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Chelation Controlled 1,3-Dipolar Cycloaddition of 5,6-Dihydro-5-phenyl-1,4-oxazin-2-one *N*-Oxide with Allyl Alcohols: A Short-step Synthesis of Clavalanine Intermediate

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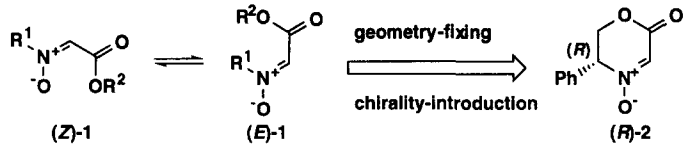
Abstract: (*R*)-5,6-Dihydro-5-phenyl-1,4-oxazin-2-one *N*-oxide {(*R*)-**2**} reacts with allyl alcohols **3a-c** in the presence of magnesium bromide from the less hindered face *via exo*-mode to afford corresponding cycloadducts **4a-c** with excellent stereoselection. Treatment of (*R*)-**2** with three equivalents of racemic secondary allyl alcohols **3d-g** under the same conditions causes partial kinetic resolution to give **4d-g** as main products among eight possible stereoisomers. Cycloadduct *ent*-**4a** from (*S*)-**2** and **3a** was converted directly to g-lactone **6**, which is known as the key synthetic intermediate of antibiotic clavalanine.

Keywords: 1,3-Dipolar Cycloaddition; chiral cyclic nitrone; magnesium bromide; clavalanine intermediate

1,3-Dipolar cycloaddition of α-alkoxycarbonylnitrones (**1**) is very attractive for construction of various nitrogen containing carbon frameworks because of the high reactivity of **1** [1-3]. Facile reductive cleavage of the nitrogen-oxygen bond in the products leads to γ-hydroxy-α-amino acid derivatives, which are useful for nitrogen containing compounds of biological interest [1,2]. However, the cycloaddition of **1** with olefins often gives mixtures of *trans*- and *cis*-isoxazolidines [3]. One of the main reasons for this drawback would be equilibration between (*E*)-**1** and (*Z*)-**1** [4]. To overcome this problem [5], we reported synthesis and cycloadditions of (*R*)- and (*S*)-5,6-dihydro-5-phenyl-1,4-oxazin-2-one *N*-oxides {(*R*)-**2** and (*S*)-**2**} which can be regarded as chiral and (*E*)-geometry fixed α-alkoxycarbonylnitrones [6]. In that work, cycloadditions



of the nitrone (*R*)-**2** with cyclic alkene or 1,1-disubstituted alkene proceeded stereoselectively in β-exo mode to give single stereoisomers, however, cycloadditions with terminal alkenes gave mixtures of diastereomers. We have now found that cycloaddition of (*R*)-**2** with allyl alcohols as terminal alkenes in the presence of magnesium bromide proceeds in highly stereoselective manner to afford corresponding cycloadducts. The cycloaddition could be applied to a facile synthesis of (3*R*,5*S*)-3-benzyloxycarbonylamino-5-hydroxy-γ-lactone, which is known as the key synthetic intermediate of antibiotic clavalanine.

On treatment of (*R*)-**2** with allyl alcohol **3a** in $ClCH_2CH_2Cl$ at room temperature for three days, smooth cycloaddition took place, however, giving a mixture of three diastereomers (Table 1, entry 1). To improve the stereoselectivity, representative Lewis acids [8] such as boron trifluoride etherate [7b-d] (entry 2), titanium

0040-4039/99/$ - see front matter
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tetraisopropoxide [9a] (entry 3), europium complex [5c] (entry 4), and magnesium bromide etherate [5a,8b] (entry 5) were examined. Although all the cycloadditions in the presence of the Lewis acids gave the same cycloadduct **4a** as the sole product, use of magnesium bromide was found to give the best result (entry 5).

