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Titanium Enolates of Thiazolidinethione Chiral Auxiliaries: Versatile Tools for Asymmetric Aldol Additions

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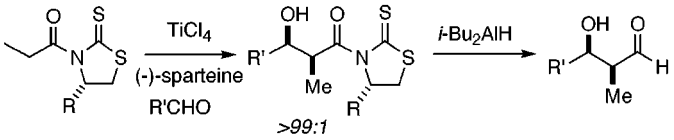
ABSTRACT



Asymmetric aldol additions using chlorotitanium enolates of 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 (–)-sparteine as the base, selectivities of 97:3 to >99:1 were obtained for the Evans syn products with 2 equivalents of base and for the non-Evans syn when 1 equiv of base was employed. The thiazolidinethione auxiliaries are easily removed, and the aldol adducts can be readily transformed to various functional groups. Even direct reduction to the aldehyde with diisobutylaluminum hydride is possible.

Chiral auxiliary-mediated asymmetric aldol additions have been studied extensively and are now an important and general method for asymmetric carbon−carbon bond formation.[1] In particular, dibutylboron enolates of acyl oxazolidinones, pioneered by Evans, are highly effective for the preparation of "Evans" syn products in asymmetric aldol additions.[2] Recent studies in our laboratory have shown that chlorotitanium enolates of oxazolidinethiones provide high diastereoselectivity as well as the ability to produce either "Evans" or "non-Evans" syn aldol adducts depending on the stoichiometry of titanium tetrachloride and nature of the amine employed.[3] However, more easily cleavable auxiliaries than oxazolidinones or oxazolidinethiones would be advantageous. We now report that the use of chlorotitanium enolates of acyl thiazolidinethione auxiliaries also results in high diastereoselectivities in aldol additions. The aldol adducts of acyl thiazolidinethiones are easily removed and can be directly converted to aldehydes as well as to other functional groups.

Synthesis of the thiazolidinethione auxiliaries[4] was readily accomplished by reduction of an amino acid to the corresponding amino alcohol[5] followed by conversion of the amino alcohol to the thiazolidinethione by exposure to carbon disulfide and 1 M KOH[6] (Figure 1). The auxiliary was then acylated with propionyl chloride in the presence of triethylamine (Figure 2).

Formation of the enolate at 0 °C using titanium tetrachloride and the appropriate amine base occurred within 20 min;

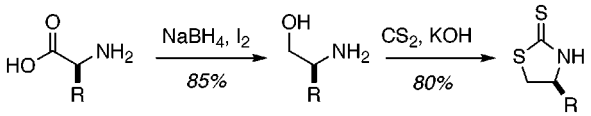


Figure 1. Synthesis of thiazolidinethione auxiliary.

(1) (a) 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.

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

(3) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, 119, 7883−7884.

(4) Nagao, Y.; Yamada, S.; Kumagai, Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem Commun.* **1985**, 1418−1419.

(5) McKennon, M. J.; Meyer, A. I. *J. Org. Chem.* **1993**, *58*, 3568−3571.

(6) Delaunay, D.; Toupet, L.; Le Corre, M.*J. Org. Chem.* **1995**, *60*, 6604−6607.

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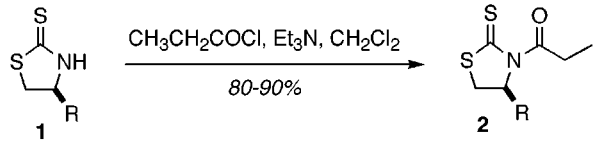


Figure 2. Acylation of thiazolidinethione auxiliary.

subsequent addition of the aldehyde led to formation of aldol adducts with excellent diastereoselectivity.[7] Interestingly, the use of diisopropylethylamine (DIEA), TMEDA, or (−)-sparteine resulted in preferential formation of non-Evans syn aldol adducts **3** when 1 equiv of titanium tetrachloride and 1 equiv of amine was employed (Tables 1 and 2). However,

Table 1. Selectivities for Propionate Aldol Additions Using Thiazolidinethione Chiral Auxiliaries with Titanium Tetrachloride and Diisopropylethylamine

auxiliary (**2**) R =	$TiCl_4$ (equiv)	aldehyde[11] (RCHO)	yield[12] (%)	**3**:**4**[13]
i-Bu	1	PhCH=CH	80	87:13
i-Bu	1	Ph	78	91:9
i-Bu	1	Me_2CH	77	87:13
i-Bu	1	Me_2CHCH_2	40	84:16
i-Bu	1	CH_2=CH	30	>99:1
i-Bu	1	MeCH=CH	53	>99:1
i-Bu	2	PhCH=CH	56	96:4
i-Bu	2	Ph	60	90:10
i-Bu	2	Me_2CH	75	95:5
i-Bu	2	Me_2CHCH_2	51	90:10
i-Bu	2	CH_2=CH	40	>99:1
i-Bu	2	MeCH=CH	44	96:4

the use of TMEDA gave excellent selectivities in all cases for Evans syn product **4** when 2 equiv of base was used. Higher selectivities and improved yields of Evans syn

