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Intramolecular Chiral Relay at Stereogenic Nitrogen. Synthesis and Application of a New Chiral Auxiliary Derived from (1*R*,2*S*)-Norephedrine and Acetone†

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(1*R*,2*S*)-Norephedrine has been employed in the synthesis of a novel 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-one via reductive alkylation with acetone, *N*-nitrosation, reduction, and cyclization. The oxadiazinone was treated with either propionyl chloride or 3-thiophenylpropionyl chloride to afford the corresponding N_3-acylated oxadiazinones **9a** and **9b**, respectively. X-ray crystallographic analysis of the N_3-thiophenylpropionyl oxadiazinone **9b** revealed that the C_2-urethane carbonyl and the N_3-carbonyl are arranged in an anti-periplanar conformation. The oxadiazinones were subsequently applied in the titanium-mediated asymmetric aldol addition reaction by treatment with titanium tetrachloride, triethylamine, and a variety of aldehydes at 0 °C. The aldol adducts **10a**−**i** and **11a**,**b** were found to have diastereoselectivities ranging from 8:1 to >99:1 favoring the formation of the non-Evans syn configuration. The absolute stereochemistry of the adduct **10a** was determined by acid hydrolysis. This process afforded the N_4-isopropyloxadiazinone **8** and (2*S*,3*S*)-3-hydroxy-2-methyl-3-phenylpropanoic acid **14** in ≥95% enantiomeric excess.

Introduction

The evolution of chiral auxiliaries over the last 30 years has yielded an incredibly diverse array of asymmetric templates for preparing enantiomerically enriched materials.[1] Oxazolidinones[2] have been central in the development of chiral auxiliaries because of their successful application in a wide variety of reactions, among which the asymmetric aldol reaction has attracted the most attention.[3] We recently disclosed our efforts in developing 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones (oxadiazinones) as viable templates for asymmetric syntheses.[4−6] We initiated our investigation of this ring system with conformational studies of N_3-acylated oxadiazinones derived either from (1*R*,2*S*)-ephedrine or (1*S*,2*S*)-pseudoephedrine (Figure 1).[4] These studies revealed that the (1*S*,2*S*)-pseudoephedrine-based oxadiazinones were conformationally labile at the N_4-nitrogen and might not be suitable candidates for chiral auxiliary applications. In contrast, the (1*R*,2*S*)-ephedrine-based oxadiazinones did not exhibit any observable conformational mobility at the N_4-nitrogen. In fact, we were able to successfully conduct asymmetric aldol addition reactions with aromatic[5] and aliphatic aldehydes[6] using this oxadiazinone (Figure 2).

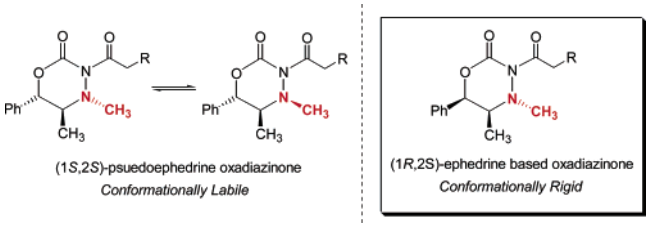

FIGURE 1. Oxadiazinones.

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(1) (a) Jones, S. *J. Chem. Soc., Perkin. Trans. 1* **2002**, 1−21. (b) Lin, G.-Q.; Li, YU.-M.; Chan, A. S. C. *Principles and Applications of Asymmetric Synthesis*; John Wiley & Sons: New York, 2001. (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; John Wiley & Sons: New York, 1995.

(2) (a) Sibi, M. P. *Aldrichim. Acta* **1999**, *32*, 93−103. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3−12. (c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875. (d) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32.

