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An improved procedure for the asymmetric aldol reaction of the titanium enolate of an N_3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one

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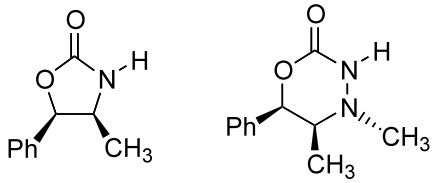
Abstract—The direct formation of the titanium enolate of N_3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one has been achieved through complexation with titanium tetrachloride at 25°C, followed by deprotonation with triethylamine (−78 to 25°C). The preformed titanium enolate has been reacted with D_2O/DCl to afford deuterated derivative **6** and also reacted with a series of aromatic and aliphatic aldehydes affording aldol adducts **4a**–**f** with crude diastereoselectivities ranging from 8:1 to 38:1.

1. Introduction

Chiral, non-racemic 1,3-oxazolidin-2-ones such as **1** have proven to be among the most effective and versatile chiral auxiliaries known to date.[1] The great success of these reagents has been demonstrated in aldol addition reactions,[2] the Diels–Alder cycloadditions,[3] 1,4-conjugate addition reactions,[4] and free radical reactions.[5] In an effort to enhance further the observed diastereoselectivities in these reactions, many research groups have attempted to introduce novel substituents onto the oxazolidinone core.[6] We became interested in the development of a structurally novel class of chiral auxiliaries that would offer greater versatility in their design, synthesis, and application. A class of heterocycle that had received little notice but might serve as an excellent asymmetric template is the 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one ring system, e.g. **2** (Fig. 1).[7]



1 **2**

Figure 1.

We have evaluated the conformational properties of these compounds and their related pseudoephedrine derivatives[8] and have applied these heterocycles in the asymmetric aldol addition reaction.[9] The conformational studies suggested that the (1*R*,2*S*)-ephedrine based oxadiazinone maintains a conformation wherein the N_4-methyl substituent of the ring blocks the *si*-face of the N_3-acyl substituent giving rise to the observed diastereoselectivities.[8b] The preliminary investigations of the efficacy of the oxadiazinone auxiliary in the asymmetric aldol were very promising (Scheme 1). The chemical yields were good and the observed diastereoselectivities ranged from 3:1 to 99:1 as determined by HPLC.[10] Unfortunately, it was not possible to conduct aldol reactions with aliphatic aldehydes bearing α-protons. This was presumed to be due to the method of inverse addition that was employed. The reaction was conducted by successive treatment of N_3-propionyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one **3** with an aldehyde, triethylamine, and finally titanium tetrachloride ($TiCl_4$). This method had been developed after many attempts to optimize the reaction conditions, and was successful for the aromatic aldehydes, but failed for the aliphatic aldehydes.[9,11] Herein, we report on efforts to improve the asymmetric aldol methodology for 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones.

2. Results and discussion

In our earlier work, we conducted the aldol reaction by inverse addition at low temperatures (−78°C) to maxi-

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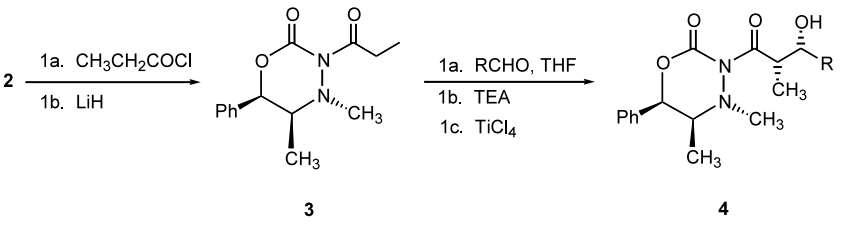
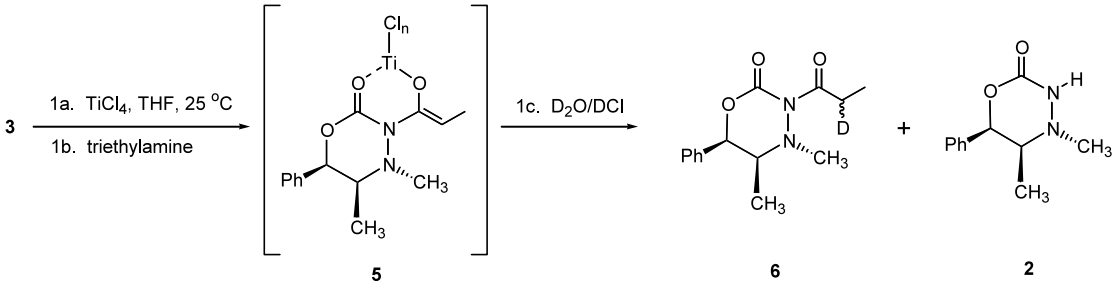


