

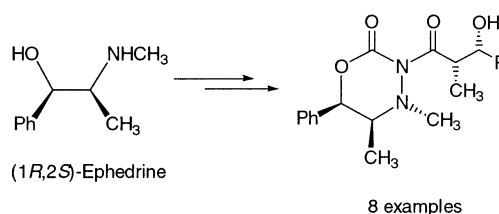
# Toward the Development of a Structurally Novel Class of Chiral Auxiliaries: Diastereoselective Aldol Reactions of a (1*R*,2*S*)-Ephedrine-Based 3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-one

David M. Casper, James R. Burgeson, Joel M. Esken, Gregory M. Ferrence, and Shawn R. Hitchcock\*

Department of Chemistry, Illinois State University, Normal, Illinois 61790-4160  
hitchcock@xenon.che.ilstu.edu

Received August 12, 2002

## ABSTRACT



Asymmetric aldol addition reactions have been conducted with (1*R*,2*S*)-ephedrine-derived 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (**2**). Diastereoselectivities range from 75:25 to 99:1 for the formation of the crude non-Evans syn adducts **8a–h**. The facial selectivity of the enolate is directed by the stereogenic *N*<sub>4</sub>-methyl substituent. Aldol adduct **8a** is readily cleaved by acid hydrolysis to afford (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropionic acid (**9**) in >95% ee.

The remarkable successes in diastereoselective carbon–carbon bond formation that have been achieved with 1,3-oxazolidin-2-ones (**1**)<sup>1</sup> derived from  $\alpha$ -amino acid-based *vic*-amino alcohols and norephedrine have spurred on much research. A significant aspect to this research is based on modifying the amino alcohol structure of the oxazolidinone for the potential enhancement of reaction diastereoselectivities.<sup>2</sup> Numerous other related chiral auxiliaries<sup>3</sup> have been developed for this purpose, but oxazolidinones have remained among the most examined, especially with regard to the asymmetric aldol reaction.<sup>1</sup> We became interested in developing a chiral auxiliary that offered an altered template away

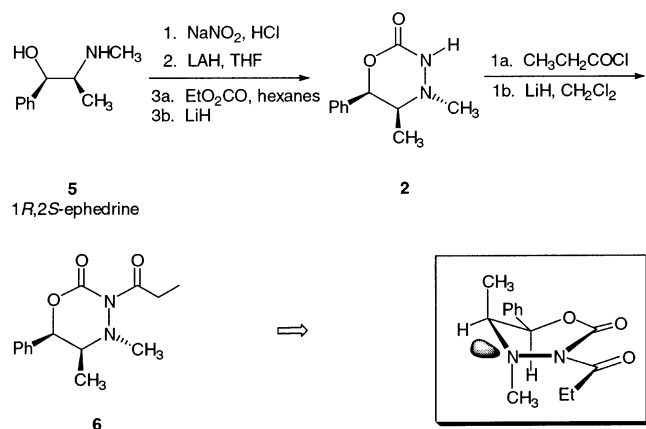
from the oxazolidinone model pioneered by Evans.<sup>1a–c</sup> In this context, 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (**2**) represent a class of heterocycles that have received little

(1) (a) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, 21, 4675. (b) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127. (c) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, 68, 83. (d) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichimica Acta* **1997**, 30, 3. (e) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, 66, 894. (f) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, 124, 392. (g) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, 4, 1127.

(2) (a) Ghosh, A. K.; Duong, T. T.; McKee, S. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1673. (b) Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A. *Tetrahedron* **1994**, 50, 6621. (c) Wang, Y.-C.; Hung, A.-W.; Chang, C.-S.; Yan, T.-H. *J. Org. Chem.* **1996**, 61, 2038. (d) Ghosh, A. K.; Cho, H.; Onishi, M. *Tetrahedron: Asymmetry* **1997**, 8, 821. (e) Andersson, P. G.; Schink, H. E.; Österlund, K. *J. Org. Chem.* **1998**, 63, 8067. (f) Anaya de Parrodi, C.; Clara-Sosa, A.; Pérez, L.; Quintero, L.; Marañón, V.; Toscano, R. A.; Aviña, J. A.; Rojas-Lima, S.; Juaristi, E. *Tetrahedron: Asymmetry* **2001**, 12, 69. (g) Guz, N. R.; Phillips, A. J. *Org. Lett.* **2002**, 4, 2253. (h) Cipiciani, A.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **2002**, 67, 2665.