(3) (a) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127−1130. (b) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393. (c) Anaya de Parrodi, C.; Clara-Sosa, A.; Perez, L.; Quintero, L.; Maranon, V.; Toscano, R. A.; Avina, J. A.; Rojas-Lima, S.; Juaristi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 69−79. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A. Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894−902. (e) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775−777. (f) Luetzen, A.; Koell, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1193−1206. (g) Sibi, M. P.; Deshpande, P. K.; Ji, J. *Tetrahedron Lett.* **1995**, *36*, 8965−8968. (h) Yan, T. H.; Lee, H. C.; Tan, C. W. *Tetrahedron Lett.* **1993**, *34*, 559−62. (i) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299−308. (j) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489−98. (k) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. (l) Bermejo-Gonzalez, F.; Perez-Baz, J.; Santinelli, F.; Mayer-Real, F. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 674−81. (m) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, 68, 83−91. (n) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42. (o) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

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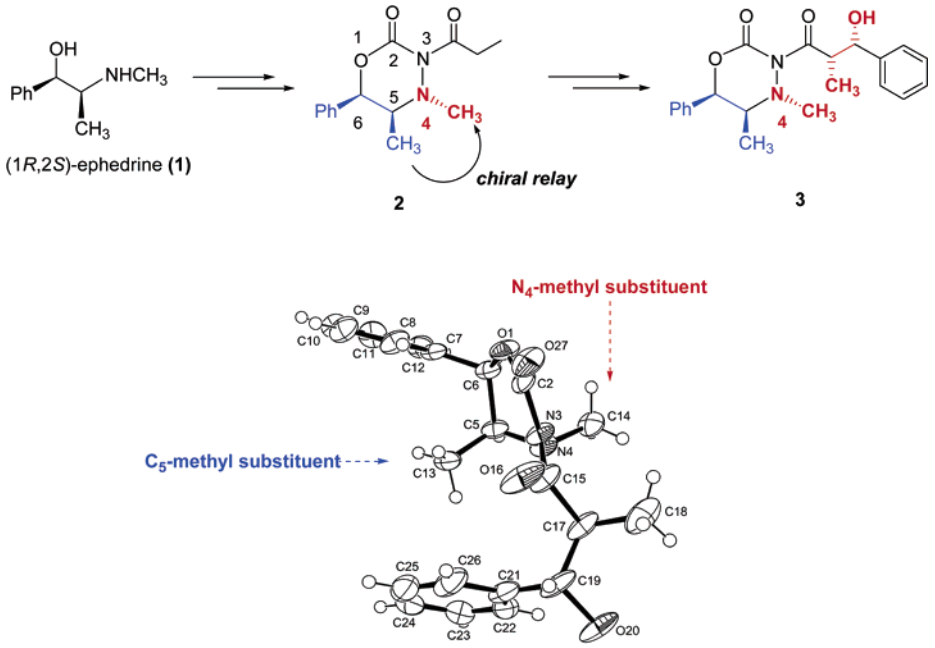
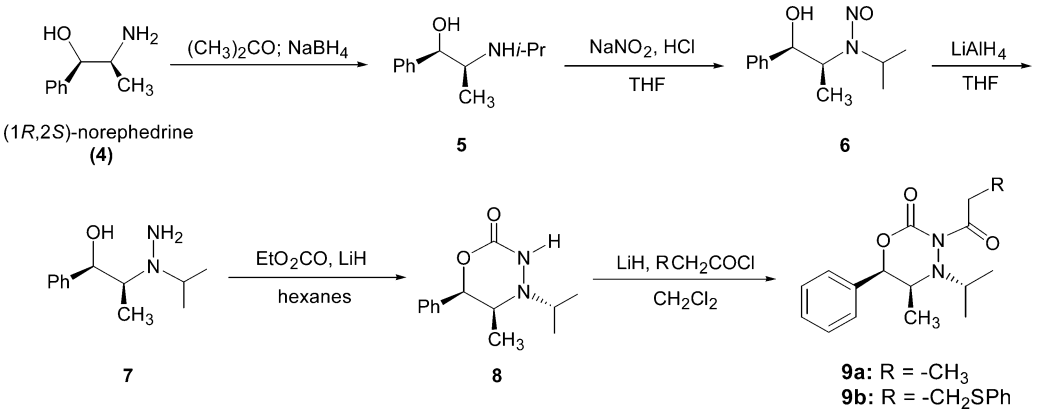


FIGURE 2. Intramolecular chiral relay with oxadiazinones.

