ORGANIC LETTERS

2000
Vol. 2, No. 5
585−588

First Asymmetric Synthesis of a 6-Alkoxy-5,6-dihydro-1,3-oxazine: A Promising Enantioselective Route to β-Amido Aldehydes

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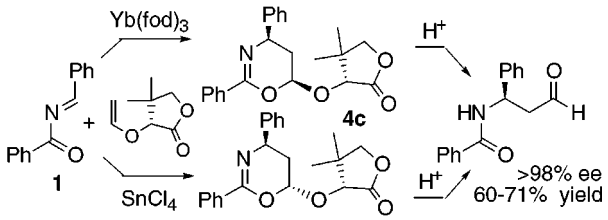
Received December 9, 1999

ABSTRACT

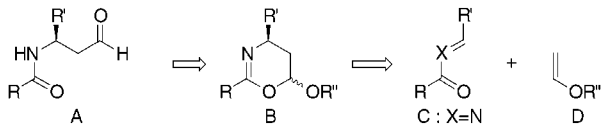


The 1,3-oxazine route to enantiopure β-amido aldehydes was investigated. Heterocycloaddition of the *N*-acyl imine 1 with (*R*)-*O*-vinylpantolactone provided the stable dihydroxazine 4c. High diastereocontrols were observed when using $Yb(fod)_3$-catalyzed or $SnCl_4$-mediated conditions, thus leading after quantitative hydrolysis to (*R*)-*N*-benzoyl-3-phenylpropanal with >98% ee.

Homochiral *N*-protected β-amino aldehydes (A) have a tremendous potential in β-peptide, modified peptide, and natural product chemistry.[1] Beyond the homologating pathways from α-amino acid derivatives, few general methods for their preparation are known: Michael addition of a chiral lithium amide to an α-unsaturated Weinreb amide,[2] addition of an ester enolate to a chiral sulfinimine.[3] Both methodologies require during the final step the careful reduction[4] of an α-methoxy amide or an ester.

To provide direct access to aldehydes A, we considered the potent precursors B which would be obtained via an asymmetric version of the (4 + 2) cycloaddition of an *N*-acyl imine (C) (or an iminium ion C′, X = NH^+) and a vinyl ether (D, Scheme 1). In fact, such cycloadditions have only been reported for a few stabilized *N*-acyl imines toward simple vinyl ethers under "thermal" conditions.[5] In most cases, heteroadducts are unstable and prone to either isomerization or uncontrolled ring opening in acidic or hydrolytic medium. More generally, reactions between C (or C′) and D remain almost unstudied under Lewis acid conditions and have not as yet provided asymmetric entry to optically active aldehydes A, whether by a cycloaddition−hydrolysis (even without isolation of B) or an α-amido-alkylation procedure.[6]

Scheme 1



This prompted us to examine how the nature of the vinyl ether substituent R″ could improve the stability of the desired

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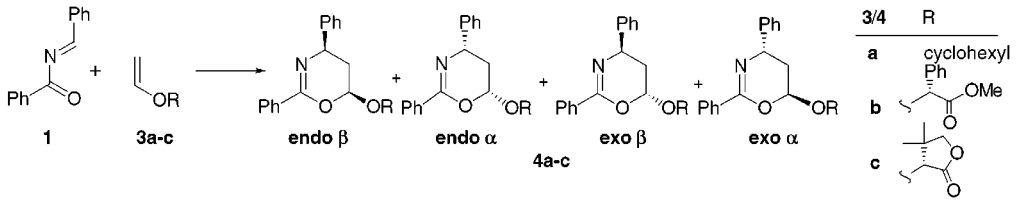
(1) Toujas, J.-L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, 713.
(2) Davies, S. G.; McCarthy, T. D. *Synlett* **1995**, 700.
(3) Davis, F. A.; Szewczyk, S. M. *Tetrahedron Lett.* **1998**, *39*, 5951.
(4) Davies, S. B.; McKervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229.
(5) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.
(6) Zaugg, H. E. *Synthesis* **1984**, 181. The $ZnBr_2$-mediated α-amido-alkylation of ethyl vinyl ether has been reported very recently: Katritzky, A. R.; Fan, W. Q.; Silina, A. *J. Org. Chem.* **1999**, *64*, 7622.

