Intermolecular 1,3-dipolar cycloaddition of chiral and geometry fixed α-alkoxycarbonylnitrone, 5,6-dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-oxide

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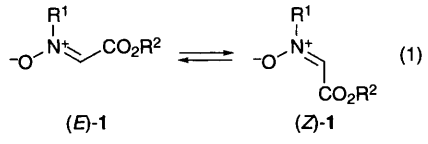
The 1,3-dipolar cycloaddition of (*R*)-5,6-dihydro-5-phenyl-2*H*-1,4-oxazin-2-one *N*-oxide[(5*R*)-2], a chiral and geometry fixed α-alkoxycarbonylnitrone, with alkenes 3–6 proceeded smoothly to afford cycloadducts 7–10 as main products *via* β-*exo* mode.

Intermolecular 1,3-cycloaddition of α-alkoxycarbonylnitrones **1** is very attractive for construction of various nitrogen-containing carbon frameworks because of the high reactivity of **1**.[1] 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.[2] However, stereoselectivities for the cycloaddition of chiral α-alkoxycarbonylnitrone have not been high enough due to equilibration between (*E*)-form [(*E*)-**1**] and (*Z*)-form [(*Z*)-**1**] (eqn. 1)[3] or due to lack of *endo-exo* selectivities.[2b,d,4] Moreover,

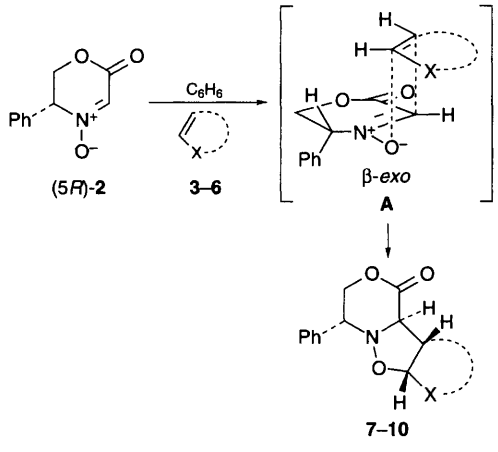


(1)

the prediction and elucidation of stereochemistry of the main cycloadduct has been often difficult. We have now designed and synthesized 5,6-dihydro-5-phenyl-2*H*1,4-oxazin-2-one*N*-oxide **2** as a chiral (*E*)-geometry fixed α-alkoxycarbonylnitrone and found that the 1,3-dipolar cycloaddition of the nitrone **2** with alkenes proceeded smoothly to afford cycloadducts *via* β-*exo* mode, predominantly.[5]

Cycloadditions of (5*R*)-**2**† with **3–6** proceeded under mild conditions to give the corresponding cycloadducts **7–10** as the main products as shown in Scheme 1 and Table 1. The stereochemistries of the main cycloadducts **7–10** were assigned by ^{1}H NMR spectra including NOE experiments. Although reactions with terminal alkenes (entries 1,2) and vinyl ether (entries 3,‡4) gave β-*exo* products accompanied by other stereoisomers, reactions with carbocyclic alkenes (entries 5,6) and 1,1-disubstituted alkenes (entries 7,8) gave exclusively single isomers. Among four possible transition states of the cycloaddition, the main products **7–10** would be produced *via* β-*exo* transition state **A** due to reduced steric hindrance.

To examine both ease of deprotection and optical purity of the products, chemical transformations were performed using the antipodal pair (4*R*)-**8b** and (4*S*)-**8b**, prepared from (5*S*)-**2**. As shown in Scheme 2, hydrogenolysis of (4*R*)-**8b** in the presence of 20% palladium hydroxide cause simultaneous reductive cleavage of both the N–O and *N*–CHPh bonds, and lactonization to afford hydrochloride (3*R*)-**11** after treatment with ethanolic hydrogen chloride. The hydrochloride (3*R*)-**11** was acylated with 3,5-dinitrobenzoyl chloride in the presence of triethylamine under the usual conditions, yielding 3,5-dinitrobenzamide (3*R*)-**12**. The antipode (3*S*)-**12** was produced in the same manner. The optical purities of (3*R*)-**12** and (3*S*)-**12** were determined as both >99% ee by chiral HPLC analyses. The analyses revealed that no racemization of **2** took place during both preparation of **2** and cycloaddition step.

