Asymmetric Aldol Additions: Use of Titanium Tetrachloride and (−)-Sparteine for the Soft Enolization of *N*-Acyl Oxazolidinones, Oxazolidinethiones, and Thiazolidinethiones

Michael T. Crimmins,* Bryan W. King, Elie A. Tabet, and Kleem Chaudhary

Venable and Kenan Laboratories of Chemistry, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

crimmins@email.unc.edu

Received September 18, 2000

Asymmetric aldol additions using chlorotitanium enolates of *N*-acyloxazolidinone, oxazolidinethione, and thiazolidinethione propionates proceed with high diastereoselectivity for the Evans or non-Evans syn product depending on the nature and amount of the base used. With 1 equiv of titanium tetrachloride and 2 equiv of (−)-sparteine as the base or 1 equiv of (−)-sparteine and 1 equiv of *N*-methyl-2-pyrrolidinone, selectivities of 97:3 to >99:1 were obtained for the Evans syn aldol products using *N*-propionyl oxazolidinones, oxazolidinethiones, and thiazolidinethiones. The non-Evans syn aldol adducts are available with the oxazolidinethione and thiazolidinethiones by altering the Lewis acid/amine base ratios. The change in facial selectivity in the aldol additions is proposed to be a result of switching of mechanistic pathways between chelated and nonchelated transition states. The auxiliaries can be reductively removed or cleaved by nucleophilic acyl substitution. Iterative aldol sequences with high diastereoselectivity can also be accomplished.

Introduction

The asymmetric aldol addition mediated by chiral auxiliaries is one of the most important and general methods for asymmetric carbon−carbon bond formation.[1] The utility of the asymmetric aldol addition has been amply demonstrated through a multitude of synthetic applications.[2] Dibutylboron enolates of *N*-acyl oxazolidinones, pioneered by Evans, are the most commonly utilized enolates and are highly effective for the preparation of Evans syn products in asymmetric aldol additions.[3] Titanium (IV)[4,5,6] enolates of *N*-acyl oxazolidinones and oxazolidinethiones, tin (IV)[2c] enolates of *N*-acyl sultams, and tin (II) enolates[7] of thiazolidinethiones have also been shown to be effective in creating well ordered transition states for aldol reactions. Evans and Yan reported the use of chlorotitanium enolates for aldol additions of *N*-acyl oxazolidinones using diisopropylethylamine or tetramethylethylenediamine as the base, but slightly lower selectivity was observed than with the dibutylboron enolates.[2−5] Also, to achieve good levels of conversion, excess aldehyde (from 2 to 5 equiv) was required.[4] The nonchelated transition state **1** has been proposed for the boron enolate (and the titanium enolate) to give the Evans syn aldol product.[8] Yan has investigated chlorotitanium enolates of camphor-derived oxazolidinethiones noting the ability to access the non-Evans syn aldol adducts. It was proposed that if chloride ion is lost, the titanium enolate can proceed through transition state **2** in which both the aldehyde and the auxiliary are coordinated to titanium and the non-Evans adduct is produced through reversal of the pi-facial orientation of the enolate in this chelated transition state.[5,6] A highly organized chelated transition state has also been proposed by Nagao and Fujita to explain the diastereoselectivity observed with tin (II) enolates of *N*-acylthiazolidinethiones.[7] The chelated transition state could be a minor competitive pathway for the titanium enolate of oxazolidinones thus lowering the diastereoselectivity. Silks recently reported the preparation of non-Evans syn aldol adducts from the titanium enolates of *N*-acylselones,[9] and Oppolzer noted a switiching to non-Evans syn adducts when tin (IV) enolates of *N*-acyl sultams were utilized in aldol additions.[2c] Results from our laboratory

(1) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917−947. Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3−12. Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(2) (a) For selected examples see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001−7031. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453. Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454−455. Evans, D. A.; Kim, A. S.; Metternich R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120* 5921−5942. Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, 56, 5747−5750. (b) Hsiao, C.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, 52, 2201−2206. (c) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767−2772.

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

(4) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.

(5) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489−2498. Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299−1308.

(6) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613−2621 and references therein. Yan, T.-H.; Hung, A.-W.; Lee, H.-C.; Chang, C.-S.; Liu, W.-H. *J. Org. Chem.* **1995**, *60*, 3301−3306.

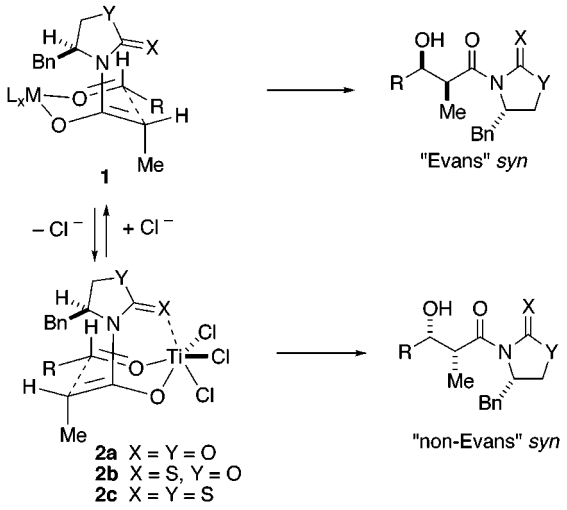
(7) Fujita, E. Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *45*, 1−36. Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M. Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1419−1420. Yamada, S.; Kumagai, T.; Ochiai, M. Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418−1419. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393. Hsiao, C.-N.; Liu, L., Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201−2206.

(8) Kim, B. M.; Williams, S. F.; Masamune, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, pp 239−275.

(9) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A. P., III. *J. Am. Chem. Soc.* **2000**, *122*, 386-387.

10.1021/jo001387r CCC: $20.00
Published on Web 01/16/2001

Scheme 1



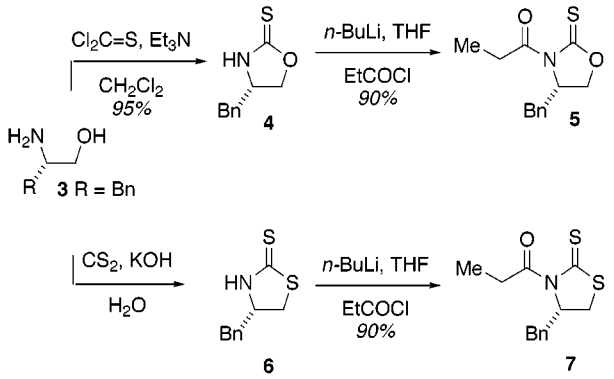
have reported the use of chlorotitanium enolates of both *N*-acyloxazolidinethiones[10] and *N*-acylthiazolidinethiones[11] for the preparation of both Evans and non-Evans syn aldol adducts. We report here a detailed account of these investigations together with additional studies and mechanistic interpretations.