Scheme 1.



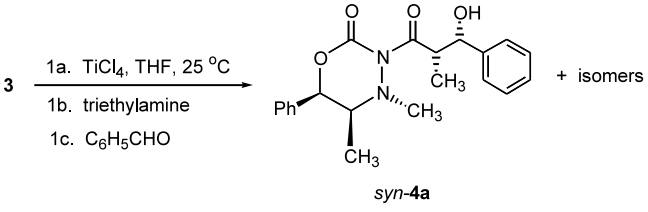
Scheme 2.

mize the chemical yield and diastereoselectivity. The inverse addition method evolved from the difficulty of deprotonation of **3** using amide bases (LiHMDS, LDA, etc.) and the uncertainties of the chemical nature of the heterocycle (i.e. potential decomposition).[12] The method of inverse addition with titanium tetrachloride worked well with aromatic aldehydes. However, with regard to aliphatic aldehydes, inverse addition was only marginally better than direct addition, and the end result was the same, i.e. aliphatic aldehydes bearing an α-proton would not undergo clean aldol addition. To address this deficiency, several control studies were conducted that were based on earlier works on titanium enolates of oxazolidinones developed by Evans (Scheme 2).[11] This work was instrumental in helping to refine the asymmetric aldol reactions with the structurally novel 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones.

Treatment of a −78°C solution of **3** (0.2-0.5 M in THF) with 1.05 equiv. of $TiCl_4$, followed by the addition of triethylamine after 25 min, gave rise to a dark red solution. This solution was stirred for 20 min and then quenched at −78°C by the addition of DCl/D_2O. Spectroscopic analysis of the isolated product indicated that there was no detectable incorporation of deuterium based on the detection limits of ^1H NMR spectroscopy.

Treatment of **3** with $TiCl_4$ at 25°C for 25 min, followed by treatment with triethylamine for 15 min at the same temperature, and quenching with DCl/D_2O afforded the α-deuterated acylated heterocycle **6** in 83% yield after chromatographic separation from the deacylation by product **2** (3%). Three control experiments were then conducted to investigate the geometry of enolate formation. The initial complexation of **3** with $TiCl_4$ was carried out at 25°C for 25 min, and triethylamine was subsequently added at 25, 0, or −78°C (Scheme 3). At all temperatures, the solution became dark red in color upon the addition of triethylamine. We could not be sure that this was a sign of complete deprotonation[11] as we had observed this same color under many reaction conditions that apparently did not involve direct enolate formation. After 15 min at the desired temperature for deprotonation, the reaction temperature was lowered to −78°C and benzaldehyde was added. The crude reaction mixture was then analyzed by ^1H NMR spectroscopy and HPLC. The formation of the non-Evans *syn*-isomer was taken as an indication that the (*Z*)-configured enolate had formed.[9]

Deprotonation of **3** with triethylamine at 25°C gave a product ratio of 1.4:1.0 favoring the non-Evans *syn*-adduct over the all other stereoisomers combined (Table 1). The ratio was significantly improved when the deprotonation was carried out 0°C. The optimal reaction conditions that afforded clean enolate formation and improved diastereoselectivity involved complexation of **3** with $TiCl_4$ at 25°C, deprotonation by triethylamine (−78→0°C) over 20 min, followed by addition of the appropriate aldehyde at −78°C. With the modified complexation and deprotonation conditions in hand, we began to pursue asymmetric aldol reactions with **3** using a variety of aldehydes including



