Hydroxy-Group Directivity in the Nitroso Ene Reaction: Diastereo- and Regioselective Amination of Chiral Allylic Alcohols

Waldemar Adam and Nils Bottke*

Institut für Organische Chemie, Universität Würzburg
Am Hubland, D-97074 Würzburg, Germany

Received May 24, 2000
Revised Manuscript Received July 12, 2000

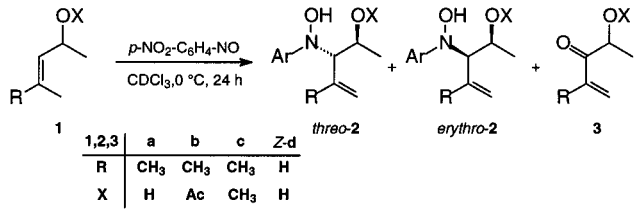
The ene reactions of singlet oxygen[1] and triazolinedione (TAD)[2] with 1,3-allylically strained chiral substrates lead to *threo*-configured ene products in high diastereoselectivities, a consequence of the hydroxy-group directivity.[3] If such stereocontrol were to operate for the isoelectronic nitroso enophile, an attractive and convenient synthetic methodology would be available for the diastereoselective amination of chiral allylic alcohols; however, the ene reaction of such olefins appears not to have been examined so far.[4] This is presumably due to the undesirable side reactions known for the nitroso ene reaction, in which the resulting hydroxylamine ene products are in situ further oxidized.[5] To circumvent these disadvantages, we recently established a new nitroso enophile, namely *p*-nitronitrosobenzene (ArNO), which affords persistent ene products.[6] Indeed, presently we demonstrate that for this nitrosoarene enophile the hydroxy-group directivity operates effectively when 1,3-allylically strained chiral allylic alcohols are employed. The desired aminated ene products have been obtained in high diastereoselectivity and regioselectivity, as well as in good yield.

The product studies of the ene reactions were conducted on the NMR scale, all unknown products were isolated from preparative runs and fully characterized. The product ratios and diastereoselectivities were determined directly on the crude reaction mixture from the peak areas of characteristic signals in the ^{1}H NMR spectra. The results are summarized in Table 1.

The allylic acohol **1a** was converted with an equimolar amount of the nitrosoarene in the nonpolar *d*-chloroform with high (92:8) diastereoselectivity (entry 1) predominantly to the *threo*-configured hydroxylamine (2*S**,3*S**)-**2a**. In d_4-methanol (69:31, entry 3) and d_6-DMSO (66:34, entry 4) significantly lower diastereoselectivities were observed. Evidently, hydrogen bonding between the 1,3-allylically strained substrate and the nitrosoarene enophile is responsible for the pronounced *threo* selectivity. In the protic methanol and the polar DMSO, the substrate/enophile hydrogen bonding is suppressed through competitive intermolecular interactions with the solvent.

Also chemical masking of the hydroxy group either by acetylation as in the ester **1b** or methylation as in the ether **1c** corraborate that substrate/enophile hydrogen bonding is at work in expressing the high *threo* diastereoselectivity for the allylic alcohol **1a** in $CDCl_3$. Thus, for the acetate **1b** (77:23, entry 7) and for the methyl ether **1c** (60:40, entry 10), the *threo* selectivity is substantially lower than that for the allylic alcohol **1a** (92:8, entry 1). Again, these results clearly establish that the hydroxy group directs the nitrosoarene ene reaction preferentially to the *threo* product through hydrogen bonding.

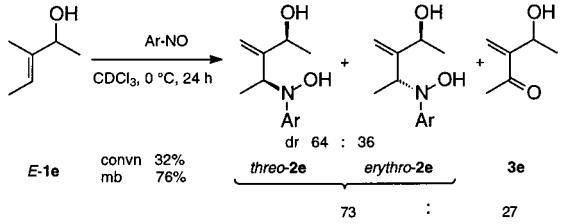
Table 1. Product Studies of the Ene Reaction of *p*-Nitronitrosobenzene (ArNO) with Allylic Substrates **1**



	olefin (equiv)	convn [%][a,b]	mb [%][a,b]	**2**:**3**[b]	diastereoselectivity[b] *threo*:*erytho*
1	**1a** (1)	81	>95	76:24	92:8
2	**1a** (2)	35	>95	92:8	>95:5
3	**1a** (1)[c]	56	79	79:21	69:31
4	**1a** (1)[d]	73	67	93:7	66:34
5	**1b** (1)	45	83	79:21	87:13
6	**1b** (2)	18	>95	83:17	80:20
7	**1b** (4)	<5	>95	94:6	77:23
8	**1c** (1)	55	85	51:49	79:21
9	**1c** (2)	17	>95	72:28	64:36
10	**1c** (4)	<5	>95	85:15	60:40
11	*Z*-**1d** (1)	51	61	> 95:5	>95:5
12	*Z*-**1d** (2)	16	92	>95:5	>95:5

[a] Conversion and mass balance (mb) relative to the allylic alcohol. [b] Determined by ^{1}H NMR spectroscopy, error ±5% of the stated value. [c] Solvent was CD_3OD. [d] Solvent was d_6-DMSO.