Results and Discussion

Given the lower selectivity of the aldol additions of chlorotitanium enolates of *N*-acyl oxazolidinones reported by Evans, it was anticipated that a more highly ordered transition state might improve the selectivity. Also, if a suitable method for asymmetric aldol reactions with chlorotitanium enolates of *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones could be developed, these aldol reactions might be complimentary to the existing Evans protocol. Initially, *N*-acyl oxazolidinethione and thiazolidinethione enolates were investigated since it was thought that they might proceed through the "chelated" transition state **2** due to the known higher affinity of sulfur for titanium, thus creating a more rigid transition state. Fowles had shown that thioxane prefers to coordinate to titanium through sulfur rather than oxygen.[12] In addition, there was a collateral advantage since the *N*-acyloxazolidinethiones and thiazolidinethiones are more easily cleaved; they undergo aminolysis at room temperature: conditions which do not cleave the corresponding oxazolidinones.[13]

Preparation of *N*-Acyloxazolidinethiones and *N*-Acylthiazolidinethiones. Oxazolidinethione **4** was readily synthesized in two steps from inexpensive, commercially available (*S*)-phenylalanine (Scheme 2). Reduction of (*S*)-phenylalanine with sodium borohydride and iodine in THF following the Meyers method provided (*S*)-phenylalaninol **3** in 95% yield.[14] Cyclization of the amino alcohol **3** with thiophosgene and triethylamine in CH_2Cl_2 gave oxazolidinethione **4** in 95% yield as a viscous oil (Note: crystallization of the oil would occur after approximately one month at 0 °C). Preparation of **4** could also be accomplished with carbon disulfide and triethylamine in THF through a modification of the method described by Corre;[15] however, lower yields were obtained due to the formation of thiazolidinethione **6** as a minor byproduct. Oxazolidinethione **4** was readily acylated with *n*-butyllithium and propionyl chloride in THF at −78 °C to provide propionyloxazolidinethione **5** in 90% yield (Scheme 2). The propionyl oxazolidinethione **5** is highly crystalline and can be purified by recrystallization from hexanes to give a pure, white crystalline solid ready for use in the aldol reactions. The thiazolidinethione **6** was prepared from (*S*)-phenylalaninol by heating in the presence of aqueous potassium hydroxide and carbon disulfide by a modification of the Corre procedure.[15] Acylation of the thiazolidinethione **6** with *n*-butyllithium and propionyl chloride was accomplished as for the oxazolidinethione. The propionylthiazolidinethione is also crystalline and readily purified by recrystallization. The *N*-acyloxazolidinethiones and thiazolidinethiones were prepared in three steps in 70−85% overall yield.

Scheme 2



Evans Syn Aldol Additions with *N*-Acyloxazolidinethiones. Titanium enolates of oxazolidinethione **5** were examined in aldol additions with a variety of aldehydes of differing structural types and at different temperatures. The diastereoselectivity, percent conversion to product, and the rate of the aldol reaction were highly dependent on the amine base and the amount of titanium tetrachloride used to generate the titanium enolate. The enolates were formed by a two-step process: (1) titanium tetrachloride was added to a solution of oxazolidinethione **5** in methylene chloride at 0 °C to produce a yellow solution or more commonly a slurry representative of a $TiCl_4$−carbonyl complex; (2) an amine base was added to immediately produce a homogeneous deep red solution characteristic of a titanium enolate **8** (Scheme 3).[16] The enolate was then treated with an aldehyde to afford mixtures of the Evans syn product **10**, the non-Evans syn product **9**, and an anti product (not shown). Titanium tetrachloride was used directly as received from Aldrich Chemical Co. No purification was necessary. All diastereomeric ratios were determined by HPLC (Dynamax-60 A, 1 mL/min, 30% EtOAc/hexanes).

Initial experiments with *N*-acyloxazolidinethione **5** were performed by generating the enolates with 1.1 equiv

(10) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.
(11) Crimmins, M. T. Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777.
(12) Fowles, G. W. A.; Rice, D. A.; Wilkins, J. D. *J. Chem. Soc. A* **1971**, 1920−1923.
(13) Nagao, Y.; Yagi, M.; Ikedo, T.; Fujita, E. *Tetrahedron Lett.* **1982**, *23*, 201−204.
(14) McMKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568−3571.
(15) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604−6607.
(16) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216.

Scheme 3

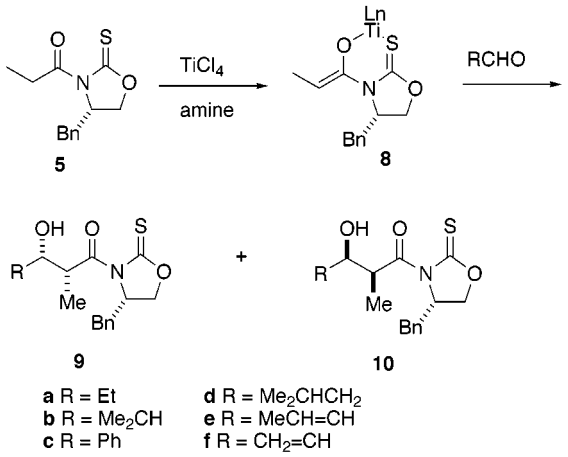


Table 1. DIEA- and TMEDA-Mediated Aldol Additions of 5

entry	base[a,b,c]	aldehyde (RCHO)[d]	% yield[e]	**10**:**9**:anti
1	DIEA[f]	Me_2CH	86[g]	85.8:13.9:0.3
2	DIEA[f]	Me_2CH	87[g]	33.7:65.9:0.4
3	TMEDA	Me_2CH	58	98.9:0.6:0.5
4	TMEDA	Et	60	93.3:6.3:0.4
5	TMEDA	Ph	60	97.6:2.4:0.0
6	TMEDA	MeCH=CH	49	98.2:1.3:0.5
7	TMEDA	Me_2CHCH_2	43	100:0.0:0.0

[a] All reactions performed at −78 °C. [b] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [c] 1.0 equiv of $TiCl_4$ and 2.5 equiv of amine were employed. [d] 1.1 equiv of aldehyde was employed. [e] Yields are for the isolated, chromatographically purified major diastereomer. [f] Reaction performed with 1.0 equiv of $TiCl_4$ and 2.5 equiv of DIEA. [g] Total yield of all aldol diastereomers.

of titanium tetrachloride and 2.5 equiv of diisopropylethylamine followed by addition of 1.1 equiv of aldehyde. The diastereoselectivity of these aldol reactions were inconsistent and appeared to be very sensitive to small changes in the Lewis acid stoichiometry. However, when 2.5 equiv of tetramethylethelenediamine (TMEDA) was employed as the base, consistently high diastereoselectivity (>98:2 Evans:non-Evans **10**:**9**) was observed as shown in Table 1. Unfortunately, using 1 equiv of aldehyde, the reactions generally failed to go to completion even after extended reaction times and isolated yields were modest (45−60%). Addition of a second equivalent of aldehyde was beneficial in improving the yields, but conditions were needed to avoid the use of greater than 1 equiv of aldehyde if expensive or synthetically prepared aldehydes were to be employed. A survey of several amines such as tributylamine, *N*-ethylpiperidine, DABCO, and DBU provided no significant advantages. Tetramethylpropylenediamine (TMPDA) did improve yields somewhat (Table 2). However, when (−)-sparteine was used to generate the titanium enolate of *N*-propionyl-oxazolidinethione **5**, a dramatic rate acceleration was observed in the aldol additions. The aldol reactions were essentially complete after 30 s to 1 min, even with 1.1 equiv of aldehyde, and diastereoselectivities were >98:2 Evans syn **10**/non-Evans syn **9** and >99:1 syn/anti (Table 3). Isolated yields with (−)-sparteine were improved substantially compared to TMEDA and TMPDA. Of equal importance was the observation that no significant reduction in selectivity occurred when the reactions were conducted at 0 °C as compared to −78 °C. Isolated yields were typically slightly higher at 0 °C due

