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ASYMMETRIC INDUCTION IN SILYL NITRONATE CYCLOADDITIONS TO OPPOLZER'S CHIRAL SULTAM DERIVATIVES

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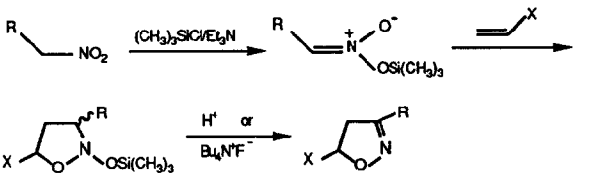
Abstract: Silyl nitronate cycloadditions to Oppolzer's chiral sultam derivatives, followed by the elimination of the silyl alcohols from the resulting *N*-silyloxyisoxazolidines, provide Δ^2-isoxazolines in good stereoselectivity (ca. 89/11). The favored transition state is suggested in the light of the X-ray crystal structure of a major cycloadduct.

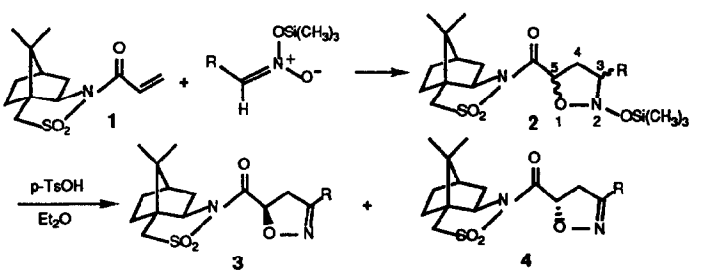
Silyl nitronates are versatile reagents for the preparation of Δ^2-isoxazolines, [2] which can be converted to β-hydroxy carbonyls, γ-amino alcohols, β,γ–unsaturated ketones, and various other functional groups.[3] With the exploratory work by Torssell and coworkers,[4] silyl nitronates can be considered as synthetic equivalents of nitrile oxides in their reaction with olefinic dipolarophiles. The resulting *N*-silyloxyisoxazolidines are readily transformed into Δ^2-isoxazolines upon treatment with acid or tetrabutylammonium fluoride (Eq. 1).[5]



Eq. 1

The asymmetric induction in nitrile oxide cycloadditions to various dipolarophiles has been studied,[6] but little has been done on the asymmetric induction in silyl nitronate cycloadditions. We now report on the asymmetric silyl nitronate cycloadditions with the Oppolzer's chiral sultam derivatives.[7]

The cycloadditions of *N*-acryloyl (2*R*)-bornane-10,2-sultam (**1**) with in situ-generated silyl nitronates formed by the *O*-silylation of the corresponding primary nitro compounds, followed by *p*-toluenesulfonic acid catalyzed elimination of trimethylsilyl alcohols from *N*-trimethylsilyloxyisoxazolidine cycloadducts **2**, produced the diastereomeric mixtures (**3** and **4**) of Δ^2-isoxazolines (Eq. 2).



Eq. 2

Table 1 summarizes some of experimental results and the series of examples presented demonstrates the generality of this procedure. A brief survey of solvent effects indicated that better diastreoselectivities were observed in nonpolar solvents such as toluene or hexane. This result parallels the solvent effect in asymmetric nitrile oxide cycloadditions.[6b] In these solvents, useful levels of asymmetric induction (typically 89/11) were consistently observed, regardless of the substituent on the silyl nitronate.

Table 1. Silyl Nitronate Cycloadditions with *N*-Acryloyl Sultams 1 or ent-1

				Δ^2-Isoxazoline Products	
Entry	Sultam	Silyl Nitronate[a]	Solvent	Major 3/Minor 4 [b]	Yield[c,d]
1	1	R=H	Toluene	89/11	96%(57%)
2	1	R=CH_3	Toluene	89/11	95%(75%)[f]
3	1	R=CH_3	Hexane	88/12	
4	1	R=CH_3	CH_2Cl_2	82/18	
5	1	R=C_2H_5	Toluene	89/11	96%(81%)
6	1	R=C_4H_9	Toluene	89/11	93%(61%)
7	1	R=C_5H_{11}	Toluene	90/10	94%(69%)
8	1	R=$CO_2C_2H_5$	Toluene	89/11	85%(60%)
9	1	R=C_6H_5	Tol/CH_2Cl_2	85/15	81%(50%)[g]
10	ent-1[e]	R=CH_3	Toluene	88/12	96%(65%)

a) Generated by the Torssell method[8] by *O*-silylation of the primary nitro compound using trimethyl silyl chloride and triethylamine at room temperature. b) Ratios determined by ^{1}H NMR. c) Isolated yield based on the sultam after chromatographic purification. d) The yield in parentheses represents the isolated yield of the major cycloadduct 3. e) The enantiomeric sultam (ent-1) was used and enantiomeric products (ent-2, ent-3, and ent-4) were obtained. f) Isolated yield of the isoxazolidine product 2. g) NMR yield.

