The Nitroso Ene Reaction: A Regioselective and Stereoselective Allylic Nitrogen Functionalization of Mechanistic Delight and Synthetic Potential

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Received April 29, 2003

Contents

I. Introduction

Nitric oxide (NO) chemistry has been intensively studied in the past decades.[1] The unexpected role of nitric oxide as a key physiological regulator has fomented intensive interdisciplinary activity in this field. The related nitroso chemistry, despite its general importance, has received comparatively little attention. In particular, the nitroso *ene* reaction (Scheme 1), discovered in 1965,[2] has not been studied to the extent that it merits. It constitutes a mild, valuable methodology for the direct regioselective and stereoselective allylic nitrogen functionalization of readily available alkenes.[4] Moreover, it may figure as a key step in the puzzling in-vivo transformations that amino compounds undergo (see section VII),[5−7] and it is an established method in the chemical modification of natural rubber.[8] Presumably, the numerous in-situ reactions that nitroso ene products suffer have restricted for many years the development and use of nitroso ene chemistry for synthetic purposes; in particular, this pertains to the direct nitrogen functionalization of olefins. This disadvantage may nowadays be readily avoided (section II.B), mainly by the use of electron-poor nitroso enophiles; alternatively, the secondary ene products may be of value for preparative purposes.

Allylamines are versatile and fundamental building blocks in organic chemistry, as exemplified in the preparation of alkaloids,[9] α- and β-amino acids,[10−13] and carbohydrate derivatives.[14] The synthesis of allylic amines may be divided into two groups: (i) nucleophilic allylic substitution (e.g., Mitsonobu reaction, Gabriel synthesis) and (ii) direct allylic amination of simple double-bond substrates (nitrene additions and ene reactions). The latter process is more economical and advantageous, since readily available alkenes are converted to valuable nitrogen-functionalized products, especially by the nitroso ene reaction (Scheme 1).[4]

A large number of publications have appeared on the mechanism of the ene reactions of the three isoelectronic species singlet oxygen ($^1O_2$),[15−17] triazolinedione (TAD),[18−20] and ArNO;[21,22] nevertheless, the nature of the involved intermediates and the structures of the transition states are not well resolved to this day. In view of the high and diverse reactivity of nitroso compounds, the nitroso ene reaction offers challenging opportunities for mechanistic exploration, as shall become apparent through recent experimental and theoretical work.

This review provides the first comprehensive coverage of the mechanistically challenging and synthetically promising nitroso ene reaction. On the basis of our recent research work and the relevant literature, we address a variety of pertinent aspects on mechanism and selectivity as well as synthetic applications and catalytic variations of the nitroso ene reaction. Biological implications shall also be briefly examined.

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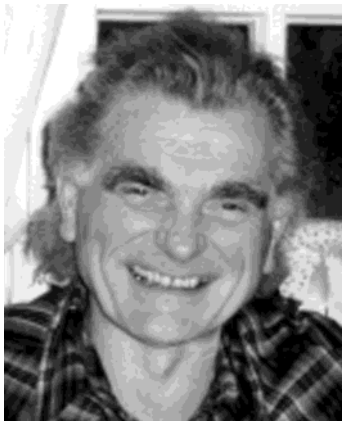
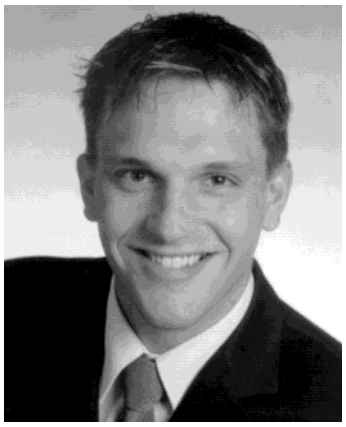
10.1021/cr030004x CCC: $44.00
Published on Web 09/05/2003

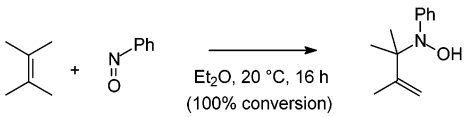


Waldemar Adam, born in 1937 in Alexanderdorf, Ukraine, received his B.Sc. degree from the University of Illinois (1958) and Ph.D. degree from MIT (1961, with F. D. Greene). He started his academic career in 1961 at the University of Puerto Rico (Rio Riedras), where he was promoted to Full Professor in 1970. In 1980 he was appointed to the Chair of Organic Chemistry at the University of Würzburg (Germany). His publication record covers more than 900 scientific papers on high-energy molecules (dioxiranes, dioxetanes), chemi- and bioluminescence, photochemistry, electron transfer, laser chemistry, cyclic peroxides, singlet oxygen, oxygen transfer, azoalkanes, diradicals, pericyclic reactions, photobiology, and biomedical applications. As of April 2003 he has retired in Puerto Rico.