Table 2. TMPDA-Mediated[a,b] Aldol Additions of 5

entry	temp[c]	aldehyde (RCHO)[d]	% yield[e]	**10**:**9**:anti
1	−78 °C	Me_2CH	62	96.4:2.7:0.9
2	0 °C	Me_2CH	69	92.9:5.1:2.0
3	0 °C	Et	72	97.6:1.6:0.8
4	0 °C	Ph	85	94.9:5.1:0.0
5	0 °C	MeCH=CH	65	93.1:6.6:0.3
6	0 °C	Me_2CHCH_2	76	96.0:3.0:1.0

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] 1.0 equiv of $TiCl_4$ and 2.5 equiv of TMPDA were employed. [c] Temperature at which the aldehyde was added. [d] 1.1 equiv of aldehyde was employed. [e] Yields are for the isolated, chromatographically purified major diastereomer.

Table 3. (−)-Sparteine-Mediated[a] Aldol Additions of 5

entry	temp[b]	aldehyde (RCHO)[c]	% yield[d]	**10**:**9**:anti
1[e]	−78 °C	Me_2CH	70	98.8:1.0:0.2
2[e]	0 °C	Me_2CH	90	97.0:2.5:0.5
3[e]	−78 °C	Et	69	97.5:1.0:1.5
4[e]	0 °C	Et	80	97.8:1.7:0.5
5[e]	−78 °C	Ph	89	98.7:1.3:0.0
6[e]	0 °C	Ph	89	97.3:2.2:0.5
7[e]	−78 °C	MeCH=CH	77	97.8:1.3:0.9
8[e]	0 °C	MeCH=CH	65	97.4:2.3:0.3
9[e]	−78 °C	Me_2CHCH_2	94	97.1:2.2:0.7
10[e]	0 °C	Me_2CHCH_2	91	97.8:2.2:0.0
11[e]	−78 °C	CH_2=CH	80	98.9:0.0:1.1
12[f]	−78 °C	Me_2CH	98	99.3:0.7:0
13[f]	−78 °C	Et	91	97.8:1.4:0.8
14[f]	−78 °C	Ph	95	95.2:4.8:0
15[f]	−78 °C	MeCH=CH	89	96.8:3.2:0
16[f]	−78 °C	Me_2CHCH_2	89	99.4:0.6:0
17[f]	−78 °C	CH_2=CH	91	99.0:1.0:0

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] Temperature at which the aldehyde was added. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer. [e] 1.0 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine were employed. [f] 1.05 equiv of $TiCl_4$, 1.0 equiv of (−)-sparteine, and 1.0 equiv. of *N*-methyl-2-pyrrolidinone were employed.

to slightly improved conversions. In the case of crotonaldehyde, the reduction in yield can be attributed to the increase in the polymerization rate of crotonaldehyde at 0 °C (Table 3, entry 8). An additional important point is that $TiCl_4$ and (−)-sparteine were used directly as received without further purification. The reason for the dramatic rate acceleration of these aldol reactions in the presence of 2.5 equiv of (−)-sparteine is not yet clear. Rate enhancement may be related to a bidentate coordination of (−)-sparteine to the metal center, although this is speculative.

Because of the cost of (−)-sparteine, the use of 2.5 equiv of the chiral base was a potential issue and conditions were sought to reduce the quantity of (−)-sparteine. If the base was coordinating to the metal, other good ligands for titanium might also prove useful. Since excess aldehyde also seemed to help the reaction rate and the degree of completion of reaction, it seemed reasonable that the aldehyde was acting as a ligand for the metal as well. If so, better Lewis basic carbonyl compounds might obviate the need for 2.5 equiv of (−)-sparteine or excess aldehyde. Since the carbonyl oxygen of an amide is more Lewis basic than an aldehyde carbonyl, the use of a tertiary amide as an unreactive ligand on the metal was explored. The use of 1.05 equiv of titanium tetrachloride, 1.0 equiv of (−)-sparteine, and 1.0 equiv of *N*-methyl-2-pyrrolidinone resulted in reaction rates, level of completion, and distereoselectivity comparable to the use of 2.5 equivlents of (−)-sparteine (entries 12−17,

Scheme 4

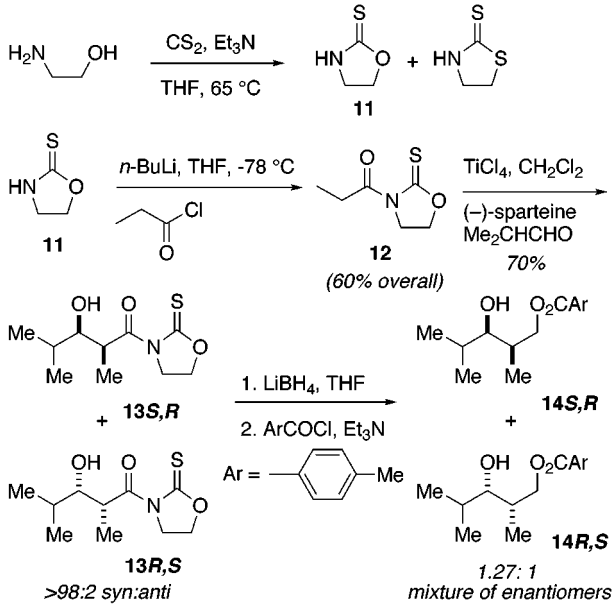


Table 3). These modified conditions were not only more cost efficient but also simplified the workup since less insoluble material was observed at the end of the reaction and filtration was significantly simplified.

To determine if the chiral architecture of (−)-sparteine was influencing the selectivity of the aldol addition, achiral *N*-propionyloxazolidinethione **12** was prepared and aldol additions of its chlorotitanium enolate were examined. Treatment of 2-amino-1-ethanol with carbon disulfide and triethylamine in THF provided a 2:1 mixture of oxazolidinethione **11** and the thiazolidinethione (Scheme 4). Acylation of oxazolidinethione **11** with *n*-BuLi and propionyl chloride gave, after purification, acylated oxazolidinethione **12** in 60% yield for two steps. Addition of isobutyraldehyde to the titanium enolate of oxazolidinethione **12** generated from 1 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine afforded the aldol products **13** in 70% yield with a 98:2 syn/anti ratio. Determination of the enantioselectivity of the aldol addition by chiral HPLC was accomplished by reductive removal of the oxazolidinethione and protection of the resulting diol as the primary *p*-toluate **14**. Analysis by chiral HPLC (Chiralcel ODH column) revealed a 1.27:1 ratio of enantiomers **14*R,S*** and **14*S,R*** (the absolute stereochemistry of the enantiomer formed in slight excess was not determined). Therefore, any asymmetric induction provided by (−)-sparteine was minimal. In addition, (−)-sparteine produced comparable rate enhancements and very similar diastereoselectivities when either enantiomer of the oxazolidinethione auxiliary was employed.