(3) (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, 98, 567. (b) Oppolzer, W.; Moretti, R.; Rhomi, S. *Tetrahedron Lett.* **1989**, 30, 5603. (c) Studer, A.; Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1995**, 78, 1185. (d) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, 117, 12368. (e) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley & Sons: New York, 1995. (f) Mulzer, J.; Langer, O.; Hiersemann, M.; Bats, J. W.; Buschmann, J.; Luger, P. *J. Org. Chem.* **2000**, 65, 6540. (g) Boeckman, R. K., Jr.; Laci, M. A.; Johnson, A. T. *Tetrahedron: Asymmetry* **2001**, 12, 205. (h) Lakner, F. J.; Negrete, G. R. *Synlett* **2002**, 4, 643.

**Scheme 1.** Preparation of the *N*<sub>3</sub>-Propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one



notice since their disclosure by Trepanier in 1968.<sup>4</sup> After nearly three decades of dormancy, Husson and co-workers successfully employed these compounds as chiral auxiliaries in diastereoselective alkylations<sup>5a</sup> and in dipolar cycloadditions.<sup>5b,c</sup>

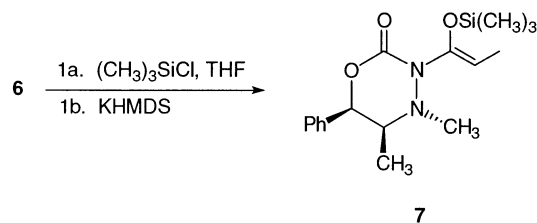
At nearly the same time as Husson and co-workers, we became interested in the chemistry of these heterocycles and conducted synthetic and conformational studies with the ephedrine-based heterocycle **2** and its related pseudoephedrine<sup>6a</sup> and norephedrine derivatives.<sup>6b</sup> We have now extended our studies into asymmetric applications and have initiated an investigation into using **2** as a chiral auxiliary in the asymmetric aldol addition reaction. Herein we report the synthesis, acylation, and diastereoselectivity observed using this auxiliary in the asymmetric aldol addition.

Synthesis of the enantiomerically enriched **2** was readily achieved by *N*-nitrosation<sup>7,8</sup> of (1*R*,2*S*)-ephedrine (**5**), followed by the reduction to the corresponding  $\beta$ -hydrazino-alcohol, and cyclization with lithium hydride and diethyl carbonate (Scheme 1). The overall yield of the heterocycle

was 60–70%.<sup>6c</sup> The auxiliary was acylated with propionyl chloride and lithium hydride to afford *N*<sub>3</sub>-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one (**6**) in 84% yield after recrystallization. Once acylated, the heterocycle adopts a twist boat conformation wherein the stereogenic *N*<sub>4</sub>-methyl substituent is arranged in a pseudoaxial position.<sup>6d</sup>

With **6** in hand, we pursued the application of this heterocycle in the asymmetric aldol reaction. Unfortunately, our initial attempts were not successful. The central problem was determined to be the formation of a stable enolate of **6**. Direct attempts to form the enolate with nonnucleophilic bases [ $\text{LDA}$ ,  $\text{MHMDS}$  ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ )] were not successful.<sup>9</sup> Finally, inverse addition (chlorotrimethylsilane/ $\text{KHMDS}$ ) was employed to trap the enolate as the corresponding enolsilane **7** (Scheme 2). We were gratified to learn that this

**Scheme 2.** Synthesis of 3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-one Enol Ether **7**



method afforded the desired enolsilane, tentatively assigned as the *Z*(*O*)-geometry,<sup>10</sup> although it was contaminated with ~10% of **6** as determined by  $^1\text{H}$  NMR.

