Asymmetric Aldol Additions with Titanium Enolates of Acyloxazolidinethiones: Dependence of Selectivity on Amine Base and Lewis Acid Stoichiometry

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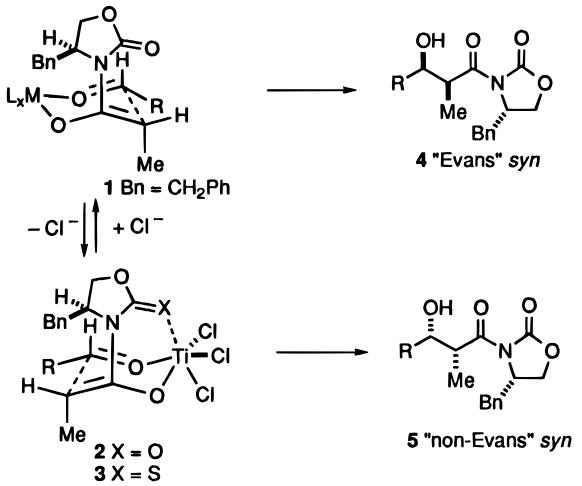
Asymmetric aldol additions have been the subject of intense synthetic and mechanistic study because of their importance in the asymmetric construction of carbon−carbon bonds. In particular, the Evans dialkylboron triflate mediated aldol reaction is a well accepted and useful method for the preparation of β-hydroxy acids and their derivatives in high enantiomeric purity (generally >250:1 diastereoselectivity, i.e. >99% ee).[1] Titanium[2−4] and tin[5] metal centers have also been shown to be effective in creating well-ordered transition states for aldol reactions. We report here our studies on the use of titanium-(IV) enolates of acyloxazolidinethiones for the preparation of either the "Evans" or "non-Evans" *syn* aldol products in high diastereomeric purity *by simply changing the stoichiometry of the Lewis acid and the nature of the amine base.*

Titanium enolates of the Evans acyl oxazolidinones have been examined, but they are less selective than the boron enolates.[2−5] Typical diastereoselectivities are 88−96% de, but much lower selectivities are observed with α,β-unsaturated aldehydes (60:40 *syn A:syn B* plus *anti*, for crotonaldehyde). Also, to achieve reasonable reaction rates and good levels of conversion, excess aldehyde (from 2−5 equiv) must be employed.[2] Therefore, the use of the titanium enolates with expensive or synthetically prepared aldehydes is prohibitive. The reduction in selectivity with titanium enolates is potentially the result of multiple mechanistic pathways operating simultaneously.[4] The transition state **1** has been proposed for the boron enolate (and the titanium enolate) to give the "Evans" *syn* aldol product.[6] If chloride ion is lost, the titanium enolate can also proceed through **2** in



which both the aldehyde and the auxiliary are coordinated to titanium.[3,4] This minor competitive pathway for the titanium enolate of oxazolidinones provides the non-Evans *syn* aldol as the product because of the change in π-facial selectivity and the overall diastereoselectivity is consequently reduced.[3,4]

In an effort to create a more highly ordered transition state for the chlorotitanium enolates, the acyloxazolidinethione enolates were investigated since they might proceed through the "chelated" transition state **3** due to the known higher affinity of sulfur for titanium. Fowles has shown that thioxane prefers to coordinate to titanium through sulfur rather than oxygen.[7] These chelated enolates were expected to be significantly more rigid than the "nonchelated" boron and chlorotitanium enolates. In addition, the *N*-acyloxazolidinethione auxiliaries are more easily cleaved. They undergo aminolysis at room temperature, conditions which do not cleave the corresponding oxazolidinones.[8] The oxazolidinethiones are readily prepared in high yield from amino alcohols, carbon disulfide, and triethylamine.[9]

