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Stereoselective Intramolecular Nitrile Oxide Cycloaddition to Chiral Allyl Ethers

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Intramolecular nitrile oxide cycloaddition reactions on (*Z*)- and (*E*)-chiral allyl ethers occur with poor to good stereoselectivity (diastereoisomeric ratios up to 86 : 14), which depends on the double bond configuration as well as on steric and stereoelectronic effects.

4,5-Dihydroisoxazoles (Δ^2-isoxazolines), important synthons for the stereodefined construction of a variety of polyfunctional molecules,[1—3] are generally synthesized by nitrile oxide cycloaddition to alkenes.[4] It has been shown that an oxygen-bearing allylic stereocentre can promote useful diastereoselectivity in *intermolecular* cycloadditions.[5—8] The factors influencing the stereochemical outcome of this reaction are still a matter of lively debate.[5—7]

Almost all the studies reported so far on cycloaddition to chiral allyl ethers concerned monosubstituted alkenes and thus could not be used to evaluate the effect of double bond configuration on the stereoselectivity of the process. A likely reason for this is the lack of regioselectivity observed for cycloadditions on 1,2-disubstituted alkenes.[1,6] In order to examine these effects without being hampered by problems of regiochemical control, we decided to study *intramolecular* nitrile oxide cycloaddition (INOC) on both (*E*)- and (*Z*)-chiral allyl ethers.†

Alcohols (**1**)—(**3**) were prepared from (*S*)-*O*-benzyl-lactaldehyde, (*R*)-2,3-*O,O*′-dibenzylglyceraldehyde, and (*R*)-2,3-*O,O*′-cyclohexylideneglyceraldehyde, respectively, by Wittig reaction with 6-hydroxyhexyl(triphenyl)phosphonium bromide,[9] which afforded the products predominantly in the (*Z*)-configuration (*Z*/*E* ratios $\geqslant$ 10 : 1; $J_{\text{CH=CH}}$ 10.7—11.0 Hz; 70—80% yield) (Scheme 1).

Isomerization to the corresponding (*E*)-alcohols was achieved by reaction with benzenethiol and azoisobutyronitrile (AIBN) in refluxing benzene (*E*/*Z* ratios $\geqslant$ 9 : 1; $J_{\text{CH=CH}}$ 15.0—15.8 Hz; 65—75% yield).[6,10] Alochols (**1**)—(**3**) were subjected to Swern oxidation (70—80% yield) and reaction with hydroxylamine hydrochloride (quantitative), to give oximes (**4**)—(**6**). Finally reaction with sodium hypochlorite generated *in situ* the nitrile oxides, which underwent intramolecular cycloaddition to give adducts (**7a,b**)—(**12a,b**) as mixtures of diastereoisomers.

As can be seen from the data reported in Table 1, useful stereoselectivity is generally obtained in this INOC reaction, despite the fact that the allylic stereocentre is not within the carbon chain connecting the 1,3 dipole and the double bond, a factor previously suggested as being important for achieving good diastereoselectivity in this reaction.[3,11]

Starting from the alkenyloximes (*Z*)-(**4**), (*Z*)-(**5**), and (*Z*)-(**6**) (entries A—C), 5,5′-*anti*[12]‡ cycloadducts (**7a**), (**9a**), and (**10a**) predominate over their 5,5′-*syn* counterparts (**7b**), (**9b**), and (**10b**), with diastereoisomeric ratios which are better than those observed in related intermolecular cycloadditions.[5—7]

The behaviour of the isomeric alkenyloximes (*E*)-(**4**), (*E*)-(**5**), and (*E*)-(**6**) (entries D—F) is different: indeed, while (*E*)-(**6**) gives the product with the 5,5′-*anti*-configuration (**12a**) in a similar excess over 5,5′-*syn* (**12b**) (entry F *vs.* C), the stereoselectivity decreases for the reaction of (*E*)-(**5**) to afford (**11a,b**) (entry E *vs.* B), and an excess of 5,5′-*syn* cycloadduct (**8b**) is produced from (*E*)-(**4**) with low selectivity (entry D *vs.* A).

The stereochemical assignment rests on the values of the coupling constants between 5- and 5′-H. *anti*-Products constantly feature *J* values larger than those of their *syn*-isomers

Table 1. Preparation of cycloadducts (**7a,b**)—(**12a,b**) from oximes (**4**)—(**6**).

Entry	Starting material	Product	% Yield	Diastereoisomeric[a] (**a** : **b**) ratios
A	(*Z*)-(**4**)	(**7a,b**)	62	80 : 20
B	(*Z*)-(**5**)	(**9a,b**)	72	83 : 17
C	(*Z*)-(**6**)	(**10a,b**)	63	86 : 14
D	(*E*)-(**4**)	(**8a,b**)	72	40 : 60
E	(*E*)-(**5**)	(**11a,b**)	87	77 : 23
F	(*E*)-(**6**)	(**12a,b**)	84	86 : 14

[a] As determined by flash chromatographic (SiO_2, diethyl ether–hexanes) separation of the products and/or by 300 MHz ^{1}H n.m.r. spectroscopy. All new compounds gave satisfactory analytical and spectral data.

