JOC Article

Novel Use of *N*-Benzoyl-*N*,*O*-acetals as *N*-Acylimine Equivalents in Asymmetric Heterocycloaddition: An Extended Enantioselective Pathway to *β*-Benzamido Aldehydes

Patricia Gizecki, Robert Dhal, Céline Poulard, Pascal Gosselin, and Gilles Dujardin*

Laboratoire de Synthèse Organique UMR CNRS 6011, Université du Maine, F-72085 Le Mans Cedex 9, France

dujardin@univ-lemans.fr

Received May 2, 2002

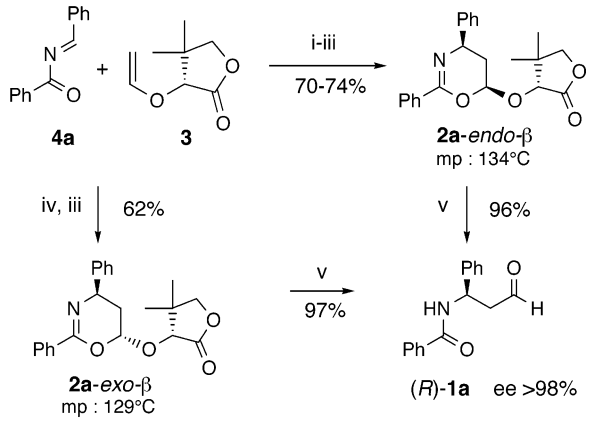
For the first time, easily available *N*-(α-methoxyalkyl)amides were successfully used as synthetic equivalents of *N*-acylimines in an asymmetric heterocycloaddition process. The facial-controlled formation of 6-alkoxydihydrooxazines was thus achieved by $SnCl_4$-promoted heterocycloaddition of (*R*)-*O*-vinyl pantolactone. By simple acidic hydrolysis of the crude heteroadducts, new *β*-aryl- and *β*-alkyl-substituted benzamido aldehydes were thus obtained in good overall yields with high enantioselectivities.

Introduction

Enantioselective access to *N*-protected *β*-aminoaldehydes remains an important tool for several reasons. First, such compounds are key intermediates in natural product chemistry (aminocyclitols,[1] piperidinic alkaloids,[2] aspartic semialdehyde, and derivatives[3]). In the field of *β*-peptide chemistry, *N*-protected *β*-aminoaldehydes may also give access to reduced peptides[4] and "carba"peptides.[5] Beyond the homologating pathways from α-amino acid derivatives,[4−6] there are few general methods for preparing enantiopure *N*-protected *β*-aminoaldehydes: Michael addition of a chiral lithium amide to an α-unsaturated Weinreb amide,[7] or addition of an ester enolate to a chiral sulfinimine.[2a] The two methods require the careful reduction of an *N*-methoxyamide or an ester in the final step.

As a first example of a novel entry in this field, we recently disclosed[8] a direct route to (*R*)-3-benzamido-3-phenylpropanal (**1a**), produced by hydrolysis of the stable[9] 6-alkoxy-5,6-dihydro-4*H*-1,3-oxazine **2a**, asymmetrically obtained from the heterocycloaddition between (*R*)-*O*-vinyl pantolactone (**3**)[10] and (*E*)-*N*-benzoyl benzaldimine (**4a**) (Scheme 1). This key cycloaddition gave high and divergent diastereoselectivities when done in the presence of a catalytic amount of $Yb(fod)_3$ (Procedure A) or of a stoichiometric amount of $SnCl_4$ (Procedure B). The two procedures, when completed by diastereomeric purification and recrystallization of the main isomer (*endo-β* for A, *exo-β* for B) and followed by acidic hydrolysis, gave efficient access to enantiopure (*R*)-(−)-3-benzamido-3-phenylpropanal (**1a**). Further experiments by our group have been directed at exploring the scope of these

SCHEME 1[a]

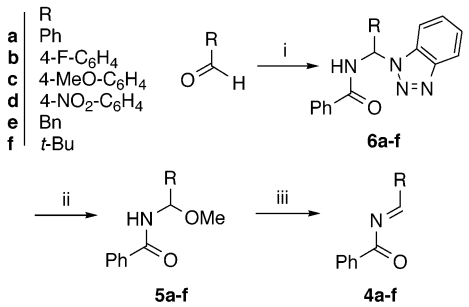


[a] Reagents and conditions: (i) 5 mol % $Yb(fod)_3$, cyclohexane, reflux, 72 h (Procedure A); (ii) chromatography over SiO_2; (iii) recrystallization (Et_2O); (iv) 1 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 0.5 h (Procedure B); (v) Amberlyst-15H$^+$, acetone, H_2O, rt, 15 h.

(1) Suami, T.; Tadano, K.; Horiuchi, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2895.
(2) (a) Davis, F. A.; Szewczyk, S. M. *Tetrahedron Lett.* **1998**, *39*, 5951. (b) Davies, S. B.; McKervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229. (c) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett.* **1993**, *34*, 2911.
(3) Coulter, C. V.; Gerrard, J. A.; Kraunsoe, J. A. E.; Moore, D. J.; Pratt, A. J. *Tetrahedron* **1996**, *52*, 7127.
(4) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 9457.
(5) (a) Rodriguez, M.; Aumelas, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 5153. (b) Rodriguez, M.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1990**, *31*, 7319. (c) Llinares, M.; Devin, C.; Azay, J.; Bergé, G.; Fehrentz, J. A.; Martinez, J. *Eur. J. Med. Chem.* **1997**, *32*, 767.
(6) Toujas, J.-L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, 713.
(7) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700.
(8) Gizecki, P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett.* **2000**, *2*, 585.
(9) This study exemplified that the nature of the vinyl ether substituent can significantly modulate the stability of the desired heteroadduct.
(10) (a) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 798. (b) For the preliminary study (Scheme 1) and the present work, the two-step method used for the preparation of (*R*)-(+)-*O*-vinyl-pantolactone **3** is an adaptation (see Experimental Section) of the previously reported procedure.[10a]

10.1021/jo0203138 CCC: $25.00
Published on Web 05/03/2003

SCHEME 2[a]



[a] Reagents and conditions: (i) benzamide, benzotriazole, toluene, Δ, $-H_2O$; (ii) MeONa, MeOH, rt; (iii) toluene, Δ.

TABLE 1. Preparation of *N*-Acylimines 4

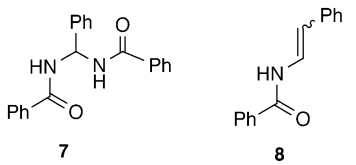
R	6	yield (%)[a]	5	yield (%)[a]	4	yield (%)[b]
Ph	**6a**[c]	59	**5a**[d]	94	**4a**	>85
p-F-C_6H_4	**6b**	60	**5b**	98	**4b**	>90
p-CH_3O-C_6H_4	**6c**[c]	63	**5c**[d]	89	**4c**	>95
p-O_2N-C_6H_4	**6d**[c]	80	**5d**[e]	98	**4d**	36
Bn	**6e**[d]	65	**5e**[d]	86	**4e**	0[g]
t-Bu	**6f**[c]	73	**5f**[f]	85	**4f**	0[h]

[a] Isolated yield. [b] Crude product. [c] Reference 12a. [d] Reference 12b. [e] Reference 13. [f] Reference 14. [g] Isomerization of **4e** into the corresponding enamide **8**. [h] No reaction.

heterocycloadditions. In the present report, we describe how the lack of availability of unstabilized *N*-acylimines can be overcome by the use of stable *N,O*-acetals **5** (Scheme 2) acting as synthetic equivalents of *N*-acylimines **4** in the Lewis acid conditions used. We describe here the enantioselective syntheses of various *β*-aryl and alkyl *β*-benzamido aldehydes with ee ranging from 90 to 97% using a straightforward sequence that avoids any intermediate purification.