The use of *N*-acyloxazolidinethiones has resulted in highly diastereoselective aldol additions of the titanium enolates even when only 1 equiv of aldehyde is employed. These aldol condensations are very sensitive to the amount of Lewis acid employed and to the nature of the amine base utilized in the reaction.[10] Use of 1 equiv of $TiCl_4$ with *i*-Pr_2EtN gave inconsistent results, but when 2.5 equiv of TMEDA was employed as the base, consistent results with selectivities of >98:2 (Evans:non-Evans **9**:**8**) were obtained. Unfortunately, the reactions generally failed to go to completion even after extended reaction times and isolated yields were modest (45−60%). When (−)-sparteine was employed as the base, a dramatic rate acceleration was observed. The reactions were complete after 30 s even with 1 equiv of aldehyde and the selectivities were >98:2 *Evans syn* ***9****:non-Evans syn* ***8*** and >99:1 *syn:anti*. Isolated yields with (−)-sparteine were improved substantially compared to those with TMEDA. Importantly, there was no reduction in selectivity when the reactions were conducted at 0 °C as compared to −78 °C and isolated yields were typically higher at 0 °C. An additional important point is that $TiCl_4$ and (−)-sparteine were used directly as received without further purification. (−)-Sparteine produced comparable rate enhancements and similar diastereoselectivies when either enantiomer of the oxazolidinethione auxiliary was employed. No apparent asymmetric induction was provided by the amine's chiral architecture. The reason for the dramatic rate acceleration of these aldol reactions in the presence of 2.5 equiv of (−)-sparteine is not yet clear.

Experiments employing 2 equiv of $TiCl_4$ and 1 equiv of *i*-Pr_2-EtN gave excellent selectivity for the "non-Evans" *syn* aldol product **8**. Selectivities are generally >95:5 for *syn:anti* and >99:1 for *non-Evans syn:Evans syn* (isolated yields 80−85%). Heathcock has reported a similar approach to the preparation of the "non-Evans" *syn* aldol product and proposed an acyclic transition state with 1 equiv of Lewis acid activating the aldehyde.[11] We believe a chelated transition state **3** resulting from abstraction of chloride ion by the second equivalent of titanium tetrachloride is operating here.[12] NMR experiments (^{1}H, 0 °C, CD_2Cl_2) support this hypothesis. A single enolate

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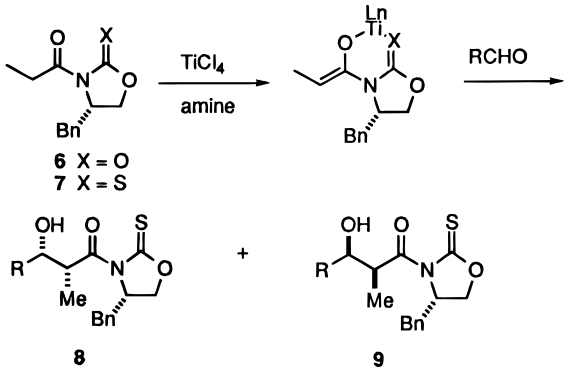
species was observed when the enolate was prepared with 1.0 equiv of titanium tetrachloride and diisopropylethylamine.[13] Addition of a second equivalent of titanium tetrachloride produced a single new species distinct from the original.[14] The species produced with 2 equiv of titanium tetrachloride 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.[14] Abstraction of chloride ion to form either a neutral trigonal bipyramidal titanium species or a chloro-bridged octahedral dimeric species is possible.[15] Either of these could react with aldehyde to produce the chelated transition state **3**. As a control experiment, 1 equiv of propionaldehyde was added to each of the three enolate species generated for the NMR experiments. As expected, the former species (from 1 equiv of $TiCl_4$) produced **9** (R = Et) as the major product and the two latter species each produced **8** (R = Et; >98:2) as the predominant product.



An added advantage of using oxazolidinethiones is that they are easily removed under mild conditions. As shown below, reductive removal is readily achieved in high yield with the inexpensive and easily handled sodium borohydride (the oxazolidinones require expensive lithium borohydride) or they can be transformed into the versatile Weinreb's amide[16] by simply stirring in the presence of imidazole and the hydroxylamine salt. Trimethylaluminum is not required. Also, the oxazolidinethiones can be directly reduced to the aldehyde with *i*-Bu_2AlH due to their increased electrophilicity.[17]

Thus, aldol reactions of the titanium enolates of acyl oxazolidinethiones can be executed with extremely high selectivities at 0 °C with readily available and easily handled reagents, and only 1 equiv of aldehyde is required. Additionally, either enantiomeric *syn* aldol product (after removal of the auxiliary) may be obtained from the same acyloxazolidinethione by simply changing the reaction conditions. A variety of aldehyde structural types, including unsaturated aldehydes are tolerated.