Evans Syn Aldol Additions with *N*-Acylthiazolidinethiones. The chlorotitanium enolates of *N*-acylthiazolidinethiones were also examined since it was thought that (1) the thiocarbonyl of the thiazolidinethione could be a better ligand for titanium and might lead to aldol additions through the chelated transition state to provide the non-Evans syn aldol adducts and (2) the thiazolidinethiones are more readily cleaved by nucleophilic attack than both oxazolidinethiones and oxazolidinones. Formation of the chlorotitanium enolate of *N*-acylthiazolidinethione **18** as described for the oxazolidinethione in the presence of 2.5 equiv of TMEDA followed by addition of

Table 4. (−)-Sparteine-Mediated Aldol Additions of 7[a]

entry	temp[c]	aldehyde (RCHO)[d]	% yield[e]	**17**:**16**
1[b]	0 °C	PhCH=CH	66	92:8
2[b]	0 °C	MeCH=CH	64	>99:1
3[b]	0 °C	CH_2=CH	77	>99:1
4[b]	0 °C	Me_2CH	75	97:3
5[b]	0 °C	Ph	62	>99:1
6[b]	0 °C	Me_2CHCH_2	71	98:2
7[f]	0 °C	PhCH=CH	77	98.6:1.4
8[f]	0 °C	MeCH=CH	84	98.1:1.9
9[f]	0 °C	CH_2=CH	84	94.2:5.8
10[f]	0 °C	Me_2CH	79	98.2:1.8
11[f]	0 °C	Ph	72	93.7:6.3
12[f]	0 °C	Me_2CHCH_2	74	96.1:3.9

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] 1.0 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine were employed. [c] Temperature at which the aldehyde was added. [d] 1.1 equiv of aldehyde was employed. [e] Yields are for the isolated, chromatographically purified major diastereomer. [f] 1.05 equiv of $TiCl_4$, 1.0 equiv of (−)-sparteine, and 1.0 equiv of *N*-methyl-2-pyrrolidinone were employed.

Table 5. TMEDA- and (−)-Sparteine-Mediated Aldol Additions of 18[a,b]

entry	base	aldehyde (RCHO)[c]	% yield[d]	**21**:**20**
1	TMEDA	PhCH=CH	75	98:2
2	TMEDA	MeCH=CH	53	>99:1
3	TMEDA	CH_2=CH	42	>99:1
4	TMEDA	Me_2CH	57	96:4
5	TMEDA	Ph	61	94:6
6	TMEDA	Me_2CHCH_2	60	96:4
7	(−)-sparteine	PhCH=CH	80	96:4
8	(−)-sparteine	MeCH=CH	66	>99:1
9	(−)-sparteine	CH_2=CH	72	>99:1
10	(−)-sparteine	Me_2CH	84	95:5
11	(−)-sparteine	Ph	85	92:8
12	(−)-sparteine	Me_2CHCH_2	81	97:3

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] 1.0 equiv of $TiCl_4$ and 2.5 equiv of diamine were employed. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer.

1.1 equiv of aldehyde gave excellent selectivities in all cases for Evans syn product **21**. As for the oxazolidinethiones, improved conversion (and resulting higher yields) to Evans syn product **21** were realized for all aldehydes examined when 2.5 equiv of (−)-sparteine was used instead of TMEDA[17] (Tables 4 and 5).[18] High selectivity and excellent yields were also realized when *N*-acylthiazolidinethione **7** was enolized with 1.05 equiv of titantium tetrachloride and 2.5 equiv of (−)-sparteine. Similar yields and selectivity were observed for *N*-acylthiazolidinethione **7** with 1 equiv of (−)-sparteine and 1 equiv of *N*-methyl-2-pyrrolidinone as observed with the *N*-acyloxazolidinethiones. The diastereomeric products are readily separated by chromatography and can often be separated by recrystallization. Since the products were yellow in color, the separation can be observed visually as the separate components move down the column.

Evans Syn Aldol Additions with *N*-Acyloxazolidinones. To determine if the soft enolization with titanium tetrachloride and (−)-sparteine was a general phenomenon, we investigated the aldol addition reactions of *N*-acyloxazolidinones. Enolization of oxazolidinone **22**

(17) Use of 1.5 equiv of diamine gave selective formation of the Evans syn product, but 2.5 equiv resulted in better selectivity.

(18) For a discussion of effects of amine structure on selectivity in aldol additions of tin(II) enolates see: Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753−756

Scheme 5

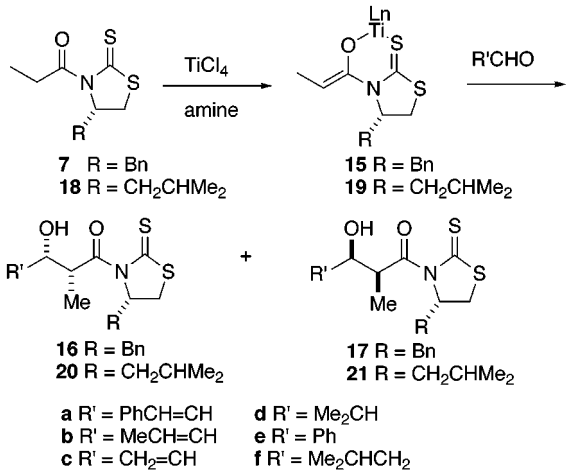


Table 6. (−)-Sparteine-Mediated Aldol Additions of 22[a]

entry	temperature	aldehyde (RCHO)[b]	yield[c]	25:24
1[d]	0 °C	Et	84	99:1
2[d]	0 °C	MeCH=CH	89	97:3
3[d]	0 °C	Me_2CH	89	98:2
4[d]	0 °C	*t*-Bu	87	97:3
5[e]	−78 °C	Me_2CH	98	98:2

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] 1.1 equiv of aldehyde was employed. [c] Yields are for the isolated, chromatographically purified major diastereomer. [d] 1.0 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine were employed. [e] 1.05 equiv of $TiCl_4$, 1.0 equiv of (−)-sparteine, and 1.0 equiv of *N*-methyl-2-pyrrolidinone were employed.

with 1.1 equiv of titanium tetrachloride and 2.5 equiv of (−)-sparteine followed by addition of 1.1 equiv of the appropriate aldehyde at 0 °C produced the Evans syn adduct **25** as the major diastereomer in high yield with excellent diastereocontrol. The isolated yields of the major diastereomer after chromatography were 84−89%. This method is operationally simple, and the cost is lower than aldol additions with dibutylboron triflate. The use of 1.05 equiv of titanium tetrachloride, 1.0 equiv of (−)-sparteine, and 1.0 equiv of *N*-methyl-2-pyrrolidinone (NMP) also proved highly efficient and selective as with the *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones (Table 6, entry 5). The advantage of the use of $TiCl_4$−(−)-sparteine−NMP for the enolization of *N*-acyloxazolidinones is that the reagents can be used as purchased, the reaction proceeds well even at 0 °C, and no oxidative workup is required. The relative cost is approximately 35−40% relative to the dibutylborontriflate procedure.

