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THE DIASTEREOSELECTIVITY OF INTERMOLECULAR NITRONE CYCLOADDITION TO CHIRAL ALLYL DERIVATIVES

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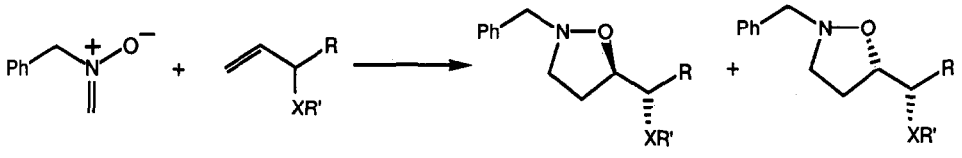
Abstract. The stereoselectivity of some intermolecular nitrone cycloadditions to alkenes featuring heterosubstituted allylic stereocenter is discussed and rationalized.

Stereoselective synthesis based on nitrone cycloaddition to alkenes [1] mostly exploit chiral dipoles as the source of stereocontrol. [2] The use of chiral dipolarophiles is much less frequent and satisfactory stereoselection has been achieved only with a few cyclic olefins and electron poor alkenes. [2,3] We recently reported on the stereoselectivity of some *intramolecular* nitrone cycloadditions to alkenes featuring an allylic stereocenter located outside the chain connecting dipole and dipolarophile. [4] To explain the stereochemical outcome of these reactions a model was proposed, [4] that was in line with that commonly invoked to rationalize the steric course of inter-[5] and intramolecular [6] nitrile oxide cycloadditions to chiral allyl compounds. To test the general validity of our hypothesis we decided to examine a series of *intermolecular* cycloadditions of a non-stereogenic nitrone to some terminal alkenes possessing a heterosubstituted allylic stereocenter. A very recent communication by Ito and Kibayashi [7] on a nitrone cycloadditon to chiral 3-benzyloxy-1-heptene prompted us to disclose our results in this field.

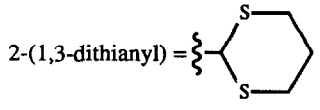
Formaldehyde N-benzyl nitrone **1**, prepared in situ from N-benzyl hydroxylamine (1.1 mol equiv; reactions were carried out on 2-30 mmol scale) and paraformaldehyde (1.7 mol equiv), was reacted for 15h in refluxing dry benzene (20ml/mmol) with 1.0 mol equiv of alkenes **2-11** in the presence of molecular sieves. [8] Purification of the crude product by flash chromatography afforded cycloadducts **12a,b-21a,b** as mixture of diastereoisomers, that in most cases could be separated (Scheme). [9] Yields and diastereoisomeric ratios, as determined by 300 MHz ^{1}H-NMR spectroscopy, are collected in Table. [10] The attribution of the relative configuration at the two stereocenters was based on chemical correlation and ^{1}H- and ^{13}C-NMR evidence. The configuration of **12b** was established as <u>syn</u> (and thus that of **12a** as <u>anti</u>) by conversion of this product into compound **23**, obtained in six steps from E-2-pentene nitrile <u>via</u> amide **22** (Scheme). Compounds **12a-14a** were then correlated to (and shown to possess the same configuration of) cycloadducts **15a-17a** either by silylation of the former or by deprotection of the latter. The <u>anti</u> configuration was assigned to **12a - 17a** and the <u>syn</u> one to **12b - 17b** on the basis of chemical shift trend considerations. [11]

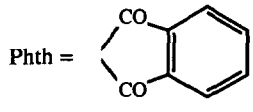
Scheme.



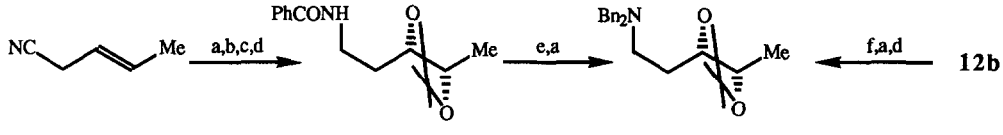
1 **2-11** **12a-21a** **12b-21b**

	X	R	R'		X	R	R'
2, 12	O	Me	H	**8, 18**	O	CH_2O-C(C_6H_{10})-	
3, 13	O	Pr-i	H	**9, 19**	NH	CH_3	COPh
4, 14	O	2-(1,3-dithianyl)	H	**10, 20**	N	CH_3	Phth
5, 15	O	Me	TBS	**11, 21**	S	CH_3	Ph
6, 16	O	Pr-i	TBS				
7, 17	O	2-(1,3-dithianyl)	TBS				