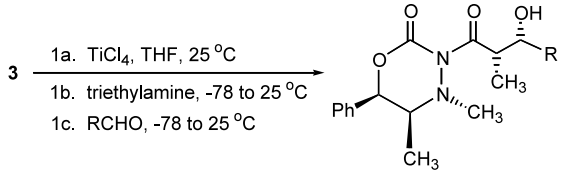
Scheme 3.

Table 1. Reaction diastereoselectivity and temperature

Entry	Temperature (°C)[a]	dr[b]
1	25	1.4:1
2	0	8:1
3	−78→25	38:1

[a] Temperature at which triethylamine is added.
[b] dr = diastereomer ratio. Diastereomeric ratio determined by HPLC and reported as major isomer: Σ other isomers.

aliphatic aldehydes bearing α-protons (Scheme 4). These aldol addition reactions were successful in terms of chemical yield and diastereoselectivity (Table 2). The proposed transition state is that of a chair-like Zimmerman–Traxler transition state wherein the N_4-methyl group of the heterocycle determines the stereochemical outcome. The stereochemistry of the products was determined by comparison to with previously prepared adducts.[9]



4a: R = -C_6H_5
4b: R = -CH_2CH_3
4c: R = -$CH(CH_3)_2$
4d: R = -C_6H_{11}
4e: R = -CH_2OBn
4f: R = -CH=CHPh

Scheme 4.

3. Conclusion

In summary, the asymmetric aldol reaction of 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones has been improved to allow for the synthesis of adducts from aliphatic aldehydes bearing α-protons. The crude diastereoselectivities were in the range of 8:1 to 38:1 for the formation of the non-Evans *syn*-adducts as determined by ^{1}H NMR. Studies are underway to employ N_3-acyloxy-oxadiazinones in asymmetric syntheses.

4. Experimental

4.1. General procedures for aldol adducts 4a–f

In a 100 mL round-bottomed flask was placed oxadiazinan-2-one **3** (0.5 g, 1.91 mmol) and dissolved in THF (5.7 mL). To this mixture was added $TiCl_4$ (0.22 mL, 2.00 mmol). This mixture was allowed to stir for 25 min then cooled to −78°C. Triethylamine (0.28 mL, 2.00 mmol) was added and the solution was immediately allowed to come to room temperature. After 15 min, the solution was again cooled to −78°C. After stirring for an additional 5 min, the appropriate aldehyde (1.3 mmol) was added and the solution was allowed to come to room temperature over a period of 4 h. The reaction was quenched by the addition of saturated aqueous solution of NH_4Cl (20 mL) and extracted with Et_2O (3×20 mL). The combined extracts were washed with brine (20 mL) and dried ($MgSO_4$). The solvents were removed by evaporation and reaction diastereoselectivity of the crude reaction mixture was determined by HPLC. The crude product was purified by column chromatography (EtOAc/hexanes, 1:1). The reported yields reflect purified material.

4.2. (2′*S*,3′*S*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methyl-3-phenylpropionyl)-4,5-dimethyl-6-phenyl-1,3,4-oxadiazin-2-one 4a

Isolated product recrystallized with Et_2O to yield **4a** in 81% yield as off-white crystals. Mp = 150–152°C; $[\alpha]_D^{24} = -25.8$ (*c* 1.00, MeOH), $R_f = 0.14$ (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.82 (d, $J = 7.2$ Hz, 3H), 1.17 (d, 3H, $J = 6.80$ Hz), 2.88 (s, 3H), 3.41 (dq, $J = 7.0$, 4.8 Hz, 1H), 4.13 (dq, $J = 7.3$, 3.7 Hz, 1H), 5.23 (d, 1H, $J = 3.2$ Hz), 6.04 (d, 1H, $J = 4.4$ Hz), 7.25–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 11.3, 12.2, 43.1, 46.9, 56.7, 73.3, 77.8, 124.7, 126.1, 127.2, 128.0, 128.1, 128.6, 135.3, 141.6, 148.0, 177.5. IR (KBr): 3435, 2979, 1715, 996, 754 cm^{-1}. EI-MS, *m*/*z* (%): 216 (1), 201 (4), 191 (12), 117 (9), 91 (12). HRMS calcd for $C_{21}H_{24}N_2O_4$ (M^++1): 369.1814. Found: 369.1813. Anal. calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.49; H, 6.62; N, 7.51.

