

# An Improved Procedure for Asymmetric Aldol Additions with *N*-Acyl Oxazolidinones, Oxazolidinethiones and Thiazolidinethiones

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Dedicated to Professor Clayton H. Heathcock

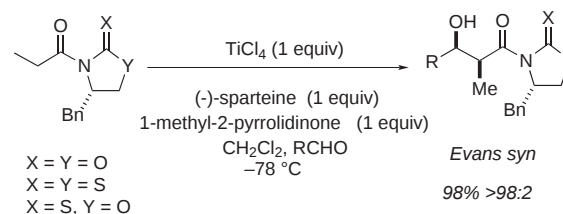
**Abstract:** Asymmetric aldol additions using chlorotitanium enolates of *N*-acyl oxazolidinones, oxazolidinethiones and thiazolidinethiones proceed with high diastereoselectivity for the 'Evans syn' product using one equivalent of titanium tetrachloride, one equivalent of diisopropylethylamine and one equivalent of *N*-methyl-2-pyrrolidinone. Typical selectivities of 94:6 to >98:2 were obtained using *N*-propionyl oxazolidinones, oxazolidinethiones and thiazolidinethiones at 0 °C with stoichiometric amounts of aldehyde. Glycolate imides also gave high selectivities and high yields using this procedure.

**Key words:** aldol reactions, asymmetric synthesis, titanium enolates, imides, glycolates

The chiral auxiliary mediated asymmetric aldol addition is one of the most general and widely used methods for asymmetric carbon-carbon bond formation.<sup>1</sup> The utility of the asymmetric aldol addition has been amply demonstrated through a multitude of synthetic applications.<sup>2</sup> The Evans protocol using dibutylboron enolates of acyl oxazolidinones is the most commonly utilized method providing the 'Evans syn' product as the major diastereomer.<sup>3</sup> Titanium(IV)<sup>4–6</sup> and tin(II)<sup>7</sup> enolates have also been shown to be effective in creating well-ordered transition states for aldol reactions. Evans and Yan have reported the use of chlorotitanium enolates of *N*-acyloxazolidinones in aldol additions, prepared by soft enolization using titanium tetrachloride and diisopropylethylamine amine.<sup>4,6</sup> However, slightly lower selectivity was observed than with the dibutylboron enolates and excess aldehyde (from 2–5 equiv) was required to achieve good levels of conversion.<sup>4,6</sup>

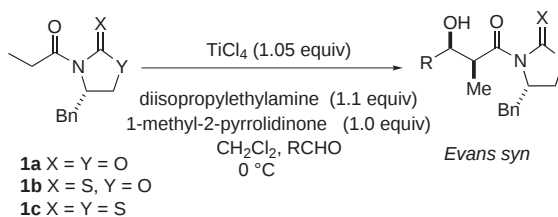
We recently reported a protocol for accessing Evans syn aldol adducts using 1 equivalent of titanium tetrachloride and 2.2 equivalents of (–)-sparteine to form the titanium enolates of *N*-acyl oxazolidinethiones, thiazolidinethiones, and oxazolidinones.<sup>8</sup> Since it was proposed that the second equivalent of (–)-sparteine was functioning simply as a ligand for titanium, an improved protocol using 1 equivalent of titanium tetrachloride, 1 equivalent of (–)-sparteine and 1 equivalent of 1-methyl-2-pyrrolidinone (NMP), as the ligand for titanium, was investigated.<sup>9</sup> The

improved TiCl<sub>4</sub>, (–)-sparteine-NMP, method was quite effective and has found increasingly wider use as an enolization method for asymmetric aldol reactions.<sup>10</sup> However, the need for the moderately expensive (–)-sparteine as the base has been the point of some concern with the method. Consequently, we recently reinvestigated the asymmetric aldol reaction with the goal of finding a set of conditions, which would obviate the need for (–)-sparteine as the base and perhaps offer improved performance in asymmetric aldol reactions of *N*-glycolyl oxazolidinones, oxazolidinethiones or thiazolidinethiones. We report here the results of our findings (Equation 1).