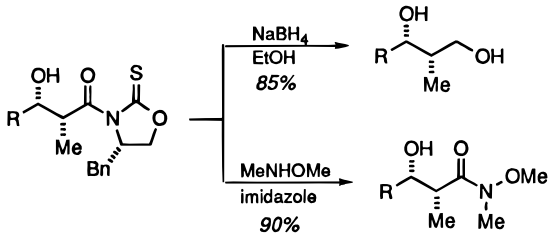
Typical Procedure. Method A: To a dry round-bottom flask under nitrogen was added 0.250 g (1.0 mmol) of the oxazolidinethione in 6 mL of CH_2Cl_2. The solution was cooled to 0 °C. Titanium (IV) chloride (2.0 mmol, 0.220 mL) was added dropwise, and the solution allowed to stir for 5 min. To the yellow slurry or suspension was added diisopropylethylamine (1.1 mmol, 0.19 mL). The dark red titanium enolate stirred for 20 min at 0 °C, then was cooled to −78 °C. Freshly distilled aldehyde (1.1 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.

Table 1

method[a,b]	aldehyde (RCHO)[c]	yield[d] (%)	**8:9:***anti*[e]
A (−78 °C)	Et	80	95.7:0.5:3.8
A (−78 °C)	Me_2CH	87	94.9:0.0:5.1
A (−78 °C)	Ph	88	97.6:0.7:1.7
A (−78 °C)	Me_2CHCH_2	75	96.7:0.0:3.3
A (−78 °C)	MeCH=CH	81	94.7:0.0:5.3
A (−78 °C)	CH_2=CH	44	99.3:0.0:0.7
B (−78 °C)	Et	60	6.3:93.3:0.4
B (−78 °C)	Me_2CH	58	0.6:98.9:0.5
B (−78 °C)	Ph	60	2.4:97.6:0.0
B (−78 °C)	MeCH=CH	49	1.3:98.2:0.5
B (−78 °C)	Me_2CHCH_2	43	0.0:100:0.0
C (0 °C)	Et	80	1.7:97.8:0.5
C (0 °C)	Me_2CH	90	2.5:97.0:0.5
C (−78 °C)	Me_2CH	70	1.0:98.8:0.2
C (0 °C)	Ph	89	2.2:97.3:0.5
C (0 °C)	MeCH=CH	65	2.3:97.4:0.3
C (0 °C)	Me_2CHCH_2	91	2.2:97.8:0.0
C (−78 °C)	CH_2=CH	80	0.0:98.9:1.1

[a] $TiCl_4$ was used as obtained from Aldrich Chemical Co. [b] Method A: 2.0 equiv of $TiCl_4$ and 1.1 equiv of *i*-Pr_2EtN were employed. Method B: 1.0 equiv of $TiCl_4$ and 2.5 equiv of TMEDA were employed. Method C: 1.0 equiv of $TiCl_4$ and 2.5 equiv of (−)-sparteine were employed. [c] 1.1 equiv of aldehyde was employed. [d] Yields are for isolated, chromatographically purified major diastereomer. [e] Ratios were determined by HPLC.

Methods B and C: To a dry round-bottom flask under nitrogen was added 0.250 g (1.0 mmol) of the oxazolidinethione 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 (method B) or (−)-sparteine (method C), 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 were the same as in Method A.



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Supporting Information Available: Spectral data (^1H, ^{13}C NMR, IR, optical rotations, and combustion analyses) for compounds **7**, **8a**−**f**, and **9a**−**f** (3 pages). See any current masthead for ordering and Internet access instructions.

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(13) ^1H NMR data for enolate generated with 1 equiv of $TiCl_4$ (CD_2Cl_2) δ 1.99 (d, J = 6.7 Hz, 3H), 3.13 (d, J = 6.0 Hz, 2H), 4.51 (dd, J = 4.0, 9.1 Hz, 1H), 4.62 (t, J = 9.1 Hz, 1H), 4.75 (q, J = 6.7 Hz, 1H), 4.80 (m, 1H), 7.29 (m, 5H).

(14) ^1H NMR data for enolate generated with 2 equiv of $TiCl_4$ or 1 equiv of $TiCl_4$ + 1 equiv of $AgSbF_6$ (CD_2Cl_2) δ 2.04 (d, J = 6.7 Hz, 3H), 3.09 (dd, J = 13.3, 4.4 Hz, 1H), 3.29 (dd, J = 13.1, 5 Hz, 1H), 4.72 (dd, J = 4.0, 9.1 Hz, 1H), 4.83 (t, J = 9.1 Hz, 1H), 4.92 (q, J = 6.7 Hz, 1H), 4.93 (m, 1H), 7.29 (m, 5H).

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