

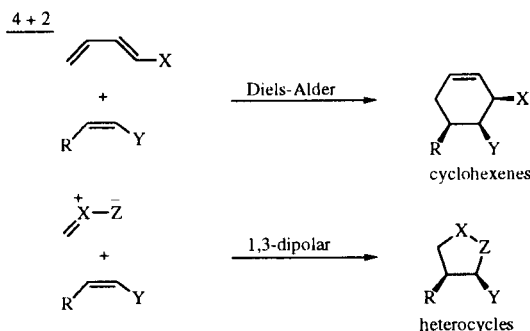
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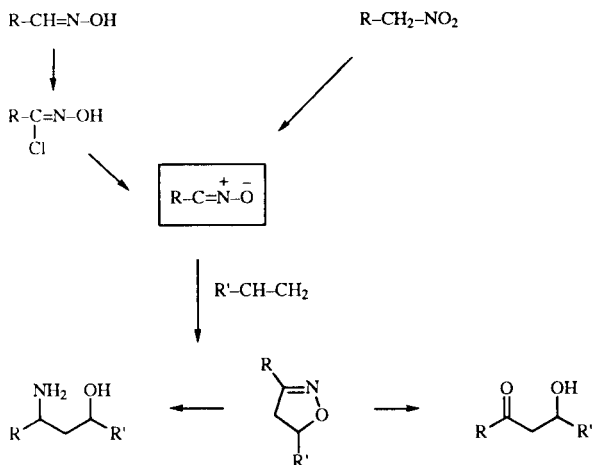
J. Heterocyclic Chem., **31**, 687 (1994).

1,3-Dipolar cycloadditions constitute the hetero analogs of the Diels-Alder reaction and usually also proceed regio and stereoselectively *via* a 4+2 addition process. These reactions involve formation of a heterocyclic ring and are of synthetic and theoretical interest.

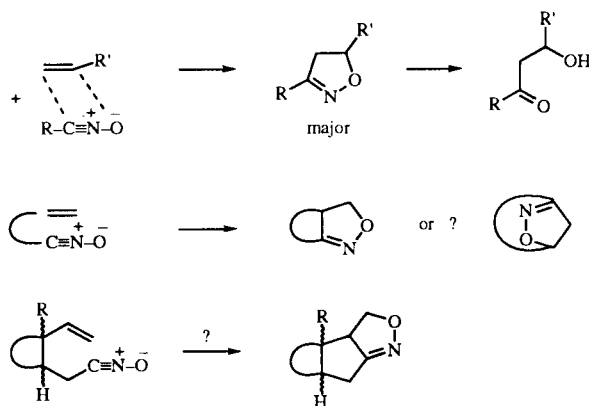
Stereoselectivity & Regioselectivity of Cycloadditions



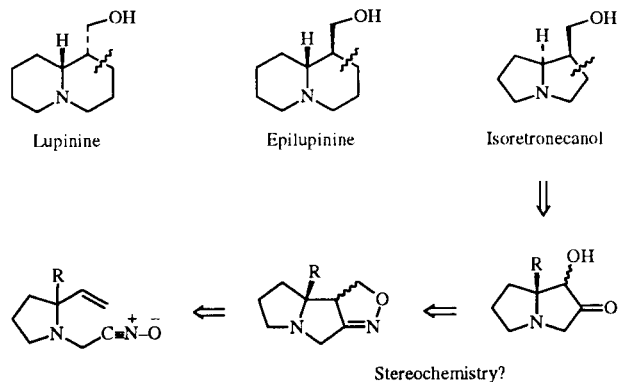
For instance, nitrile oxide olefin cycloadditions serve as useful starting materials for bifunctional systems such as amino alcohols, keto alcohols or unsaturated ketones, *via* cleavage of the N-O bond of the primarily formed isoxazoline. Nitrile oxides are usually prepared either from aldoximes by chlorination and dehydrochlorination or from primary nitro compounds by reaction with phenyl isocyanate.



Nitrile oxide olefin cycloadditions proceed regioselectively to produce mainly 5-substituted isoxazolines. Such intramolecular cycloadditions lead to simultaneous double annulation with formation of two rings, which can be either 4-substituted isoxazolines, due to geometric constraints or 5-substituted isoxazolines, due to favorable frontier molecular orbital interactions. Of interest to us was to be able to predict the stereochemistry of newly generated centers in the intramolecular cycloaddition.

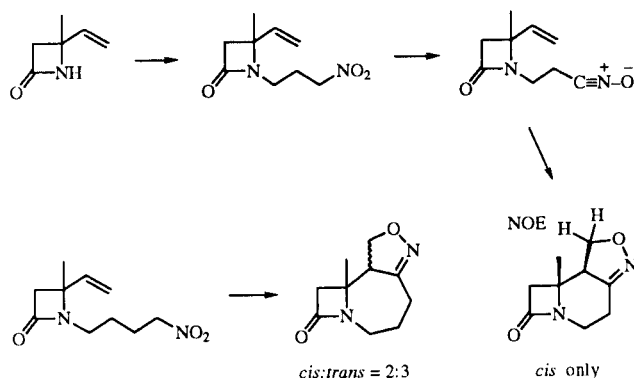


Such reactions should be useful in the synthesis of pyrrolizidine or quinolizidine alkaloids, such as the necine or lupinine systems, where the stereochemistry differs only near the ring junction. A retrosynthetic analysis for pyrrolizidine systems leads us to an intramolecular nitrile oxide olefin cycloaddition (INOC) of a vinylpyrrolidine, as the step in which the stereochemistry is determined.