Non-Evans Syn Aldol Reactions with *N*-Acyloxazolidinethiones. Because of the noticeable sensitivity of the diastereoselectivity of the oxazolidinethione aldol reactions to small changes in the Lewis acid stoichiometry, a survey of effects of various amines, their stoichiometry, and the stoichiometry of the titanium tetrachloride was undertaken. After further investigation, it was observed that employing 2 equiv of $TiCl_4$ and 1 equiv of *i*-Pr_2EtN gave excellent selectivity for the non-Evans syn aldol product **9** (Scheme 3). Selectivities were generally >95:5 for syn/anti and >99:1 for non-Evans syn/Evans syn (isolated yields generally 80−85%). The major aldol addition product formed was the non-Evans syn adduct when using 1 equiv of DIEA, TMEDA, or (−)-sparteine when 2 equiv of titanium tetrachloride were added. The

Scheme 6

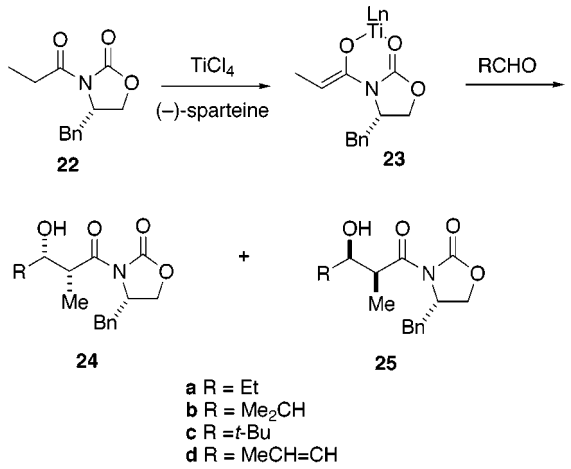


Table 7. Non-Evans Syn Aldol Additions with Oxazolidinethione 5[a]

entry	amine (1.1 equiv)[b]	aldehyde (RCHO)[c]	% yield[d]	**9**:**10**:anti
1	DIEA	Et	80	95.7:0.5:3.8
2	DIEA	MeCH=CH	81	94.7:0.0:5.3
3	DIEA	CH_2=CH	44	99.3:0.0:0.7
4	DIEA	Me_2CH	87	94.9:0.0:5.1
5	DIEA	Ph	88	97.6:0.7:1.7
6	DIEA	Me_2CHCH_2	75	96.7:0.0:3.3
7	(−)-sparteine	Et	72	93.6:6.4:0.0
8	(−)-sparteine	MeCH=CH	80	92.9:0.0:7.1
9	(−)-sparteine	CH_2=CH	55	95.3:0.0:4.7
10	(−)-sparteine	Me_2CH	79	94.1:0.0:5.9
11	(−)-sparteine	Me_2CHCH_2	84	95.5:0.0:4.5

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] 2.0 equiv of $TiCl_4$ and 1.1 equiv of amine were employed. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer.

use of (−)-sparteine resulted in somewhat cleaner reactions in most cases than was observed with DIEA.

Non-Evans Syn Aldol Reactions with *N*-Acylthiazolidinethiones. Interestingly, the major aldol addition product was the non-Evans syn adduct with *N*-acylthiazolidinethiones regardless of the titanium tetrachloride stoichiometry (1 or 2 equiv) when only 1 equiv of amine was utilized. Thus, DIEA, TMEDA, or (−)-sparteine provide the non-Evans syn adducts **16** and **20** as the major products (Tables 8−10). The thiazolidinethiones allow access to either Evans syn or non-Evans syn simply by changing the base stoichiometry to 2 or 1 equiv, respectively, without the need for changing the Lewis acid stoichiometry.

Mechanistic Implications. *N*-Acyloxazolidinones, *N*-acyloxazolidinethiones, and *N*-acylthiazolidinethiones all produce Evans syn aldol adducts when their chlorotitanium enolates are formed in the presence of 2 equiv of (−)-sparteine. In these instances, the nonchelated transition state **1** is operative possibly due to coordination of the second equivalent of diamine to the metal center, thus preventing coordination of the imide or thioimide carbonyl to the metal. The same factors that govern the boron enolate transition states would then be operative resulting in the Evans syn product. The second equivalent of diamine may also play a role in avoiding the need for excess aldehyde, since if the diamine is bound to titanium, no vacant coordination sites would be available for coordination of a second equivalent of aldehyde. Evidence

Table 8. DIEA-Mediated Aldol Additions of 18[a]

auxiliary	equiv $TiCl_4$[b]	aldehyde (RCHO)[c]	% yield[d]	**20**:**21**
R = *i*Bu	1	PhCH=CH	80	87:13
R = *i*Bu	1	Ph	78	91:9
R = *i*Bu	1	Me_2CH	77	87:13
R = *i*Bu	1	Me_2CHCH_2	40	84:16
R = *i*Bu	1	CH_2=CH	30	>99:1
R = *i*Bu	1	MeCH=CH	53	>99:1
R = *i*Bu	2	PhCH=CH	56	96:4
R = *i*Bu	2	Ph	60	90:10
R = *i*Bu	2	Me_2CH	75	95:5
R = *i*Bu	2	Me_2CHCH_2	51	90:10
R = *i*Bu	2	CH_2=CH	40	>99:1
R = *i*Bu	2	MeCH=CH	44	96:4

[a] 1.1 equiv of amine was employed. [b] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer.

Table 9. Non-Evans Syn Aldol Additions with TMEDA and (−)-Sparteine with 18[a]

auxiliary	base[b]	aldehyde (RCHO)[c]	% yield[d]	**20**:**21**
R = *i*Bu	TMEDA	PhCH=CH	52	97:3
R = *i*Bu	TMEDA	MeCH=CH	74	92:8
R = *i*Bu	TMEDA	CH_2=CH	51	>99:1
R = *i*Bu	TMEDA	Me_2CH	50	>99:1
R = *i*Bu	TMEDA	Ph	62	92:8
R = *i*Bu	TMEDA	Me_2CHCH_2	52	92:8
R = *i*Bu	(−)-sparteine	PhCH=CH	63	92:8
R = *i*Bu	(−)-sparteine	MeCH=CH	79	98:2
R = *i*Bu	(−)-sparteine	CH_2=CH	42	>99:1
R = *i*Bu	(−)-sparteine	Me_2CH	63	95:5
R = *i*Bu	(−)-sparteine	Ph	64	91:9
R = *i*Bu	(−)-sparteine	Me_2CHCH_2	65	93:7

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. 1.1 equiv of $TiCl_4$ was employed. [b] 1.0 equiv of amine was employed. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer.