Results and Discussion

Our preliminary heterocycloaddition study showed that *N*-acylimine **4a**, when prepared by previous procedures,[11] led to some nonreproducible results. To overcome this obstacle, we developed an alternative method for preparing **4a**, based on the thermal dehydromethoxylation of the readily available *N,O*-acetal **5a**[12] (Scheme 2, Table 1, R = Ph). Under the mild conditions used (toluene, 110 °C), *N*-acylimine **4a** was cleanly obtained, without any formation of side products such as bis-amide **7**,[13] and was successfully used as heterodiene toward vinyl ether **3**.



(11) Kupfer, R.; Meier, S.; Wurthwein, E. U. *Synthesis* **1984**, 688.
(12) (a) Katritzky, A. R.; Pernak, J.; Fan, W.-Q.; Saczewski, F. *J. Org. Chem.* **1991**, *56*, 4439. (b) Katritzky, A. R.; Fan, W.-Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547. (c) Katritzky, A. R.; Pernak, J.; Fan, W.-Q. *Synthesis* **1991**, 868.
(13) Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron*, **1967**, *23*, 2869.

Extending the scope of the method to various 3-aryl and 3-alkyl analogues of 3-benzamido-3-phenylpropanal **1a** required the preparation of various *N*-benzoyl aryl- or alkylaldimines via the corresponding *N,O*-acetals **5b**−**f** (Scheme 2, Table 1). The *N,O*-acetals **5b**−**f** were prepared by Katritzky's method[12] in satisfactory yields. In the case of **5f** (R = *t*-Bu), the convenient preparation of the intermediate benzotriazole adduct **6f** by azeotropic removal of water required the catalytic use of TsOH (5 mol %). Contrary to our expectations, the thermal dehydromethoxylation of *N,O*-acetals **5b**−**f** gave heterogeneous results. Although highly successful for some arylated substrates (**5b**, R = *p*-F-Ph; **5c**, R = *p*-MeO-Ph), the above-mentionned conditions (toluene, reflux) proved sluggish for **5d** (R = *p*-O_2N-Ph) and totally ineffective for alkyl substrates **5e**,**f**. For **5e** (R = Bn), complete isomerization of **4e** into the corresponding enamide **8**[15] was observed. For **5f** (R = *t*-Bu), no reaction was observed.

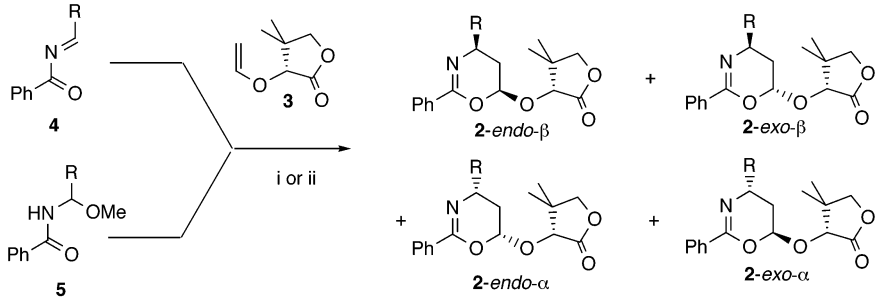
As previously observed for *N*-acyl imine **4a**, the Yb(fod)$_3$-catalyzed heterocycloaddition of (*R*)-*O*-vinyl pantolactone (**3**) with *N*-acylimines **4b** and **4c** led with high yields to the selective formation of the *endo-β* and *exo*-α diastereoisomers (Scheme 3, Table 2). Assignment of the stereostructures for **2b** and **2c** thus obtained was based on consistent comparisons between NMR data of each isomer (Table 3)[16] and those of **2a**-*endo-β* and **2a**-*exo*-α, for which the configuration was previously established by crystallographic analysis and chemical correlation (Table 3).[8] As expected, the stability of the dihydroxazines was satisfactory again, as exemplified by the isolation of the major diastereomer **2b**-*endo-β* after chromatography or recrystallization in 64% and 51% yield, respectively. However, relative to the case of **2a**, the overall diastereoselectivity *endo-β*/*exo*-α significantly decreased (Table 2, entries 4 and 6 vs 1).

An interesting feature was that reaction with **3** also proceeded when *N*-acylimines **4a**−**c** were produced in situ from *N,O*-acetals **5a**−**c** under the thermal conditions used (refluxing cyclohexane or toluene). ^{1}H NMR showed evidence of the transient *N*-acylimine formation.[17] With Yb(fod)$_3$ as the catalyst, *endo-β* selectivity increased (Table 2, entry 3 vs 2) as previously observed when starting from preformed *N*-acylimine,[8] but to a lesser extent.[18] Thus, considering our final goal, diastereomeric distribution of the cycloadducts produced under these in situ conditions remained unsatisfactory because of the low overall *β*/α selectivity (≤80/20, entries 3, 5, 7, and 8).

From this stereochemical point of view, results that are more valuable were obtained with the use of stoichiometric amounts of $SnCl_4$ at low temperature. Conversion of *N*-acylimines **4b** and **4c** into the dihydrooxazines **2b**

(14) Lokensgard, J. P.; Fischer, J. W.; Bartz, W. *J. Org. Chem*, **1985**, *50*, 5609.
(15) Enamide functionality of **8** was characterized in ^{1}H NMR by its vinylic proton at 6.27 ppm (d, J = 14.8 Hz, *E* geometry).
(16) As a typical example of the correlations that can be established between ^{1}H diastereotopic signals of compounds **2a**−**c**, the chemical shifts of the *N,O*-acetalic protons H-6 are in the following range: δ *endo-β* > δ *exo*-α > δ *exo-β*.
(17) This observation is consistent with the fact that no Yb(fod)$_3$-catalyzed reaction occurred between **3** and the *N,O*-acetal **5f** from which the corresponding *N*-acylimine **4f** could not have been obtained.
(18) A possible rationale would be the poisonous effect of the in situ formed methanol on the lanthanide salt.

SCHEME 3[a]



[a] Reagents and conditions: (i) Procedure A: 5 mol % $Yb(fod)_3$, cyclohexane or toluene, reflux, 72 h; (ii) Procedure B: 1 equiv of $SnCl_4$, CH_2Cl_2, −78 °C, 0.5 h.

TABLE 2. Heterocycloaddition of 3 with Preformed or in Situ-Formed *N*-Acylimines 4a−c

	starting material (eq/**3**)	cond.[a] (time)	adduct	conv. **2**/**3**[c]	diastereomeric distribution of **2**				isolated yield of **2** (%)[j]
					***endo*-β**	*exo*-β	*endo*-α	*exo*-α	
1	**4a** (1)	A (3 d)	**2a**	100	**90**	0	0	10	74 (pure **2a**-*endo*-β)
2	**5a** (2)	C (3 d)	**2a**	65	38	6	1	55	
3	**5a** (2)	A (3 d)	**2a**	100	72	8	2	18	
4	**4b** (1.2)	A (3 d)	**2b**	100	**86**	0	0	14	64 (pure **2b**-*endo*-β)[d]
5	**5b** (2)	A (3 d)[e]	**2b**	>95	67	11	0	22	
6	**4c** (2)	A (8 d)[f]	**2c**	72	64	2	0	34	
7	**5c** (1.5)	A (8 d)[e]	**2c**	78	63	10	0	27	
8	**5d** (2)	A (1 d)[e]	**2d**	48	57	3	0	40	
9	**4a** (1.5)	B (0.5 h)	**2a**	100[g]	13	87	0	0	64 (pure **2a**-*exo*-β)
10	**4b** (1.5)	B (0.5 h)	**2b**	100[h]	9	91	0	0	
11	**4c** (2)	B (1 h)[a]	**2c**	100[i]	8	86	5	1	

[a] Procedure A: 5% mol of $Yb(fod)_3$, cyclohexane, reflux. Procedure B: 1 equiv mol of $SnCl_4$, CH_2Cl_2, −78°C. Procedure C: no catalyst, cyclohexane, reflux. [b] −90 °C. [c] By ^1H NMR. [d] 51% after crystallization. [e] Solvent: toluene. [f] Solvent: toluene/cyclohexane, 1:3. [g] 2% of aldehyde **1a**. [h] 1% of aldehyde **1b**. [i] 3% of aldehyde **1c**. [j] After chromatography on SiO_2.

