Anti-Selective Aldol Reactions with Titanium Enolates of *N*-Glycolyloxazolidinethiones
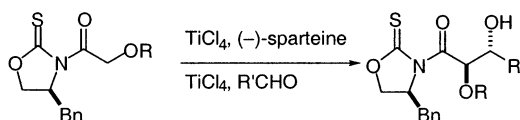
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ABSTRACT

A highly diastereoselective anti aldol addition utilizing a variety of *N*-glycolyloxazolidinethiones has been developed. Enolization of an *N*-glycolyloxazolidinethione with titanium (IV) chloride and (–)-sparteine followed by addition of an aldehyde activated with additional TiCl₄ resulted in highly anti-selective aldol additions, typically with no observable syn isomers. Allyl-protected glycolates demonstrated the highest levels of selection and yields, although *O*-benzyl and *O*-methyl glycolyloxazolidinethiones also performed well.

The stereoselective glycolate aldol addition is a useful carbon–carbon bond-forming process, giving rise to differentially protected 1,2-diols. Methods for producing the syn diastereomers include the Evans boron enolate aldol addition[1] using *N*-glycolyloxazolidinones, which has proven to be very successful with a wide variety of aldehydes and protecting groups.[2] Additionally, the titanium enolates of *N*-glycolyloxazolidinones and *N*-glycolyloxazolidinethiones have demonstrated high syn selectivities with good yields.[3] Masamune's norephedrine esters have also been used to generate the syn adducts.[4] Effective methods for obtaining the anti aldol adducts from glycolate enolates, however, are less prevalent. Moderately selective anti aldol reactions of tin(II) enolates of *N*-acylthiazolidinethiones and *N*-acyl-oxazolidinones have been observed by Mukaiyama[5] and Evans,[6] respectively. Alternative auxiliary-based approaches include the use of oxapyrone boron enolates[7] or selone auxiliaries.[8] Chiral tin(II) Lewis acids[9] have also been moderately successful. Here we report a general method for anti-selective glycolate aldol additions using a variety of substrates and aldehydes through a simple and inexpensive procedure, mediated by the 4-benzyl-oxazolidine-2-thione auxiliary.

Our initial investigation of the glycolate anti aldol addition revealed that the thiazolidinethione auxiliary[10] **1** (Figure 1)
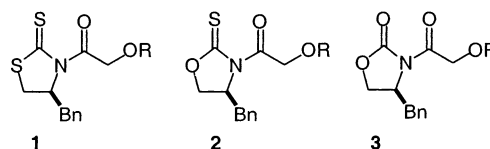

Figure 1. Chiral auxiliary variants.

gave excellent anti selectivity; however, up to 20 mol % of the free auxiliary was detected in the product. This competing deacylation during the course of the reaction resulted in low

(1) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.

(2) Selected examples: Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998–3017. Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113–3122. Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549.

(3) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476. Crimmins, M. T.; King, B. W.; Zuercher, W. J.; Choy, A. L. *J. Org. Chem.* **2000**, *65*, 8499–8509.

(4) Andrus, M. B.; Sekhar, B. B. V. S.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197–7201.

(5) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753–756.

(6) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961–1963.

yields. Fortunately, switching to the oxazolidinethione auxiliary **2** alleviated this problem, providing similar levels of asymmetric induction accompanied by only trace amounts of deacylation. In contrast, the oxazolidinone auxiliary **3** (R = allyl) produced both anti diastereomers (ca. 1.2:1) accompanied by approximately 10% of the syn isomers. Several oxazolidinethiones were studied, with 4-benzyl-oxazolidine-2-thione **2** showing the highest level of asymmetric induction.

The effect of the glycolate ether group was explored in an effort to optimize the selectivity and expand the scope of the reaction. The *O*-allyl- (**4**) and *O*-benzyl-protected (**5**) glycolates (Figure 2) were chosen on the basis of their ability
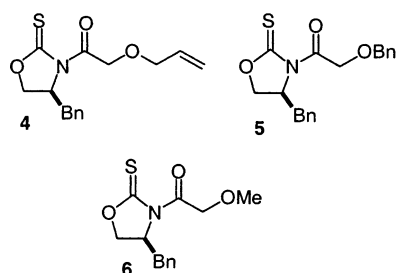
Figure 2. Substrates for anti aldol additions.

to withstand the Lewis acidic reaction conditions while providing easy removal of the protecting group. The *O*-methyl glycolate **6** was also examined. All three substrates provided good anti selection; however, the *O*-allyl glycolate proved to be the most diastereoselective and delivered the anti adducts in the highest yields for all aldehydes tested.