Table 2. Selectivities for Propionate Aldol Additions Using Thiazolidinethione Chiral Auxiliaries with Titanium Tetrachloride and Diamines (1 Equiv)

auxiliary (**2**) R =	base	aldehyde (RCHO)	yield (%)	**3**:**4**
i-Bu	TMEDA	PhCH=CH	52	97:3
i-Bu	TMEDA	MeCH=CH	74	92:8
i-Bu	TMEDA	CH_2=CH	51	>99:1
i-Bu	TMEDA	Me_2CH	50	>99:1
i-Bu	TMEDA	Ph	62	92:8
i-Bu	TMEDA	Me_2CHCH_2	52	92:8
i-Bu	(−)-sparteine	PhCH=CH	63	92:8
i-Bu	(−)-sparteine	MeCH=CH	79	98:2
i-Bu	(−)-sparteine	CH_2=CH	42	>99:1
i-Bu	(−)-sparteine	Me_2CH	63	95:5
i-Bu	(−)-sparteine	Ph	64	91:9
i-Bu	(−)-sparteine	Me_2CHCH_2	65	93:7
CH_2Ph	(−)-sparteine	PhCH=CH	58	97:3
CH_2Ph	(−)-sparteine	MeCH=CH	45	>99:1
CH_2Ph	(−)-sparteine	CH_2=CH	49	>99:1
CH_2Ph	(−)-sparteine	Me_2CH	60	98:2
CH_2Ph	(−)-sparteine	Ph	52	>99:1
CH_2Ph	(−)-sparteine	Me_2CHCH_2	57	98:2

product **4** were realized for all aldehydes studied when 2 equiv of (−)-sparteine was used instead of TMEDA[8] (Table 3).[9] Isolation of diastereomeric products proceeded very

Table 3. Selectivities for Propionate Aldol Additions Using Thiazolidinethione Chiral Auxiliaries with Titanium Tetrachloride and Diamines (2 Equiv)

auxiliary (**2**) R =	base	aldehyde (RCHO)	yield (%)	**3**:**4**
i-Bu	TMEDA	PhCH=CH	75	2:98
i-Bu	TMEDA	MeCH=CH	53	<1:99
i-Bu	TMEDA	CH_2=CH	42	<1:99
i-Bu	TMEDA	Me_2CH	57	4:96
i-Bu	TMEDA	Ph	61	6:94
i-Bu	TMEDA	Me_2CHCH_2	60	4:96
i-Bu	(−)-sparteine	PhCH=CH	80	4:96
i-Bu	(−)-sparteine	MeCH=CH	66	<1:99
i-Bu	(−)-sparteine	CH_2=CH	72	<1:99
i-Bu	(−)-sparteine	Me_2CH	84	5:95
i-Bu	(−)-sparteine	Ph	85	8:92
i-Bu	(−)-sparteine	Me_2CHCH_2	81	3:97
CH_2Ph	(−)-sparteine	PhCH=CH	66	8:92
CH_2Ph	(−)-sparteine	MeCH=CH	64	<1:99
CH_2Ph	(−)-sparteine	CH_2=CH	77	<1:99
CH_2Ph	(−)-sparteine	Me_2CH	75	3:97
CH_2Ph	(−)-sparteine	Ph	62	<1:99
CH_2Ph	(−)-sparteine	Me_2CHCH_2	71	2:98

easily. The products were yellow in color, which allowed for visual chromatography where separation of components could be seen directly on a silica gel column.

The major aldol addition product formed was the non-Evans syn adduct when using 1 equiv of DIEA, TMEDA,

(7) **Typical Procedure.** To a dry round-bottom flask under nitrogen was added 0.2330 g (1.0 mmol) of the thiazolidinethione in 5 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium(IV) chloride (0.121 mL, 1.1 mmol) was added dropwise, and the solution was allowed to stir for 5 min. To the red suspension was added (−)-sparteine (0.572 mL, 2 mmol). The dark red enolate was stirred for 20 min at 0 °C. Freshly distilled aldehyde (1.1 mmol) was added dropwise and the resulting mixture stirred for 1 h at 0 °C. The reaction was quenched with half-saturated ammonium chloride, and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2, and the combined extracts were dried over magnesium sulfate, filtered, and concentrated. HPLC analysis of the unpurified product revealed the isomer ratios. Purification by flash column chromatography afforded the major diastereomer.

(8) Using 1.5 equiv of diamine gave selective formation of the Evans syn product, but 2 equiv resulted in better selectivity.

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

(10) The configuration of the aldol adducts was verified by correlation to authentic samples after removal of the auxiliary.

(11) Aldehydes were freshly distilled prior to use.

(12) All new compounds were characterized by ^1H and ^{13}C NMR and optical rotation. Yields are for isolated, chromatographically purified products.