TABLE 3. Selected ^1H NMR Spectroscopic Data for Dihydrooxazines 2a−f

adduct **2**	R	H-6 *endo*-β (ax) δ ppm ($^3J_{6-5ax}$ Hz)	H-6 *endo*-α (ax) δ ppm ($^3J_{6-5ax}$ Hz)	H-6 *exo*-α (eq) δ ppm ($^3J_{6-5ax}$ Hz)	H-6 *exo*-β (eq) δ ppm ($^3J_{6-5ax}$ Hz)
2a	Ph	5.99 (8.9)	5.67 (9.4)	5.89 (3.0)	5.53 (3.0)
2b	*p*-F-C_6H_4	6.01 (8.4)	5.68	5.94 (3.0)	5.53 (3.0)
2c	*p*-CH_3O-C_6H_4	5.98 (8.9)	5.67	5.87 (3.0)	5.52 (3.0)
2d	*p*-O_2N-C_6H_4	6.05 (7.9)	5.76	5.86	5.60 (2.5)
2e	Ph-CH_2	5.76 (7.9)		5.80 (3.0)	5.45 (3.0)
2f	*t*-Bu	5.74 (9.8)			5.56 (3.0)

and **2c** was complete in less than 1 h, and as for **2a**, the two β isomers were produced in both cases with a high selectivity (Table 2, entries 9−11). Nevertheless, extension of the method was severely restricted by the unavailability of the requisite *N*-acylimines **4**. This prompted us to examine how *N*,*O*-acetals **5** or even their precursors **6** could give access to the target heteroadducts **2** under nonthermal conditions. For that purpose, given its well-known ability to promote *N*-acyliminium chemistry together with the positive results obtained with neutral acylimines (vide infra), $SnCl_4$ appeared as the appropriate Lewis acid. At −78 °C, the $SnCl_4$-promoted reaction between the benzotriazolyl adduct **6a**[19] (in excess) and vinyl ether **3** gave only low conversion of the latter (<10%) into **1a**. By contrast, under the same conditions (−78 °C), an efficient reaction occurred between **3** and the *N*,*O*-acetal **5a**. Dihydrooxazine **2a** was produced as the main product together with small amounts of aldehyde **1a** (Table 4, entry 1). Furthermore, the stereochemical outcome of this reaction showed an amazing similarity with those that prevailed when starting from **3** and **4a** (Table 2, entry 9): the two β isomers were obtained again almost exclusively in an 84/16 *exo*/*endo* ratio. This unexpected result, very positive in terms of synthetic potential, poses some questions about the real nature of the reactive intermediate produced by the *N*,*O*-acetal in the presence of $SnCl_4$.[20] At −10 °C, under stoichiometric conditions, *N*,*O*-acetal **5a** gave rise to a nearly quantitative reaction with vinyl ether **3** (Table 4, entry 2). This new procedure also proved fruitful for new substrates. Thus, dihydrooxazines **2d**−**f** bearing respectively a *p*-nitrophenyl, benzyl, or *tert*-butyl group at C-4 were

(19) Katritzky's group recently reported the $ZnBr_2$-mediated α-amidoalkylation of ethyl vinyl ether with the use of **6**-type *N*-(1-benzotriazol-1-alkyl)amides: Katritzky, A. R.; Fan, W. Q.; Silina, A. *J. Org. Chem.* **1999**, *64*, 7622.

(20) As suggested with *N*-acylimine **4a** in our previous paper,[8] the *endo*/*exo* stereodivergency observed with *N*,*O*-acetal **5a**−**c** between $Yb(fod)_3$-catalyzed and $SnCl_4$-promoted reactions most probably indicates two different mechanisms. The first role of $SnCl_4$ would be to promote the formation of the electrophilic reactive heterodiene from the *N*,*O*-acetal **5a**−**c**. As the present time, we have little evidence about (i) the real nature of this intermediate (neutral *N*-acylimine or more likely *N*-acyliminium salt[21]) and (ii) the subsequent putative influence of the stannic salt ($SnCl_3OMe$ or $SnCl_4$) on the expected stepwise mechanism that would involve this intermediate.

TABLE 4. $SnCl_4$-Promoted Reaction of 3 and *N,O*-Acetals 5

	5	5:3[a] ratio	temp (°C)	time (min)	adduct 2	conv./5[b,c]	2:1 ratio	diastereomeric distribution of 2[c] endo-β	exo-β	endo-α	exo-α
1	**5a**	1:1	−78	15	**2a**	67	97:3	16	84	0	0
2	**5a**	1:1	−10	15	**2a**	100	99:1	18	80.5	0	1.5
3	**5b**	1:1	−10	15	**2b**	80	99:1	13	85.5	0	1.5
4	**5c**	1:1	−10	15	**2c**	82	99:1	14	83	0	3
5	**5d**	1:1	−10	15	**2d**	36	91:9	20	75	3	2
6	**5d**	1:2	−10	15 d	**2d**	63	82:18[d]	20	77	3	0
7	**5e**	1:2	−78	30		0					
8	**5e**	1:2	−10	30	**2e**	71	100:0	22	77	0	1
9	**5f**	1:1.5	−10	30	**2f**	69	100:0	24	76	0	0

[a] 1 equiv of $SnCl_4$, CH_2Cl_2, −78°C (Procedure B). [b] Into **2**/**1** mixture. [c] Estimated by ^1H NMR. [d] No improvement with 30 min reaction.

conveniently obtained, but not isolated,[22] from the corresponding *N,O*-acetals **5d**−**f** (Table 4), provided that the conditions fit with the reactivity of the substrate. Indeed, compared to the other aryl-substituted *N,O*-acetals **5a**−**c** under the same conditions, *N,O*-acetal **5d** (R = *p*-NO_2-C_6H_4) proved less reactive (−10 °C, 1:1 ratio, entry 5).[23] In this case, more convenient conditions were found with an excess of vinyl ether **3** (entry 6). **5e** and **5f** proved reactive only at −10 °C in an extended time (entry 7), and thus again an excess of vinyl ether **3** was necessary because of its sensitivity under these harsher conditions (entries 8 and 9). However, homogeneous high levels of *β*-stereoselectivity were observed in both aryl and alkyl series (*β*: α ratio ≥97:3).

For all heteroadducts **2b**−**f** obtained with $SnCl_4$, assignment of the *exo-β* topicity to the main isomer was based on a consistent ^1H NMR correlation with **2a**-*exo-β*[8] (Table 3). In each case, the *exo-β* proton H-6 is significantly high-field displaced (≤5.60 ppm) relative to the H-6 protons of other configurations. The *exo* character is evidenced by the weak value of the coupling constant (3.0 Hz or less) with the vicinal axial proton.

Since all the $SnCl_4$-promoted heterocycloadditions of **3** we tested (using either **4** or **5** as the co-reactant) led to a high overall *β*-control (≥97:3), acidic hydrolysis of the dihydrooxazines thus obtained was performed without any prior purification (Scheme 4, Table 5). Treatment of the crude heteroadducts **2a**−**f** with Amberlyst 15-H^+ in aqueous acetone at room temperature gave the desired *β*-benzamido aldehydes **1a**−**f** in 43−80% overall yields, with an efficient simultaneous recovery of the chiral auxiliary. ^1H NMR measurements with use of (+)-Eu(tfc)$_3$ as the chiral shift reagent gave homogeneous ee values ranging from 90 to 97%.[24]

Finally, assignment of the absolute configuration or each *β*-benzamido aldehyde **1** was unambiguously deduced from the *exo-β* character of its main cyclic precursor. To ascertain the configuration of the *β*-benzyl-*β*-benzamido aldehyde **1e**, additional proof was introduced by way of the X-ray crystallographic structure (see Supporting Information) of the corresponding *β*-benzyl-*β*-benzamidoacetal **9** deriving from (+)-1,4-bis-*O*-(4-chlorobenzyl)-D-threitol[25] (Scheme 5).