Oliver Krebs, born in 1974 in Nördlingen, Germany, has studied chemistry at the University of Würzburg since 1994, where he received his diploma degree in 2000 (Procter & Gamble Research Award) and his doctoral degree in 2002 (Lower-Franconian Science Award) in Professor Adam's group for his research on the ene reaction of nitrosoarenes, singlet oxygen, and triazolinedione. Sponsored by DAAD (German Academic Exchange Service), he conducted a joint research project with Professors Michael Orfanopoulos and Manolis Stratakis at the University of Crete, Greece, as part of his doctoral work. Currently, he is a Postdoctoral Fellow in Professor Richard J. K. Taylor's research group at the University of York, England, engaged in natural product synthesis.

Scheme 1. Reaction of Nitrosobenzene with Tetramethylethylene; An Early Example of the Nitroso Ene Process (ref 3)

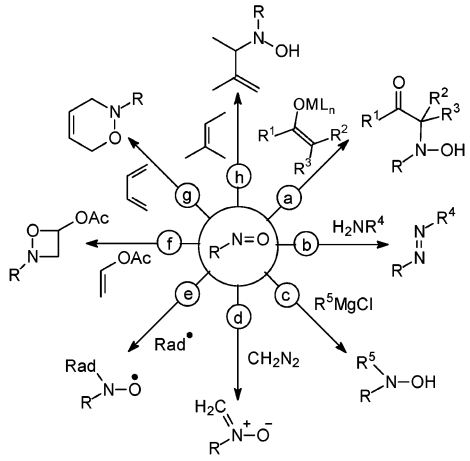


II. Reactivity of Nitroso Compounds

A. As Versatile Reagents

The nitroso functional group undergoes a variety of reactions, which include additions, isomerizations, oxidations, as well as reductions.[23,24] Their versatile reactivity results in numerous side reactions, which is one of the reasons why nitroso compounds have received limited attention in organic synthesis; nevertheless, such diversity should be advantageous for developing new and efficient synthetic methods based on nitroso chemistry.

Scheme 2. Use of Nitroso Compounds in Organic Synthesis



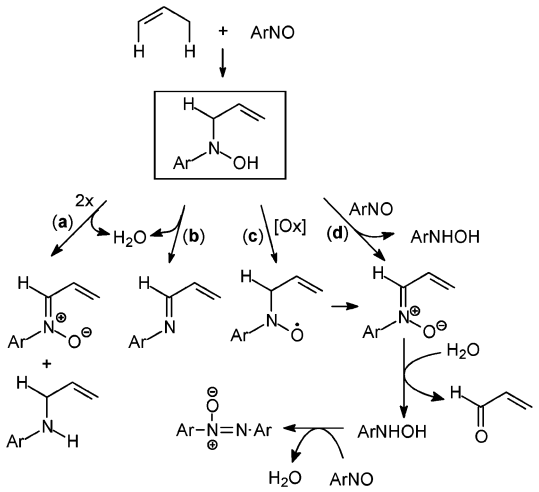
Examples of the various transformations that nitroso compounds undergo are displayed in the form of the rosette in Scheme 2. As electrophilic species, they undergo additions with enolates (path a),[25−27] amines (path b),[28] and Grignard reagents (path c).[29−31] With diazomethane, nitrones are formed (path d)[32] and it is well-known that nitroso compounds are good radical scavengers (path e).[33−35] The [2+2] (path f)[36,37] and [4+2] (path g)[38−41] cycloadditions of nitroso compounds are established transformations, as well as the ene reaction (path h).[3,4] By the use of chiral nitroso compounds or chiral partner substrates, excellent diastereoselectivities have been obtained in the nitroso aldol reaction (path a),[25,27] in [4+2] cycloadditions (path g),[38,42,43] and in the ene reaction (path h); the latter shall be discussed in detail in section V.

