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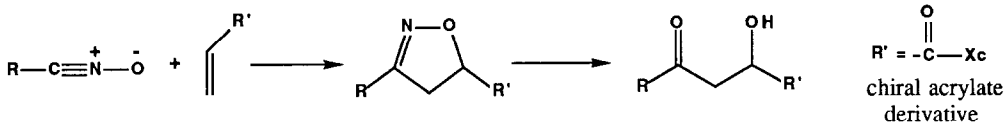
The Preparation of Optically Active Δ^2-Isoxazolines. A Model for Asymmetric Induction in the Non Lewis Acid Catalyzed Reactions of Oppolzer's Chiral Sultam

Dennis P. Curran,*[1a] Byeang Hyean Kim, James Daugherty,[1b] and Timothy A. Heffner
Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA

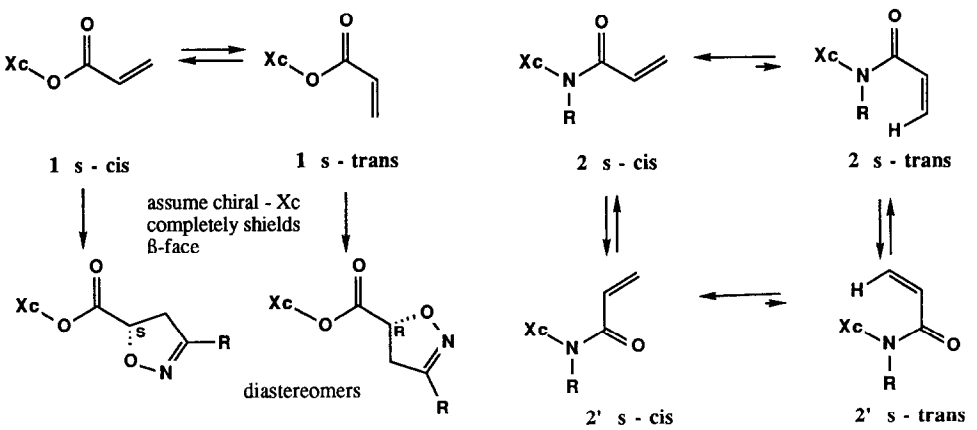
Abstract: *Good diastereoselectivity (ca. 90/10) is reported in the cycloaddition reactions of Oppolzer's chiral sultam with nitrile oxides. A model is proposed which may apply to other non Lewis acid promoted reactions of this sultam.*

Δ^2-Isoxazolines are central intermediates in the cycloadditive strategy for the preparation of β-hydroxy carbonyls (Eq. 1).[2] The ability to prepare optically active β-hydroxy carbonyls by this route hinges on the development of methods for asymmetric induction in nitrile oxide cycloadditions. One of the most straightforward approaches involves the cycloaddition reaction of a nitrile oxide with a chiral acrylate dipolarophile.[3]



Eq. 1

The use of chiral acrylate derivatives as dienophiles in Diels-Alder cycloadditions is a productive route to optically active cyclohexenes.[4,5] However, the observation of high asymmetric induction in Diels-Alder reactions may not directly translate to ostensibly similar nitrile oxide cycloadditions. Indeed, a variety of chiral acrylate esters which provided excellent diastereoselectivity in Lewis acid catalyzed Diels-Alder reactions showed low to modest selectivity in nitrile oxide cycloadditions.[4] The reasons for this are summarized in Eq. 2. In cycloaddition reactions with chiral acrylate ester derivatives, both the direction of attack of a reagent and the rotameric preference of the acrylate must be controlled to observe high diastereoselectivity. The direction of attack is controlled by the auxiliary (X_C). In Diels-Alder reactions, the low rotameric preference of esters (**1** s-cis ⇌ **1** s-trans) is