SCHEME 4

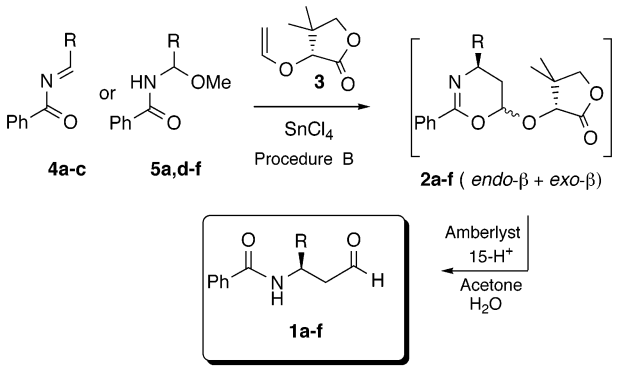


TABLE 5. Enantioselective Synthesis of *β*-Amidoaldehydes 1a−f (without purification of intermediate adducts 2a−f)

	R	starting material	preparation method for 2	aldehyde 1	overall yield[a] (%)	ee[c] (%)
1	Ph	**4a**	Table 2, entry 9	(*R*)-**1a**	63[b]	97
2	*p*-F-C_6H_4	**4b**	Table 2, entry 10	(*R*)-**1b**	80[b]	97
3	Ph	**5a**	Table 4, entry 2	(*R*)-**1a**	63	96
4	*p*-F-C_6H_4	**5b**	Table 4, entry 3	(*R*)-**1b**	62	96
5	*p*-CH_3O-C_6H_4	**5c**	Table 4, entry 4	(*R*)-**1c**	62	93
6	*p*-O_2N-C_6H_4	**5d**	Table 4, entry 6	(*R*)-**1d**	45	90
7	Bn	**5e**	Table 4, entry 8	(*S*)-**1e**	70	96
8	*t*-Bu	**5f**	Table 4, entry 9	(*R*)-**1f**	43	97

[a] Per **5** unless otherwise noted. [b] Per **3**. [c] Determined by ^1H NMR with 25−100 mol % of (+)-Eu(tfc)$_3$.

Conclusion

In summary, the present study demonstrates the synthetic usefulness of $SnCl_4$ as a Lewis acid promotor for the asymmetric synthesis of type-**2** dihydrooxazines. First, through the novel use of *N,O*-acetals **5**,[26] this method can be applied to a wide range of starting compounds, easily obtained from the corresponding aldehyde via Katritzky's procedure. In addition, much benefit can be gained from the unique stereochemical outcome that prevails when **3** is used under these Lewis acid conditions, to obtain the corresponding *β*-benzamido

(21) Meester, W. J. N.; Rutjes, F. P. J. T.; Hermkens, P. H. H.; Hiemstra, H. *Tetrahedron Lett.* **1999**, *40*, 1601.

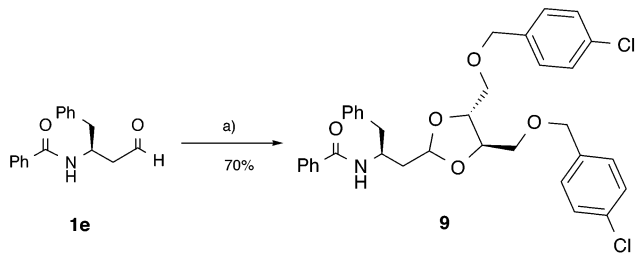
(22) Contrariwise to dihydroxazines **2a**−**c**, dihydroxazines **2d** (R = $C_6H_4NO_2$) and **2e** (R = Bn) showed a weak stability over SiO_2 and column chromatography gave low yields of purified product (17% for **2e**).

(23) This fact agrees with the total lack of reactivity we observed under the same conditions when using imino ester **5g** (R = CO_2Me) if we assume that the reaction is disfavored when *N,O*-acetal is substituted by an electron-withdrawing group.

(24) The (*R*)-(+)-*O*-vinyl-pantolactone **3** used in this study was found to have 98.5% ee (determined by chiral GC, see Experimental Section).

(25) Tamoto, K.; Sugimori, M.; Terashima, S. *Tetrahedron* **1984**, *40*, 4617.

SCHEME 5[a]



[a] Reagents and conditions: (a) (+)-1,4-bis-*O*-(4-chlorobenzyl)-D-threitol, *p*-TsOH·H_2O, C_6H_6, Δ.

aldehydes **1**, as yet not described to our knowledge, with a valuable enantioselectivity and by a very simple preparative pathway. Extension of this methodology to other types of *N*-substituted *N*,*O*-acetals is under investigation in our laboratory.

Experimental Section

General Methods. Reagents were purchased from commercial suppliers and used without purification. Commercial (*R*)-(−)-pantolactone was recrystallized from xylene before use (99.5% ee, determined by chiral GC). All solvents were dried following standard procedures. Chromatography was performed with 40−60 μm silica gel under medium pressure (1 bar). All melting points are uncorrected. Infrared spectra were performed on an FT spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on 200- and 400- MHz spectrometers in $CDCl_3$ with TMS as reference. LCMS (EI or CI) were performed on a particle beam mass spectrometer. High-resolution mass spectra were performed at the University of Rennes I.

General Procedure for the Preparation of Benzotriazole Derivatives 6a−f.[12] A solution of an aldehyde (0.05 mol), benzotriazole (5.96 g, 0.05 mol), and benzamide (6.06 g, 0.05 mol) in anhydrous toluene (or benzene for **6f**) (50 mL) was heated to reflux for 48−72 h with azeotropic distillation of water. After concentration in vacuo, the residue was treated with ethyl ether (100 mL) and the resulting solid was separated by filtration.

***N*-[Benzotriazol-1-yl-(4-fluorophenyl)methyl]benzamide (6b).** Colorless crystal (60,5%), mp 163−164 °C (MeOH); IR (Nujol) 3305, 1637, 1514, 1232, 1155, 1090, 845, 787, 742, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (1H, d, J = 8.4 Hz), 8.21 (1H, d, J = 7.9 Hz), 8.09 (1H, d, J = 8.4 Hz), 7.95 (3H, m), 7.58 (2H, m), 7.50 (4H, m), 7.43 (1H, t, J = 7.4 Hz), 7,27 (2H, t, J = 9.2 Hz). Anal. Calcd for $C_{20}H_{15}FN_4O$: C, 69.36; H, 4.37; F, 5.49; N, 16.18. Found: C, 69.37; H, 4.43; F, 5.43; N, 16.21.

General Procedure for the Preparation of *N*,*O*-Acetals 5a−f.[12b] The benzotriazole derivative **6** (10 mmol) was added to a solution of sodium methoxide (2 mmol) in methanol (10 mL), and the mixture was stirred at room temperature for one night. After dilution with water (20 mL), or adjustment to pH 7 with HCl for products **5c** and **5e**, the precipitate was separated by filtration. After solubilization of the product in dichloromethane or ethyl acetate, the organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by column chromatography (silica gel 20/1; toluene/AcOEt from 100:0 to 97:3).

***N*-[(4-Fluorophenyl)(methoxy)methyl]benzamide (5b).** Colorless crystal (98%), mp 106−108 °C (CH_2Cl_2); IR (Nujol) 3271, 1643, 1525, 1223, 1092, 982, 845, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, d, J = 6.9 Hz), 7.54 (1H, t, J = 7.4 Hz), 7.46 (4H, m), 7.06 (2H, t, J = 8.6 Hz), 6.57 (1H, d, J = 9.4 Hz), 6.36 (1H, d, J = 9.4 Hz), 3.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 162.3 (d, $^1J_{C-F}$ = 247.2 Hz), 134.8 (d, $^4J_{C-F}$ = 3.0 Hz), 133.2, 131.8, 128.3, 127.4 (d, $^3J_{C-F}$ = 8.4 Hz), 126.8, 115.1 (d, $^2J_{C-F}$ = 22.1 Hz), 81.0, 55.8. Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; F, 7.13; N, 5.44. Found: C, 69.51; H, 5.44; F, 7.16; N 5.41.