SCHEME 1



In terms of the asymmetric aldol addition reaction of N_3-acyloxadiazinones, the asymmetry of the (1*R*,2*S*)-ephedrine fragment of the oxadiazinone is not directly responsible for the observed diastereoselectivity. It is postulated that the stereochemical impact of the ephedrine fragment (C_5-methyl and C_6-phenyl of the oxadiazinone) is transmitted to the appendant N_3-enolate by way of intramolecular chiral relay via the stereogenic N_4-nitrogen (Scheme 1).[7,8] This postulate is supported by the X-ray crystallographic data of aldol adduct **3**.[5] The X-ray crystal structure[9] suggests that the proximity of the N_4-methyl group to the N_3-substituent is the dominant mechanism of asymmetric induction in the course of the carbon−carbon bond-forming process during the aldol addition reaction. Herein, we describe our efforts in enhancing the observed diastereoselectivities of the aldol addition reaction by modification of the N_4-position.

Results and Discussion

Preparation of the N_3-Acyl-N_4-isopropyloxadiazinones. With a rationale for the observed diastereoselectivity in hand, we sought to improve the asymmetric induction of the oxadiazinone-directed aldol reaction by modification of the N_4-substituent. Thus, (1*R*,2*S*)-norephe-

(4) (a) Casper, D. M.; Blackburn, J. R.; Maroules, C. D.; Brady, T.; Esken, J. M.; Ferrence, G. M.; Standard, J. M.; Hitchcock, S. R. *J. Org. Chem.* **2002**, *67*, 8871−8876. (b) 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*, 9789−9798.

(5) Casper, D. M.; Burgeson, J. R.; Esken, J. M.; Ferrence, G. M.; Hitchcock, S. R. *Org. Lett.* **2002**, *4*, 3739−3742.

(6) Casper, D. M.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2003**, *14*, 517−521.

(7) Sibi and co-workers have demonstrated intermolecular chiral relay between a chiral, nonracemic Lewis acid and its interaction with an achiral pyrazolidinone. The conformation preference of the stereogenic N_1-nitrogen is determined by the structure of the chiral Lewis acid. Please see: Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444−8445.

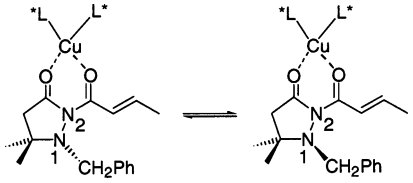
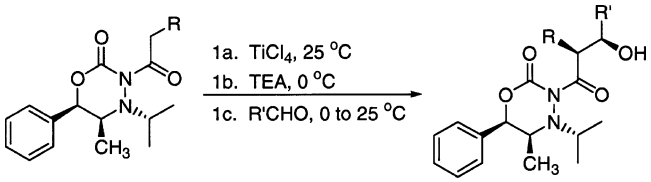


TABLE 1. Asymmetric Aldol Reactions Leading to Aldol Adducts 11a−i and 12a,b



entry	oxadiazinone	aldehyde R′CHO	adduct	crude dr[a]	purified dr[a]	yield[b] (%)
1	**9a** (R = −CH_3)	C_6H_5CHO	**10a**	>99:1[c]	>99:1[c]	78
2	**9a** (R = −CH_3)	*p*-ClC_6H_4CHO	**10b**	>99:1[c]	>99:1[c]	73
3	**9a** (R = −CH_3)	(*E*)-C_6H_5CH=$CHCHO$	**10c**	>99:1[c]	>99:1[c]	85
4	**9a** (R = −CH_3)	*p*-$CH_3OC_6H_4CHO$	**10d**	>99:1[c]	>99:1[c]	31
5	**9a** (R = −CH_3)	*p*-$NO_2C_6H_4CHO$	**10e**	38:1[c]	39:1[c]	74
6	**9a** (R = −CH_3)	1-$C_{10}H_7CHO$	**10f**	8:1[c]	>99:1[c]	59
7	**9a** (R = −CH_3)	2-$C_{10}H_7CHO$	**10g**	99:1[c]	99:1[c]	98
8	**9a** (R = −CH_3)	$(CH_3)_3CCHO$	**10h**	10:1[c]	29:1[c]	96
9	**9a** (R = −CH_3)	$(CH_3)_2CHCHO$	**10i**	49:1[c]	>99:1[c]	97
10	**9b** (R = −CH_2SPh)	C_6H_5CHO	**11a**	99:1[c]	>99:1[c]	82
11	**9b** (R = −CH_2SPh)	$C_6H_5CH_2OCH_2CHO$	**11b**	≥19:1[d]	≥19:1[d]	45