**Equation 1** Diastereoselective aldol additions using TiCl<sub>4</sub>, (–)-sparteine, and NMP

Our initial attempts to further improve conditions for the chlorotitanium enolate aldol reaction focused on finding a suitable base to substitute for (–)-sparteine. Tetramethylethylenediamine (TMEDA), also a diamine, seemed a logical choice since it had shown some promise in our original survey of conditions with oxazolidinethiones.<sup>8</sup> However, the combination of TiCl<sub>4</sub>, TMEDA, and NMP gave inferior selectivity to the TiCl<sub>4</sub>, (–)-sparteine, NMP method and generally gave lower overall conversion. After surveying other tertiary amines, the best combination was found to be 1.05 equivalents of titanium tetrachloride, 1.1 equivalents of diisopropylethylamine and 1.0 equivalent of *N*-methyl-2-pyrrolidinone. Utilizing these conditions with only 1.1 equivalents of the desired aldehyde

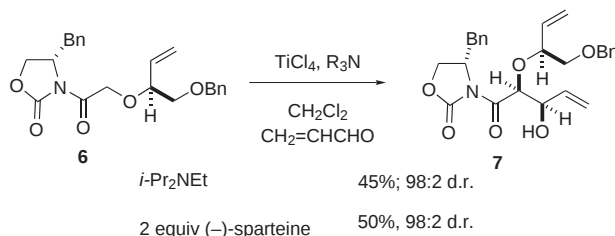


**Equation 2** Diastereoselective aldol additions using TiCl<sub>4</sub>, *i*-Pr<sub>2</sub>NEt, and NMP

provided high levels of conversion and high selectivities even at 0 °C.<sup>11</sup>

All three imide auxiliaries: oxazolidinones, oxazolidinethiones and thiazolidinethiones were found to function well under these conditions to afford the Evans *syn* product as the major diastereomer. It is important to note that our early studies indicated the use of diisopropylethylamine as base without added NMP gave inconsistent results with *N*-propionyloxazolidinethiones,<sup>8a</sup> and provided the non-Evans *syn* adducts with *N*-propionylthiazolidinethiones.<sup>8b</sup> Table 1 shows the results of a survey of several aldehydes with each of the three propionyl imides **1a**, **1b**, **1c** (Equation 2). This new protocol provides a cost effective, operationally simple procedure for the execution of diastereoselective aldol additions with *N*-acyl oxazolidinones, oxazolidinethiones and thiazolidinethiones.

The success of the new protocol for the aldol addition with *N*-propionylimides prompted an investigation to its applicability to aldol additions of simple and more complex *N*-glycolylimides, since we have utilized aldol adducts of *N*-glycolylimides in a number of syntheses of complex cyclic ethers.<sup>12</sup> Using either the standard Evans dibutylboryl enolates or chlorotitanium enolates through various enolization methods had met with limited success with complex glycolylimides. Typically, levels of conversion were low compared to *N*-propionylimide aldol reactions. For



**Equation 3** Previous results with glycolate aldol reactions

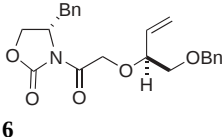
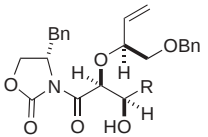
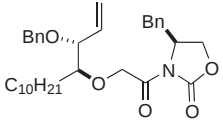
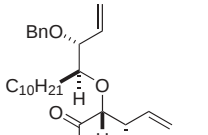
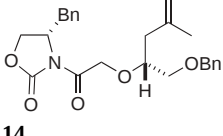
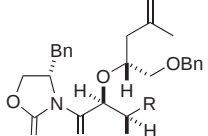
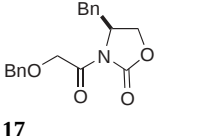
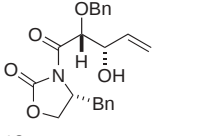
example, when the enolate of *N*-acyloxazolidinone **6** was prepared with 1 equivalent titanium tetrachloride and diisopropylethylamine and then treated with acrolein (Equation 3), the yield of the aldol adduct was only about 45%. The (–)-sparteine protocol improved the efficiency slightly, but the yield was still disappointingly low (50%). When imide **6** was treated with 1 equivalent of titanium tetrachloride and 2.5 equivalents<sup>13</sup> of diisopropylethylamine plus 1 equivalent of NMP, the conversion of the reaction was substantially improved to 78% with high levels of diastereoselectivity.<sup>14</sup> Furthermore, the improved reaction conditions are general for a variety of *N*-glycolyloxazolidinones as illustrated in Table 2.