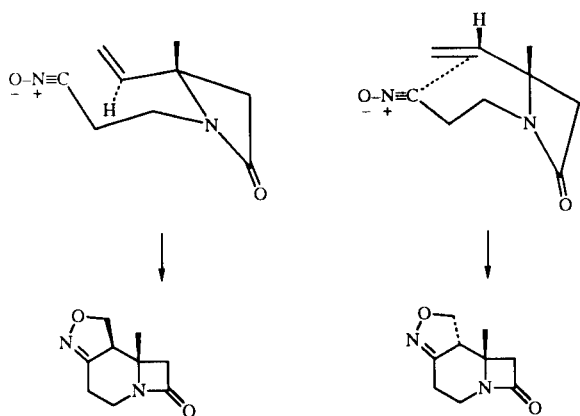


Since vinylpyrrolidines are unstable compounds, we decided to examine these reactions first on the readily

available vinylazetidiones. Mono-*N*-alkylation of these lactams with dibromoalkanes in the presence of solid KOH followed by replacement of the remaining bromine with nitrite ions led to the unsaturated nitro compound. The latter on reaction with PhNCO gave a nitrile oxide which spontaneously cyclized to afford in nearly quantitative yield the annulation product as a single isomer (*cis*). By contrast when a 7-membered ring was formed in the cyclization a mixture of *cis-trans* isomers resulted.



An examination of models for the parallel transition states for the reaction indicated that a chair-like TS should lead to the *cis* isomer, while a boat-like TS should afford the *trans* product. In more flexible larger rings the difference in energy between transition states should be much smaller, thus leading to a mixture of isomers.

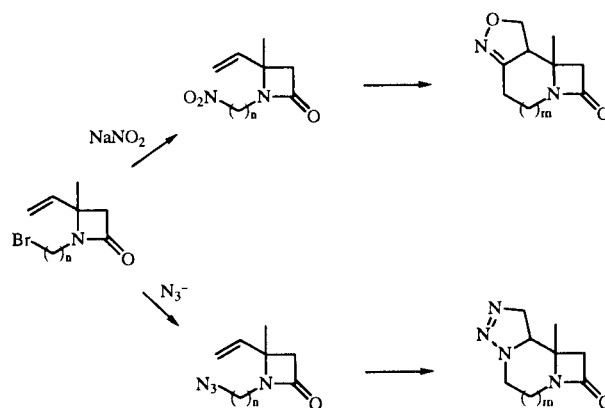


A more quantitative assessment was possible by means of MM2 calculations carried out in collaboration with Professor Padwa at Emory University. Both ground state and transition state calculated energy differences between *cis* and *trans* isomers bear out our results.

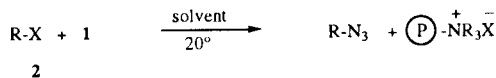
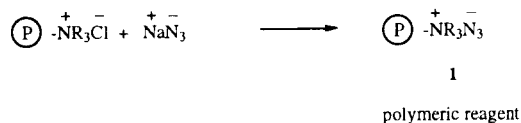
Molecular Mechanics Calculations (Padwa)

Structure	Calcd.		Found
	<i>E</i> (<i>cis-trans</i>)		
	-3.01 kcal	G.S.	100
	-1.54 kcal	T.S.	
	-0.61 kcal	G.S.	40/60
	-0.23 kcal	T.S.	

We then tried to compare the nitrile oxide olefin cycloadditions with related azide olefin cycloadditions. However azide displacement of the starting bromide required heat and proceeded poorly.

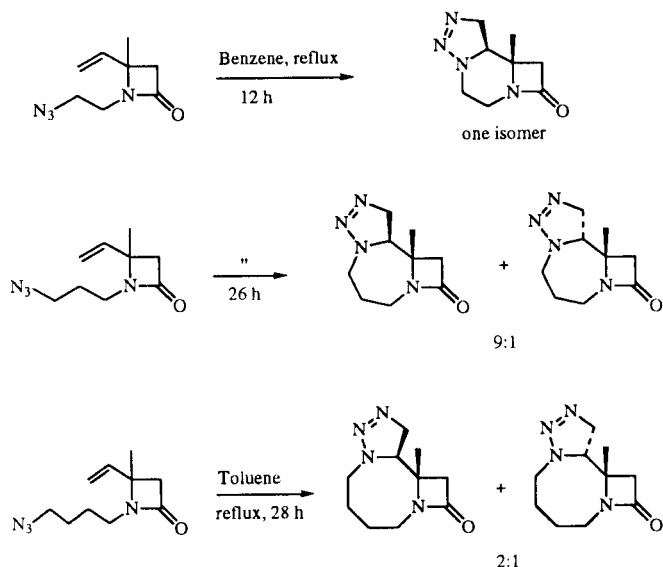


We were able to accomplish the azide displacement in nearly quantitative yield by utilizing our recently discovered polymeric azide reagent **1**, which usually reacts with alkyl halides or sulfonates at room temperature in essentially quantitative yield, without the necessity of distillation or chromatographic separations.