10.1021/ol991326j CCC: $19.00
Published on Web 02/09/2000

Table 1. Effect of Lewis Acid Activation on Reactivity, *endo*/*exo*, and Facial Control in the Reaction of **1** and **3a**−**c**



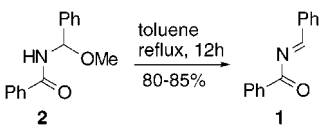
				crude product **4**[f]						
					% *endo*		% *exo*		isolated product **4**	
entry	**3**[a]	**4**	catalyst	% convn of **3** to **4**	*β*	α	*β*	α	combined yield,[h] %	% yield of **4**-*β* isomer
1	**3a**	**4a**	none[b]	70	40		60		nd[i]	
2	**3a**	**4a**	5% $Yb(fod)_3$[b]	95	65		35		70	
3	**3b**	**4b**	none[b]	42	28	18	27	27	nd	
4	**3b**	**4b**	5% $Yb(fod)_3$[b]	86	65	27	4	4	60	30[h]
5	**3c**	**4c**	none[b]	60	44	0	0	56	nd	
6	**3c**	**4c**	5% $Yb(fod)_3$[b]	>95	90	0	0	10	88	74,[h] 70[j]
7	**3c**	**4c**	5% $Eu(fod)_3$[b]	75	77	0	0	23	nd	52,[h] 50[j]
8	**3c**	**4c**	5% $Eu(fod)_3$[c]	95	76	0	0	24	70	
9	**3c**	**4c**	5% $Pr(fod)_3$[b]	60	57	0	0	43	nd	
10	**3c**	**4c**	10% $Yb(OTf)_3$[d]	20[g]			>95		<15	
11	**3c**	**4c**	10% $Cu(OTf)_2$[d]	0					0	
12	**3c**	**4c**	1 equiv of TMSOTf[e]	>95	12	5	78	5	nd	
13	**3c**	**4c**	1 equiv of $SnCl_4$[e]	>95	13	0	87	0	90	62[j]
14	**3c**	**4c**	5% $SnCl_4$[e]	5			>90		nd	
15	**3b**	**4b**	1 equiv of $SnCl_4$[e]	>95	85	6	9	0	85	nd

[a] Reaction conditions: **1** (1 equiv), **3a**−**c** (1 equiv). [b] Cyclohexane, reflux, 1 d for **3a**, 2 d for **3b**, 3 d for **3c**. [c] 10 d. [d] CH_2Cl_2, room temperature, 1 d. [e] CH_2Cl_2, −78 °C, 0.5 h. [f] Conversion and product ratios were determined by ^1H NMR. [g] 80% decomposition of **1**. [h] Obtained after chromatography on silica gel. [i] Not determined (uncomplete reaction). [j] Obtained after a single recrystallization in Et_2O of the crude product.

heteroadduct and would allow its formation under Lewis acid conditions with the aim, if R″ is chosen chiral, of causing an acceptable degree of facial discrimination during the cycloaddition process.[7]

For this systematic study, (*E*)-*N*-benzoylbenzaldimine (**1**) was used as the model 4Π cycloreactant. When prepared according to previous procedures,[8,9] this unstabilized *N*-acyl imine led to unreproducible results in the following cycloaddition study. Thus **1** was prepared on a large scale by thermal dehydromethoxylation of the readily available *N*,*O*-acetal **2**[10] (Scheme 2). The mild conditions used (toluene, 110 °C) proved to be efficient in avoiding formation of side products.[9]

Scheme 2



A preliminary study of the reaction between **1** and vinyl ethers deriving from various achiral alcohols showed interesting features. As expected, the stability of dihydroxazines thus obtained proved to be dependent on the nature of the acetal moiety: those derived from cyclohexyl vinyl ether (**3a**) and benzyl vinyl ether tolerated SiO_2 purification conditions quite well in contrast with those obtained from ethyl, isobutyl, and *tert*-butyl vinyl ethers. Nevertheless, in the thermal conditions used (cyclohexane, reflux, 1 d), such cycloadditions were sluggish (30−70% conversion) and nonselective (Table 1, entry 1).

These facts suggested further investigations under Lewis acid conditions. Starting from equal amounts of **3a** and **1**, complete conversion was achieved after 1 day when using 5 mol % of $Yb(fod)_3$. Product **4a** was isolated as a 3:2 *cis*/*trans* mixture in 50−70% yield (entry 2). These catalyzed conditions proved to be fruitfully applicable to chiral vinyl ethers **3b** and **3c**.[11] Applying them to methyl *O*-vinylmandelate (**3b**) led to a significant improvement of both the conversion (86 *vs* 42% after 2 days) and the overall *endo* selectivity (12/1 *vs* 1/1; entries 3 and 4).[12] Owing to the poor degree of facial selectivity, the major *cis* isomer was isolated

(7) For a successful related approach to the Taxol A-ring side chain starting from **1** and a chiral ketene acetal in thermal conditions, see: Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889.