[a] Diastereomer ratios reported as major isomer/Σ other isomers. [b] Chemical yield of the purified product after chromatography or recrystallization. [c] Diastereomer ratio determined by HPLC. [d] Diastereomer ratio determined by 400 MHz ^1H NMR where the detection limit is taken to be no greater than 19:1.

drine **(4)** was reductively alkylated with acetone and sodium borohydride[10a] to afford *N*-isopropylnorephedrine derivative **5**[10b] in 95% yield after recrystallization (Scheme 1).[11] This product was quantitatively converted to the *N*-nitrosamine **6**[12] by treatment with sodium nitrite and HCl and, in turn, was reduced to afford *β*-hydroxyhydrazine **7** (78%) after recrystallization. Finally, the hydrazine was cyclized with lithium hydride and diethyl carbonate to afford the target heterocycle **8**.[13] To pursue the asymmetric aldol reactions, oxadiazinone **8** was acylated with either propionyl chloride or 3-thiophenylpropionyl chloride[14] to afford N_3-acylated oxadiazinones **9a** and **9b**, respectively.

X-ray Crystallography. Single-crystal X-ray diffraction analysis of **9b** revealed that the urethane C_2-carbonyl and the N_3-carbonyl groups are arranged in an anti-periplanar conformation as evidenced by the 172.5-(2)° [O(18)−C(17)−C(2)−O(28)] torsion angle (Figure 3).[15] This was initially unexpected as the dominant conformation of the carbonyls for (1*R*,2*S*)-ephedrine- and (1*S*,2*S*)-pseudoephedrine-based oxadiazinones is the syn-periplanar arrangement based on X-ray crystallographic data[4,5] and ^{13}C NMR spectroscopy.[4] It is believed that the syn-periplanar conformation arises from lone pair repulsion between the N_4-nitrogen lone pair and the N_3-carbonyl lone pair. In contrast, the conformation of the carbonyls in oxadiazinone **9b** (and **9a**) probably originates from repulsive interactions between the N_4-isopropyl group and the N_3-substituent.

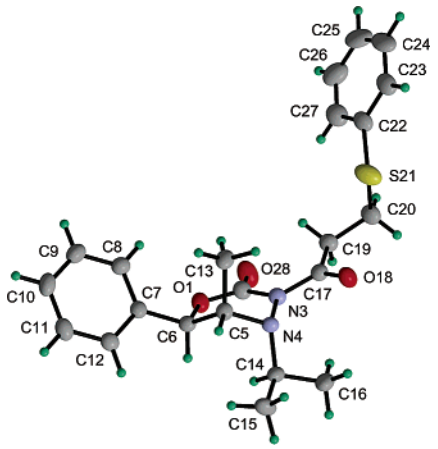


FIGURE 3. View of molecular structure of **9b** showing the atom labeling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 50% probability level. Hydrogen atoms have been drawn arbitrarily small and are not labeled.

Asymmetric Aldol Reactions. The acylated auxiliaries **9a** and **9b** were complexed with titanium tetra-

(8) (a) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, P.; Jasperse, C. P.; Sibi, M. P. *Chem.—Eur. J.* **2003**, *9*, 28−35. (b) Quaranta, L.; Corminboeuf, O., Renaud, P. *Org. Lett.* **2002**, *4*, 39−42.

(9) Solvation effects must also be taken into account when conformations of the oxadiazinones are being considered in the liquid state. Yet, the X-ray crystallographic data of aldol adduct **3** would suggest that the aldehyde must approach away from the N_4-methyl substituent.

(10) (a) We have previously synthesized oxadiazinone derivatives based on (1*R*,2*S*)-norephedrine. See: Hitchcock, S. R.; Casper, D. M.; Nora, G. P.; Blackburn, J. R.; Bentley, J. T.; Taylor, D. C. *J. Heterocycl. Chem.* **2002**, *39*, 823−828. (b) Other oxadiazinones prepared from (1*R*,2*S*)-norephedrine via condensation with cyclohexanone or D-camphor that have been recently synthesized in our laboratories. Work is underway in applying these oxadiazinones to asymmetric syntheses.

(11) Baxter, E. W.; Reitz, A. B. Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents. In *Org. React.* (Overman, L. E., Ed.) **2002**, 59, pp 3−714.