Table 2. Diastereoselective aldol additions

Entry	Compound	RCHO	Diastereomeric ratios[a]		Yield (%)[b]
			Crude	Purified	
1	**4a**	C_6H_5CHO	38:1	50:1	81
2	**4b**	C_2H_5CHO	18:1	20:1 (89:1)[c]	66 (58)[c]
3	**4c**	$(CH_3)_2CHCHO$	19:1	63:1	91
4	**4d**	$C_6H_{11}CHO$	26:1	32:1	95
5	**4e**	$BnOCH_2CHO$	8:1	12:1	76
6	**4f**	C_6H_5CH=$CHCHO$	14:1	18:1 (54:1)[c]	80 (54)[c]

[a] Diastereomer ratios reported as major isomer: Σ other isomers; ratios determined by HPLC.
[b] Chemical yield of the purified product after chromatography and recrystallization.
[c] The values in parentheses are the results after a second recrystallization.

4.3. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2-methylpentanoyl)-4,5-dimethyl-6-phenyl-1,3,4-oxadiazin-2-one 4b

Isolated product recrystallized with Et_2O to yield **4b** in 66% yield as white crystals. Mp = 91–93°C; $[\alpha]_D^{25}$ = +5.2 (*c* 0.97, MeOH), R_f = 0.51 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J = 6.0 Hz, 3H), 1.00 (dt, J = 6.8, 0.8 Hz, 3H), 1.23 (dd, J = 7.2, 1.2 Hz, 3H), 1.47 (m, 2H), 1.57 (m, 1H), 2.99 (s, 3H), 3.47 (dq, J = 7.2, 1.2 Hz, 1H), 3.88 (dq, J = 6.8, 2.2 Hz, 1H), 6.09 (d, J = 4.4 Hz, 1H), 7.29–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.2, 10.6, 12.2, 26.6, 43.9, 43.7, 56.4, 72.6, 77.7, 124.5, 127.9, 128.3, 135.2, 147.9, 178.0. IR (KBr): 3543, 2975, 1723, 1716, 734, 702 cm^{-1}. EI-MS, *m*/*z* (%): 207 (3), 206 (40), 118 (20), 99 (5), 91 (4). HRMS calcd for $C_{17}H_{24}N_2O_4$: 320.1736. Found: 320.1736. Anal. calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.65; H, 7.51; N, 8.79.

4.4. (2′*S*,3′*R*,5*S*,6*R*)-3,4,5,6-Tetrahydro-3-(3-hydroxy-2,4-dimethylpentanoyl)-4,5-dimethyl-6-phenyl-1,3,4-oxadiazinan-2-one 4c

Isolated product recrystallized with Et_2O to yield **4c** in 91% yield as white crystals. Mp = 98–100°C; $[\alpha]_D^{24}$ = +7.4 (*c* 1.02, MeOH), R_f = 0.24 (EtOAc/hexanes, 1:1). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 4.4 Hz, 3H), 1.21 (dd, J = 7.6, 1.2 Hz, 3H), 1.73 (m, 1H), 3.00 (s, 3H), 3.44 (dq, J = 7.2, 2.4 Hz, 1H), 3.62 (d, J = 9.2 Hz, 1H), 4.08 (dq, J = 7.2, 1.2 Hz, 1H), 6.08 (d, J = 4.8 Hz, 1H), 7.26–7.44 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.2, 12.5, 18.8, 19.4, 30.6, 41.8, 43.3, 56.9, 76.5, 78.0, 124.7, 128.2, 128.7, 135.4, 148.2, 178.8. IR (KBr): 3523, 2960, 1716, 1141 cm^{-1}. EI-MS, *m*/*z* (%):285 (1), 260 (5). HRMS calcd for $C_{18}H_{26}N_2O_4$ (M^++1): 335.1971. Found: 335.1971. Anal. calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.49; H, 7.88; N, 8.40.