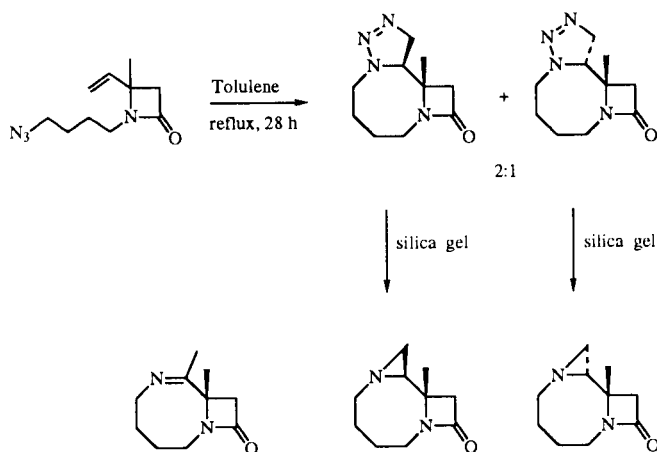


Follow reaction by GC to disappearance of **2**, filter polymer, obtain pure RN₃

The azido olefins thus prepared were heated to accomplish the dipolar cycloaddition with formation of fused triazolines. Here, as in the nitrile oxide case, formation of a six-membered ring proceeded stereospecifically to yield a single product, the *cis* isomer, while formation of 7- and 8-membered rings led to *cis trans* mixtures.

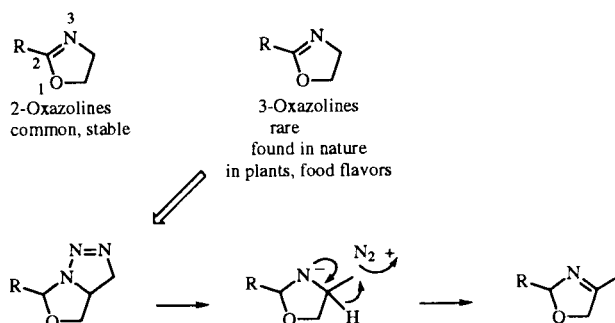


The newly formed triazolines decomposed on silica gel in a stereospecific manner to form fused aziridines in the case of the 8-membered ring diazocines, while in the case of the 6-membered ring analogs imino compounds resulted.

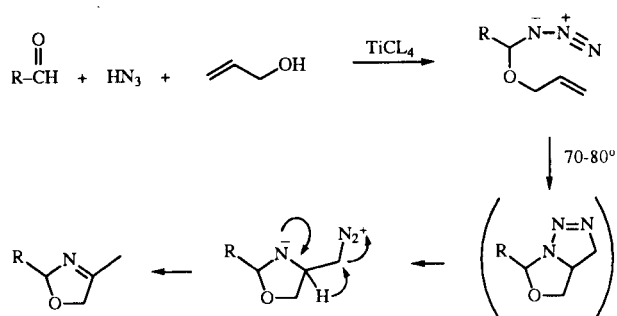


The latter pathway led us to consider decomposition of fused triazolines as a route to 3-oxazolines. Though 3-oxazolines are sometimes found in nature in plants or are

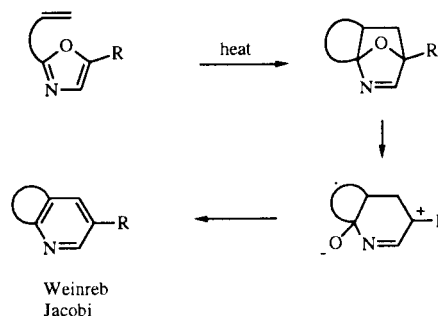
food flavoring agents, they are much less stable and more difficult to prepare than the well known 2-oxazolines.