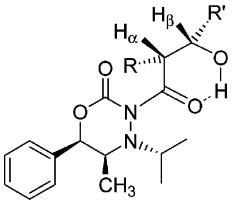
(12) Saavedra, J. E.; Farnworth, D. W.; Pei, G.-K. *Synth. Commun.* **1988**, *18*, 313−322. *It should be noted that many N-nitrosamines are potentially dangerous carcinogens and should be handled with due caution.* See: Loeppky, R. N., Michejda, C. J., Eds. Nitrosamines and Related *N*-Nitroso Compounds: Chemistry and Biochemistry; ACS Symposium Series 553; American Chemical Society: Washington, DC, 1994.

(13) The heterocycle is routinely prepared on multigram scale (5−40 g).

(14) The 3-thiophenylpropionic acid was prepared by reaction of thiophenol and 3-bromoproionic acid in the presence of an excess of lithium hydride. The 400 MHz ^1H NMR spectrum was identical with the known literature examples. See: Anh, Y.; Cohen, T. *J. Org. Chem.* **1994**, *59*, 3142−3150.

(15) X-ray crystallographic data for **9b** is collected in the Supporting Information.

TABLE 2. Stereochemical Assignment



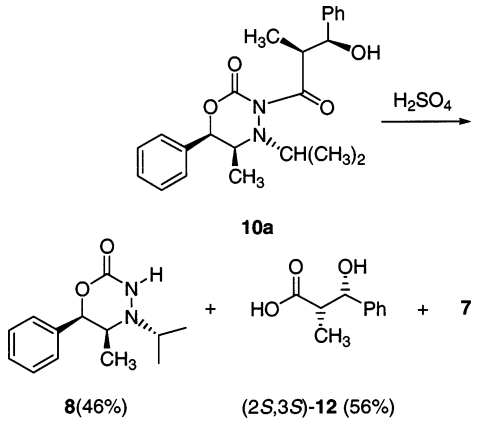
entry	product	δ (ppm)	J (Hz)	$[\alpha]^{25}_D$	configuration[a]
1	**10a**	4.18	2.8	−117.9	2′*S*,3′*S*,4*R*,5*S*,6*R*
2	**10b**	4.12	3.4	−123.8	2′*S*,3′*S*,4*R*,5*S*,6*R*
3	**10c**	4.08	3.3	−96.5	2′*S*,3′*S*,4*R*,5*S*,6*R*
4	**10d**	4.14	3.8	−120.1	2′*S*,3′*S*,4*R*,5*S*,6*R*
5	**10e**	4.19	1.6	−127.6	2′*S*,3′*S*,4*R*,5*S*,6*R*
6	**10f**	4.45	4.8	−103.5	2′*S*,3′*S*,4*R*,5*S*,6*R*
7	**10g**	4.29	3.2	−131.2	2′*S*,3′*S*,4*R*,5*S*,6*R*
8	**10h**	4.27	1.6	−104.9	2′*S*,3′*S*,4*R*,5*S*,6*R*
9	**10i**	4.11	1.8	−104.6	2′*S*,3′*R*,4*R*,5*S*,6*R*
10	**11a**	4.41	2.6	−172.1	2′*R*,3′*S*,4*R*,5*S*,6*R*
11	**11b**	4.31	4.0	−144.1	2′*R*,3′*S*,4*R*,5*S*,6*R*

[a] Stereochemistry determined by analogy to the hydrolysis product of **10a**.

chloride (1 equiv) at 25 °C for a period of 25 min. The reaction mixture was cooled to 0 °C, and triethylamine was added to effect enolate formation. After 1 h, the aldehyde (1 equiv) was added. This process successfully yielded the aldol adducts **10a**,**b**,**d**−**g** and **11a** in high yield and diastereoselectivity (Table 1). However, in the case of aliphatic aldehydes, 2 equiv of titanium tetrachloride as well as 2 equiv of triethylamine were employed to effect complete conversion. This process yielded aldol adducts **10c**,**h**,**i** and **11b** in good to excellent chemical yield and good diastereoselectivity (Table 1). Interestingly, the addition of 2 equiv of $TiCl_4$ and triethylamine did not change the stereochemical course of the reactions.[16,17] We were gratified to learn that the diastereoselectivities observed in this work were superior to those obtained from the aldol reactions with the ephedrine based oxadiazinone **2**. In fact, the reactions involving the (1*R*,2*S*)-ephedrine-based oxadiazinone **2** were originally conducted at low temperature (enolate formation and aldehyde addition at −78 °C).[5] The reactions of the (1*R*,2*S*)-norephedrine-based oxadiazinones **9a** and **9b** (this work) were conducted at 0 °C due to low conversion at lower temperatures. Nonetheless, these reactions produced high diastereoselectivities despite operating at higher temperatures. Unfortunately, aldehydes that had high steric requirements (entries 6 and 8) gave lower stereoselectivities.[18]