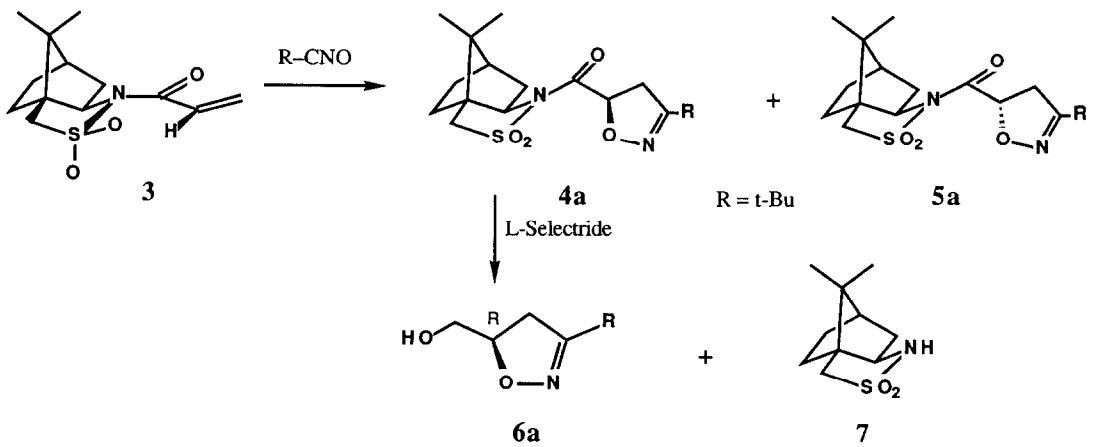
Eq. 2

often controlled by addition of Lewis acids.[3,6] The use of strong Lewis acids to promote nitrile oxide cycloadditions has not yet succeeded, presumably because of the Lewis basicity of the nitrile oxide. Thus, even though the direction of attack of a nitrile oxide may be well controlled, a low diastereomer ratio can result due to competing attack on s-cis and s-trans rotamers. The development of highly diastereoselective nitrile oxide cycloadditions is a challenging goal.

The use of chiral 3°-acrylamides provides a potential solution to the rotamer problem encountered with esters. Planar s-trans rotamers should be strongly disfavored (see Eq. 2). However, acrylamides such as **2** may now have two low energy rotamers about the C–N bond, **2** and **2'**, which would again produce diastereomeric products if attacked by a reagent from the same direction. Considering the requirements for nitrile oxide cycloadditions, we were attracted to the Oppolzer chiral sultam derivatives, such as **3**, which are among the most practical and fascinating chiral auxiliaries presently available.[5]

The cycloaddition of **3** with in situ-generated 2,2-dimethylpropane nitrile oxide in hexane produced a 95/5 mixture of diastereomers **4a** and **5a** (Eq. 3). After flash chromatography, the major diastereomer **4a** was isolated in pure form in 73% yield. The stereochemical outcome of the cycloaddition was ascertained by chemical correlation. Reduction of **4a** with L-Selectride™ (THF, 25 °C) provided an easily separable mixture of optically pure isoxazoline **6a** and recovered sultam **7** (which was reconverted to **3**). The absolute configuration of **6a** was assigned as R by comparison with an authentic sample of R-**6a** prepared in our laboratories by another (less selective) route.[3]

Eq. 3



The series of examples presented in Table 1 demonstrates the generality of this procedure. A brief survey of solvent effects indicated that the best diastereoselectivities were obtained in non-polar solvents such as hexane, benzene, or toluene. In these solvents, diastereomer ratios near 90/10 were consistently observed regardless of the substituent on the nitrile oxide. In all of the cases in Table 1, it was possible to isolate the major diastereomer by chromatography or crystallization and to excise (and recover) the chiral auxiliary by L-Selectride reduction. The gross structures of alcohols **6** were confirmed by the preparation of racemic samples by standard cycloadditions with allyl alcohol. In addition to **6a**, the stereochemistry of two other products was rigorously determined by either chemical correlation (**6b**),[3] or x-ray crystallography (**4c**, see below). The stereochemistry of the