The mode selectivity of the nitroso reactions with double bonds (paths f−h) has as yet not been systematically studied. With dienes, the [4+2] cycloaddition is usually the exclusive pathway.[38] With alkenes that bear an allylic hydrogen atom, the ene reaction usually prevails.[3,4,21] The [2+2] cycloaddition mode is rare but is observed between trichloronitrosomethane and perhalogenated or electron-rich alkenes.[36,37] In contrast to the isoelectronic heteroatom enophiles singlet oxygen and triazolinedione, product mixtures derived from the competition between these pericyclic reaction modes are unusual for nitroso compounds,[44] i.e., they advantageously exhibit a high mode selectivity. Of the transformations in Scheme 2, the nitroso ene reaction has received relatively little attention for preparative purposes; the reasons are outlined in the next section.

B. As Enophiles

In view of their low LUMO energy, nitroso compounds belong to the class of most reactive enophiles; however, compared to the heteroatom enophiles

Scheme 3. In-situ Transformations of the Hydroxylamines Derived from the Nitroso Ene Reaction



singlet oxygen[17,45] and triazolinedione,[18,46] relatively few papers have appeared on the nitroso ene reaction. Whereas the nitroso [4+2] cycloaddition[38] has been extensively investigated and its synthetic potential documented (see section II.A), this is not the case for the ene reaction. In fact, the little data that is available is quite scattered, and no definitive review exists to date on this remarkable pericyclic process. Presumably, the low persistence of the initially formed hydroxylamine ene product toward subsequent in-situ reaction such as oxidation, disproportionation, and elimination has curbed the interest in applying the potentially useful ene reaction for synthetic purposes. The more common in-situ products, generated from the initial ene adducts, are displayed in Scheme 3 and comprise nitrones, nitroxides, imines, amines, and azoxy compounds.[4,47,48]

Ene products derived from electron-rich nitroso compounds (e.g., 4-nitrosophenol, *N*,*N*-dimethyl-4-nitrosoaniline) undergo almost entirely disproportionation along path a.[49−51] On treatment with acids and bases or on heating, the resulting hydroxylamine dehydrates to the corresponding imine (path b),[23,52] a process that is part of the Ehrlich−Sachs reaction.[53]

The oxidation of the ene products from various nitrosoarenes and tetramethylethylene by adventitious oxygen or by an "excess" of nitroso compound leads to the relatively persistent nitrosyl radicals path c (see also Scheme 2, path e), which have been well studied by means of ESR spectroscopy.[54−57] Trace amounts of nitroxides are formed in almost all nitroso ene reactions, except for electron-poor substrates (see below); these radicals cause signal broadening in the NMR spectra, which severely complicates the product analysis. Nevertheless, to obtain well-resolved NMR spectra directly on the product mixture without workup, ca. 5 mg of phenylhydrazine or diphenylhydrazine should be added immediately before the analysis, which removes the undesirable paramagnetic impurities.[44]

Hydroxylamines that bear a hydrogen atom at the N-substituted carbon (e.g., the ene products from di- or trisubstituted alkenes) may be further oxidized to nitrones (path d in Scheme 3), which are labile species and undergo polymerizations,[58] 1,3-cycloadditions,[59,60] or are solvolyzed.[61,62] The solvolysis leads to the respective carbonyl compounds (e.g., the enones) and the hydroxylamine; the latter condenses with another equivalent of the nitroso compound to an azoxyarene, and the resulting water hydrolyzes more nitrone (path d, subsequent reaction). Since this process consumes two moles of the nitroso compound, the conversion of the alkene is significantly decreased and in many cases, especially for less reactive olefins, azoxyarenes may be observed as the major or exclusive products.

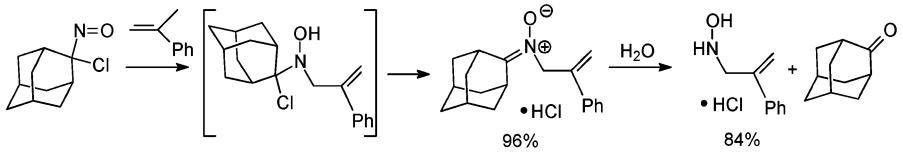
Fortunately, electron-withdrawing groups at the nitroso functionality not only increase the enophilic reactivity, but also afford relatively persistent hydroxylamine products toward further in-situ transformations. Therefore, to minimize such problems, most recent work on the nitroso ene reaction has employed electron-poor enophiles, e.g., α-chloro nitroso compounds,[63−65] acyl nitroso compounds,[66−68] pentafluoronitrosobenzene,[21,22,60] and 4-nitronitrosobenzene.[69] Since electron-poor nitroso species are also relatively strong oxidizing agents, path d has still been observed as a (minor) side reaction for such nitroso enophiles.