Even though it was possible to “trap” the enolate as enolsilane **7** via inverse addition, it was not possible to use this method to conduct aldol reactions. When these conditions were employed in the presence of aldehydes, the major product was deacylation of **6** to afford **2**. We next explored the use of chlorotitanium enolates as a more viable pathway into the aldol reaction.<sup>1e,11</sup> Unfortunately, the aldol addition reaction of **6** via  $\text{TiCl}_4$  and an amine base followed by addition of the aldehyde was not successful. The reaction was modified so that the aldehyde was present as the chlorotitanium enolate was formed. Thus, **2** was dissolved in  $\text{THF}$ , and to this solution was added stoichiometric benzaldehyde and an amine base. Titanium tetrachloride was then added last to create the putative chlorotitanium enolate in the presence of the aldehyde. We were gratified to learn

(4) (a) Trepanier, D. L.; Elbe, J. N.; Harris, G. H. *J. Med. Chem.* **1968**, *11*, 357. (b) Trepanier, D. L.; Harris, J. N. US Patent 3,377,345, 1968; *Chem. Abstr.* **1969**, 70, 78026c.

(5) (a) Roussi, F.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1998**, *39*, 8081. (b) Roussi, F.; Bonin, M.; Chiaroni, A.; Micouin, L.; Riche, C.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 3727. (c) Roussi, F.; Chauveau, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2000**, 1170.

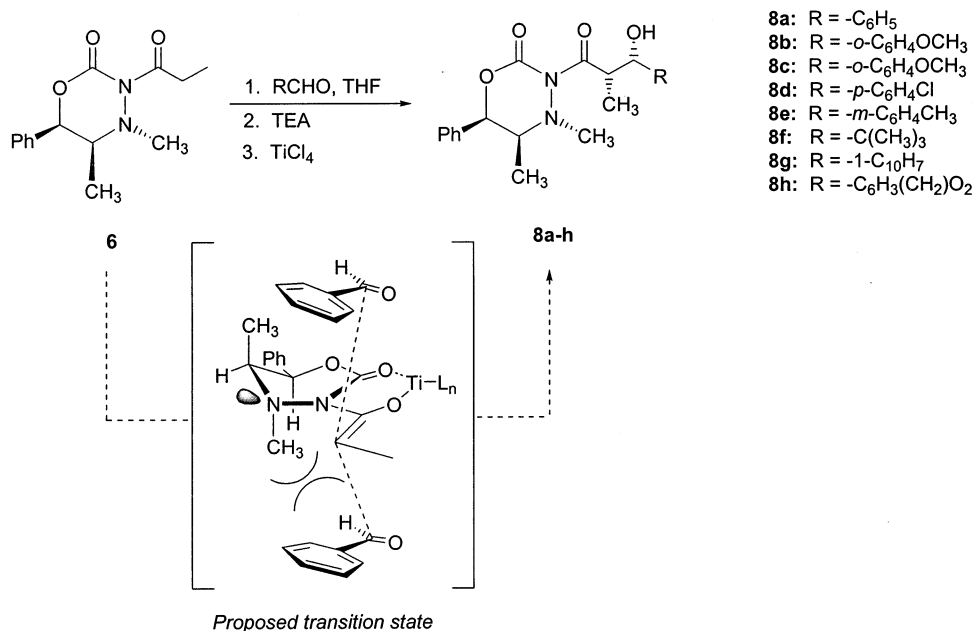
(6) (a) Hitchcock, S. R.; Nora, G. P.; Casper, D. M.; Squire, M. D.; Maroules, C. D.; Ferrence, G. M.; Szczepura, L. F.; Standard, J. M. *Tetrahedron* **2001**, *57*, 9789. (b) Casper, D. M.; Nora, G. P.; Blackburn, J. R.; Bentley, J. T.; Taylor, D. C.; Hitchcock, S. R. *J. Heterocycl. Chem.* **2002**, *39*, 823. (c) The heterocycle is synthesized on multigram scales (5–25 g) in a period of 2 days with no chromatography. (d) This conformation has been observed by X-ray crystallography (ref 6a) for the *N*<sub>3</sub>-phenylacetyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one derived from (1*R*,2*S*)-ephedrine and represents the most stable conformer in the solid state. The conformation adopted in solution may be dependent on other factors, including solvation effects.