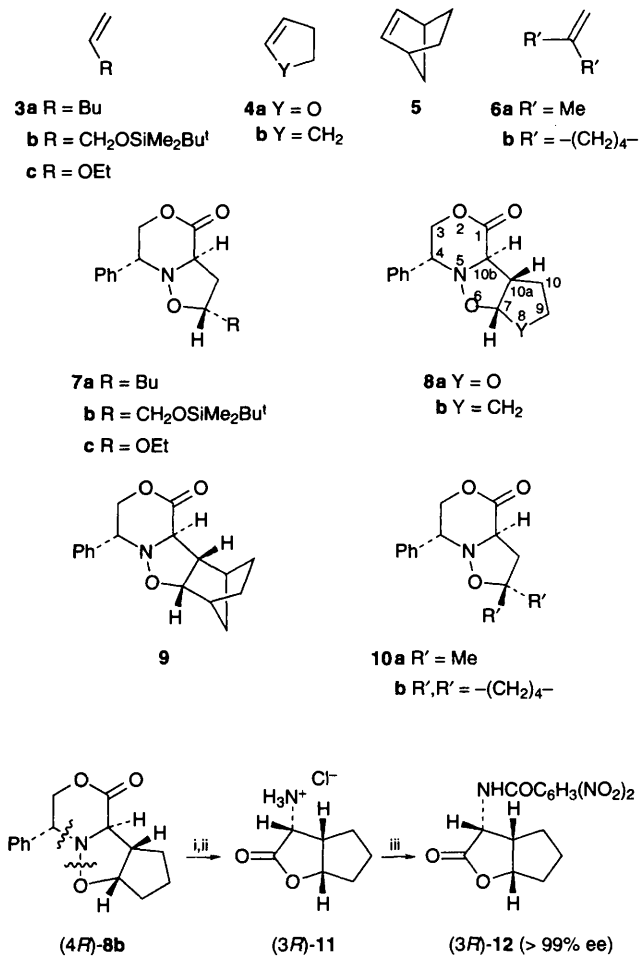


Scheme 1

Table 1 Intermolecular cycloaddition of (5*R*)-**2** with alkenes **3–6**

Entry	Alkene	Conditions	Ratio of stereoisomers	Yield (%)[a]	Main product[b]
1	**3a**	60 °C, 8 h	85:7:8[c]	86	**7a**
2	**3b**	60 °C, 12 h	75:5:11:9[c]	89	**7b**
3	**3c**	room temp. 16 h	83:8:9[c]	87	**7c**
4	**4a**	room temp. → 40 °C, 19 h	87:13[c]	83	**8a**
5	**4b**	room temp. 30 h	single isomer[d]	90	(4*R*)-**8b**
6	**5**	room temp. 9 h	single isomer[d]	92	**9**[e]
7	**6a**	room temp. → 50 °C, 32 h	single isomer[d]	87	**10a**
8	**6b**	60 °C, 25 h	single isomer[d]	95	**10b**

[a] Total yields of stereoisomers. [b] Unless otherwise noted, each of the stereostructures was elucidated by NOE difference spectrum. [c] The ratio was obtained from HPLC analysis. [d] No other isomer was detected by 270 MHz ^{1}H NMR. [e] The stereostructure was elucidated by the NOESY spectrum.



Scheme 2 *Reagents and conditions*: i, 20% $Pd(OH)_2$–C, H_2 (6 atm.), AcOH, room temp.; ii, HCl–EtOH, 90% from (4*R*)-**8b**; iii, 3,5-dinitrobenzoyl chloride, Et_3N, THF

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Footnotes

† The nitrone (5*R*)-**2**, mp 64–66 °C, $[\alpha]_D$ +80 ($CHCl_3$), was prepared from (*R*)-phenylglycinol by indirect oxidation, to the *N*-hydroxy derivative,[6] followed by condensation with methyl glyoxylate. The antipodal nitrone (5*S*)-**2** was prepared in the same manner.

‡ In contrast to this reaction, reaction of the related five-membered cyclic nitrone with **3c** requires high pressure conditions to give the corresponding cycloadduct.[5a] In general, 6-membered ring nitrones have higher reactivities than 5-membered ones.[7]

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