(8) Kupfer, R.; Meier, S.; Wurthwein, E. U. *Synthesis* **1984**, 688.

(9) Previous conditions involved distillation at 200−210 °C in a vacuum: Breuer, S. W.; Bernath, T.; Ben-Ishai, D. *Tetrahedron* **1967**, *23*, 2869. Thermolysis of **2** at 180 °C gave decomposition of the imine and formation of benzylidene-bis-benzamide: Chiacchio, U.; Corsaro, A.; Compagnini, A.; Purello, G. *J. Chem. Soc., Chem. Commun.* **1983**, 671.

(10) Katritzky, A. R.; Fan, W. Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547.

(11) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 798.

(12) Relative configurations were established by NMR NOE studies.

in a low yield. With the *O*-vinylpantolactone (**3c**), the same catalytic and *endo* selective effects were observed (entries 5 and 6), but in this case the facial discrimination proved to be complete. Indeed, after 3 days in refluxing cyclohexane[13] in the presence of 5 mol % of $Yb(fod)_3$, **4c** was obtained as a mixture of two *cis*/*trans* isomers in a 9/1 ratio (entry 6). Chromatography afforded the crystalline major isomer of **4c** in a 74% yield. Nearly the same result was obtained after a simple crystallization of the crude product from Et_2O. The absolute configuration (4*R*,6*S*,2′*S*) of this adduct was established by X-ray crystallography (Figure 1)[14] and is consistent

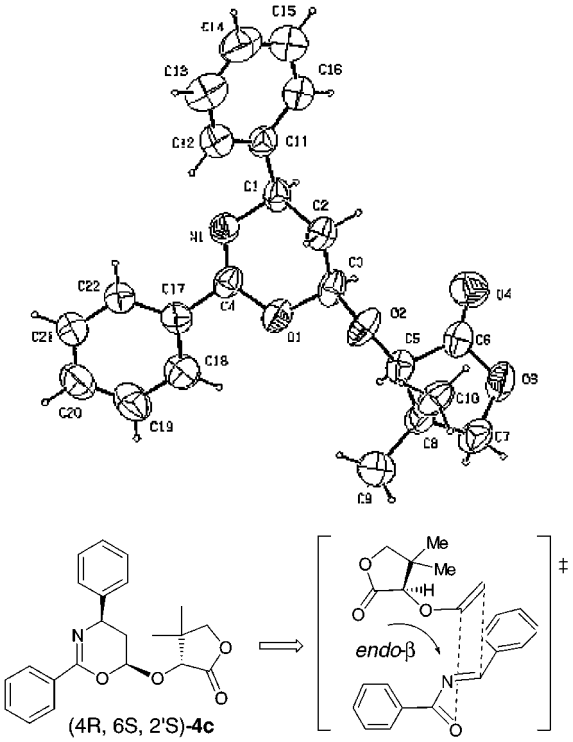


Figure 1. Crystal structure of the adduct **4c**-*endo*-β obtained in $Yb(fod)_3$-catalyzed conditions and related transition state.

with an *endo*-β approach of the dienophile in the expected concerted transition state. The *exo*-α stereostructure could be assigned to the minor isomer after identification of the **4c**-*exo*-β isomer obtained by isomerization of the **4c**-*endo*-β isomer.[15]

With $Eu(fod)_3$ or $Pr(fod)_3$ as the catalyst, facial discrimination remained the same but catalytic and *endo* selective effects decreased until disappearance from latest to earliest rare earth salts (entries 6−9). Yb(III) and Cu(II) triflate activation caused dominant or exclusive decomposition of the acyl imine **1** (entries 10 and 11). However, the selective formation in low yield of the *exo*-β isomer in the former case suggested a determining influence of the catalyst−Lewis acidity on the mechanistic features of the reaction (entry 10). This stereodivergence was fully demonstrated when the reaction between **1** and **3c** was performed in TMSOTf- or $SnCl_4$-mediated conditions at low temperature (entries 12−14). Interestingly, after conventional aqueous workup, dihydroxazine **4c** was obtained in a high combined yield and showed a large predominancy for the "*exo*-β" [16] isomer over the "*endo*-β". Moreover, in the second case, only both β isomers were obtained in a 6/1 *trans*/*cis* ratio (entry 13). After crystallization in Et_2O, the pure major adduct **4c**-"*exo*-β" was obtained in 62% yield. Finally, when the previous conditions were reapplied to **1** and **3b**, dihydroxazine **4b** was readily obtained with an unexpected "*endo*-β" selectivity (entry 15). These last facts strongly suggest that the $SnCl_4$-mediated formation of adducts **4** follows a stepwise mechanism: an acyclic stannic intermediate (zwitterionic or not,[17] Figure 2)

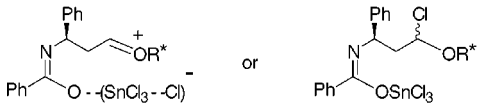


Figure 2.

would undergo a subsequent ring closure with a *cis*/*trans* preferency depending on the nature of the R* group (entries 13 and 15).