(7) The *N*-nitrosamine of (1*R*,2*S*)-ephedrine was prepared previously: Hitchcock, S. R.; Nora, G. P.; Hedberg, C.; Casper, D. M.; Buchanan, L. S.; Squire, M. D.; West, D. X. *Tetrahedron* **2000**, *56*, 8799. **Caution:** It should be noted that many *N*-nitrosamines are potentially carcinogenic and should be handled with great care. For more information on *N*-nitrosamines, see: Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D., Ed.; ACS Monograph Series 182; American Chemical Society; Washington, DC, 1984.

(8) A variety of methods were explored to circumvent the usage of the *N*-nitrosamine. These methods included electrophilic amination pathways. See: (a) Kim, M.; White, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 1172. (b) Greck, C.; Bischoff, L.; Ferreira, F.; Genet, J. P. *J. Org. Chem.* **1995**, *60*, 7010. (c) Greck, C.; Genet, J. P. *Synlett* **1997**, 741. (d) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *112*, 8329. These methods proved to be more cumbersome and expensive than the nitrosation procedure in which the *N*-nitrosamine spontaneously crystallizes during the removal of solvents after extraction. The transformation and yield are both nearly quantitative.

(9) We have also had difficulties in forming the enolate of the *N*<sub>3</sub>-propionyl pseudoephedrine-based heterocycle using the same nonnucleophilic bases. The dominant product observed in these reactions is deacylation.

**Scheme 3.** Asymmetric Aldol Reactions of **6**



that aldol reaction occurred in high chemical yield and good diastereoselectivity to provide aldol adducts **8a–h** (Scheme 3). The diastereoselectivities are listed in Table 1. The

**Table 1.** Stereoselective Aldol Additions of the Enolate Derived from **6**

entry	RCHO	diastereomeric ratios <sup>a</sup> syn:Σ(all other diastereomers)		% yield <sup>b</sup>
		crude	purified	
<b>8a</b>	C <sub>6</sub> H <sub>5</sub> CHO	95:5	>99:1	73
<b>8b</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	97:3	96:4	93
<b>8c</b>	<i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CHO	99:1	99:1	84
<b>8d</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO	87:13	88:12 <sup>c</sup>	97
<b>8e</b>	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CHO	93:7	99:1	59
<b>8f</b>	(CH <sub>3</sub> ) <sub>3</sub> CCHO	75:25	97:3	70
<b>8g</b>	1-C <sub>10</sub> H <sub>7</sub> CHO	93:7	99:1	91
<b>8h</b>	(CH <sub>2</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CHO	93:7	97:3	62

<sup>a</sup> Diastereomer ratios determined by HPLC. <sup>b</sup> Chemical yield of the purified product after chromatography and recrystallization. <sup>c</sup> Ratio of diastereomers was increased to 97:3 after a second recrystallization.

selectivity of this aldol reaction is believed to be due to the presence of the stereogenic N<sub>4</sub>-methyl group. The optimal position of this group is in the pseudoaxial position due to allylic strain interactions with the N<sub>3</sub>-acyl substituent.<sup>6a</sup> It must also be noted that the C<sub>5</sub>-methyl and C<sub>6</sub>-phenyl substituents may also have an impact on the course of the reaction with regard to the approach of the aldehyde. However, on the basis of <sup>1</sup>H NMR and X-ray crystallographic analysis of **8a**, the N<sub>4</sub>-methyl group is the primary substituent that guides the stereochemical course of the reaction in terms of facial selectivity of the enolate.