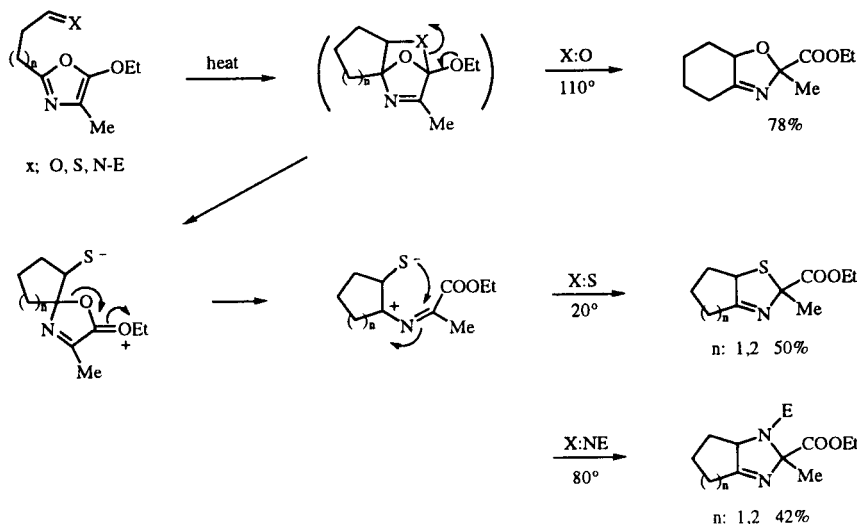
We devised a route to 3-oxazolines by heating unsaturated azido ethers, which in turn were readily prepared from aldehydes, hydrazoic acid and an allyl alcohol.



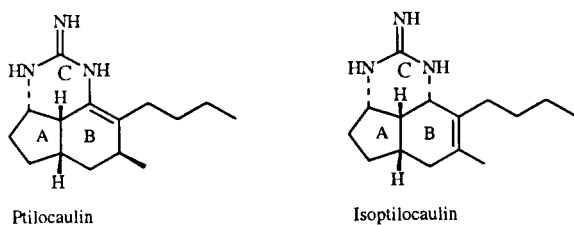
Another route to 3-oxazolines might be *via* Diels-Alder reactions to oxazoles. Intramolecular olefin additions to oxazoles have been shown to proceed readily but they lead to pyridine derivatives.



When we studied intramolecular Diels-Alder reactions of heteroenes (C=O, C=S, C=N) with oxazoles, we found that it was possible to obtain novel 3-oxazolines, 3-triazolines or 3-imidazolines by this route.



Another application of the stereoselective nitrile oxide olefin cycloaddition is shown in the synthesis of ptilocaulin, an antileukemic, antimicrobial agent isolated from a marine sponge.



Isolation: Caribbean sponge *Ptilocaulis* aff. *P. Spiculifer*
1981; Rinehart, *et al*

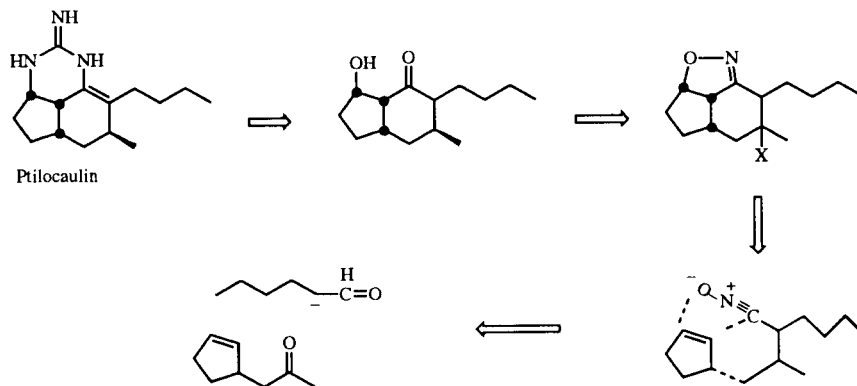
Broad spectrum antimicrobial
Broad spectrum activity against colon and mammary adenocarcinoma,
leukemia

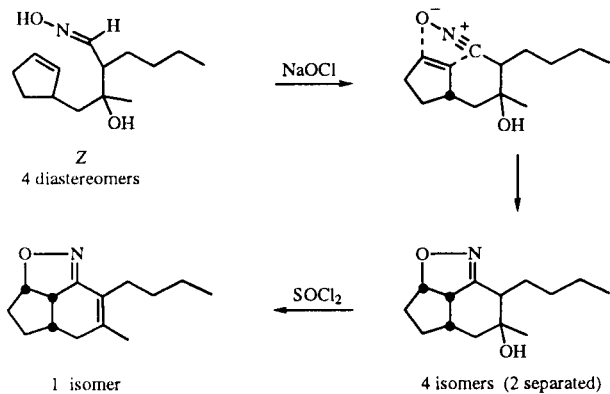
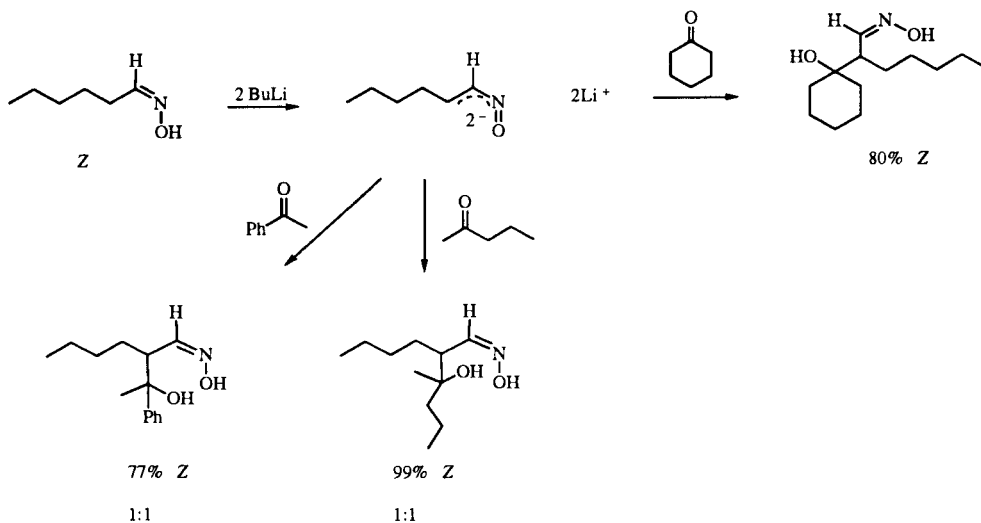
A retrosynthetic analysis for the introduction of the four stereocenters in ptilocaulin leads us to an intramolecular nitrile oxide olefin cycloaddition.