General Procedure for the Preparation of *N*-Acylimines 4a−d. By adaptation of the Breuer's method,[13] a solution of freshly chromatographed *N*,*O*-acetal **5** (1 mmol) in anhydrous toluene (15 mL) under nitrogen was stirred at 110 °C for 24−60 h. After concentration in vacuo, *N*-acylimine **4** was obtained without further purification.

***N*-[(*E*)-4-Fluorobenzylidene]benzamide (4b).** Yellowish crystal (100%, purity ≥90%), mp 82−83.5 °C (toluene); IR (Nujol) 1674, 1520, 1354, 1049, 852, 715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (1H, s), 8.16 (2H, dd, J = 8.4 and 1.5 Hz), 8.00 (2H, dd, J = 8.9 and 5.4 Hz), 7.60 (1H, t, J = 7.4 Hz), 7.49 (2H, t, J = 7.6 Hz), 7.21 (2H, dd, J = 8.9 and 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7, 165.8 (d, $^1J_{C-F}$ = 255.6 Hz), 163.2, 133.5, 133.2, 132.2 (d, $^3J_{C-F}$ = 9.2 Hz), 130.9 (d, $^4J_{C-F}$ = 3.0 Hz), 130.1, 128.5, 116.3 (d, $^2J_{C-F}$ = 22.1 Hz). HRMS calcd for $C_{14}H_{10}FNO$ $[M]^{\bullet+}$ 227.0746, found 227.0743.

(*R*)-(+)-*O*-Vinyl Pantolactone (3). By adaptation of the previous method,[10a] to a solution of the crude mixed acetal (4.94 g, 24.4 mmol, quantitatively obtained from (*R*)-(−)-pantolactone and ethyl vinyl ether[10a]) in anhydrous dichloromethane (30 mL) under argon was added dropwise at 0 °C triethylamine (1.2 equiv, 29.3 mmol, 4.1 mL) and then trimethylsilyl trifluoromethanesulfonate (1.1 equiv, 26.9 mmol, 4.9 mL). The reaction mixture was allowed to warm at room temperature and was stirred for 4 h. The cooled solution was treated at 0 °C with aqueous 1 M NaOH (7.4 mL) and then immediately diluted with pentane (300 mL). The resulting organic layer was washed (H_2O), dried ($MgSO_4$), and concentrated in vacuo at room temperature. Purification by column chromatography (silica gel 15/1; cyclohexane/AcOEt from 95:5 to 80:20) afforded the vinyl ether **3** as a colorless oil (2.70 g, 70%). The enantiopurity of (*R*)-(+)-*O*-vinyl pantolactone **3** was determined by chiral GC (column: Restek-β Dex Sm (25m × 0.25 mm), inlet 200 °C, detector 200 °C, oven 120 °C for 1 min then 2 °C/min until 180 °C): t_R = 8.4 min, (*R*)-(+)-**3**, t_R = 9.4 min, (*S*)-(−)-**3**, ee 98.5%.

Preparation of Dihydrooxazines 2 with Yb(fod)$_3$: Procedure A (with final purification). 6-[(2*R*)-3,3-Dimethyl-γ-butyrolactone-2-yl]oxy-4-(4-fluorophenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazines (2b-*endo*-β) (4*R*,6*S*) and (2b-*exo*-α) (4*S*,6*S*). A solution of *N*-acylimine **4b** (556 mg, 2.45 mmol), (*R*)-(+)-*O*-vinylpantolactone (**3**) (318 mg, 2.04 mmol), and Yb(fod)$_3$ (107 mg, 0.1 mmol) in dry cyclohexane (40 mL) was refluxed under nitrogen for 3 d. After concentration in vacuo, the crude product (*endo*-β/*exo*-α: 86/14) was chromatographed (silica gel 50/1, toluene/AcOEt 99:1 to 95:5) to yield in order of elution the pure dihydrooxazines **2b**-*exo*-α (56 mg, 9%) and **2b**-*endo*-β (381 mg, 64%).

2b-*endo*-β: amorphous white solid;^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 6.9 Hz), 7.48 (1H, t, J = 7.1 Hz), 7.41 (2H, t, J = 7.4 Hz), 7.39 (2H, dd, J = 8.4 and 5.4 Hz), 7.05 (2H, ∼t, J ∼ 8.9 Hz), 6.01 (1H, dd, J = 8.4 and 3.4 Hz), 4.79 (1H, dd, J = 10.3 and 4.4 Hz), 4.45 (1H, s), 4.05 and 4.01 (2H, 2d, J = 8.9 Hz), 2.62 (1H, ddd, J = 13.3, 4.4, and 3.4 Hz), 1.87 (1H, ddd, J = 13.3, 10.3, and 8.4 Hz), 1.27 (3H, s), 1.02 (3H, s); MS (EI) m/z (%) 393 $[M]^{\bullet+}$ (4.7), 270 $[M - C_6H_9O_2]^+$ (11), 123 (25.5), 105 $[C_7H_5O]^+$ (100), 77 $[C_6H_5]^+$ (44.4).

2b-*exo*-α: colorless crystal, mp 159−160 °C (toluene); IR (Nujol) 1784, 1655, 1508 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

(26) To our knowledge, **5**-type compounds have never been used for the preparation of **2**-type 6-alkoxy dihydrooxazines. By contrast, the successful use of *N*,*O*-acetals as iminium precursors in the asymmetric preparation of β-aminocarbonyl compounds is well documented, see: (a) Ferraris, D.; Young, B.; Dudding, T.; Leckta, T. *J. Am. Chem. Soc.* **1998**, *120*, 4849. (b) Kise, N.; Ueda, N. *Org. Lett.* **1999**, *1*, 1803. (c) Kise, N.; Ueda, N. *J. Org. Chem.* **1999**, *64*, 7511. (d) Pilli, R. A.; Alves, C. F.; Böckelmann, M. A.; Mascarenhas, Y. P.; Nevy, J. G.; Vencato, I. *Tetrahedron Lett.* **1999**, *40*, 2891. (e) Ferraris, D.; Young, B.; Dudding, T.; Leckta, T. *J. Am. Chem. Soc.* **2002**, *124*, 67 and references therein.

8.06 (2H, d, J = 6.9 Hz), 7.48 (1H, t, J = 7.4 Hz), 7.42 (4H, m), 7.07 (2H, ~t, J = 8.6 Hz), 5.94 (1H, br s), 4.90 (1H, dd, J = 12.3 and 4.9 Hz), 4.47 (1H, s), 4.08 and 4.01 (2H, 2d, J = 8.9 Hz), 2.50 (1H, ddd, J = 13.8, 4.9, and 2.0 Hz), 1.87 (1H, ddd, J = 13.8, 12.3, and 3.0 Hz), 1.13 (3H, s), 1.09 (3H, s); MS (EI) m/z (%) 383 $[M]^{\bullet+}$ − (1), 270 $[M - C_6H_9O_2]^+$ (13.4), 151 (8), 123 (19.3), 105 $[C_7H_5O]^+$ (100), 77 $[C_6H_5]^+$ (22.9). Anal. Calcd for $C_{22}H_{22}FNO_4$: C, 68.92; H, 5.78; F, 4.95; N 3.65. Found: C, 68.47; H, 5.77; F, 5.08; N, 3.68.

6-[(2*R*)-3,3-Dimethyl-γ-butyrolactone-2-yl]oxy-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazines (2c-*endo*-β) (4*R*,6*S*) and (2c-*exo*-α) (4*S*,6*S*). A solution of *N*,*O*-acetal **5c**[12b] (333 mg, 1.23 mmol, 1.5 equiv), (*R*)-(+)-*O*-vinyl pantolactone (**3**) (124 mg, 0.79 mmol), and Yb(fod)$_3$ (42 mg, 0.04 mmol) in dry toluene (16 mL) was refluxed under nitrogen for 8 d. After concentration in vacuo, the crude product was chromatographed (silica gel 30 /1, toluene/AcOEt 100:0 to 95:5) to yield in order of elution the pure dihydrooxazine **2c**-*exo*-α (85.5 mg, 27%) and a (84:16) mixture of the dihydrooxazines **2c**-*endo*-β and **2c**-*exo*-β (139.3 mg, 45%).