Determination of Stereochemistry. The relative stereochemistry of the aldol adducts was determined to be the syn configuration by evaluation of the vicinal coupling constants [N_3-COCH$_\alpha$(CH$_3$)CH$_\beta$(OH)R)] of the adducts (Table 2). The value of the coupling constants for adducts **10a**−**i** and **11a**,**b** were in the expected range for syn-configured aldol adducts.[19]

The determination of the absolute stereochemistry was conducted through hydrolysis of adduct **10a** (eq 1).



Treatment of **10a** with 6 M sulfuric acid for 2 h at reflux afforded the norephedrine-derived heterocycle **8** (46%) and desired β-hydroxy acid **12** (56%). The remaining mass balance consisted of the β-hydroxyhydrazine **7** and byproducts. The generation of **7** is believed to come from an endocyclic ring-opening process[20] followed by hydrolysis of the amide bond to the N_3-substituent. This alternate pathway is most likely attributed to steric factors associated with the N_4-isopropyl group. Attempts to conduct base hydrolysis[21] were not successful and gave rise to ring-opening processes, elimination of the aldol side chain (α,β-unsaturation), or retro-aldol processes. The crude ^{1}H NMR spectrum of the isolated β-hydroxy acid **12** suggested that there was no detectable sign of epimerization.

The absolute stereochemistry of the β-hydroxyacid **12** was determined by comparison of the optical rotation to literature values: an observed value of $[\alpha]^{24}_D$ −35 (*c* 0.8, $CHCl_3$) versus the literature value of $[\alpha]_D$ −29.3 (*c* 0.8, $CHCl_3$)[22] for the (2*S*,3*S*)-isomer.[23] The enantiomeric purity of (2*S*,3*S*)-**12** was estimated to be greater than 95% enantiomeric excess based on the optical rotation.

(16) With regard to the aldol adducts derived from the aliphatic aldehydes, the characteristic signals for the 400 MHz ^{1}H NMR spectra (as well as the HPLC traces) remained unchanged after increasing the amount of titanium chloride from 1 to 2 equiv.

(17) In contrast to the oxadiazinones, the stereochemical outcome of asymmetric aldol reactions with oxazolidinones exhibits a strong dependence on the stoichiometric amount of titanium tetrachloride employed. See: Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883−7884.

(18) In some cases steric interactions may have given rise to poor selectivity, possibly via alternate transition states, i.e., a boatlike transition state vs a chair like transition state. See ref 3a.

(19) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1−115. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; John, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066−1081.

(20) The undesired endocyclic ring opening process is postulated to be a result of the steric environment of the N_4-nitrogen proximal to the N_3-acyl moiety. See: (a) Prashad, M.; Kim, H.-Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750−1753. (b) Ishizuka, T.; Kunieda, T. *Tetrahedron Lett.* **1987**, *28*, 4185−4187.

(21) Peroxide-assisted saponification (NaOH, H_2O_2) also failed to give the desired β-hydroxyacid in significant yield. This may be due to the susceptibility of the N_4-nitrogen to oxidation. See: (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144. (b) Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187−1189.

(22) (a) Vicario, J. L.; Badia, D.; Dominguez, E.; Rodriguez, M.; Carrillo, L. *J. Org. Chem.* **2000**, *65*, 3754−3760. (b) Fringuelli, F.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1995**, *60*, 7006−7009. (c) Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. *Tetrahedron Lett.* **1994**, *35*, 2373−2376. (d) Davies, S. G.; Edwards, A. J.; Evans, G. B.; Mortlock, A. A.; *Tetrahedron* **1994**, *50*, 6621−6642. (e) van Draanen, N. A.; Arsenyiadis, A.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499−2506. (f) Heathcock, C. H.; White, C. T.; Morrison, J. H.; VanDerveer, D. *J. Org. Chem.* **1981**, *46*, 1296−1309.