The relative configuration of the major diastereomer of the aldol addition reaction was determined to be the syn

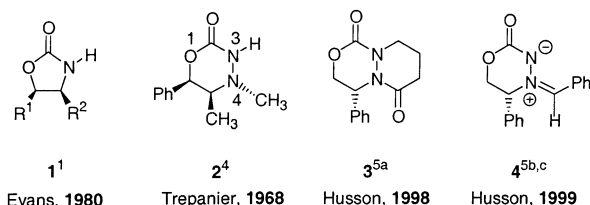
configuration via the <sup>1</sup>H NMR coupling constants for the vicinal protons of the aldol adduct (Table 2).<sup>2f,12</sup>

**Table 2.** <sup>1</sup>H NMR Coupling Constants for **8a–h**

entry	R	δ H <sub>a</sub> (ppm)	J <sub>H<sub>a</sub>-b</sub> (Hz)	configuration
<b>8a</b>	C <sub>6</sub> H <sub>5</sub> –	4.13	3.7	(2′S,3′S,5S,6R) <sup>a</sup>
<b>8b</b>	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> –	4.09	3.7	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8c</b>	<i>o</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> –	4.25	4.4	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8d</b>	<i>p</i> -Cl C <sub>6</sub> H <sub>4</sub> –	4.09	3.3	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8e</b>	<i>m</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> –	4.11	3.7	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8f</b>	(CH <sub>3</sub> ) <sub>3</sub> C–	4.22	2.6	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8g</b>	1-C <sub>10</sub> H <sub>7</sub> –	4.34	3.3	(2′S,3′S,5S,6R) <sup>b</sup>
<b>8h</b>	(CH <sub>2</sub> O) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> –	4.06	3.7	(2′S,3′S,5S,6R) <sup>b</sup>

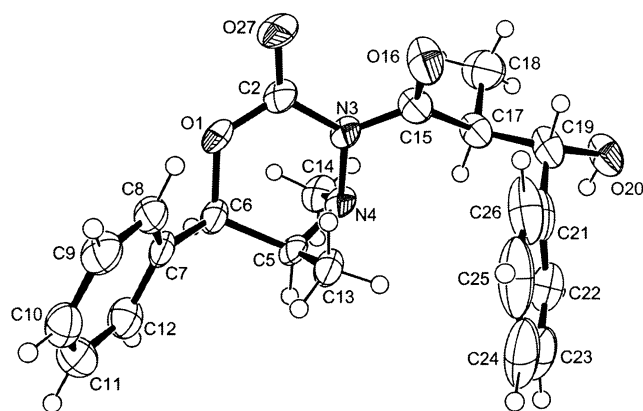
<sup>a</sup> Configuration determined by X-ray crystallography. <sup>b</sup> Absolute configuration determined by analogy with **8a**.

The absolute configuration of the aldol adduct was determined by evaluation of the hydrolyzed product. Adduct **8a** was subjected to acid hydrolysis<sup>13</sup> to afford the parent heterocycle **2** in nearly quantitative yield and the 3-hydroxy-2-methyl-3-phenylpropionic acid (**9**) in 71% yield after a single recrystallization (Scheme 4). The optical rotation value of [α]<sub>D</sub> –29.5° (*c* 1.02, CH<sub>2</sub>Cl<sub>2</sub>) revealed that the recovered carboxylic acid was obtained as the (2*S*,3*S*)-enantiomer in >95% ee (lit.<sup>14</sup> [α]<sub>D</sub> –29.3° (*c* 0.8, CHCl<sub>3</sub>)). X-ray crystal-



**Figure 1.** Evolution of 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-ones.

lographic analysis of aldol adduct **8a** confirmed the stereochemical assignment (Figure 2).<sup>15</sup> The collected results



**Figure 2.** ORTEP diagram of **8a** with 50% probability ellipsoids shown. Hydrogen atoms are drawn arbitrarily small for clarity.

suggested a Zimmerman–Traxler transition state in which the *re*-face of the *Z*(O)-configured enolate of **6** and the *si*-face of the aldehyde are combined (Scheme 3).<sup>16</sup>

With the exception of trimethylacetaldehyde, aliphatic aldehydes did not undergo reaction cleanly.<sup>17</sup> The reaction was sluggish, and the dominant product was deacylation, which suggested that chlorotitanium enolate of **6** was not sufficiently nucleophilic to capture the aldehydes. Triethy-

(10) 1,3-Oxazolidin-2-ones are known to have a strong preference for the formation of the *Z*(O)-configured enolate. The 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-ones most likely form *Z*(O)-enolates as well. See: Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737 and references contained therein.