Aldol additions utilizing these substrates began with the generation of their respective titanium enolates under conditions previously developed in our laboratory employing titanium(IV) chloride and (−)-sparteine.[10] As expected, addition of an aldehyde directly to the enolate selectively provided the Evans syn diastereomer. However, treatment of the same aldehyde with additional TiCl$_4$, prior to addition of the aldehyde to the enolate, led to selective formation of one anti isomer. In most instances, the syn diastereomers were not observed. The degree of anti selection was highly dependent on the amount of TiCl$_4$ used to activate the aldehyde. The results, depending on the aldehyde, can be generalized as follows: *saturated aldehydes gave higher selectivities using >2 equiv of TiCl$_4$ to each equivalent of aldehyde, while α,β-unsaturated aldehydes required >3 equiv of TiCl$_4$ for optimum results*. Examples illustrating this effect are shown in Table 1.

A general one-pot procedure for the anti aldol addition was ultimately developed on the basis of the observation that

(7) Andrus, M. B.; Sekhar, B. B. V. S.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035−3037.
(8) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III. *J. Am. Chem. Soc.* **2000**, *122*, 386−387.
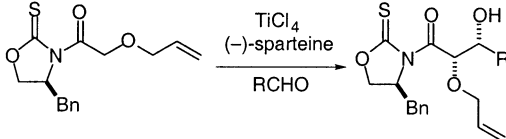(9) Kobayashi, S.; Kawasuji, T. *Tetrahedron Lett.* **1994**, *35*, 3329−3332.
(10) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902.

Table 1. Variation of Precomplexing TiCl$_4$[a]

aldehyde	TiCl$_4$:aldehyde	selectivity[b]
⟩—CHO	2.3:1.0 1.5:1.0	87:13 78:28
⟋⟍CHO	3.1:1.0 2.3:1.0	95:5 84:16

[a] Substrate = **4**. Performed with method A. [b] Ratios indicate major diastereomer with respect to all other diastereomers. Ratios were determined by 400 MHz ^{1}H NMR of the unpurified material.

precomplexation of the aldehyde can occur in situ. After the enolate was formed by exposure of the *N*-glycolyloxazolidinethione to TiCl$_4$ and (−)-sparteine at −78 °C, the remainder of the TiCl$_4$ was added directly to the enolate solution followed immediately by addition of the aldehyde (method A).[11] Alternatively, the aldehyde could be treated with the additional Lewis acid in a separate flask followed by cannula transfer to the enolate (method B).[12] Both methods provided the anti adducts with similar selectivities and yields.

The results for various aldehydes are presented in Table 2. The *O*-allyl glycolate **4** provided the anti adducts of

Table 2. Anti Aldol Additions[a]

subst.	aldehyde[b]	A$_1$:A$_2$:syn[c]	yield(%)[d]	adduct[e]
4	H$_3$CCHO	94:6:0	84	**7a**
4	⟍⟋⟍CHO	97:3:0	74	**7b**
4	⟍⟋⟍⟋CHO	94:6:0	74	**7c**
4	⟩⟨CHO	87:13:0	61	**7d**
4	⟋⟍CHO	95:5:0	58	**7e**
4	⟍⟋⟍CHO	73:23:4	56	**7f**
4	⬡—CHO	65:24:11	56	**7g**
5	⟍⟋⟍⟋CHO	88:12:0	64	**8a**
5	⟋⟍CHO	74:26:0	48	**8b**
6	H$_3$CCHO	86:4:10	62	**9a**
6	⟍⟋⟍⟋CHO	84:11:5	63	**9b**
6	⟋⟍CHO	88:12:0	59	**9c**

[a] All additions were performed using method A. [b] Aldehydes were freshly distilled over Ca$_2$SO$_4$ prior to use. [c] Isomeric ratios were determined by 400 MHz ^{1}H NMR analysis of the unpurified material. [d] Yields of major diastereomer. Determined by combined chromatographic separation and NMR analysis. [e] Adducts **7a**−**d**, **8a**, and **9b** were performed using 2.3 equiv of TiCl$_4$:aldehyde. Adducts **7e**−**g**, **8b**, and **9a,c** were performed using 3.1 equiv of TiCl$_4$:aldehyde.

aliphatic aldehydes in consistently high selectivities and good yields, without significant formation of the syn isomers (typically <3%). Isomeric ratios up to 97:3 for the two anti products, A_1 and A_2, were observed for unhindered aldehydes (adducts **7a**−**c**); however, isobutyraldehyde gave a slightly lower selectivity of 87:13, possibly due to the steric demands of the isopropyl group (**7d**). The anti selectivities for α,β-unsaturated and aromatic aldehydes with **4** were less consistent, ranging from 95:5 with acrolein (**7e**) to 73:23(:4 syn) with crotonaldehyde (**7f**). Benzaldehyde gave the poorest selectivity (**7g**). The *O*-benzyl **5** and *O*-methyl **6** substrates also performed well with aliphatic aldehydes, although the selectivities and yields were significantly lower than with **4** (**8a** and **9a,b**). These substrates also gave varying results with acrolein, providing the aldol adducts in a 74:26 ratio for **5** (**8b**) and 88:12 for **6** (**9c**). The relative and absolute configuration of aldol adduct **9a** was confirmed by X-ray analysis. The stereochemistry of adduct **7a** was confirmed by chemical conversion of **9a** to **7a**.[13] The stereochemistry of the remaining aldol adducts was inferred by comparison of NMR data.