In summary, a new cost effective, operationally simple protocol for the execution of diastereoselective aldol additions with *N*-acyl oxazolidinones, oxazolidinethiones

**Table 1** Aldol Additions with *N*-Propionyl Oxazolidinones, Oxazolidinethiones and Thiazolidinethiones<sup>11</sup>

| Entry | Aldol Substrate | Aldehyde                                     | Product                                                                 | Yield (%)                        | Diastereoselectivity |
|-------|-----------------|----------------------------------------------|-------------------------------------------------------------------------|----------------------------------|----------------------|
| 1     |                 | $\text{Me}_2\text{CHCHO}$                    |                                                                         | 99                               | 97:3                 |
| 2     | <b>1a</b>       | $\text{C}_5\text{H}_{11}\text{CHO}$          | <b>2a</b> R = <i>i</i> -Pr<br><b>3a</b> R = $\text{C}_5\text{H}_{11}$ – | 75                               | 93:7                 |
| 3     | <b>1a</b>       | $\text{C}_6\text{H}_5\text{CHO}$             | <b>4a</b> R = $\text{C}_6\text{H}_5$ –                                  | 97                               | 94:6                 |
| 4     | <b>1a</b>       | $\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$ | <b>5a</b> R = $\text{C}_6\text{H}_5\text{CH}=\text{CH}$ –               | 97                               | 95:5                 |
| 5     |                 | $\text{Me}_2\text{CHCHO}$                    |                                                                         | 98 (–78 °C to 0 °C)<br>97 (0 °C) | >98:2<br>97:3        |
| 6     | <b>1b</b>       | $\text{C}_5\text{H}_{11}\text{CHO}$          | <b>2b</b> R = <i>i</i> -Pr<br><b>3b</b> R = $\text{C}_5\text{H}_{11}$ – | 97                               | 94:6                 |
| 7     | <b>1b</b>       | $\text{C}_6\text{H}_5\text{CHO}$             | <b>4b</b> R = $\text{C}_6\text{H}_5$ –                                  | 95                               | 93:7                 |
| 8     | <b>1b</b>       | $\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$ | <b>5b</b> R = $\text{C}_6\text{H}_5\text{CH}=\text{CH}$ –               | 97                               | 96:4                 |
| 9     |                 | $\text{Me}_2\text{CHCHO}$                    |                                                                         | 99                               | 98:2                 |
| 10    | <b>1c</b>       | $\text{C}_5\text{H}_{11}\text{CHO}$          | <b>2c</b> R = <i>i</i> -Pr<br><b>3c</b> R = $\text{C}_5\text{H}_{11}$ – | 97                               | 96:4                 |
| 11    | <b>1c</b>       | $\text{C}_6\text{H}_5\text{CHO}$             | <b>4c</b> R = $\text{C}_6\text{H}_5$ –                                  | 99                               | 96:4                 |
| 12    | <b>1c</b>       | $\text{C}_6\text{H}_5\text{CH}=\text{CHCHO}$ | <b>5c</b> R = $\text{C}_6\text{H}_5\text{CH}=\text{CH}$ –               | 98                               | 96:4                 |