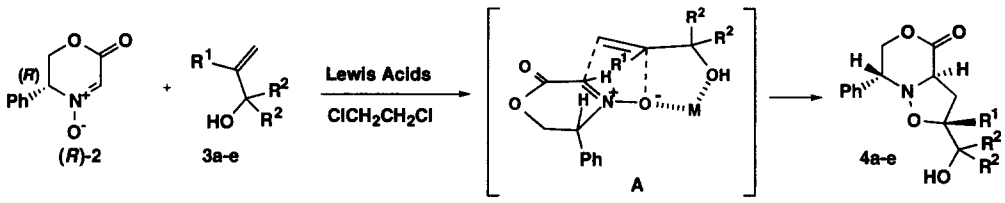
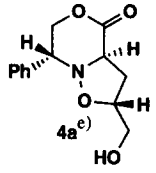
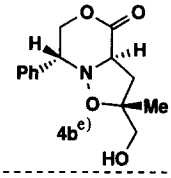
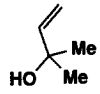
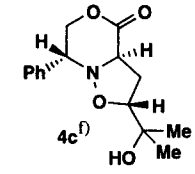
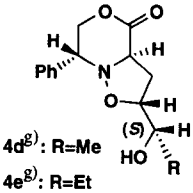
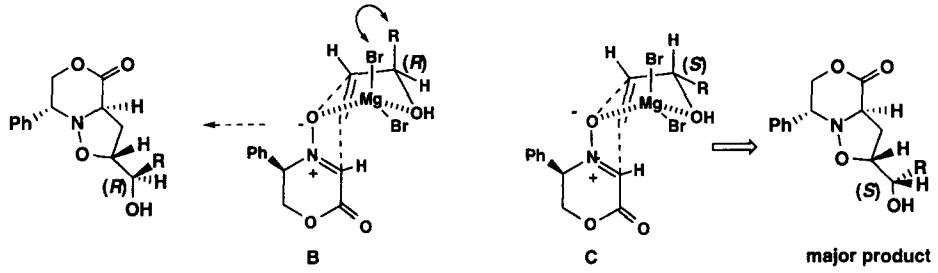


Table 1. Cycloaddition of (*R*)-**2** with allyl alcohols (**3a-g**) in the presence of Lewis acids.[a)]

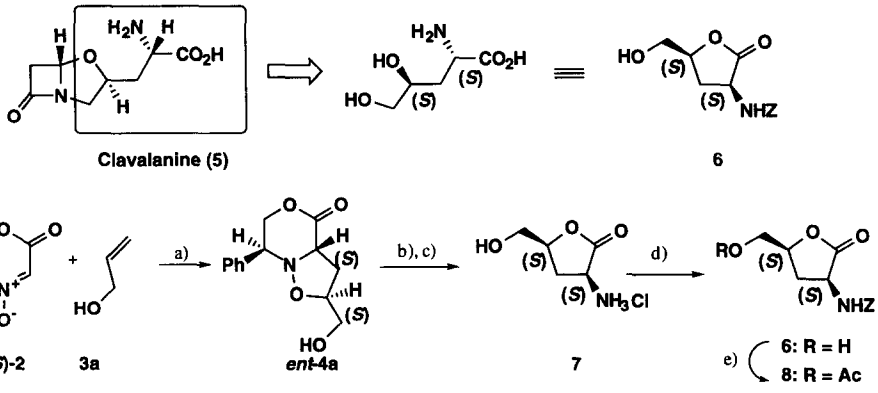
Entry	Allyl Alcohol	Conditions	Yield (%)	Ratio[b)]	Main Product[c)]
1	 **3a** 1.5 eq	rt, 72 h[d)]	99	75:19:5	 4a[e)]
2		1.5 equiv. BF_3•OEt_2, rt, 4 days	49	single isomer	
3		1.5 equiv. $Ti(O^iPr)_4$, rt, 5 days	60	single isomer	
4		1.5 equiv. $Eu(fod)_3$, rt, 3 days	71	single isomer	
5		1.5 equiv. $MgBr_2$•OEt_2, rt, 3 h	89	single isomer	
6	 **3b** 1.5 eq	1.5 equiv. $MgBr_2$•OEt_2 50 °C, 16 h	84	single isomer	 4b[e)]
7	 **3c** 1.5 eq	1.5 equiv. $MgBr_2$•OEt_2 50 °C, 24 h	30	single isomer	 4c[f)]
8	 **3d: R=Me** **3e: R=Et** **3f: R=cyclohexyl** **3g: R=Ph** 1.5 eq	3 equiv. **3d**, 3 equiv. $MgBr_2$•OEt_2 rt, 4 h	89	79:15:6	 **4d[g)]: R=Me** **4e[g)]: R=Et** **4f[h)]: R=cyclohexyl** **4g[h)]: R=Ph**
9		3 equiv. **3e**, 3 equiv. $MgBr_2$•OEt_2 rt, 4 h	93	82:18	
10		3 equiv. **3f**, 3 equiv. $MgBr_2$•OEt_2 rt, 4 h	92	83:17	
11		3 equiv. **3g**, 3 equiv. $MgBr_2$•OEt_2 50 °C, 3.5 h	59	80:20	