TBS = $SiMe_2Bu$-t



12b $\xrightarrow{g}$ **20a** $\xrightarrow{h,b}$ **19a**

12b $\xrightarrow{i}$ **21a**

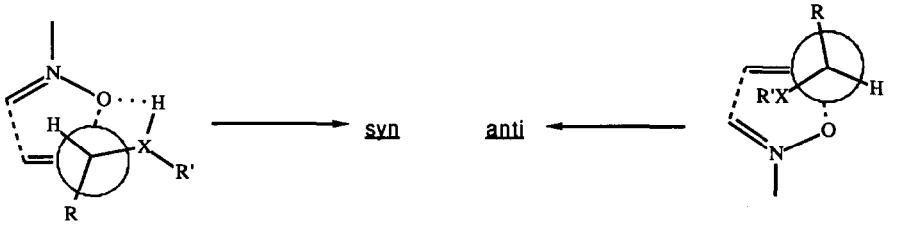
Reagents: a: $LiAlH_4$; b: PhCOCl, Py; c: OsO_4, Me_3NO; d: $Me_2C(OMe)_2$, PTS; e: $PhCH_2Br$, NaH; f: $PhCH_2Br$; g: PPh_3, phtalimide, DEAD; h: H_2N-NH_2 H_2O; i: PhSSPh, Bu_3P.

Table. Diastereoselectivity in the synthesis of adducts **12-21** by cycloaddition of **1** to **2-11**.

Entry	Alkene	Product	Yield %	**a:b** ratio
1	**2**	**12 a,b**	68	29 : 71
2	**3**	**13 a,b**	70	27 : 73
3	**4**	**14 a,b**	66	24 : 76
4	**5**	**15 a,b**	47	63 : 37
5	**6**	**16 a,b**	23	90 : 10
6	**7**	**17 a,b**	42	76 : 24
7	**8**	**18 a,b**	64	85 : 15
8	**9**	**19 a,b**	67	39 : 61
9	**10**	**20 a,b**	60	52 : 48
10	**11**	**21 a,b**	81	65 : 35

This is in agreement with the results reported for similar cycloadditions, [4,6,7] that also suggest (together with comparison of NMR data [4,6]) the indicated configuration for isoxazolidine **18a,b**. Starting from compound syn **-12b** it was also possible to establish the relative stereochemistry of cycloadducts **19a,b-21a,b**. Indeed, reaction of **12b** with PhSSPh and Bu_3P [12] gave anti **-21a**, while a standard Mitsunobu protocol [13] correlated syn **-12b** with anti **-19a** via the phthalimido derivative **20a** (Scheme).

As can be seen from the data reported in Table the stereoselection of the cycloadditions ranges from poor to good. Allylic stereocenters capable of hydrogen bond formation with the oxygen of the nitrone (entries 1-3,8) lead to the preferential formation of syn products; [7,14] anti cycloadducts predominate in the other cases (entries 4-7,10,11), the stereoselection increasing with increasing bulkiness of the R residue (entries 4-6), or when a homoallylic oxygen is present (entry 7). Some of these trends have already been observed in intramolecular nitrone, [4] and in inter- and intramolecular nitrile oxide cycloadditions to related substrates. [2,5,6,15]



A X=O, N-EWG **B** X=O, S

We therefore propose transition structures **A** and **B** for the cycloadditions described in this manuscript. With hydrogen bond forming substituents, nitrone attacks anti to the R group with the allylic hydrogen inside and the heteroatom outside, respectively. The presence of large R and of strongly electronwithdrawing R' groups should increase the syn stereoselection of this process. [15] On the other hand stereoelectronically favored [5,6] "inside heteroatom model" **B** (analogous to Houk's "inside alkoxy" model [5]) is preferred when X is a lone pair bearing heteroatom and the substrate is not capable of hydrogen bond formation. Also in this case large R groups should increase the stereoselectivity of the reaction, as confirmed by our experimental results. Thus nitrone and nitrile oxide intermolecular cycloadditions to chiral allyl derivatives likely proceeds via similar transition states. Additional experiments and theoretical work are currently underway in our laboratories to confirm the general applicability of these models.

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8. J. Wityak, S. J. Gould, S. J. Hein, D. A. Keszler, J. Org. Chem., **52**, 2179, 1987.
9. All new compounds gave analytical and spectral data in agreement with the proposed structures.
10. NMR spectra were recorded at 55° C in $CDCl_3$, to avoid line broadening observed at RT. For an analogous case see ref. 8.
11. Compound **15-17**: HC-ON and HC-OSi resonate at higher field in all the major isomers and at lower field in all the minor isomers; for C-ON and C-OSi the opposite trend was observed. Compound **12-14**: HC-ON resonate at higher field in all the minor isomers; for HC-OH the opposite trend was observed.
12. D. G. Cleary, Synthetic Comm., **19**, 737, 1989; and references therein.
13. O. Mitsunobu, Synthesis, 1, 1981.
14. For related examples see: S. Mzengeza, R. A. Whitney, J. Org. Chem., **53**, 4074, 1988.
15. For a very recent example of secondary amide group directed, syn -selective nitrile oxide cycloaddition see: D. P. Curran, S.-M. Choi, S. A. Gothe, F. Lin, J. Org. Chem., **55**, 3710, 1990.

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