2c-*endo*-β: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, J = 6.9 Hz), 7.46 (1H, t, J = 7.1 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.34 (2H, d, J = 8.6 Hz), 6.90 (2H, d, J = 8.6 Hz), 5.98 (1H, dd, J = 8.9 and 3.4 Hz), 4.76 (1H, dd, J = 10.8 and 4.4 Hz), 4.45 (1H, s), 4.03 and 4.00 (2H, 2d, J = 8.9 Hz), 3.81 (3H, s), 2.61 (1H, ddd, J = 13.3, 4.4, and 3.4 Hz), 1.85 (1H, ddd, J = 13.3, 10.8, and 8.9 Hz), 1.27 (3H, s), 1.04 (3H, s); MS (EI) m/z (%) 395 $[M]^{\bullet+}$ (2.7), 282 $[M - C_6H_9O_2]^+$ (8.3), 239 (10.8), 105 $[C_7H_5O]^+$ (100), 77 $[C_6H_5]^+$ (25.6).

2c-*exo*-α: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, J = 7.4 Hz), 7.46 (1H, t, J = 7.4 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.35 (2H, d, J = 8.4 Hz), 6.92 (2H, d, J = 8.9 Hz), 5.87 (1H, ~t, J = 2.5 Hz), 4.85 (1H, dd, J = 12.3 and 4.9 Hz), 4.40 (1H, s), 4.04 and 3.97 (2H, 2d, J = 8.9 Hz), 3.82 (3H, s), 2.47 (1H, ddd, J = 13.8, 4.9, and 2.0 Hz), 1.88 (1H, ddd, J = 13.8, 12.3, and 3.0 Hz), 1.23 (3H, s), 1.19 (3H, s); SM (EI) m/z 395 $[M]^{\bullet+}$ (2.2), 282 $[M - C_6H_9O_2]^+$ (17.8), 105 $[C_7H_5O]^+$ (100), 77 $[C_6H_5]^+$ (24.8). HRMS calcd for $C_{23}H_{25}NO_5$ $[M]^{\bullet+}$ 395.17327, found 395.1718.

General Procedures for the Preparation of Dihydrooxazines 2 with $SnCl_4$ without Purification. Procedure B (with *N*-acylimine 4). To a cooled solution at −78 °C under nitrogen of (*R*)-(+)-*O*-vinyl pantolactone (**3**) (1 equiv) and *N*-acylimine **4** (1.5−2 equiv) in dichloromethane (15 mL/mmol) was rapidly added dropwise $SnCl_4$ (1 equiv, 1 M in dichloromethane). After being stirred (30 to 60 min), the mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL/mmol). After return to room temperature and extraction with dichloromethane (2 × 15 mL/mmol), the resulting organic layer was dried ($MgSO_4$) and concentrated in vacuo at room temperature. The crude dihydrooxazine **2** is used for hydrolysis without further purification (analytical samples were obtained by chromatography).

Procedure C (with *N*,*O*-acetal 5). To a cooled solution at −10 °C under nitrogen of *N*,*O*-acetal **5** (1 equiv) and (*R*)-(+)-*O*-vinyl pantolactone (**3**) (1.5−2 equiv) in dichloromethane (15−30 mL/mmol) was rapidly added $SnCl_4$ (1 equiv, 1 M in dichloromethane). After being stirred (15 to 30 min), the mixture was quenched with saturated aqueous $NaHCO_3$ solution (30 mL/mmol) and treated as in protocol B.

6-[(2*R*)-3,3-Dimethyl-γ-butyrolactone-2-yl]oxy-4-(4-fluorophenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (2b). (i) Obtained with procedure B as a foam (*exo*-β/*endo*-β: 91/9) from (*R*)-(+)-*O*-vinyl pantolactone **3** (1 eq, 210 mg, 1.34 mmol) and *N*-acylimine **4b** (1.5 equiv, 470 mg, 2.07 mmol) at −78 °C (30 min). Isomer (4*R*,6*R*) (**2b**-*exo*-β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, J = 6.9 Hz), 7.39 (5H, m), 7.05 (2H, t, J ~ 8.8 Hz), 5.53 (1H, t, J = 3.0 Hz), 4.91 (1H, dd, J = 11.3 and 4.9 Hz), 4.27 (1H, s), 4.02 and 3.93 (2H, 2d, J = 8.9 Hz), 2.35 (1H, ddd, J = 13.8, 4.9, and 3.0 Hz), 1.87 (1H, ddd, J = 13.8, 11.3, and 3.0 Hz), 1.28 (3H, s), 1.17 (3H, s). (ii) Obtained with procedure C as a foam (*exo*-β/*endo*-β/*exo*-α 85.5/13/1.5) from (*R*)-(+)-*O*-vinyl pantolactone **3** (1 equiv, 130 mg, 1 mmol) and *N*,*O*-acetal **4b** (1 equiv, 260 mg, 1 mmol) at −10 °C (15 min).

6-[(2*R*)-3,3-Dimethyl-γ-butyrolactone-2-yl]oxy-4-(4-methoxyphenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (2c). Obtained with procedure C as a foam (*exo*-β/*endo*-β/*exo*-α 83/14/3) from *N*,*O*-acetal **5c**[13] (1 equiv, 200 mg, 0.735 mmol) and (*R*)-(+)-*O*-vinyl pantolactone **3** (1 equiv) in dichloromethane (11 mL) at −10 °C (15 min). Isomer (4*R*,6*R*) (**2c**-*exo*-β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, J = 6.9 Hz), 7.51 (1H, t, J = 8.6 Hz), 7.40 (2H, t, J = 7.9 Hz), 7.32 (2H, d, J = 8.9 Hz), 6.91 (2H, d, J = 8.9 Hz), 5.52 (1H, dd, J = 3.4 and 3.0 Hz), 4.90 (1H, dd, J = 10.8 and 4.9 Hz), 4.25 (1H, s), 4.03 and 3.92 (2H, 2d, J = 8.9 Hz), 3.81 (3H, s), 2.33 (1H, ddd, J = 13.5, 4.9, and 3.4 Hz), 1.92 (1H, ddd, J = 13.5, 10.8, and 3.0 Hz), 1.27 (3H, s), 1.17 (3H, s).

6-[(2*R*)-3,3-Dimethyl-γ-butyrolactone-2-yl]oxy-4-(4-nitrophenyl)-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (2d) Obtained with procedure C as a foam (*exo*-β/*endo*-β/*endo*-α 77/20/3) from *N*,*O*-acetal **5d**[13] (1 equiv, 175 mg, 0.61 mmol) and (*R*)-(+)-*O*-vinyl pantolactone **3** (2 equiv) in dichloromethane (18 mL) at −10 °C (15 min). Isomer (4*R*,6*R*) (**2d**-*exo*-β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (2H, d, J = 8.6 Hz), 8.05 (2H, d, J = 7.4 Hz), 7.64 (2H, d, J = 8.6 Hz), 7.47 (1H, t, J = 7.4 Hz), 7.41 (2H, t, J = 7.4 Hz), 5.60 (1H, t, J = 2.5 Hz), 5.05 (1H, dd, J = 11.8 and 4.9 Hz), 4.32 (1H, s), 4.04 and 3.96 (2H, 2d, J = 8.9 Hz), 2.42 (1H, ddd, J = 13.8, 4.9, and 2.5 Hz), 1.85 (1H, ddd, J = 13.8, 11.8, and 2.5 Hz), 1.31 (3H, s), 1.19 (3H, s). HRMS calcd for $C_{23}H_{22}N_2O_6$ $[M]^{\bullet+}$ 410.14779, found 410.1471. Selected data for **2d**-*endo*-β: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (1H, dd, J = 7.9 and 3.4 Hz, H-6), 4.92 (1H, dd, J = 10.1 and 5.2 Hz), 4.44 (1H, s). Selected data for **2d**-*endo*-α: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, m).