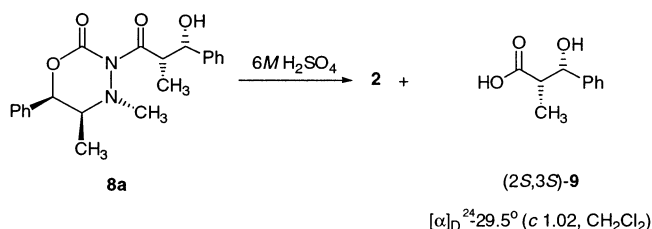
(11) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. See also ref 2f.

(12) Coupling constants for all of the derivatives were in the range of 2.6–4.4 Hz as would be expected for the *syn* configuration. See: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwenhze, M. S.; Darin, J. G.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, W. J., III. *J. Org. Chem.* **2002**, *67*, 4284 and references therein. See also refs 1g (anti adducts) and 2f (*syn* adducts).

(13) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carillo, L. *J. Org. Chem.* **2000**, *65*, 3754.

(14) (a) van Draanen, N. A.; Arseniyadis, A.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499–2506. (b) Davies, S. G.; Doisneau, G. J.-M.; Procter, J. C.; Sangane, H. *Tetrahedron Lett.* **1994**, *35*, 2373–2376. (c) Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1995**, *60*, 7006 and references therein.

#### Scheme 4. Acid Hydrolysis of **8a**



lamine (TEA) proved to be superior to Hunig's base (ethyldiisopropylamine), as there were only trace amounts of product when the more sterically hindered base was employed. It was also determined that the use of the 2 equiv of  $\text{TiCl}_4$  was less effective than the use of a single equivalent with regard to overall yield and diastereoselectivity. It was also determined that the order of addition of  $\text{TiCl}_4$  and the amine base was not critical for success.<sup>11,17</sup>

We have demonstrated that asymmetric aldol addition reactions are viable with an 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-one serving as the chiral auxiliary, although further research is necessary to refine the aldol reaction involving aliphatic aldehydes. The crude diastereoselectivities ranged from 75:25 to 95:5 for the formation of the non-Evans *syn* adduct as determined by  $^1\text{H}$  NMR and X-ray crystallography. Studies are underway to further investigate the reactivity of the 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-ones, especially with regard to the directing, stereogenic  $\text{N}_4$ -nitrogen.

**Acknowledgment.** We thank Dr. Marjorie Jones for HPLC support. We also thank Paddi Ekhlassi of the Analytical Research and Development Department of Pfizer Global Research and Development in La Jolla, CA for optical activity measurements. We also thank Dr. Robert McDonald and the University of Alberta Structure Determination Laboratory for the collection of low temperature CCD X-ray data. We gratefully acknowledge financial support for D. M. Casper and J. M. Esken from Abbott Laboratories for summer research. We also acknowledge continued support from Merck & Co., Inc. We also thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

**Supporting Information Available:** Experimentals for compounds **7**, **8a–h**, and (2*S*,3*S*)-**9**, copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **7**, **8a–h**, and (2*S*,3*S*)-**9**, and X-ray crystal data for **8a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL026721F

(15) Akin to other 3,4,5,6-tetrahydro-2H-1,3,4-oxadiazin-2-ones that we have reported, **8a** adopts a half chair conformation.<sup>6</sup> The X-ray crystal structure also reveals that the  $\text{N}_4$ -methyl group does indeed adopt a *trans*-1,2-diaxial arrangement with the  $\text{C}_5$ -methyl group. In effect, the  $\text{N}_4$ -position determines the facial selectivity of the enolate and the  $\text{C}_5$ -methyl group influences of the facial selectivity of the aldehyde. In addition, the urethane carbonyl and the  $\text{N}_3$ -carbonyl adopt a nearly parallel configuration as evidenced by the  $33.9^\circ \text{O}(27)–\text{C}(2)–\text{C}(15)–\text{O}(16)$  torsion angle.

(16) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(17) The reaction has been successful with nonenolizable aldehydes, but the chlorotitanium enolate does not react well with enolizable aldehydes. Research is underway to address this deficiency. See: Harrison, C. R. *Tetrahedron Lett.* **1987**, *28*, 4135.