The reaction of α-chloronitroso enophiles does not lead to the expected primary hydroxylamine ene product; instead, the latter eliminates in situ HCl and affords the persistent nitrone hydrochloride salt. The nitrone hydrochloride salt is readily hydrolyzed to the respective ketone and the hydroxylamine (Scheme 4).[63] Through this methodology primary amines become accessible.

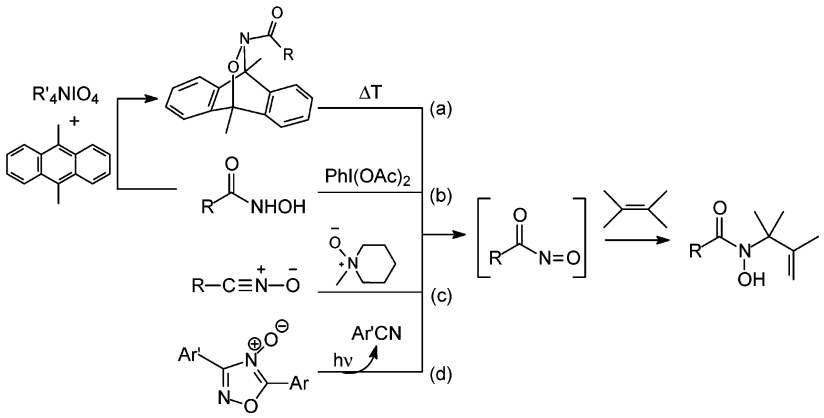
Alkenes, which contain only aliphatic substituents, e.g., 2-methyl-2-butene or 2-methylpropene, are not sufficiently reactive toward α-chloronitrosoadamantane.[63] Our own experiments showed that α-chloronitrosocyclohexane[70] and α,α-dichloronitrosoethane[71,72] do not react with 2-methyl-2-butene within 10 days at 20 °C. For the latter enophile, presumably steric obstruction decreases the reaction rate. Nevertheless, in section V.B (stereoselectivity), α-chloronitroso sugar derivatives are presented, which are much more reactive and react also with alkenes with only alkyl substituents. Presumably, the inductive effect (−I) of the α-ether functionality in these sugar derivatives is responsible for the increased ene reactivity. Consequently, α-chloro-*β*-ethoxynitrosoethanes[73,74] should be sufficiently reactive enophiles to afford attractive ene products for the synthesis of primary amines. As side products, *β*-chloro hydroxylamines are obtained, which presumably are formed by the nucleophilic attack of a chloride ion on the aziridine *N*-oxide intermediate of the ene reaction (see section III).[66]

Acyl−nitroso compounds are probably the most reactive nitroso enophiles[4] and also well-known to engage in [4+2] cycloaddition.[75−78] They are attractive aminating agents due to the fact that the carbonyl group at the nitrogen site may be readily removed or derivatized ("amidating agents").[66] Several in-situ preparative routes have been developed to make these highly reactive nitroso compounds available for synthetic applications (Scheme 5).

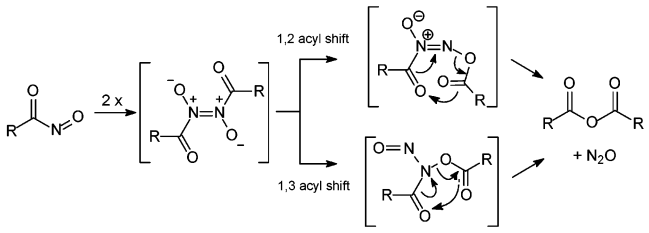
Scheme 4. Ene Reaction of α-Chloronitrosoadamantane with 2-Phenylpropene and Subsequent Hydrolysis



Scheme 5. In-situ-Generated Nitroso Carbonyl Compounds for the Ene Reaction with Tetramethylethylene (TME)



Scheme 6. Proposed Mechanism for the Decomposition of Acyl Nitroso Compounds to the Corresponding Anhydrides



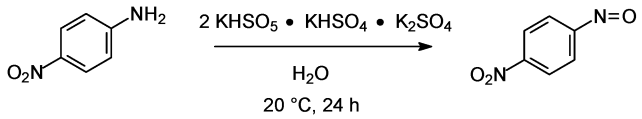
In this context, the direct in-situ oxidation of hydroxamic acids with periodates is not possible,[75−77] because this oxidant destroys the ene product. To circumvent this problem, the acyl nitroso species is first trapped in situ by [4+2] cycloaddition with dimethylanthracene (DMA).[66] The resulting cycloadducts, which are inert toward further oxidation, may be thermolized at relatively low temperature (ca. 100 °C) to release the free nitroso species in the absence of an oxidant (path a).