Since aldol reactions between aldehyde enolates and ketones are difficult to accomplish we turned our attention to the aldol reaction of aldoximes with ketones. We found that of the two isomeric oximes only the *Z*-isomer forms a dianion that undergoes aldol condensation with ketones in good yield.

Fortunately, pure *Z*-oximes can be obtained by recrystallization and the aldol reaction proceeded well. Although a mixture of four diastereomers were obtained, the nitrile oxide olefin cycloaddition step proceeded stereospecifically, as indicated by conversion of all four isomers to a single *cis-cis* isomer upon elimination of water.

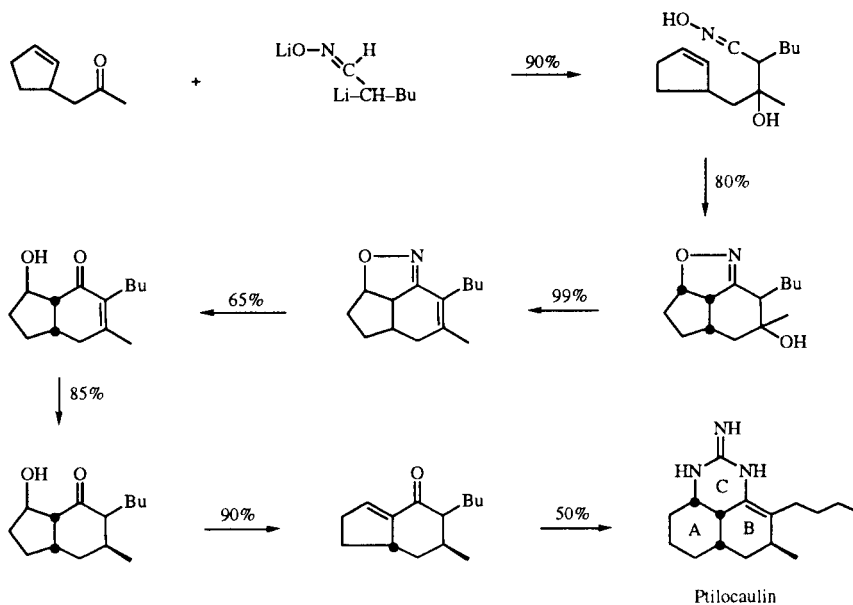
The synthesis of ptilocaulin was accomplished in 7 steps. The introduction of the β -methyl group was possible by means of LiEtNH_2 . Lithium chelation keeps the conformation of the hydrindanone locked so that protona-

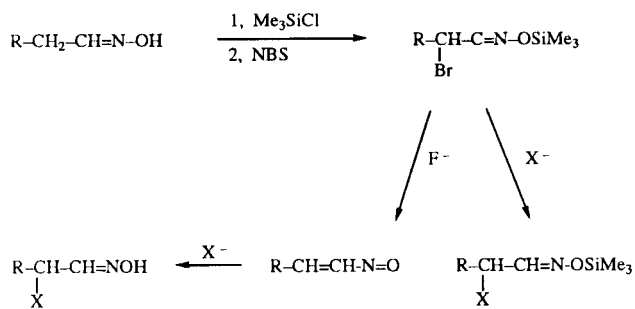




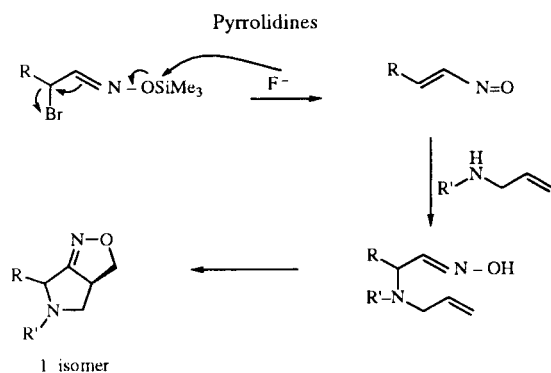
tion of the anion can take place axially from the α -side, leading to the β -methyl isomer.