Table 1 Nitrile Oxide Cycloadditions with *N*-Acryloyl Sultams 3 or ent-3

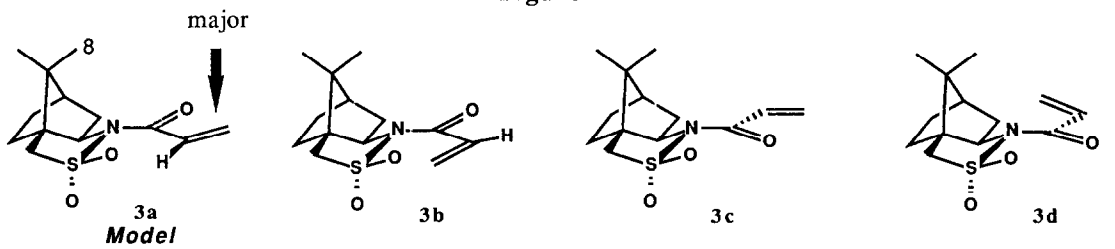
Entry	Sultam	Nitrile Oxide[a]	Solvent	4/5 Ratio	Yield of 4[c]	Yield of 6[c]	$[\alpha]_D$[e]
a	**3**	R=C(CH$_3$)$_3$	hexane	95/5	73%	61%	−127°
	3	R=C(CH$_3$)$_3$	toluene	90/10			
	3	R=C(CH$_3$)$_3$	CH_2Cl_2	81/19			
	3	R=C(CH$_3$)$_3$	THF	85/15			
	3	R=C(CH$_3$)$_3$	MeOH	85/15			
	ent-3[d]	R=C(CH$_3$)$_3$	hexane	95/5	73%[d]	52%[d]	+124°
b	**3**	R=Ph	hexane	95/5	59%	61%	−161°
c	**3**	R=CH$_3$	hexane	90/10	72%	64%	−172°
d	**3**	R=CH$_2$CH$_3$	hexane	90/10	74%	62%	−154°[f]
e	**ent-3**[d]	R=CH$_2$CH$_2$  [b]	benzene	88/12	85%[d]	85%[d]	+114°[g]

Footnotes to the Table: a) Generated by the Huisgen method by 1,3-dehydrohalogenation of the oxime chloride unless indicated. b) Generated by the Mukaiyama method by dehydration of the nitro compound. c) Isolated yield after chromatographic purification. d) The enantiomeric sultam (ent -**3**) was used and enantiomeric products (ent-**4** and ent-**6**) were produced. e) optical rotations were measured in chloroform at 25 °C, c = 1.0. f) c = 0.7. g) c = 4.0.

other products was assigned by analogy. Thus, the method provides a direct route to simple, optically pure isoxazolines. These are valuable precursors for synthesis since they can be selectively functionalized by a variety of means prior to cleavage of the heterocyclic ring.[2]

These results provide insight into the likely transition states in the reaction of **3** with nitrile oxides, in particular, and with other reagents in general. Of the four planar conformations of **3**, three (**3b-d**) are unlikely to be energetically significant in the ground state or the transition state due to either unfavorable dipole-dipole interactions (C=O and S–O aligned, **3c,d**) or steric destabilization (s-trans, **3b,d**). Only conformer **3a** lacks these interactions and its importance in the ground state has been recognized by Oppolzer.[6] An x-ray crystal structure (Figure 2) shows that **3a** is indeed the favored conformer in the solid state,[7] and crystal structures of related sultams show the same conformation.[8]

Figure 1



If reagents attack conformer **3a**, then a transition state model for the the facial selectivity of the cycloaddition is defined. The major product results from "top-side" attack of the incoming nitrile oxide. Additional, circumstantial evidence for this model comes from the x-ray crystal structure of cycloadduct **4c** shown in Figure 3.[7] This structure bears a remarkable resemblance to the proposed model **3a**. Indeed, the sense of asymmetric induction of derivatives of **3** in other reactions such as osmylation[9a] and palladium-catalyzed hydrogenation[9b] is the same as in the nitrile oxide cycloadditions and we suggest that the model **3a** is directly applicable to these results. The accompanying manuscript by Oppolzer and coworkers provides independent evidence which supports the applicability of model **3a** to cycloadditions and related reactions.[10] This model does not apply to the Lewis acid promoted reactions of **3**, because (as Oppolzer has indicated) chelation alters the conformer preference.[5]