Scheme 1. 1,2-Allylic Strain in the Nitrosoarene Ene Reaction with the Allylic Substrate *E*-**1e**



The stereochemically labeled and 1,3-allylically strained alcohol *Z*-**1d** (entry 12) displayed exclusive (>95:5) *threo* diastereoselectivity; the *erythro* ene product was not detected by ^{1}H NMR spectroscopy. Under identical conditions, the complementary diastereomer *E*-**1d** is unreactive toward the *p*-nitronitrosobenzene enophile. That 1,2-allylic strain exercises no appreciable diastereoselective control was demonstrated by the substrate *E*-**1e** (Scheme 1), for which the *threo/erythro* ratio is only 64:36. In contrast, the *Z*-**1e** isomer did not undergo the nitrosoarene ene reaction. The reactivities of the various substrates are for convenience collected in Figure 1 and underline the recently established high *twix* regioselectivity of the nitrosoarene ene reaction.[6]

The relative configurations of the ene products were determined by ^{1}H NMR spectroscopy. For this purpose, the hydroxylamines **2** were cyclized with 2,2-dimethoxypropane under acid catalysis to the corresponding 1,3,4-dioxazines **4** (Scheme 2). The *threo* configuration of these conformationally rigid derivatives was assessed by the $J^{1,3}$(H,H) coupling constant for the protons of the vicinal CH groups (*threo* 8.8 Hz). This clearly speaks for their 180° arrangement and establishes the *threo* configuration.

* Address correspondence to this author. Fax: +49931/888 4756. E-mail: adam@chemie.uni-wuerzburg.de.

(1) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 5041−5049. Adam, W.; Brünker, H. G. *J. Am. Chem. Soc.* **1995**, *117*, 3976−3982. Adam, W.; Brünker, H.-G.; Kumar, A. S.; Peters, E.-M.; Peters, K.; Schneider, U.; von Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899−1905.

(2) Adam, W.; Nestler, B.; Pastor, A.; Wirth T. *Tetrahedron Lett.* **1998**, *39*(17), 2625−2629. Stratakis, M.; Vassilikogiannakis, G.; Orfanopoulos M. *Tetrahedron Lett.* **1998**, *39*(16), 2393−2396. Gau, A.-H.; Lin, G.-L.; Uang, B.-J.; Liao, F.-L.; Wang, S.-L. *J. Org. Chem.* **1999**, *64*, 2194−2201.

(3) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703−710.

(4) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226−5227. Greene, F. D. In *Stereochemistry and Reactivity of Systems containing π-Electrons*; Watson, W. H., Ed.; Verlag Chemie International: Deersfield Beach, FL, 1983; pp 197−240.

(5) Knight, G. T.; Pepper, B. *Tetrahedron* **1971**, *27*, 6201−6208.

(6) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791−6792.

10.1021/ja001752w CCC: $19.00
Published on Web 09/26/2000

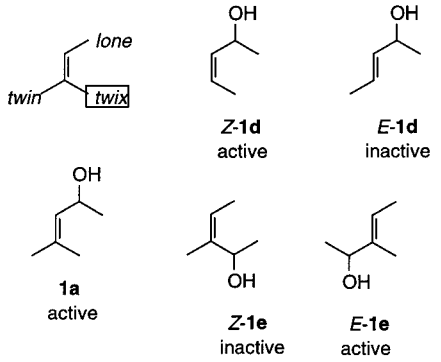
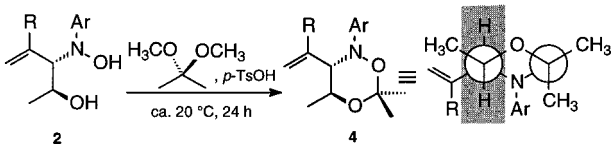
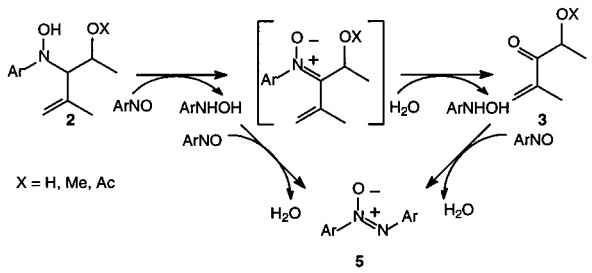


Figure 1. The ene reactivity with *twix* regioselectivity between the nitrosoarene and the chiral allylic alcohols **1**.