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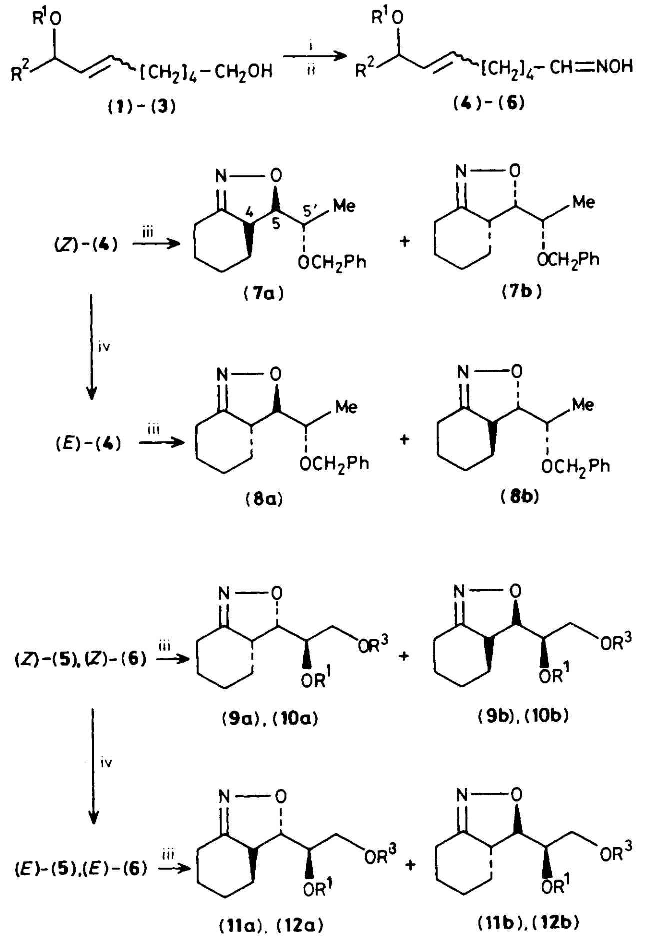
† Recently Houk *et al.* studied the stereoselectivity of some related INOC reactions. We are grateful to Prof. Houk for a valuable exchange of information.

‡ The relative configuration at C-4 and C-5 of (**7a,b**)—(**12a,b**) is determined by the configuration at the double bond of the starting alkenes (**4**)—(**6**). Thus from (*Z*)- and (*E*)-alkenes, products with 4,5 *syn*- and 4,5-*anti*-configurations are obtained, respectively.



(1), (4) $R^1 = CH_2Ph$, $R^2 = Me$
(2), (5) $R^1 = CH_2Ph$, $R^2 = CH_2OCH_2Ph$
(3), (6) $R^1, R^2 = \overline{CH_2[CH_2]_4C}\text{–}OCH_2\text{–}$
(9), (11) $R^1 = R^3 = CH_2Ph$
(10), (12) $R^1, R^3 = \overline{CH_2[CH_2]_4C}<$

Scheme 1. *Reagents:* i, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2; ii, $NH_2OH{\cdot}HCl$, AcONa, EtOH, H_2O; iii, 0.3 M NaOCl, CH_2Cl_2, 0 °C, iv, PhSH, AIBN, benzene, 80 °C.

as already observed in analogous substrates.[6,13] For products from (*Z*)-alkenes: $J_{anti} = 8.4$—8.7 Hz; $J_{syn} = 3.8$—6.2 Hz. For products from (*E*)-alkenes: $J_{anti} = 6.0$—8.0 Hz; $J_{syn} = 4.3$—6.0 Hz.§

These results require a few comments. The reactions of (*Z*)-alkenyloximes can be nicely rationalized by both the proposed models;[5,6] the *intramolecular* nature of the process is likely to be responsible for the enhancement in diastereoselectivity. Even if an estimate of their relative contribution to product formation is difficult, inspection of molecular models indicates that to avoid severe steric congestion the allylic hydrogen would prefer an 'inside'[5] position as depicted in Figure 1.

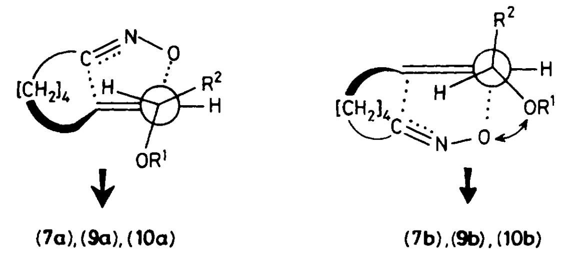


Figure 1

Repulsive interactions[7] between the oxygens of the incoming nitrile oxide and of the alkoxy group would account for the preferential formation of adducts (**7a**), (**9a**), and (**10a**).¶

In principle the lack of steric interactions around the double bond of (*E*)-alkenes should lead, for (*E*)-(**4**)—(*E*)-(**6**), to a distribution of cycloadducts similar to that observed in analogous intermolecular cycloadditions.[5—7] However, the proposed models[5,6] can rationalize only the preferential formation of (**11a**) and (**12a**) but not that of (**8b**), which remains inexplicable.

In conclusion, the results indicate that the sense and the extent of stereoselectivity of INOC reactions with chiral allyl ethers depends on steric and stereoelectronic factors, a definite trend being found only in the case of (*Z*)-derivatives. In order to gain more information on the reaction course, molecular mechanics calculations are currently underway.

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§ In the case of compound (**11a,b**), very similar coupling constants were observed for *anti*- and *syn*-isomers. The relative configuration was established by conversion of pure (**12a**) into (**11a**).

¶ Recently Vedejs[14] has shown that osmylation (a reaction closely related to nitrile oxide cycloaddition[5,7,14]) of (*Z*)-(α)-heterosubstituted chiral allylic derivatives always affords predominantly *anti* rather than *syn* products, suggesting transition states for their formation similar to those proposed in Figure 1.