As mentioned previously, selective formation of the Evans syn diastereomer occurred upon addition of the free aldehyde to the preformed enolate without prior activation. Select examples using substrate **4** are shown in Table 3. Notably,
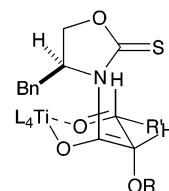
Table 3. Syn Aldol Additions[10]

conditions	aldehyde	selectivity[c]	yield (%)[d]
A[a]	⌒⌒CHO	93:7	57
B[b]	⌒⌒⌒CHO	93:7	74
B	⌒⌒CHO	90:10	78

[a] (−)-Sparteine (1 equiv). [b] (−)-Sparteine (1 equiv) + *N*-methylpyrrolidinone (1 equiv). [c] Determined by 400 MHz ¹H NMR analysis of the unpurified material. [d] Based on chromatographic isolation of the major diastereomer.

adding 1 equiv of *N*-methylpyrrolidinone to the enolization procedure[14] resulted in a significant increase in yields, similar

Figure 3. Proposed syn transition state.

to previously demonstrated examples using propionate substrates.[10]

Proposed transition states for both the syn and anti aldol additions are shown in Figures 3 and 4. For the syn

Figure 4. Proposed anti transition state.

diastereomer, the reaction has previously been proposed to proceed via a six-member chairlike transition state as shown.[10] On the basis of the observation that precomplexing the aldehyde with a Lewis acid leads to the anti isomer, we believe that addition to the enolate occurs via an open transition state, as suggested by Heathcock to explain propionate anti aldol additions using *N*-acyloxazolidinones.[15] In addition, the glycolate oxygen may coordinate to the TiCl₄ that serves to activate to the aldehyde as shown. Positioning the aldehyde substituent away from the auxiliary leads to the observed anti product. The involvement of the glycolyl oxygen in coordination to the metal bound to the aldehyde is supported by the observation that the *N*-propionyl oxazolidinethione produces the non-Evans syn diastereomer under the same conditions.

Synthetic manipulation of the aldol adducts can be readily accomplished via cleavage of the oxazolidinethione auxiliary and differentiation of the 1,2-diol. Removal of the auxiliary to multiple functional groups, including the versatile Weinreb

(11) **Method A.** The *N*-glycolyloxazolidinethione glycolate (0.172 mmol) and 5 mL of dichloromethane were added to a dry round-bottom flask under argon. After the mixture was cooled to −78 °C, titanium(IV) chloride (0.023 mL, 0.206 mmol) was added dropwise and the solution was allowed to stir for 10 min. A freshly prepared solution of (−)-sparteine (0.103 mL, 0.206 mmol; 2 M in dichloromethane) was added dropwise to the mixture, and the solution was allowed to stir for 40 min. TiCl₄ (0.057 mL, 0.516 mmol or 0.075 mL, 0.688 mmol if the aldehyde was α,β-unsaturated) was added directly to the enolate solution. After the mixture was stirred for 1 min, freshly distilled aldehyde (0.224 mmol) was added dropwise to the reaction. The reaction was allowed to stir for 15 min and quenched with half-saturated ammonium chloride. The organic layer was separated and the aqueous layer extracted twice with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude mixture was analyzed by ¹H NMR followed by column chromatography purification.
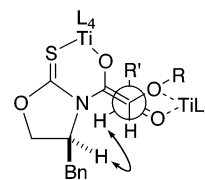
(12) **Method B.** See enolate formation in method A. To a separate dry flask was added 5 mL of CH₂Cl₂ and TiCl₄ (0.057 mL, 0.516 mmol or 0.075 mL, 0.688 mmol if the aldehyde was α,β-unsaturated), and the mixture was cooled to −78 °C. Freshly distilled aldehyde (0.224 mmol) was added to the TiCl₄ solution. The resulting mixture was transferred via cold cannula to the enolate after 10 s. The reaction was allowed to stir for 15 min followed by workup as in method A.

(13) See Supporting Information.

(14) −-Sparteine (1 equiv) + *N*-methylpyrrolidinone (1 equiv).

(15) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747−5750.

amide, can be performed under mild conditions.[10] Furthermore, deprotection of the benzyl and allyl ethers[16] allows for further manipulation of glycolyl hydroxyl.

In summary, a new anti aldol process has been developed utilizing the titanium enolate of various *N*-glycolyloxazolidinethiones and a titanium(IV) chloride activated aldehyde. *O*-Methyl, *O*-benzyl, and *O*-allyl glycolyloxazolidinethiones provided the anti adducts in high selectivities and yields using a simple one-pot procedure.

Supporting Information Available: Experimental procedures for oxazolidinethione substrates, spectral data of all new compounds, and correlation studies of aldol adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

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