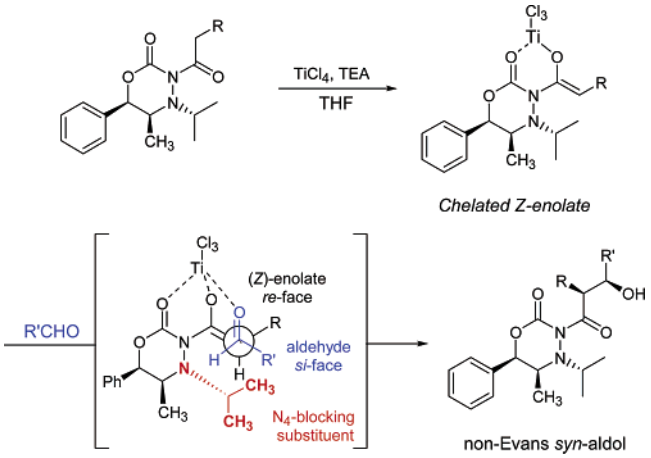


FIGURE 4. Proposed transition state.

Mechanistic Implications of Stereochemistry. Previous efforts with the (1*R*,2*S*)-ephedrine-based N_3-propionyloxadiazinone[5,6] suggest that enolization with $TiCl_4$ and triethylamine leads to the *Z*(O)-enolate.[24] The preference for the *Z*(O)-enolate is not unexpected as related chiral imides such as the oxazolidinones are also known to afford the same enolate geometry.[25] When oxadiazinones **9a** and **9b** undergo enolization with $TiCl_4$ and triethylamine, their respective enolates are believed to be engaged in a chelated chair conformation (Figure 4). The absolute stereochemistry of the products was determined to possess the non-Evans syn-aldol stereochemistry (see previous section). This suggests that the diastereoselectivity of the aldol reaction of oxadiazinones **9a** and **9b** originates from a chairlike Zimmerman−Traxler transition state in which the *re*-face of the putative *Z*(O)-titanium enolate of the N_3-substituent reacts with the *si*-face of the aldehyde (Figure 4).[26]

Conclusion

In summary, we have rationally designed, synthesized, and applied a structurally novel chiral auxiliary derived from (1*R*,2*S*)-norephedrine and acetone. The success of the asymmetric induction in the transition state is due to the chiral relay effect of the ephedrine core (C_5-methyl and C_6-phenyl through the N_4-isopropyl substituent. When applied in the titanium mediated asymmetric aldol reaction, the auxiliary affords aldol adducts **10a**−**i** and **11a**,**b** in good to excellent chemical yield and, in general, high diastereoselectivities. The reaction is believed to occur via a Zimmerman−Traxler transition state involving a chelated *Z*(O)-titanium enolate. A significant limitation to this oxadiazinone system is the resistance to cleavage under mild conditions. Studies are underway to address the cleavage of the chiral auxiliary and its further application in asymmetric synthesis.

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Supporting Information Available: Experimental details and characterization data (400 MHz ^{1}H NMR spectra, 100 MHz ^{13}C NMR spectra) for **5**, **6**, **8**, **9a**,**b**, **10a**−**i**, **11a**,**b**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The *β*-hydroxy acid **12** had a specific rotation that was greater than the expected −29.3. On the basis of ^{1}H and ^{13}C NMR spectroscopy and melting point determination, the compound was identical to the literature examples cited in ref 22. Mp (2*S*,3*S*)-**12** = 87.5−89 °C (lit.[22f] Mp (2*R*,3*R*)-enantiomer = 87−88 °C). ^{1}H NMR ($CDCl_3$, ppm): *δ* 1.16 (d, *J* = 7.0 Hz, 3H), 2.86 (dq, *J* = 7.3, 4.0 Hz, 1H), 5.18 (d, *J* = 3.6 Hz, 1H), 7.28−7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, ppm): *δ* 10.2, 46.2, 73.4, 125.9, 127.7, 128.3, 140.9, 181.1.

(24) The *Z*(O)-enolate geometry for the N_3-acylated oxadiazinones has not been rigorously established. The formation of the *Z*(O)-enolate is based on evaluation of the products of the asymmetric aldol reaction.

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