While amides can be monoalkylated with dibromoalkanes, this is not an efficient process with amines. Therefore, a new approach to unsaturated amine nitrile oxides was sought *via* the introduction of an aldoxime function into an unsaturated amine. The route by reaction with an α -bromoaldoxime was not feasible because, unlike most α -bromoketoximes, α -bromoaldoximes are not stable. They are also not available by bromination of aldoximes. We solved this problem by silylating the oxime which now can be α -brominated with NBS. The resulting silylated oximes can undergo direct substitution or better by treatment with F^- .

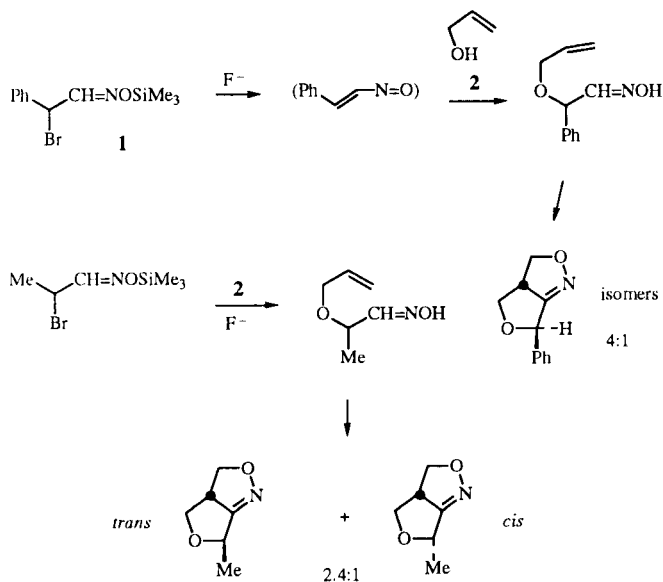




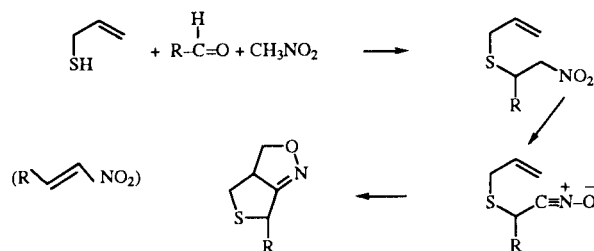
In this manner allylamines can be treated with *O*-silyl- α -bromoaldoximes and the resulting unsaturated oximes converted with NaOCl to the nitrile oxides, which spontaneously cyclize to afford stereospecifically functionalized pyrrolidines.



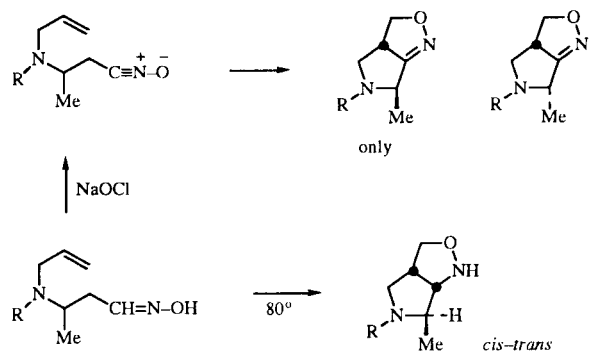
The reaction also can be applied to the synthesis of functionalized cyclic ethers, though with lower stereoselectivity.



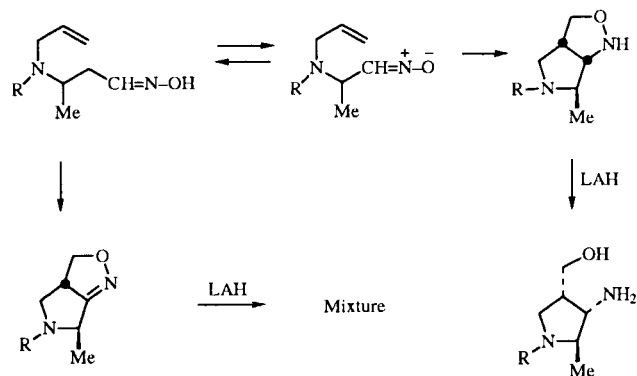
The above method was not applicable to formation of tetrahydrothiophenes, because of the sensitivity of the thioether to halogenating conditions. Hence, an alternative pathway *via* the nitrothio ether was devised. The nitro compounds were prepared in a one pot reaction from aldehydes, nitromethane and an unsaturated thiol.