Comparing the effects of the various Lewis acids tested led us to the following conclusions: (a) oxophilic Lewis acids ($Yb(fod)_3$, $Eu(fod)_3$, $SnCl_4$, TMSOTf) are efficient catalytic or stoichiometric promoters of **4** formation, (b) a prevalent azaphilicity of $Cu(OTf)_2$ could explain its degradative effect upon the *N*-acyl imine **1**,[18] and (c) the concerted character of the heterocycloaddition seems strongly dependent on the nature of the Lewis acid employed. Such a control on the concerted−*endo* selective−*vs* stepwise pathway had been previously exemplified in dihydropyran syntheses.[19]

From these results, different asymmetric pathways were selectable in order to perform a straightforward synthesis of (*R*)- (or *S*)-*N*-benzoyl-3-phenylpropanal (**5**).

(13) Use of other solvents gave lower conversion and/or selectivity.

(14) $C_{22}H_{23}NO_4$, (M = 780.83); crystal dimensions 0.36 × 0.33 × 0.33 mm, trigonal, space group $P32$, a = 11.144 (2) Å, c = 27.418(7) Å, V = 2949(1) Å^3, Z = 6, D_x = 1.235 mg·m^{-3}, μ = 0.85 cm^{-1}, T = 293 K. Automatic CAD4 NONIUS diffractometer, Mo Kα radiation (λ = 0.7107 Å), scan method $\omega/2\theta$, 7156 data measured, 4953 independent reflections, R(int) = 0.008. After Lorenz and polarization corrections, the structure was solved with SIR-97 which revealed the non-hydrogen atoms. After anisotropic refinement, all the hydrogen atoms were found using Fourier difference. The whole structure was refined with SHELXL97 by the full least-squares techniques (use of F magnitude; x, y, z, β_{ij} for C, O, and N atoms, x, y, z, in riding mode for H atoms; 488 variables and 4953 observations; calc $w = 1/(\sigma^2(F_o^2) + (0.0983P)^2 + 0.55P)$ where $P = (F_o^2 + 2F_c^2)/3$ with the resulting R = 0.064, R_w = 0.14, and S_w = 1.053 (residual $\Delta\rho < 0.20\epsilon$ Å^{-3}).

(15) This isomerization was performed in refluxing toluene with 5% of $Yb(fod)_3$ overnight.

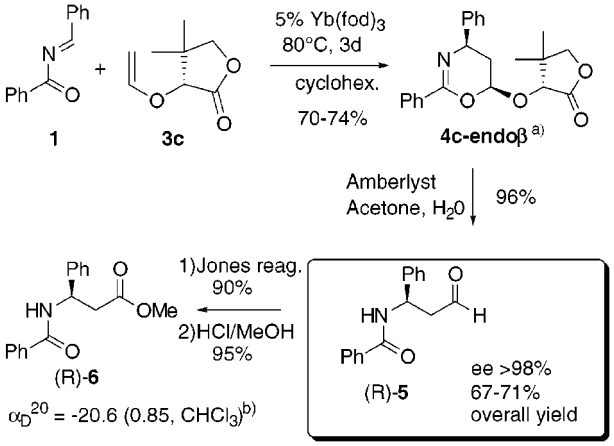
(16) For entries 10−15 (Table 1), "*exo*/*endo*" isomers were so named since a nonconcerted mechanism for their formation is expected (vide supra).

(17) The total lack of turnover (Table 1, entries 14 and 15) observed with $SnCl_4$ may suggest an irreversible evolution of the latter.

(18) It must be mentionned that the structure of **1** does not allow the formation of a stable Cu(II)-chelated complex, in contrast to that of α-imino esters. The enantioselective alkylation of *N*-tosyl-α-imino esters using a Cu(I) chiral complex was recently reported: Ferraris, D.; Young, B.; Dudding, T.; Leckta, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548.