Recently, acyl nitroso compounds have been generated in situ for the ene reaction by the oxidation of hydroxamic acids with $PhI(OAc)_2$ (path b)[67] or nitrile oxides by *N*-methylmorpholine-*N*-oxide (path c).[68] An alternative novel entry to in-situ-generated acyl nitroso enophiles is the photolysis of 1,2,4-oxadiazole-4-oxides (path d).[79,80]

A limiting factor for the use of acyl nitroso enophiles is their high reactivity toward nucleophilic functional groups. Also, their decomposition into the corresponding anhydride with the evolution of dinitrogen oxide gas is a problem (Scheme 6).[76,78,80] Hence, only unfunctionalized alkenes give fair yields of ene product with acyl nitroso compounds.

4-Nitronitrosobenzene does not exhibit such undesirable reactivity and constitutes a "well-behaved" enophile, which we advantageously exploited in our work. It is persistent and tolerates other functional

Scheme 7. Preparation of 4-Nitronitrosobenzene from 4-Nitroaniline by Oxidation



groups, e.g., even the hydroxy group. This yellow-colored powder is readily prepared by oxidation of commercially available 4-nitroaniline with potassium monopersulfate (Scheme 7).[81,82]

As an enophile, 4-nitronitrosobenzene undergoes clean reactions with tri- and tetrasubstituted olefins. The reactivity (k_{rel}) of trisubstituted olefins with a variety of *lone* substituents (Figure 1)[83] toward this nitroso enophile has been shown to depend on electronic, steric, and coordinative effects. Thus, an ethyl group at the *lone* site accelerates the reaction rate somewhat, but the bulky *tert*-butyl group decreases the ene reactivity significantly. The electron-withdrawing methoxy and acetoxy groups in a substrate (−I effect) decrease the reactivity, whereas the hydroxy group enhances reactivity through coordination of the enophile by hydrogen bonding (see also section V.A).

[*Note*: For the regiochemical differentiation of the three alkyl groups in trisubstituted olefins the following codification is used (see Figure 5.2): Attention is focused on the central alkyl substitutent, which is

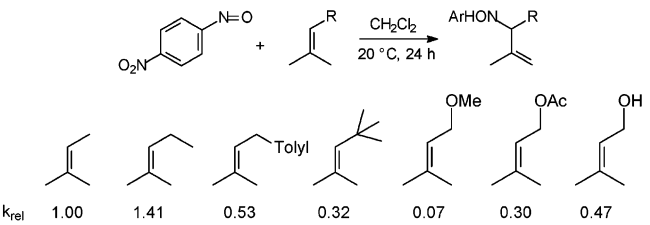


Figure 1. Ene reactivity (relative rates) of *lone*-substituted 2-methyl-2-butenes with 4-nitronitrosobenzene.

defined as the *twixt* group (R_{twix}, for simplification the last "t" has been dropped); "twixt" comes from old English and means "between", i.e., R_{twix} is between a geminal and vicinal alkyl group. The other geminal substitutent is then designated as the *twin* group (R_{twin}), and the remaining vicinal substituent as the *lone* one (R_{lone}).]

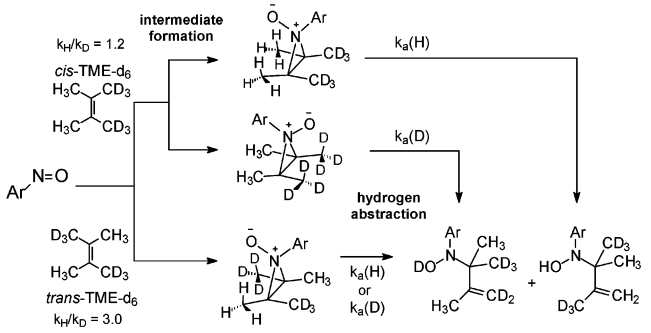
The formation of nitrones by the oxidation of the resulting ene adducts (see Scheme 3, path d) is observed only as minor (<10%) side product in the ene reaction of 4-nitronitrosobenzene with 2-methyl-2-butene, 2-methyl-2-pentene, and mesitylol.[47,62,83] Conversely, electron-poor olefins such as tiglic acid derivatives[84] undergo a clean ene reaction, since the ene product is deactivated and, therefore, resistant toward further oxidation. Unfortunately, disubstituted alkenes react with 4-nitronitrosobenzene to form a rather complex product mixture but no ene products.