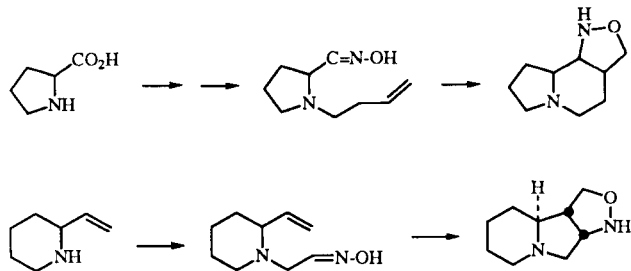
While studying the reaction unsaturated amino oximes, we found that simple heating led to cyclization affording a fused isoxazolidine. Even though three new stereocenters were created the cycloaddition was stereospecific.



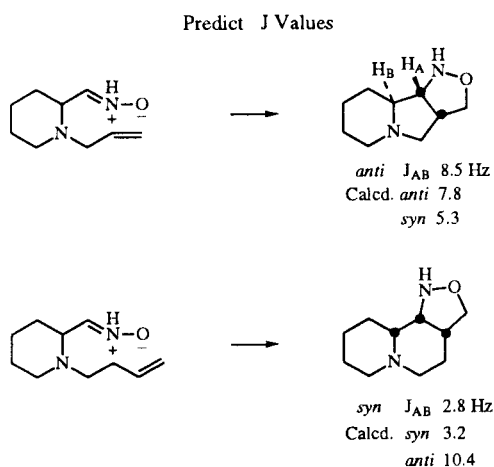
The oxime olefin cycloaddition apparently proceeds *via* a proton shift to an NH-nitrone, which is trapped intramolecularly by the double bond.



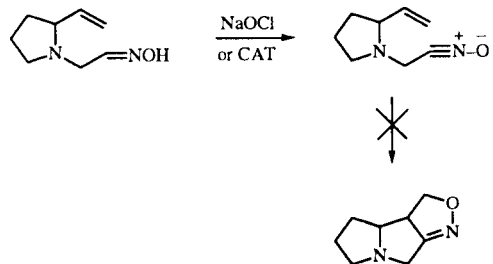
Some examples of the intramolecular oxime olefin cycloaddition (IOOC) leading to indolizidines functionalized in either the 6- or the 5-membered ring are shown.



Molecular mechanics calculations, carried out in collaboration with Professor Padwa permit correlation and prediction of coupling constants in these systems. As before, formation of 6-membered rings give the syn product, while formation of 5-membered rings produce the anti isomer exclusively.

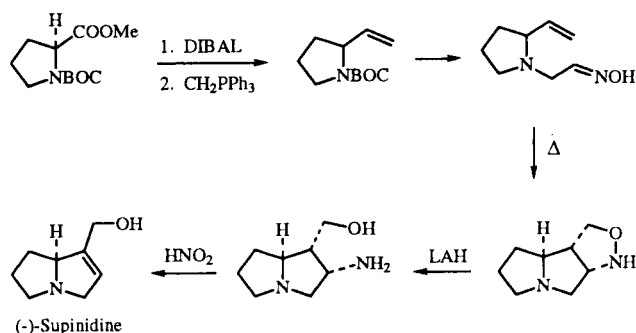


When we attempted to apply the nitrile oxide olefin cycloaddition to the formation of pyrrolizidine alkaloids, we found that virtually no cycloaddition occurred.

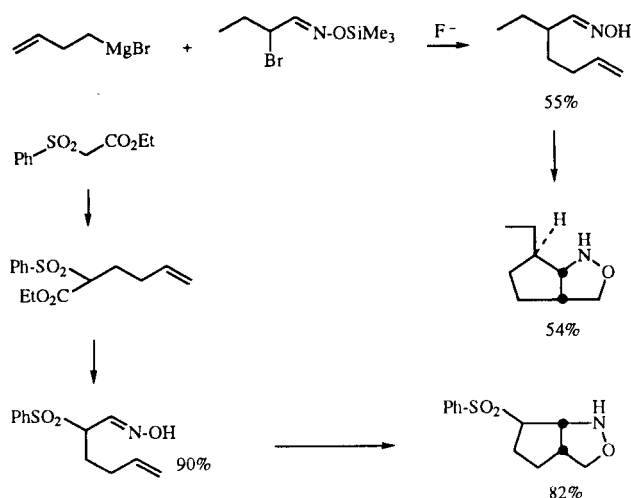


On the other hand the oxime olefin cycloaddition of the vinylpyrrolidine derived from proline proceeded well and

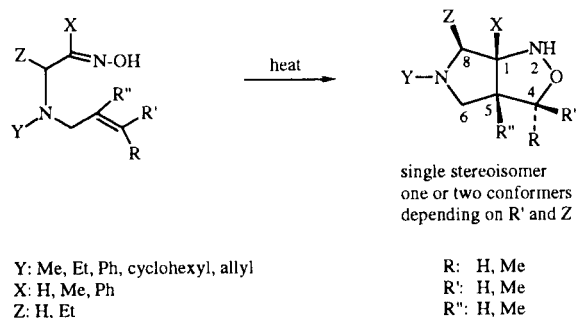
led in a few steps to the synthesis of (-)-supinidine.



The oxime olefin cycloaddition is also applicable to formation of cyclopentane derivatives.