4.5. (2′*S*,3′*R*,5*S*,6*R*)-3-(3-Cyclohexyl-3-hydroxy-2-methyl-propionyl)-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-1,3,4-oxadiazin-2-one 4d

Isolated product **4d** in 95% yield as a colorless oil; $[\alpha]_D^{24}$ = +3.0 (*c* 1.20, MeOH), R_f = 0.53 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.86 (d, J = 7.2 Hz, 3H), 0.95–0.1.03 (m, 4H), 1.19 (d, J = 6.8 Hz, 3H), 1.13–1.28 (m, 2H), 1.67 (d, J = 12.0 Hz, 2H), 1.77 (d, 12.4 Hz, 2H), 2.14 (d, J = 12.8 Hz, 1H), 2.98 (s, 3H), 3.46 (dq, J = 6.8, 4.8 Hz, 1H), 3.69 (dd, J = 8.4, 2.0 Hz, 1H), 4.05 (dq, J = 7.2, 2.4 Hz, 1H), 6.07 (d, J = 4.4 Hz, 1H), 7.28–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 10.1, 12.6, 25.9, 26.0, 28.7, 29.8, 40.0, 41.4, 43.4, 56.9, 75.3, 78.0, 124.5, 127.9, 128.4, 135.2, 147.9, 178.4. IR (neat): 3510, 2928, 1771, 1720, 996, 736, 700 cm^{-1}. EI-MS, *m*/*z* (%): 262 (1), 206 (33), 118 (100). HRMS calcd for $C_{21}H_{30}N_2O_4$ (M^++1): 375.2284. Found: 375.2283.

4.6. (2′*S*,3′*S*,5*S*,6*R*)-3-(4-Benzyloxy-3-hydroxy-2-methylbutyryl)-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-1,3,4-oxadiazin-2-one 4e

Isolated product **4e** in 76% yield as a colorless oil; $[\alpha]_D^{24}$ = −1.3 (*c* 0.98, MeOH), R_f = 0.62 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.84 (d, J = 7.2 Hz, 3H), 1.25 (d, J = 6.8 Hz, 3H,), 2.90 (s, 3H), 3.40 (dq, J = 6.4, 2.0 Hz, 1H), 3.55 (dd, J = 6.0, 2.0 Hz, 1H), 4.01 (dq, J = 6.8, 2.4 Hz, 1H), 4.07–4.14 (m, 1H), 4.23 (q, J = 7.3, 5.2 Hz, 1H), 4.55 (d, J = 1.6 Hz, 2H), 6.03 (d, 1H, J = 4.4 Hz), 7.27–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 12.2, 12.4, 42.3, 43.3, 56.8, 70.7, 71.5, 73.2, 77.8, 124.8, 127.6, 127.7, 128.2, 128.3, 128.6, 135.4, 137.9, 148.1, 177.1. IR (neat): 3466, 2938, 1770, 1715, 1136, 736, 700 cm^{-1}. EI-MS, *m*/*z* (%): 324 (1), 206 (37), 118 (100). HRMS calcd for $C_{23}H_{28}N_2O_5$ (M^++1): 413.2077. Found: 413.2077.