Figure 2 ORTEP plot of **3**

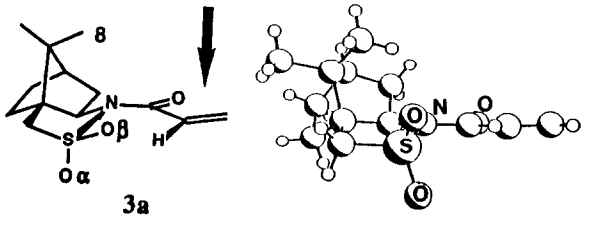
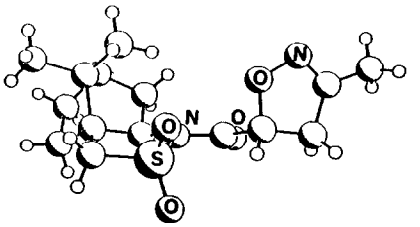


Figure 3 ORTEP plot of **4c**



An intriguing question remains: why do reagents prefer to approach the top side of **3a**? We advance two tentative hypotheses: 1) The faces of the *N*-acryloyl sultam are disposed differently with respect the two S–O bonds. The S–Oα bond projects directly "down" from the plane of the acrylamide while the S–Oβ bond projects outward. Thus, Oα may provide a steric or electronic encumbrance to "bottom-side" attack (see Figure 2). 2) The nitrogen atom is partially pyramidalized with the lone pair directed towards the face of the alkene that is attacked by the reagent.[11] The possible stereoelectronic directing effects of pyramidal nitrogens have been the topic of recent investigations,[12] and this hypothesis is further elaborated by Professor Oppolzer.[10,13] Additional research will be required to better understand the operative stereochemical control element(s).

References and Notes

1 (a) Recipient of a Sloan Foundation Fellowship, 1985-87; Dreyfus Teacher-Scholar, 1985-89; Eli Lilly Grantee, 1985-87. Merck Faculty Development Awardee, 1986-87. National Institutes of Health Research Career Development Awardee, 1987-92. (b) University of Pittsburgh undergraduate research participant.

2 (a) Curran, D. P. *Advances in Cycloaddition*, JAI: Greenwich, CN., 1988, p129. (b) Jäger, V.; Grund, H.; Franz, R.; Ehrler, R. *Lect. Heterocyc. Chem.* **1985**, *8*, 79. (c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

3 Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 2137.

4 Paquette, L. A. , in *Asymmetric Synthesis*, Vol 3, Morrison, J. D., Ed., Academic Press: Orlando, FL, Chapter 7.

5 Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969, see especially Section 3.3. The original printing of this excellent review contains printer errors. A version is reprinted in the Errata section of *Tetrahedron* **1987**, *42*, Issue 18.

6 Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876.

7 (a) Details of these structures are being submitted to the Cambridge Crystallographic File. We thank Dr. J. Abola and Mr. K. Parris for the crystallographic work. (b) The crystal structure of **ent-3** was actually determined. The mirror image of this structure is deliberately printed to facilitate comparison.

8 Bernardinelli, G.; Oppolzer, W.; Schneider, P. *Acta Cryst. C* **1987**, *43*, 1000. Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta.* **1984**, *67*, 1397.

9 (a) Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta.* **1987**, *70*, 1666. (b) Oppolzer, W.; Mills, R. J.; Reglier, M. *Tetrahedron Lett.* **1986**, *27*, 183. Assuming α-attack was favored due to steric hindrance from the C-8 ß-methyl group, chelated models were advanced to explain the stereoselectivites in these reactions.

10 Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. accompanying manuscript in this issue. See also, footnote 1 on page 1668 of ref 9a.

11 This pyramidalization may be caused by a "pinching" effect of the five-membered ring. The relevant C3-N-S angles are significantly less than 120°: **3a** = 111.0°, **4c** = 112.5°. The structures in ref. 8 have similar angles.

12 For recent discussions of stereoelectronic effects of pyramidal amides on alkylations, see: Seebach, D.; Juaristi, E.: Miller, D. D.; Schicrli, C.; Weber, T. *Helv. Chim. Acta.* **1987**, *70*, 237. Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105.

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