(13) Diasteromeric ratios were determined by HPLC.

or (−)-sparteine regardless of the amount of titanium tetrachloride added.[10] This can be attributed to a proposed highly ordered chelated transition state (Figure 3). We

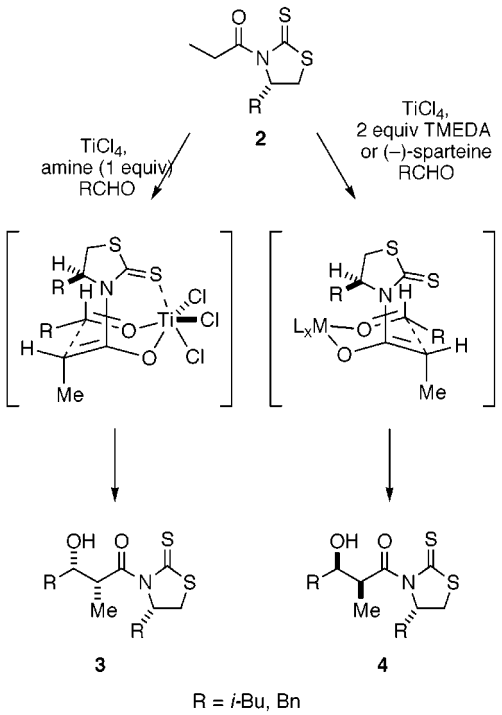
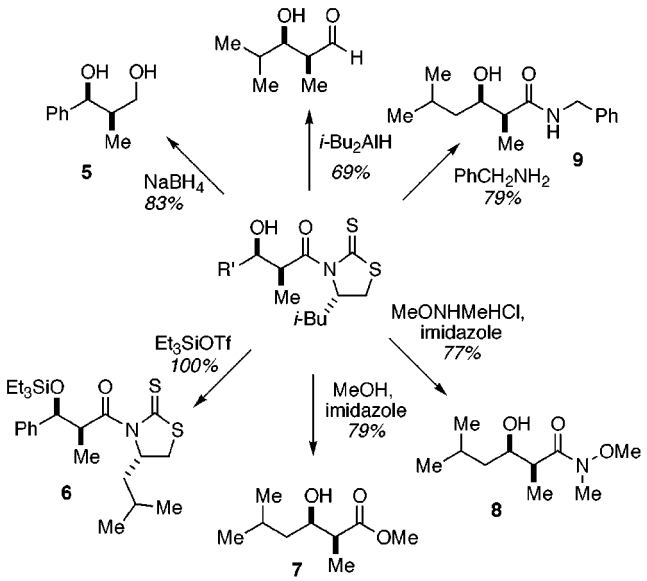


Figure 3. Proposed transition states for aldol additions using titanium enolates of thiazolidinethiones.

previously observed that, with oxazolidinethiones, use of 1 equiv of $TiCl_4$ led to formation of the Evans syn product. Addition of an additional 1 equiv of $TiCl_4$ led to formation of non-Evans syn aldol adduct. However, in the case of thiazolidinethiones, the increased nucleophilicity of the auxiliary apparently results in formation of the highly ordered chelated transition state with only 1 equiv of titanium tetrachloride to yield the non-Evans syn product preferentially. Interestingly, when 2 equiv of TMEDA or (−)-sparteine was used, a reversal of selectivity was observed to give the Evans syn aldol adduct in excellent selectivity. The diamine may participate by coordinating to the titanium, disfavoring the chelation of the thiocarbonyl to the metal center (Figure 3).

The aldol adducts formed can be converted to a variety of derivatives (Scheme 1). Treatment with $NaBH_4$ resulted

Scheme 1. Conversion of Aldol Adduct to Various Products



in efficient conversion to the diol. Conversion to the Weinreb amide was possible simply by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and imidazole.[14] Conversion to the amide via substitution using a primary amine also proceeded cleanly. Most importantly, conversion to the aldehyde using *i*-$BuAl_2H$ was possible.[15] In addition, formation of esters was effected with an alcohol and imidazole.[16] In all cases, liberation of the deacylated auxiliary results. Because of the relatively high acidity of the thiazolidinethione, it is readily removed from the reaction mixture with a basic wash using 1 M NaOH and can be recovered by acidification.[17] The ability to separate the auxiliary from the cleavage products by simple extraction is a distinct advantage of both the oxazolidinethione and thiazolidinethione auxiliaries.

In summary, aldol additions of the chlorotitanium enolates of acyl thiazolidinethiones deliver highly selective aldol reactions favoring non-Evans syn products **3** when using 1 equiv of DIEA, TMEDA, or (−)-sparteine as the base and Evans syn products **4** with 2 equiv of TMEDA or (−)-sparteine. The products are easily isolated and can be converted directly to the aldehyde as well as to a variety of other functionalities. Recovery of the auxiliary is effected by basic extraction of the product mixture.

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Supporting Information Available: Spectral data for Evans syn products **4a**−**l**, non-Evans products **3a**−**f**, and cleavage products **5**−**9**. This material is available via the Internet at http://pubs.acs.org.

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(14) 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.

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

(16) 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.

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