Table 10. Non-Evans Syn Aldol Additions with (−)-Sparteine with 7[a]

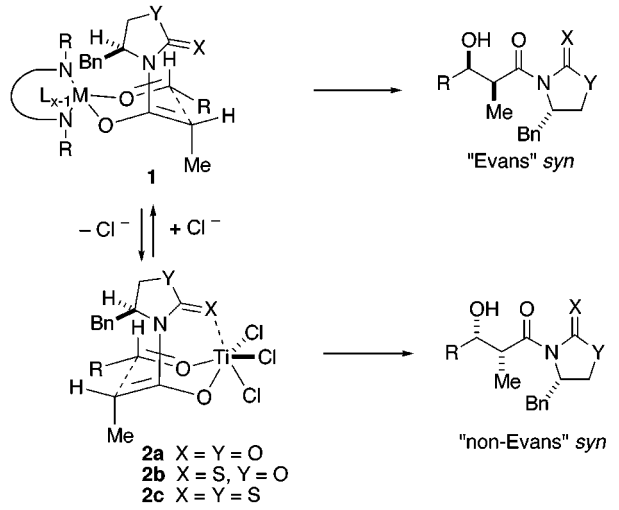
auxiliary	base[b]	aldehyde (RCHO)[c]	yield[d]	**16**:**17**
R = CH_2Ph	(−)-sparteine	PhCH=CH	58	97:3
R = CH_2Ph	(−)-sparteine	MeCH=CH	45	>99:1
R = CH_2Ph	(−)-sparteine	CH_2=CH	49	>99:1
R = CH_2Ph	(−)-sparteine	Me_2CH	60	98:2
R = CH_2Ph	(−)-sparteine	Ph	52	>99:1
R = CH_2Ph	(−)-sparteine	Me_2CHCH_2	57	98:2

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. 1.1 equiv of $TiCl_4$ were employed. [b] 1.0 equiv of amine were employed. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for the isolated, chromatographically purified major diastereomer.

for coordination of 1 equiv of diamine to the metal center is particularly strong in the case of the thiazolidinethiones where the facial selectivity of the aldol is reversed upon addition of a second equivalent of diamine without the addition of a second equivalent of titanium tetrachloride.

The fact that thiazolidinethiones produce non-Evans syn aldol adducts with 1 equiv of (−)-sparteine and 1 equiv of titanium tetrachloride can be attributed to a highly ordered chelated transition-state (Scheme 7). The thiocarbonyl of thiazolidinethiones is more nucleophilic than the oxazolidinone carbonyl or the oxazolidinethione carbonyl, thus the non-Evans product apparently results from formation of the highly ordered chelated transition-state with only 1 equiv of titanium tetrachloride. When 2 equiv of TMEDA or (−)-sparteine were used, a reversal of selectivity was observed to give the Evans syn aldol adduct in excellent selectivity. The diamine is presumably coordinating to the titanium disfavoring the chelation of the thiocarbonyl to the metal center (Scheme 7).

Scheme 7



Oxazolidinethiones provide the Evans syn adducts with 1 equiv of titanium tetrachloride and the non-Evans syn products upon addition of a second equivalent of $TiCl_4$. Heathcock has reported a similar approach to the preparation of the non-Evans syn aldol products by adding additional Lewis acids to boron enolates and has proposed an acyclic transition state with 1 equiv of Lewis acid activating the aldehyde.[19] In the case of oxazolidinethiones, we propose the chelated transition state, originally proposed by Nagao and Fujita,[7] for the formation of the non-Evans syn adducts. Oppolzer had previously proposed a switching from the standard Zimmerman-Traxler model to the Nagao chelated model to explain the change in selectivity observed with tin (IV) enolates of *N*-acyl sultams.[2c] While the oxazolidinethione carbonyl is not sufficiently nucleophilic to displace chloride ion and coordinate to the metal center of the chlorotitanium enolate, upon addition of a second equivalent of titanium tetrachloride, chloride ion is abstracted from the metal center opening a coordination site on the metal.[20] NMR experiments support this hypothesis. A single enolate species was observed when the enolate was prepared with 1.0 equiv of titanium tetrachloride and diisopropylethylamine. Addition of a second equivalent of titanium tetrachloride produced a single new species distinct from the original. The species produced with 2 equiv of titanium tetrachloride was also produced when the enolate was prepared with 1.0 equiv of titanium tetrachloride and diisopropylethylamine followed by addition of 1.0 equiv of silver hexafluoroantimonate. Abstraction of chloride ion to form either a neutral trigonal bipyramidal titanium species or a chloro bridged octahedral dimeric species is possible.[21] Either of these could react with aldehyde to produce the chelated transition state **2** (Scheme 7).

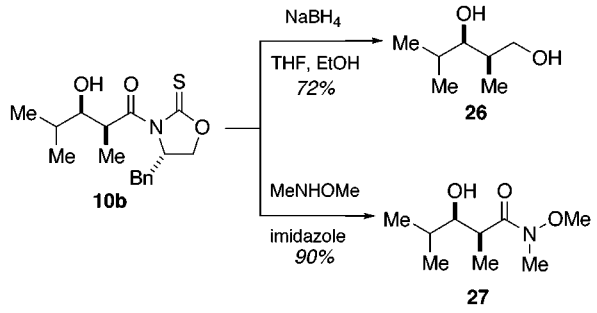
Synthetic Manipulation of Aldol Adducts. The aldol adducts of both *N*-acyloxazolidinethiones and *N*-

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

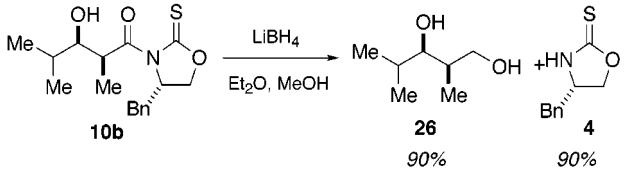
(20) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986−2987.

(21) For a discussion of the structural features of complexes of titanium tetrachloride with carbonyl functionality see: Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Chem. Ber.* **1996**, *129*, 1361−1368.

Scheme 8



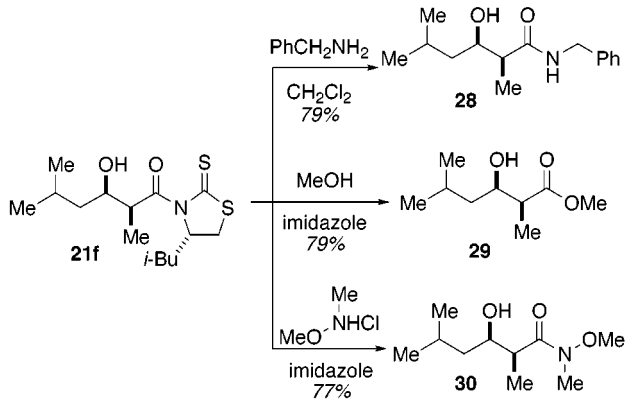
Scheme 9



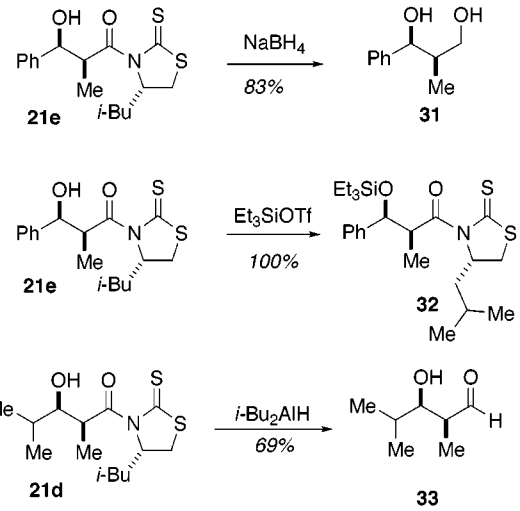
acylthiazolidinethiones can be readily converted to other functional groups. Both the oxazolidinethiones and thiazolidinethiones are cleaved under milder conditions than the oxazolidinones. As illustrated in Schemes 8 and 9, the oxazolidinethiones such as **10b** can be reductively removed with either lithium borohydride or the less expensive sodium borohydride to produce the diols such as **26**. Yields are typically somewhat higher with lithium borohydride, however. A major practical advantage that was discovered during the total synthesis of (−)-callystatin A[22] was the ability to recover the oxazolidinethione auxiliary in high yield by simple base extraction with aqueous NaOH. For example, treatment of intermediate **10b** with lithium borohydride in Et_2O and methanol followed by base extraction with aqueous 14% NaOH provided alcohol **26**[3] in 90% yield (Scheme 9). Neutralization of the water layer with aqueous 10% HCl and subsequent extraction with methylene chloride and concentration gave 90% recovery of oxazolidinethione **4**. The facile reductive removal of the oxazolidinethione auxiliary of **10b** is noteworthy given the difficulty often encountered in the reductive cleavage of oxazolidinone auxiliaries in hindered systems.