First, the pure dihydroxazine **4c**-*endo*-β (obtained in Yb(fod)$_3$-catalyzed conditions) was treated with Amberlyst 15-H$^+$ in aqueous medium[20] and furnished the expected benzamidoaldehyde (*R*)-**5** in quantitative yield. The enantiomeric excess of this new compound[21] was shown to be >98% by ^{1}H NMR measurement using 25 mol % of Eu(tfc)$_3$ and was confirmed by the optical rotation of the known corresponding methyl ester **6** (Scheme 3).[22,23]

Scheme 3

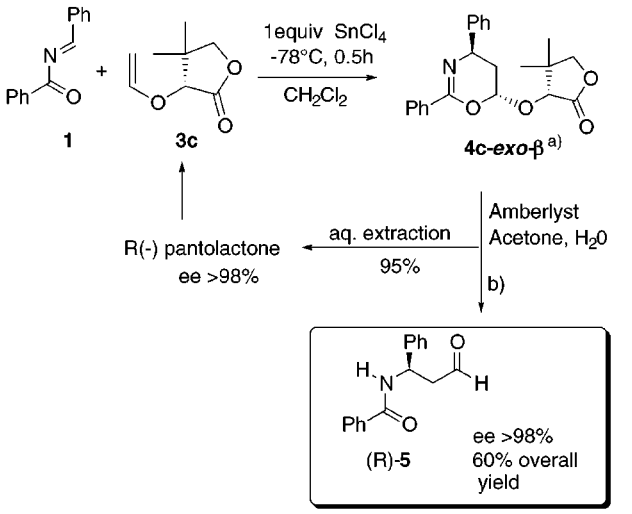


[a] Mp = 134 °C. [b] Lit.[23] $\alpha^{20}_D = -20.2$ (*c* 1.2, $CHCl_3$).

On the other hand, the pure dihydroxazine **4c**-*exo*-β, obtained using $SnCl_4$-mediated conditions, was treated with Amberlyst under the same conditions and gave (*R*)-**5** with >98% ee in 60% overall yield (Scheme 4).[24]

It must be emphasized that these two two-step syntheses did not require any chromatographic purification since the chiral auxiliary is efficiently removed by aqueous extraction.[25] After five operations, unchanged (*R*)-(−)-pantolactone was thus recovered in 95% yield from **3c**. As a consequence, isolation of **5** with a high chemical purity resulted from the simple evaporation of the residual organic layer.

Scheme 4



[a] Crystallized from the ethereal crude product solution, mp = 129 °C. [b] Simply obtained by evaporation of the final organic phase (AcOEt).

In summary, we disclosed efficient routes to (*R*)-*N*-benzoyl-3-phenylpropanal via a stable 6-alkoxy-5,6-dihydro-4*H*-1,3-oxazine, asymmetrically obtained from (*R*)-*O*-vinylpantolactone and (*E*)-*N*-benzoylbenzaldimine in appropriate Lewis acid conditions. Considering the interesting features of this two-step sequence (enantiodivergency,[26] easy and nearly quantitative recovery of the chiral auxiliary, obtention of high enantio- and chemical purities even without any chromatographic separation of diastereomers or byproducts), experiments are currently directed at exploring the scope of the key cycloaddition with various *N*-acyl imines.

Supporting Information Available: Experimental procedures, full characterization, and stereochemical assignment for **1**, **4b**, **4c**, and **5**; complete X-ray structural data of **4c**-*endo*-β (performed by Dr. L. Toupet). This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Heterocycloadditions between Danishefsky's dienes and aldehydes follow a normal electron demand, concerted mechanism when using $ZnCl_2$ or Eu(fod)$_3$, while aldol-like cyclization is presumed with BF_3•Et_2O: Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. In inverse electron demand results with $SnCl_4$ suggest a Mukayaima−Michael cyclization cascade reaction instead of the expected pericyclic pathway observed with Eu(fod)$_3$: Dujardin, G.; Martel, A.; Brown, E. *Tetrahedron Lett.* **1998**, *39*, 8647 and references therein.

(20) Coppola, G. M. *Synthesis* **1984**, 1021.

(21) Mp = 131 °C; $\alpha^{20}_D \sim 0$ (*c* 1, $CHCl_3$); stable for months under N_2.

(22) By the same method, the *endo*-β structure was assigned to the major isomer of **4b** (Table 1, entries 4 and 15).

(23) Hanessian, S.; Sanceau, J. Y. *Can. J. Chem.* **1996**, *74*, 621.

(24) Alternatively, (*R*)-**5** had been prepared via the crude corresponding dihydroxazine (94% ee) in 63% overall yield after SiO_2 chromatography.

(25) Resulting loss of aldehyde **5** is less than 2%.

(26) Both enantiomers of pantolactone are commercially available.