It was possible to isolate the major diastereomer 3 by chromatography in good yield and to excise the chiral auxiliary by L-Selectride® reduction. The absolute stereochemistry of the newly generated C5 stereogenic center of the major product 3 was rigorously determined as *R* by chemical correlation (R=CH_3, C_6H_5), by comparison of the optical rotations of the resulting Δ^2-isoxazoline alcohols by L-Selectride® reduction with those of the authentic compounds prepared by nitrile oxide cycloaddition method (R=CH_3, C_2H_5),[6b] and by X-ray crystallography (ent-2, R=CH_3, see Figure1). The stereochemistry of the other products was assigned by analogy. It is noteworthy that only two diastereomers out of four possible isomers of *N*-trimethylsilyloxyisoxazolidine 2 were formed in the cycloadditions of 1 or ent-1 with methyl substituted silyl nitronate. The major cycloadduct in each case was separated by chromatography and attempts were made to grow a single crystal for X-ray crystallography. Finally, the X-ray crystal structure of the major product in the cycloaddition of ent-1 was obtained (Figure 1).[9]

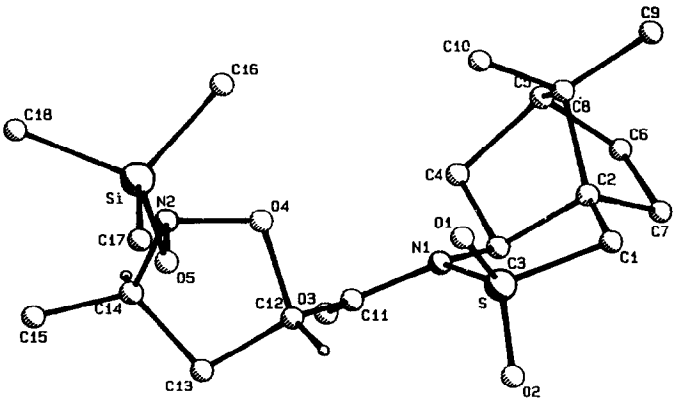
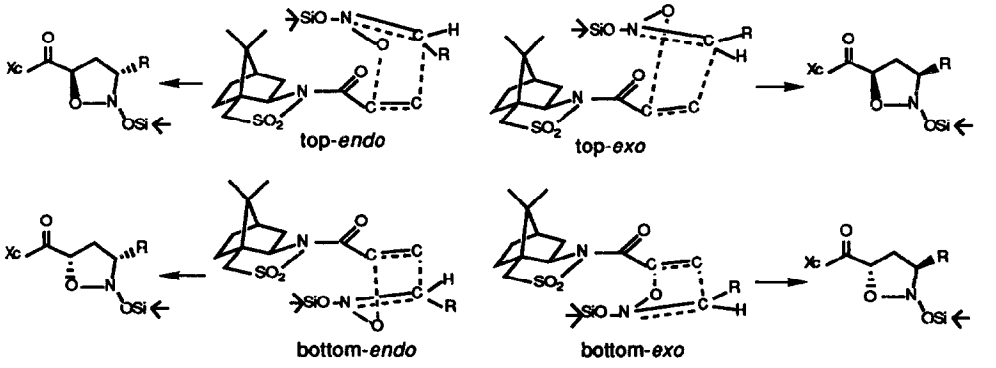


Figure 1. X-ray crystal structure of the major isomer of ent-**2** (R=CH_3).

The stereochemical outcomes in the cycloadditions of **1** or ent-**1** with silyl nitronates can be rationalized by inspection of the transition state models in Scheme 1. The ground state conformer in solid state of ent-**1** has already been determined as the C=O/C=C *s-cis* conformer by X-ray crystallography.[6b,10] Like nitrone cycloadditions,[11] the stereochemistry of silyl nitronate cycloaddition is controlled by the facial selectivity (top vs. bottom face attack) and the *endo-exo* selectivity. The C5 stereogenic center is governed by the facial selectivity and the C3 stereogenic center is related to the *endo-exo* selectivity in silyl nitronate cycloadditions. Among the four possible transition states (Scheme 1), the major product may result from the top-*endo* transition state. This transition state is stabilized by the favorable secondary orbital interactions between the molecular orbitals of silyl nitronate nitrogen and carbonyl carbon of *N*-acryloyl sultam, and it alleviates a steric or electronic encumbrance between incoming silyl nitronate and one of sulfonamide oxygens in the chiral dipolarophile.[6b] Additional, circumstantial evidence for this assignment comes from the X-ray crystal structure of the major cycloadduct in the cycloaddition of ent-**1** with methyl substituted silyl nitronate (Figure 1). This structure clearly shows that the major cycloadduct closely resembles the proposed top-*endo* transition state.

Scheme 1 (Xc=(2*R*)-bornane-10,2-sultam auxiliary).



Asymmetric silyl nitronate cycloaddition, followed by the elimination of silyl alcohol, provides a useful route to optically active Δ^2-isoxazolines. The application of this method to natural product synthesis is under active investigation.

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References and Notes

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9. Crystallographic details: $C_{18}H_{32}N_2O_5Si_1S_1$, M_r = 416.62, orthorhombic, $P2_12_12_1$, a=7.627(1), b=11.436(2), c=25.783(2) Å, V=2249.0(5) Å^3, Z=4, D_X=1.230, monochromated Mo $K\alpha$ radiation ($\lambda(K\alpha_1$=0.7093 Å), μ=2.2 cm^{-1}, $F(000)$=896, T=295K, Enraf-Nonius CAD4 diffractometer; 1625 unique reflections measured; 912 reflections observed ($I > 3\sigma(I)$); solved by Patterson and difference Fourier methods; full-matrix least-squares refinement; non-hydrogen atoms anisotropic; hydrogen atoms included at calculated positions; Final agreement indices: $R(F)$=0.049, $R_W(F)$=0.050. Thermal parameters and bond lengths and angles are available from the Cambridge Crystallographic Data Centre.
10. For the related X-ray crystal structure, see Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397.
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