Scheme 2. Determination of the *threo* Configuration for the Nitrosoarene Ene Products



Scheme 3. Formation of the Enone **3a** and Azoxybenzene **5** from the Primary Ene Product **2a** through Subsequent Oxidation by the Nitrosoarene

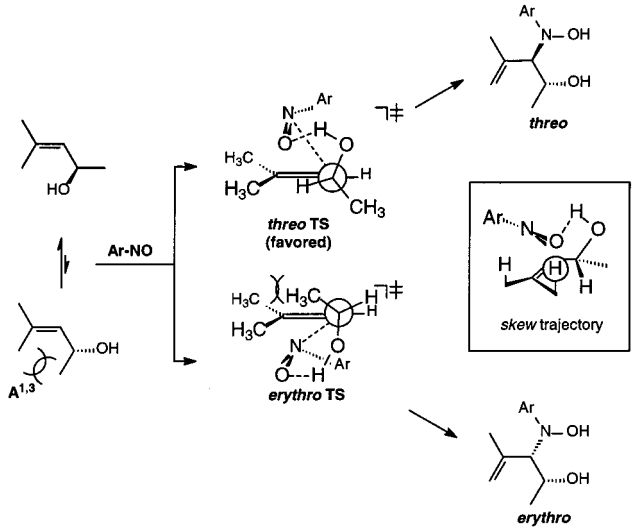


In all of these nitrosoarene ene reactions, the enones **3** were formed (Scheme 3). The amount of enone strongly depended on the substrate/enophile ratio, i.e., the larger the olefin excess, the less the amount of the enone that formed (Table 1). For example, in the case of the methyl ether **1c**, the product/enone ratio increased from 51:49 for an equimolar amount of olefin (entry 8) to 85:15 for 4 equiv (entry 10). Mechanistically pertinent, the diastereomeric ratio increased from 60:40 for 4 equiv (entry 8) to 79:21 for 1 equiv (entry 10). The same trend was observed for the ester substrate **1b** (entries 5−7). The enone formation is attributed to dehydrogenation of the hydroxylamine ene product **1** by the nitrosoarene[7] to the nitrone and subsequent hydrolysis by adventitious water. The released hydroxylamine ArNHOH condenses in situ with the ArNO to generate the azoxyarene **5**, which was observed in amounts nearly equal to the enone **3**.

The *threo* selectivity is rationalized mechanistically in terms of the established hydroxy-group directivity, which is the combination of 1,3-allylic strain and hydrogen bonding (Scheme 4).[1,2] Thus, the enophilic attack of the nitrosoarene on the *twix*

(7) Knight, G. T.; Loadman, M. J. R *J. Chem. Soc. (B)* **1971**, 2107−2112.

Scheme 4. Hydroxy-Group Directivity (*threo* Selectivity) in the Ene Reaction of Nitrosoarenes with 1,3-Allylically ($A^{1,3}$) Strained Alcohols



substituent[6] along the *skew* trajectory is directed by the allylic hydroxy functionality through hydrogen bonding in the chiral substrate, which is conformationally aligned on account of 1,3-allylic strain. The *threo* transition state is favored over the *erythro* one because 1,3-allylic strain is minimized and, therefore, the *threo* diastereomer is the main product.

This mechanistic model also accounts for the reactivity behavior of the chiral substrates in Figure 1. The ene-inactive *E*-**1d** possesses no *twix* substituent, while for *Z*-**1e** the *twix* site is occupied by the chiral alcohol functionality and hydrogen bonding presumably prevents the ene reaction.[1,8] The poor diastereoselectivity of the *E*-**1e** substrate (Scheme 1) is due to the lack of 1,3-allylic strain.

In summary, the nitrosoarene ene reactivity has been tamed sufficiently such that a highly *threo*-selective allylic amination of 1,3-allylically strained substrates has been achieved. In fact, the extent of the diastereoselectivity for the nitrosoarene ene reaction is superior to that of the well-studied singlet oxygen and triazolinedione enophiles.[1,2] An additional advantage is that a high *twix* regioselectivity operates for the nitrosoarene enophile. This combination of high *threo* diastereoselectivity and high *twix* regioselectivity offers attractive synthetic opportunities for the controlled amination of chiral 1,3-allylically strained hydroxy-functionalized olefins.

Acknowledgment. For financial support we thank the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm: "Peroxidchemie") and the Fonds der Chemischen Industrie (doctoral fellowship for N.B.).

Supporting Information Available: Complete experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA001752W

(8) Adam, W.; Peters, K.; Peters, E.-M.; Schambony, S. B. *J. Am. Chem. Soc.* **2000**, *122*, 7610−7611.