a) Unless otherwise noted, all reactions were carried out in 1,2-dichloroethane. b) The ratios were obtained by HPLC analyses and/or integrations of 270MHz NMR spectra. c) All the main products were fully characterized by IR, ^{1}H NMR, mass, high resolution mass spectra and/or elemental analyses and optical rotations. d) The reaction was made without Lewis acid in benzene. e) The stereochemistry was established by NOE experiments. f) The stereochemistry was assigned as the same sense of **4a,b**. g) The configuration of the secondary alcohol was assigned by the modified Mosher method [10]. h) The stereochemistry was assigned as the same sense of **4d,e**.

Thus, cycloaddition of (*R*)-**2** with 1.5 equivalent of **3a** in the presence of 1.5 equivalent of magnesium bromide etherate in $ClCH_2CH_2Cl$ at room temperature was completed in 3 hr to afford **4a** in 89% yield. This exclusive diastereoselectivity can be interpreted by considering the transition state model **A** (M=$MgBr_2$) bearing doubly coordinated magnesium bromide, through which the reaction proceeded intramolecularly. In the case employing methacryl alcohol **3b**, the reaction took place similarly to give **4b** in high yield, although it required mild heating conditions (entry 6). Furthermore, the yield of cycloaddition decreased when tertiary allyl alcohol **3c** was used under the same conditions of the reaction using **3b** probably due to the low Lewis basicity of the bulky allyl alcohol **3c** (entry 7). Next, enantiomer-recognition by the cycloaddition of (*R*)-**2** was examined. Thus, the nitrone was conducted with three equivalents of racemic secondary allyl alcohols **3d-g** in the presence of magnesium bromide etherate to give **4d-g** as the major stereoisomers in high yields (entry 8-11). It should be noted that one stereoisomer was formed in ca. 80% of the eight possible diastereomers of the products in each reaction. While the detailed mechanism remains unknown, this enantiomer-recognition may be explained by taking into account the transition state models **B** and **C**. Model **B** from (*R*)-**2** and (*R*)-allyl alcohol would have significant steric interaction between the bromine atom and the alkyl group of the allyl alcohol. Accordingly, the nitrone-magnesium complex would select (*S*)-allyl alcohol to give the major product *via* model **C**.



Based on these results, we applied the magnesium bromide mediated cycloaddition to the direct synthesis of (3*S*,5*S*)-3-benzyloxycarbonylamino-5-hydroxy-γ-lactone (**6**) [11], known as the key intermediate of an antibiotic clavalanine (**5**) [11a]. Thus, the cyclic nitrone (*S*)-**2**, the enantiomer of (*R*)-**2**, was treated with **3a** under the conditions indicated in Table 1, entry 5, providing *ent*-**4a** in 89% yield as the sole product. Hydrogenolysis of *ent*-**4a** in the presence of 20% palladium hydroxide caused simultaneously reductive



a) $MgBr_2$, $ClCH_2CH_2Cl$, 89% b) H_2, 20% $Pd(OH)_2$-C c) HCl-EtOH d) ZCl, THF, $NaHCO_3$, 89% from *ent*-**4a** e) Ac_2O, py

cleavage of *N-O* bond and *N*-benzyl position, and lactonization to afford hydrochloride **7** after treatment with ethanolic hydrogen chloride. Finally, the lactone hydrochloride **7** was protected with benzyl chloroformate to give the desired **6** in 89% yield from *ent*-**4a**. Since the reported optical rotational value of **6** is very small, lactone **6** was further converted to its acetate **8**, $[\alpha]_D^{20}$ +50.0 (*c* 1.02, $CHCl_3$) {*lit.* [11a] $[\alpha]_D^{25}$ +47.1 (*c* 0.99, $CHCl_3$)}. The present method for lactone **6** has advantages over the reported methods [11] in terms of availability of the enantiomers, high stereoselection, short reaction step, and high overall yield of the product.

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