman, P.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349–1357.
(24) Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Märki, H. P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161–8174.