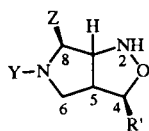
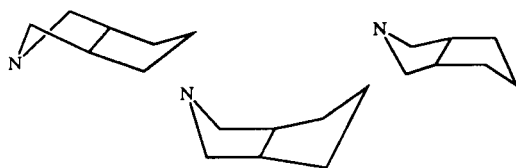
When we examined the products of the oxime aminoolefin cycloaddition, we found that not only a single stereoisomer but in some cases a single conformer was formed.



This permitted an evaluation of preferred conformations in these azabicyclo[3.3.0]octanes, by means of nmr.

Conformations of Azabicyclo[3.3.0]octanes

difficult to determine



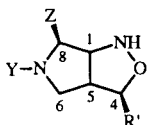
allows to measure

$J_{1,2}$ $J_{1,8}$

$J_{4,5}$ $J_{5,6}$

Y, Z, R': alkyl

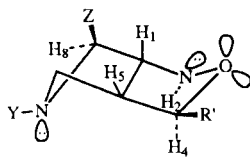
We found that an alkyl group at position 4 prefers a pseudo equatorial orientation which predisposes the molecule to conformation 1. On the other hand, an alkyl substituent at C-7 favors conformer 2. In cases where both conformers were produced, equilibration studies indicate a free energy of conversion of approximately 13 kcal/mol, which is probably due to the energy barrier for *N*-inversion around the N-O bond.



measure: $J_{1,2}$ $J_{1,8}$

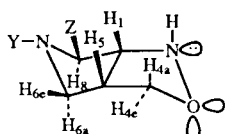
$J_{4,5}$ $J_{5,6}$

Y: Me, Et, Ph, cyclohexyl, allyl



1

R': Me
Z: H, Et



2

Z: Et

R' = alkyl, favors conformer 1 (>10:1) Z = alkyl, favors conformer 2 (>10:1)

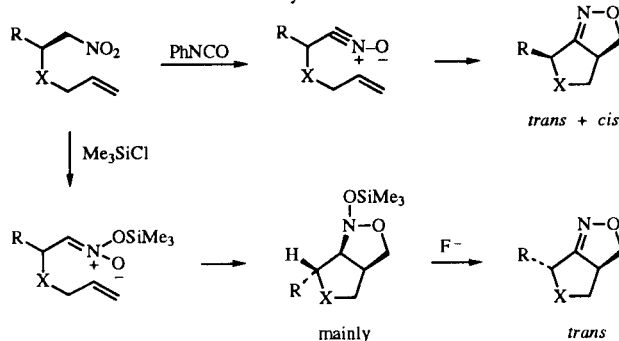
Z and R' = H, give 1:2 to 2:1 mixtures of 1:2

conformer interconversion (NMR): $\Delta G^\ddagger = 13.2 + 0.3$ kcal/mol

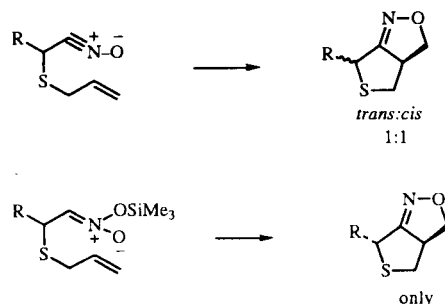
In order to improve stereoselectivity during nitrile oxide olefin cycloadditions, we studied conversion of the nitroolefins to silyl nitronates. Cycloaddition of the latter occurred with high stereoselectivity and led after elimination of TMS-OH to isoxazolines as a single isomer.

In this manner it was possible to improve the stereoselectivity during formation of the tetrahydrothiophenes from 1:1 to >99:1. A similar stereospecificity was observed in the formation of a variety of substituted tetrahydrofurans and cyclopentanes *via* intramolecular silyl nitronate olefin cycloadditions (ISOC).

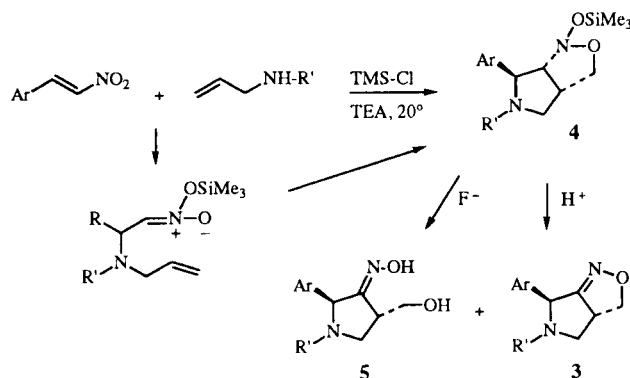
Silyl nitronates



Nitrile Oxide vs Silyl Nitronate (Thiophenes)



We then tried to apply the silyl nitronate reaction to formation of pyrrolidines. Addition of amines to nitro olefins is reversible; however if the reaction is carried out in the presence of TMS-Cl, the silyl nitronates, formed as intermediates, underwent cycloaddition to produce pyrrolidines.



Acknowledgment.

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