Transamination to the Weinreb's amide occurs by exposure of the *N*-acyloxazolidinethione to *N*,*O*-dimethylhydroxylamine hydrochloride and imidazole in dichloromethane (Scheme 8).[23] Trimethylaluminum is not required. A typical procedure involves the sequential addition of 3 equiv of imidazole and 1 equiv of *N*,*O*-dimethylhydroxylamine hydrochloride to a methylene chloride solution of an oxazolidinethione substrate such as **10b** (1 equiv). Base extraction allows for the separation of the oxazolidinethione auxiliary from the amide without chromatographic separation. These reactions are believed to proceed by initial displacement of the oxazolidinethione by imidazole followed by further substitution of the imidazole by the hydroxylamine. It is critical that the hydroxyl group be unprotected for successful execution of these transaminations.[24]

Scheme 10



Scheme 11



The *N*-acylthiazolidinethione aldol adducts are also reductively cleaved with either lithium borohydride or sodium borohydride as with the oxazolidinethiones (Scheme 11). Most importantly, direct conversion to the aldehyde using *i*Bu_2AlH was possible (Scheme 11).[25] Conversion to the secondary amide via substitution using a primary amine or the Weinreb's amide with N−MeOMe−HCl and imidazole also proceeded cleanly in dichloromethane (Scheme 10). In addition, formation of esters can be achieved with an alcohol and imidazole (Scheme 10).[26] In all cases, liberation of the deacylated auxiliary results. As with the oxazolidinethiones, because of the relatively high acidity of the thiazolidinethione, it is readily removed from the reaction mixture with a basic wash using 1M NaOH and can be easily recovered by acidification.[27] The ability to separate the auxiliary from the cleavage products by simple extraction is a distinct advantage of both the oxazolidinethione and thiazolidinethione auxiliaries.

Iterative Aldol Additions. Certainly one of the most advantageous aspects of the aldol reactions described above is the ability to switch from Evans to non-Evans

(22) Crimmins, M. T.; King, Bryan W. *J. Am. Chem. Soc.* **1998**, *120*, 9084−9085.

(23) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1997**, 4171−4174. Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, 12, 989−993.

(24) Evans, D. A.; Gage, J. R.; Leighton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

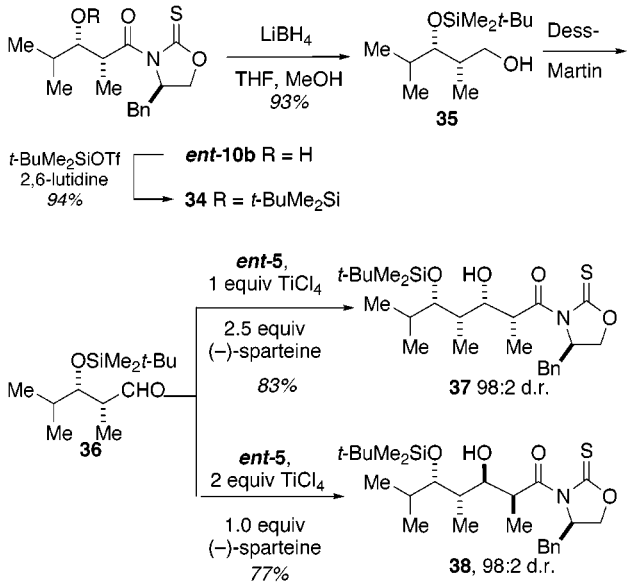
(25) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett.* **1995**, 36, 2097−2100.

(26) With oxazolidinethione auxiliaries, this product can also be obtained but the use of DMAP is required, see: Su, D.; Wang, Y.; Yan, T. *Tetrahedron Lett.* **1999**, 40, 4197−4198.

(27) This procedure cannot be used in the case of the aldehyde, which is easily epimerized under basic conditions.

syn aldol adducts by simply changing the reaction conditions, thus nullifying the need for the auxiliary of the opposite chirality. To demonstrate the utility of the *N*-acyloxazolidinethione auxiliaries in this context, an iterative aldol sequence with both possible syn−syn tetrads was carried out. Aldol adduct ***ent*-10b** from *N*-acyloxazolidinethiones ***ent*-5** and isobutyraldehyde was protected as its triethylsilyl ether **34**, and then the auxiliary was reductively removed with lithium borohydride to give the primary alcohol **35**. Dess−Martin oxidation of the alcohol provided the aldehyde **36** which was exposed to both the Evans syn conditions [1 equiv of $TiCl_4$, 2.5 equiv (−)-sparteine] and the non-Evans syn conditions [2 equiv of $TiCl_4$, 1.0 equiv (−)-sparteine] to provide the syn−syn−syn adduct **37** and the syn−anti−syn adduct **38**, respectively. Both adducts were formed in high yield with excellent diastereoselectivity demonstrating the ability to access either syn tetrad depending on the reaction conditions. The formation of a syn−syn tetrad by iterative aldol additions of *N*-acyloxazolidinethiones was utilized in a recent synthesis of (−)-callystatin A[22] and has been exploited by Sulikowski in an approach to a fragment of apoptolidin.[28]

Scheme 12



Summary

Aldol addition reactions of the titanium enolates of *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones have been executed with extremely high selectivities and yields with readily available and easily handled reagents and with 1.1 equiv of aldehyde. Either enantiomeric syn aldol product (after removal of the auxiliary) may be obtained from the same *N*-acyloxazolidinethione or thiazolidinethione by simply changing the reaction conditions. A variety of aldehyde structural types, including unsaturated aldehydes, are tolerated. The combination of 1.0 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine [or 1 equiv of (−)-sparteine and 1 equiv of *N*-methyl-2-pyrrolidinone] has provided excellent selectivity for the Evans syn aldol product and has shown a dramatic rate enhancement. Outstanding selectivity for the non-Evans syn aldol product was obtained with 2 equiv of $TiCl_4$ and 1.1 equiv of (−)-sparteine for the oxazolidinethiones and 1 equiv of $TiCl_4$ and 1.1 equiv of (−)-sparteine for the thiazolidinethiones. In addition, the thione auxiliaries are more easily removed than the corresponding oxazolidinones and can be recovered by simple base extraction of the crude reaction mixtures. These points exemplify the practicality of the oxazolidinethione and the thiazolidinethione mediated aldol methodology. The titanium tetrachloride-(−)-sparteine-*N*-methyl-2-pyrrolidinone method also holds practical advantages in the asymmetric aldol additions with *N*-acyloxazolidinones.