4-Benzyl-6-[(2*R*)-3,3-dimethyl-γ-butyrolactone-2-yl]oxy-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (2e). Obtained with procedure C as a foam (*exo*-β/*endo*-β/*exo*-α 77/22/1) from *N*,*O*-acetal **5e**[12b] (1 equiv, 401 mg, 1.57 mmol) and (*R*)-(+)-*O*-vinyl pantolactone (**3**) (2 equiv) in dichloromethane (47 mL) at −10 °C (30 min). Isomer (4*S*,6*R*) (**2e**-*exo*-β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 6.4 Hz), 7.38 (3H, m), 7.35 to 7.20 (5H, m), 5.45 (1H, dd, J = 3.0 and 2.5 Hz), 4.14 (1H, s), 4.02 (1H, s), 3.97 and 3.87 (2H, 2d, J = 8.9 Hz), 3.19 (1H, dd, J = 13.3 and 5.9 Hz), 2.79 (1H, dd, J = 13.3 and 8.4 Hz), 1.96 (1H, ddd, J_{AB} = 13.8, 4.9, and 2.5 Hz), 1.62 (1H, ddd, J = 13.8, 11.0, and 3.0 Hz), 1.19 (3H, s), 1.07 (3H, s). HRMS calcd for $C_{16}H_{18}NO_4$ $[M - CH_2Ph]^+$ 288.1236, found 288.1246. Selected data for **2e**-*endo*-β: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, dd, J = 7.9 and 3.4 Hz), 4.40 (1H, s), 2.19 (1H, ddd, J = 13.8, 4.9, and 3.4 Hz), 1.65 (1H, ddd, J = 13.8, 8.9, and 7.9 Hz). Selected data for **2e**-*exo*-α: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, ~t, J = 2.5 Hz).

4-*tert*-Butyl-6-[(2*R*)-3,3-dimethyl-γ-butyrolactone-2-yl]-oxy-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (2f). Obtained with procedure C as a foam (*exo*-β/*endo*-β 76/24) from *N*,*O*-acetal **5f**[14] (1 equiv, 94.5 mg, 0.43 mmol) and (*R*)-(+)-*O*-vinyl pantolactone (**3**) (1.5 equiv) in dichloromethane (13 mL) at −10 °C (30 min). Isomer (4*R*,6*R*) (**2f**-*exo*-β): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, J = 6.4 Hz), 7.39 (3H, m), 5.56 (1H, dd, J = 3.0 and 2.0 Hz), 4.19 (1H, s), 4.00 to 3.90 (2H, m), 3.40 (1H, dd, J = 12.5 and 4.9 Hz), 2.04 (1H, ddd, J = 13.3, 4.9, and 2.0 Hz), 1.65 (1H, ~dt, J = 13.3 and 3.0 Hz), 1.22 (3H, s), 1.13 (3H, s), 1.01 (9H, s). Selected data for **2f**-*endo*-β: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (1H, dd, J = 9.8 and 3.0 Hz), 4.45 (1H, s), 3.25 (1H, dd, J = 12.3 and 4.4 Hz), 2.35 (1H, m).

General Procedure for the Preparation of β-Amidoaldehydes 1a−f: Hydrolysis[27] of Crude Dihydrooxazines 2a−f. A solution of dihydrooxazine **2** (1 mmol, see Table 5) in a mixture of acetone (8 mL) and water (2 mL) was stirred with Amberlyst-15 H^+ (320 mg) at room temperature under nitrogen for one night. After filtration and concentration in vacuo, the residue was dissolved in dichloromethane (20 mL), and the organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residual (*R*)-(−)-pantolactone was removed by sublimation

with use of a bulb-to-bulb distillation apparatus (100 °C, 10^{-1} Torr, 1 h) and the β-amidoaldehyde **1** thus obtained was chromatographed (silica gel 50/1; toluene/AcOEt 100:0 to 80:20).

(3*R*)-3-Benzamido-3-(4-fluorophenyl)propanal (*R*)-1b. (i) Obtained from the crude dihydrooxazine **2b** (Procedure B, 1.34 mmol) as an amorphous white solid (289 mg, 80%); IR (Nujol) 3330 (NH), 2729 (C*H*O), 1716 (HC=O), 1637 (HNC=O), 1525 (C=C Ar), 1228, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s), 7.77 (2H, d, J = 6.9 Hz), 7.52 (1H, t, J = 7.4 Hz), 7.44 (2H, t, J = 7.4 Hz), 7.36 (2H, dd, J = 8.4 Hz and J_{H-F} = 4.9 Hz), 7.05 (2H, ~t, J ~ 8.6 Hz), 6.93 (1H, d, J = 7.9 Hz), 5.69 (1H, m, J = 5.9 Hz), 3.24 (1H, ddd, J = 17.2, 5.9, and 2.0 Hz), 3.08 (1H, ddd, J = 17.2, 6.2, and 1.2 Hz); ^{13}C NMR + DEPT 135 (100 MHz, $CDCl_3$) δ 200.4 (C), 166.8 (C), 162.1 (C, d, $^1J_{C-F}$ = 246.4 Hz), 136.3 (C, d, $^4J_{C-F}$ = 3.1 Hz), 133.8 (C), 131,8 (C), 128.6 (CH), 128.2 (CH, d, $^3J_{C-F}$ = 8.4 Hz), 127.0 (CH), 115.7 (CH, d, $^2J_{C-F}$ = 21.4 Hz), 48.7 (CH_2), 48.4 (CH). HRMS calcd for $C_{16}H_{14}FNO_2$ $[M]^{\bullet+}$ 271.1008, found 271.1008. $[\alpha]^{20}_D$ −2.85 (*c* 0.43, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 30% mol, C*H*O) $\delta_{(R)}$ 9.97 (98.5%), $\delta_{(S)}$ 9.93 (1.5%); ee 97%. (ii) Obtained from the crude dihydrooxazine **2b** (Procedure C, 1 mmol) as an amorphous white solid (169 mg, 62%).^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 55% mol, C*H*O) $\delta_{(R)}$ 10.15 (98%), $\delta_{(S)}$ 10.06 (2%); ee 96%.

(3*S*)-3-Benzamido-4-(methoxyphenyl)propanal (*S*)-1c. Obtained from the pure dihydrooxazine **2c**-*exo*-α (Procedure A, 0.2 mmol) as a yellowish oil (23 mg, 40%); IR (Nujol) 3321 (NH), 2834 (C*H*O), 1722 (HC=O), 1637 (HNC=O), 1178, 1032, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, s), 7.75 (2H, d, J = 6.9 Hz), 7.49 (1H, t, J = 7.4 Hz), 7.40 (2H, t, J = 7.4 Hz), 7.29 (2H, d, J = 8.6 Hz), 6.95 (1H, br s), 6.87 (2H, d, J = 8.6 Hz), 5.65 (1H, ~q, J ~ 7 Hz), 3.78 (3H, s), 3.18 (1H, dd, J = 16.7 and 6.9 Hz), 3.01 (1H, dd, J = 16.7 and 5.9 Hz); ^{13}C NMR + DEPT 135 (100 MHz, $CDCl_3$) δ 200.4 (C), 166.4 (C), 158.9 (C), 133.7 (C), 132.1 (C), 131,4 (CH), 128.3 (CH), 127.5 (CH), 126.7 (CH), 114.0 (CH), 55,0 (CH_3), 48.6 (CH_2), 48.3 (CH). HRMS calcd for $C_{17}H_{17}NO_3$ $[M]^{\bullet+}$ 283.1208, found 283.1213. $[\alpha]^{20}_D$ −17 (*c* 0.965, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 25% mol, C*H*O) $\delta_{(S)}$ 9.92; ee >98%.