4.7. (2′*S*,3′*R*,5*S*,6*R*)-3-(3-Hydroxy-2-methyl-5-phenyl-pent-4-enoyl)-4,5-dimethyl-6-phenyl-[1,3,4]-oxadiazinan-2-one 4f

Isolated product recrystallized with Et_2O to yield **4f** in 80% yield as off-white crystals. Mp = 136–137°C; $[\alpha]_D^{24}$ = −2.3 (*c* 1.00, MeOH), R_f = 0.67 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.84 (d, J = 6.8 Hz, 3H), 1.26 (d, J = 7.6 Hz, 3H), 2.95 (s, 3H), 3.41 (dq, J = 7.2, 4.4 Hz, 1H), 4.04 (dq, J = 7.2, 3.6 Hz, 1H), 4.74 (m, 1H), 6.04 (d, J = 4.4 Hz, 1H), 6.26 (dd, J = 16.4, 6.0 Hz, 1H), 6.72 (dd, J = 22.8, 1.2 Hz, 1H), 7.20–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 11.8, 12.3, 43.2, 45.2, 56.6, 72.7, 77.2, 77.9, 124.7, 126.3, 127.4, 128.1, 128.3, 128.5, 128.9, 131.0, 135.2, 136.4, 148.3, 177.1. IR (KBr): 3436, 2973, 1714, 1256, 1181, 1144, 984, 958, 747, 697 cm^{-1}. EI-MS, *m*/*z* (%): 262 (1), 206 (33), 118 (100). HRMS calcd for $C_{23}H_{28}N_2O_5$ (M^++1): 395.1971. Found: 395.1971. Anal. calcd for $C_{23}H_{28}N_2O_5$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.71; H, 6.60; N, 7.23.

4.8. (5*S*,6*R*)-3-(2-Deuteriopropionyl)-3,4,5,6-tetrahydro-4,5-dimethyl-6-phenyl-1,3,4-oxadiazin-2-one 6

Oxadiazinone **3** (0.5 g, 1.91 mmol) and dissolved in THF (5.73 mL) and to this mixture was added $TiCl_4$ (0.22 mL, 2.00 mmol). This mixture was allowed to stir for 25 min then cooled to −78°C. Triethylamine (0.28 mL, 2.00 mmol) was added and the solution was immediately allowed to come to room temperature. After 15 min, the reaction was quenched by the addition of D_2O/DCl (1 M, 1.0 mL) and the solution and allowed to stir for an additional 5 min. The solution was extracted with Et_2O (3×20 mL), washed with $NaHCO_3$ (3×20 mL), brine (3×20 mL), and the combined extracts were dried ($MgSO_4$) at which point the solvents were removed by evaporation. The crude product was purified by column chromatography (EtOAc/hexanes, 1:1). The isolated product recrystallized with Et_2O to yield **6** in 83% yield as white crystals. Mp = 136–137°C; R_f = 0.70 (EtOAc). ^{1}H NMR ($CDCl_3$): δ 0.85 (d, J = 7.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 2.98 (s, 3H), 3.40–

3.51 (m, 2H), 6.05 (d, $J=4.4$ Hz, 1H), 7.29–7.42 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 8.92, 12.4, 30.8, 31.0, 31.2, 43.2, 56.7, 77.6, 124.8, 128.1, 128.6, 135.6, 148.3, 174.5. IR (KBr): 2981, 1724 cm^{-1}. EI-MS, m/z (%): 263 (1), 206 (33), 118 (100). HRMS calcd for $C_{14}H_{17}DN_2O_3$ (M^++1): 264.1452. Found: 264.1457. Anal. calcd for $C_{14}H_{17}DN_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.86; H, 7.27; N, 10.64.

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10. The average diastereoselectivity that was observed was 91:9 from eight examples. Reaction with trimethylacetaldehyde gave poor results (75:25). See Ref. 9.
11. Presumably, the α-proton bearing aldehydes underwent competitive side reactions such as enolization and self condensation. See: Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
12. The acylation of oxadiazinone **2** has proven to be not straightforward. Direct treatment with many bases (*n*-BuLi, MHMDS (M = Na, K, Li) leads to very inefficient acylation. We were also concerned with other potential decomposition pathways. For example, see: Allen, A.; Anselme, J.-P. *Tetrahedron Lett.* **1996**, *37*, 5039–5040.