Experimental Section

(*S*)-4-Benzyl-1,3-oxazolidine-2-thione (4)[15]. To a solution of 4.11 g (27.18 mmol) of l-phenylalaninol and 9.47 mL (6.88 g, 67.95 mmol) of triethylamine in 100 mL of CH_2Cl_2 at 0 °C was added a solution of 2.07 mL (3.13 g, 27.18 mmol) of thiophosgene in 2 mL of CH_2Cl_2. After the mixture was stirred for 30 min at 0 °C, the reaction was quenched with 10% $NaHSO_4$. The layers were separated, and the organic layer was washed with 1 M NH_4OH, dried over Na_2SO_4, decanted, and concentrated. The crude material could be purified by column chromatography to provide 4.98 g (95%) of oxazolidinethione **4**[15] as a viscous oil (crystallization of the oil would slowly occur after approximately one month at 0 °C) but was generally carried to the acylation step without purification: $[\alpha]^{24}_D$ −95.4° (c = 1.1, CH_2Cl_2); IR (neat) 3450, 3050 br, 1485, 1325, 1260, 1220, 1205, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.40−7.10 (m, 5H), 7.06 (br s, 1H), 4.71 (t, J = 8.9 Hz, 1H), 4.45−4.18 (m, 2H), 3.01−2.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 189.3, 135.1, 129.0, 128.9, 127.3, 74.6, 57.6, 40.2.

(*S*)-3-(1-Oxopropyl)-4-benzyl-1,3-oxazolidine-2-thione (5). To a cooled solution (−78 °C) of 12.86 g (66.54 mmol) of oxazolidinethione **4** in 300 mL of THF was added dropwise 41.6 mL (66.54 mmol) of *n*-butyllithium (1.6 M in hexanes). After stirring the lithiated oxazolidinethione for 15−20 min, 6.94 mL (7.39 g, 79.85 mmol) of propionyl chloride was added. The reaction was allowed to stir at −78 °C for 15 min prior to warming to room temperature and stirring for 30 min. The reaction was quenched with aqueous 10% K_2CO_3, and the volatiles were removed. The aqueous layer was extracted with CH_2Cl_2 (2×) and the organic layer concentrated. Purification of the residue by column chromatography afforded 14.93 g (90%) of *N*-acyloxazolidinethione **5** as a white solid: $[\alpha]^{24}_D$ +127.3° (c = 0.49, CH_2Cl_2); IR (neat) 1695, 1400, 1360, 1310, 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, J = 7.2 Hz, 3H), 2.75 (dd, J = 13.1, 9.5 Hz, 1H), 3.11−3.51 (m, 3H), 4.20−4.38 (m, 2H), 4.91 (m, 1H), 7.15−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 185.3, 174.8, 135.2, 129.3, 128.9, 127.3, 70.21, 59.88, 37.55, 31.29, 8.45. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.59; H, 6.04; N, 5.58.

Typical Procedure for $TiCl_4$ (2 equiv), *i*-Pr_2NEt, or (−)-Sparteine (1.1 equiv). To a dry round-bottom flask under nitrogen was added 0.25 g (1.00 mmol) of the oxazolidinethione in 6 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium (IV) chloride (2.00 mmol, 0.22 mL) was added dropwise and the solution allowed to stir for 5 min. To the yellow slurry or suspension was added diisopropylethylamine or (−)-sparteine (1.10 mmol). The dark red titanium enolate was stirred for 20 min at 0 °C, then was cooled to −78 °C. Freshly distilled aldehyde (1.10 mmol) was added dropwise. The resulting mixture was stirred for 1 h at −78 °C and then was warmed to 0 °C. The reaction was quenched with half-saturated ammonium chloride (6 mL), and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and concentrated. HPLC analysis of the crude revealed the isomer ratios. Purification by column chromatography of the crude material afforded the major diastereomer.

Typical Procedure for $TiCl_4$ (1 equiv), Diamine (2.5 equiv). To a dry round-bottom under nitrogen was added 1.00 mmol of the *N*-propionyloxazolidinone, oxazolidinethione, or

(28) Sulikowski, G. A.; Lee, W.-M.; Jin, B.; Wu, B. *Org. Lett.* **2000**, 2, 1439−1442.

thiazolidinethione in 6 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium (IV) chloride (1.05 mmol, 0.115 mL) was added dropwise and the solution allowed to stir for 5 min. To the yellow slurry or suspension was added the diamine [TMEDA or (−)-sparteine, 2.5 mmol]. The dark red enolate was stirred for 20 min at 0 °C. Freshly distilled aldehyde (1.1 mmol) was added dropwise and the reaction stirred for 1 h at 0 °C. Workup and procedure was the same as above.

Typical Procedure for $TiCl_4$ (1 equiv), (−)-Sparteine (1 equiv), *N*-Methyl-2-pyrrolidinone (1 equiv). A solution of the *N*-acyloxazolidinethione, *N*-acyloxazolidinone, or *N*-acylthiazolidinethione (1.23 mmol) in 10 mL of CH_2Cl_2 was cooled to 0 °C. $TiCl_4$ (0.14 mL, 1.29 mmol) was added, and the mixture was stirred for 5 min. (−)-Sparteine (0.28 mL, 1.23 mmol) was added dropwise slowly. After complete addition, the mixture was stirred at 0 °C for 20 min. The mixture was cooled to −78 °C, and 1-methyl-2-pyrrolidinone (0.12 mL, 1.23 mmol) was added. The mixture was stirred for 10 min followed by addition of freshly distilled isobutyraldehyde (0.12 mL, 1.35 mmol) dropwise. The mixture was stirred for 1 h at −78 °C, gradually warmed to 0 °C, and stirred for 1h. The reaction was quenched with half-saturated NH_4Cl and warmed to 25 °C. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 0.389 g of alcohol (98%).

Typical Procedure for $TiCl_4$ (1 equiv), (−)-Sparteine (1 equiv). To a dry round-bottom flask under nitrogen was added the thiazolidinethione (1.00 mmol) in 6 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium (IV) chloride (1.00 mmol, 0.11 mL) was added dropwise, and the solution allowed to stir for 5 min. To the yellow slurry or suspension was added diisopropylethylamine or (−)-sparteine (1.00 mmol). The dark red titanium enolate was stirred for 20 min at 0 °C, then was cooled to −78 °C. Freshly distilled aldehyde (1.10 mmol) was added dropwise. The resulting mixture stirred for 1 h at −78 °C and then was warmed to 0 °C. The reaction was quenched with half-saturated ammonium chloride (6 mL) and the layers separated. The organic layer was dried over sodium sulfate, filtered, and concentrated. HPLC analysis of the crude revealed the isomer ratios. Purification by column chromatography of the crude material afforded the major diastereomer.

Acknowledgment. We thank Professor James P. Morken and for helpful discussions. Financial support of our programs by the NIH and the NSF is acknowledged with thanks. Thanks are also due to the Wellcome Foundation for a fellowship to B.W.K and E.A.T. and to Organic Reactions for sponsoring a Division of Organic Chemistry Fellowship for B.W.K.

Supporting Information Available: Supporting Information Available: Spectral data (^1H, ^{13}C NMR, IR, and optical rotations) for compounds **7**, **9a**−**f**, **10a**−**f**, **20a**−**f**, **21a**−**f, 26**−**38** are available. This information is available free of charge via the Internet at http://pubs.acs.org.

JO001387R