(3*R*)-3-Benzamido-3-(4-methoxyphenyl)propanal (*R*)-1c. Obtained from the crude dihydrooxazine **2c** (Procedure C, 0.735 mmol) as a yellowish oil (181 mg, 62%); ^1H NMR (400 MHz, $CDCl_3$) according to **(*S*)-1c**. $[\alpha]^{20}_D$ +15 (*c* 1.335, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 65% mol, C*H*O): $\delta_{(R)}$ 10.17 (96.5%), $\delta_{(S)}$ 10.10 (3.5%); ee 93%.

(3*R*)-3-Benzamido-3-(4-nitrophenyl)propanal (*R*)-1d. Obtained from the crude dihydrooxazine **2d** (Procedure C, 0.61 mmol) as a yellowish amorphous solid (82 mg, 45%); IR (Nujol) 3271 (NH), 2729 (C*H*O), 1720 (HC=O), 1637 (HNC=O), 1520 (NO_2), 1346 (NO_2) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, s), 8.21 (2H, d, J = 8.9 Hz), 7.79 (2H, d, J = 6.9 Hz), 7.56 (2H, d, J = 8.9 Hz), 7.53 (1H, m), 7.46 (1H, t, J = 7.6 Hz), 7.17 (1H, m), 5.76 (1H, ~q, J ~ 6.1 Hz), 3.32 (1H, ddd, J = 17.7, 5.7, and 1.2 Hz), 3.18 (1H, dd, J = 17.7 and 5.7 Hz). HRMS calcd for $C_{16}H_{14}N_2O_4$ $[M]^{\bullet+}$ 283.12084, found 283.1213. $[\alpha]^{20}_D$ −6 (*c* 1.13, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 30% mol, C*H*O): $\delta_{(R)}$ 10.06 (95%), $\delta_{(S)}$ 9.97 (5%); ee 90%.

(3*S*)-3-Benzamido-4-phenylbutanal (*S*)-1e.[28] Obtained from the crude dihydrooxazine **2e** (Procedure C, 1.57 mmol) as a colorless amorphous solid (318 mg, 74%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (1H, ~t, J ~ 1.0 Hz), 7.68 (2H, dt, J = 6.9 and 1.5 Hz), 7.50 (1H, tt, J = 7.4 and 1.5 Hz), 7.42 (2H, tt, J = 7.4 and 1.5 Hz), 7.33 (2H, tt, J = 7.4 and 1.5 Hz), 7.26 (1H, m), 7.22 (2H, dt, J = 6.9 and 1.5 Hz), 6.54 (1H, d, J = 8.5 Hz), 4.76 (1H, m), 3.10 (1H, dd, J = 13.3 and 6.9 Hz), 2.98 (1H, dd, J = 13.3 and 7.9 Hz), 2.79 (1H, ddd, J = 17.3, 5.4, and 1.0 Hz), 2.74 (1H, ddd, J = 17.7, 5.9, and 2.0 Hz); ^{13}C NMR + DEPT 135 (100 MHz, $CDCl_3$) δ 201.4 (C), 167.0 (C), 137.3 (C), 134.2 (C), 131,6 (C), 129.2 (CH), 128.8 (CH), 128.6 (CH), 127.0 (CH), 126.9 (CH), 46.9 (CH), 46.7 (CH_2), 40.1 (CH). HRMS calcd for $C_{17}H_{17}NO_2$ $[M]^{\bullet+}$ 267.12593, found 267.1259. $[\alpha]^{20}_D$ −12 (*c* 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 25% mol, C*H*O): $\delta_{(S)}$ 9.94 (98%), $\delta_{(R)}$ 9.88 (2%); ee 96%.

(3*R*)-3-Benzamido-4,4-dimethylbutanal (*R*)-1f. Obtained from the crude dihydrooxazine **2f** (Procedure C, 0.43 mmol) as a colorless amorphous solid (42 mg, 43%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, dd, J = 1.0 and 4.4 Hz), 7.73 (2H, d, J = 7.4 Hz), 7.51 (1H, t, J = 7.1 Hz), 7.44 (2H, t, J = 7.6 Hz), 6.20 (1H, d, J ~ 9.4 Hz), 4.61 (1H, ~dt, J ~ 10.3 and 3.9 Hz), 2.79 (1H, ddd, J = 14.5, 3.9, and 1.0 Hz), 2.46 (1H, ddd, J = 14.5, 10.3, and 4.4 Hz), 1.03 (9H, s). HRMS calcd for $C_{14}H_{19}NO_2$ $[M]^{\bullet+}$ 233.14158, found 233.1412, $[M - C_2H_3O]^+$ 190, $[M - t\text{-Bu}]^+$ 176. $[\alpha]^{20}_D$ +13 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, (+)-Eu(tfc)$_3$ 100% mol, C*H*O): $\delta_{(R)}$ 10.81 (98.5%), $\delta_{(S)}$ 10.72 (1.5%); ee 97%.

Determination of the Absolute Configuration of Aldehyde 1e: Preparation of the Amido Acetal 9. A mixture of **1e** (0.250 g, 0.95 mmol), (+)-1,4-bis-*O*-(4-chlorobenzyl)-D-threitol (mp 72−74 °C, $[\alpha]^{20}_D$ +6.0 ± 0.5 (*c* 3, $CHCl_3$); 0.372 g, 1 mmol), and *p*-TsOH·H_2O (9.5 mg, 0.05 mmol) in C_6H_6 (13 mL) was heated at reflux for 13h in a Dean−Stark apparatus. After being cooled, the mixture was diluted with CH_2Cl_2 (15 mL), then neutralized by adding powdered K_2CO_3 (0.8 g). Filtration and concentration in vacuo, followed by purification by column chromatography (silica gel 20/1; cyclohexane/AcOEt from 9:1 to 8:2), afforded acetal **9** as a thick oil (0.42 g, 70%) (R_f 0.32; cyclohexane/AcOEt 9:1), that slowly crystallized as colorless needles, mp 92−94 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$) 7.73 (2H, d, J = 7.7 Hz), 7.46 (1H, t, J = 7.5 Hz), 7.34 (2H, t, J = 7.7 Hz), 7.22 (13H, m), 6.75 (1H, d, J = 7.2 Hz), 5,22 (1H, d, J = 4.5 Hz), 4.52 (1H, m), 4.50 (2H, s), 4.46 (2H, 2d, J = 12.1 Hz), 4.05 and 3.96 (2H, 2dt, J = 6.7 and 4.9 Hz), 3.56 (4H, m), 3.14 (1H, dd, J = 13.4 and 4.8 Hz), 2.86 (1H, dd, J = 13.4 and 8.1 Hz), 1.98 (1H, dt, J = 14.7 and 4.4 Hz), 1.88 (1H, ddd, J = 14.7, 8.8, and 4.6 Hz); ^{13}C NMR + DEPT 135 (100 MHz, $CDCl_3$) δ 166.7 (C), 137.8 (C), 136.2 (C), 136.1 (C), 134.8 (C), 133.5 (C), 131.3 (C), 129.6 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 126,8 (CH), 126,5 (CH), 103.3 (CH), 77.9 (CH), 77.0 (CH), 72.7 (CH_2), 70.3 (CH_2), 48.1 (CH), 40.5 (CH_2), 36.2 (CH_2).

Acknowledgment. We thank Dr. Vincent Maisonneuve (Laboratoire des Fluorures UMR CNRS 6010, Université du Maine, F-72085 Le Mans Cedex 9, France) for performing the X-ray crystallography of compound **9**.

Supporting Information Available: Crystal structure data for **9** and copies of ^1H NMR spectra of all new compounds lacking elemental analysis, including ee determination by ^1H NMR with use of chiral shift reagent in the case of **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0203138

(27) Coppola, G. M. *Synthesis* **1984**, 1021.
(28) Greenlee, W. J.; Allibone, P. L.; Perlow, D. S.; Patchett, A. A.; Ulm, E. H.; Vassil, T. C. *J. Med. Chem.* **1985**, *28*, 434.