**Table 2** Aldol Additions with *N*-Glycolyl Oxazolidinones<sup>14</sup>

| Entry | Aldol Substrate                                                                     | Aldehyde                                 | Product                                                                                                                                                                         | Yield (%) | Diastereoselectivity |
|-------|-------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------------|
| 1     |    | CH <sub>2</sub> =CHCHO                   | <br>7 R = CH=CH <sub>2</sub><br>8 R = C <sub>12</sub> H <sub>25</sub> –                        | 72        | 97:3                 |
| 2     | 6                                                                                   | C <sub>12</sub> H <sub>25</sub> CHO      | 8 R = C <sub>12</sub> H <sub>25</sub> –                                                                                                                                         | 74        | 95:5                 |
| 3     | 6                                                                                   | TIPSO(CH <sub>2</sub> ) <sub>3</sub> CHO | 9 R = TIPSO(CH <sub>2</sub> ) <sub>3</sub> –                                                                                                                                    | 76        | 96:4                 |
| 4     | 6                                                                                   | TMSC≡CCHO                                | 10 R = TMSC≡C–                                                                                                                                                                  | 79        | 95:5                 |
| 5     | 6                                                                                   | TIPSC≡CCHO                               | 11 R = TIPSC≡C–                                                                                                                                                                 | 93        | 96:4                 |
| 6     |    | CH <sub>2</sub> =CHCHO                   |                                                                                                | 77        | 95:5                 |
| 7     |    | CH <sub>2</sub> =CHCHO                   | <br>15 R = CH <sub>2</sub> =CH–<br>16 R = CH <sub>2</sub> =CHCH <sub>2</sub> CH <sub>2</sub> – | 83        | 96:4                 |
| 8     | 14                                                                                  | C <sub>6</sub> H <sub>5</sub> CHO        | 16 R = CH <sub>2</sub> =CHCH <sub>2</sub> CH <sub>2</sub> –                                                                                                                     | 84        | 96:4                 |
| 9     |  | CH <sub>2</sub> =CHCHO                   |                                                                                              | 84        | 91:9                 |

and thiazolidinethiones has been developed and should significantly improve the utility of this important reaction. Additionally, the successful implementation of the aldol reaction of chlorotitanium enolates of highly substituted and stereochemically complex *N*-glycolyloxazolidinones should lead to many useful applications in the synthesis of complex advanced intermediates for synthesis of cyclic ethers and related substances. These applications are currently in progress and will be reported in due course.

### Acknowledgment

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- (11) **Typical Procedure for Formation of Evans *syn* Adducts from *N*-Propionylimides 1a, 1b, and 1c.** To a dry round-bottom flask under argon was added 1.00 mmol of the appropriate *N*-acyloxazolidinone, *N*-acyloxazolidinethione, or *N*-propionylthiazolidinethione, and 10 mL CH<sub>2</sub>Cl<sub>2</sub>. After cooling to 0 °C, TiCl<sub>4</sub> (0.115 mL, 1.05 mmol) was added dropwise and the solution was allowed to stir for 15 min. Diisopropylethylamine (0.191 mL, 1.10 mmol) was added dropwise to the mixture and the solution was allowed to stir for 40 min. 1-Methyl-2-pyrrolidinone (0.096 mL, 1.00 mmol for *N*-acyloxazolidinone and *N*-acyloxazolidinethione; 0.192 mL, 2.00 mmol for *N*-propionylthiazolidinethione) was added at 0 °C and the mixture was stirred for an additional 10 min. Freshly distilled aldehyde (1.10 mmol) was then added directly to the enolate. The reaction was allowed to stir for 1–2 h followed by addition of half-sat. NH<sub>4</sub>Cl. The organic layer was separated and the aqueous layer extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The initial product mixture was analyzed by <sup>1</sup>H NMR followed by purification by column chromatography.
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- (13) The use of 2.5 equiv of diisopropylethylamine for *N*-glycolylimides (compared to the use of 1.1 equiv of diisopropylethylamine for *N*-propionyl imides) improved the levels of conversion in the aldol reaction.
- (14) **Typical Procedure for Formation of Evans *syn* Adducts from *N*-Glycolylimides.** To a dry round-bottom flask under argon was added 1.00 mmol of the appropriate *N*-acyloxazolidone, *N*-acyloxazolidinethione, or *N*-propionylthiazolidinethione, and 10 mL CH<sub>2</sub>Cl<sub>2</sub>. After cooling to –78 °C, TiCl<sub>4</sub> (0.115 mL, 1.05 mmol) was added dropwise and the solution was allowed to stir for 15 min. Diisopropylethylamine (0.434 mL, 2.50 mmol) was added dropwise to the mixture and the solution was allowed to stir for 1–2 h. 1-Methyl-2-pyrrolidinone (0.096 mL, 1.00 mmol) was added at –78 °C and the mixture was stirred for an additional 10 min. Freshly distilled aldehyde (2.00–4.00 mmol) was then added directly to the enolate. The reaction was allowed to stir for 1–2 h at –78 °C and then warmed to –40 °C for 1–2 h followed by addition of half-sat. NH<sub>4</sub>Cl. The organic layer was separated and the aqueous layer extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated. The initial product mixture was analyzed by <sup>1</sup>H NMR followed by purification by column chromatography.