The advantages of the 4-nitronitrosobenzene enophile as a probe for mechanistic studies are its ready accessibility, its pronounced persistence, its good yields of ene products, and its appreciable steric demand resulting in excellent regiochemical and stereochemical control. The disadvantage for synthetic applications as allylic aminating reagent is the need to release the free amino group. Unfortunately, a suitable dearylation is to date only known for the *p*-methoxyphenyl group.[85−87] The latter derivative is a much less reactive enophile compared to 4-nitronitrosobenzene (see section II.B).

III. Mechanism

In the first definitive mechanistic study of the nitroso ene reaction, Greene and co-workers employed Stephenson's isotope test with F_5C_6NO as enophile (Scheme 8).[21] The intramolecular isotopic competition in *cis*- and *trans*-2,3-dimethyl-but-2-ene-d_6 (*cis*-TME-d_6 and *trans*-TME-d_6) disclosed for this enophile a negligible kinetic isotope effect (KIE) for the *cis*-TME-d_6 substrate ($k_H/k_D \approx 1$) but a large one for *trans*-TME-d_6 ($k_H/k_D \gg 1$). To accommodate these KIE data, it was proposed that an aziridine-*N*-oxide intermediate is formed irreversibly in the rate-determining first step of the ene reaction. Once the three-membered-ring intermediate has been generated from the *cis*-TME-d_6, the terminal oxygen atom of the enophile points either to the undeuterated or deuterated side of the alkene and there is no isotopic H/D competition. In contrast, for the three-membered-ring intermediate derived from *trans*-TME-d_6, isotopic discrimination occurs in the product-forming second step (H or D abstraction), which accounts for the large k_H/k_D value that has been observed (Scheme 8).

Scheme 8. Formation of the Aziridine-*N*-oxide Intermediate and Hydrogen Abstraction in the Ene Reaction of ArNO (Ar = F_5C_6) with Deuterium-Labeled Tetramethylethylenes



In contrast, in our recent studies with 4-nitronitrosobenzene as enophile, the Stephenson's isotope test provided experimental evidence for the *reversible* formation of the aziridine-*N*-oxide intermediate (Table 1).[88] As expected, the ene reaction of this nitrosoarene with *trans*-TME-d_6 (fourth column) and *gem*-TME-d_6 (last column) show high intramolecular primary KIE ($k_H/k_D \gg 1$). For *cis*-TME-d_6 (third column) and for the intermolecular competition between TME-d_0 and TME-d_{12} (second column), the KIE values are substantially smaller but mechanistically most revealing because they require *reversible* generation of the aziridine-*N*-oxide intermediate.

Since the **TS1** and **TS2** transition states of the two reaction steps have similar activation energies, reversal competes with hydrogen or deuterium abstraction (Scheme 9). For the abstraction process, a primary KIE may operate, which should perturb the product distribution of the intramolecular competition in the *cis*-TME-d_6 substrate and of the intermolecular competition in the TME-d_0/TME-d_{12} pair. Since D abstraction is retarded compared to H abstraction, more of the intermediate $\mathbf{AI}_D$ reverts than $\mathbf{AI}_H$. Accordingly, more of the ene reaction is channeled along the H-abstracting path and $k_H/k_D > 1$ is observed (Scheme 9). By means of a steady-state kinetic analysis, the rate constant for reversibility (k_r) versus for abstraction (k_a) has been calculated to be $k_r = k_a(D) = 1/3\ k_a(H)$. Thus, for the intended D abstraction, reversal is about three times more pronounced than for H abstraction.

The partitioning of the aziridine *N*-oxide either back to the alkene or forward to the nitroso ene product is not unique. It was already observed for independently synthesized aziridine *N*-oxides![89] As shown in Scheme 10, thermolysis of the authentic aziridine *N*-oxides **A** and **B** at −30 °C affords exclusively the ene product in the case of the *cis*-configured **A**, whereas equal amounts of ene and reversal products, namely, the alkene and the nitroso compound, are obtained for the *trans*-configured **B**, in which hydrogen abstraction is hindered through steric factors.

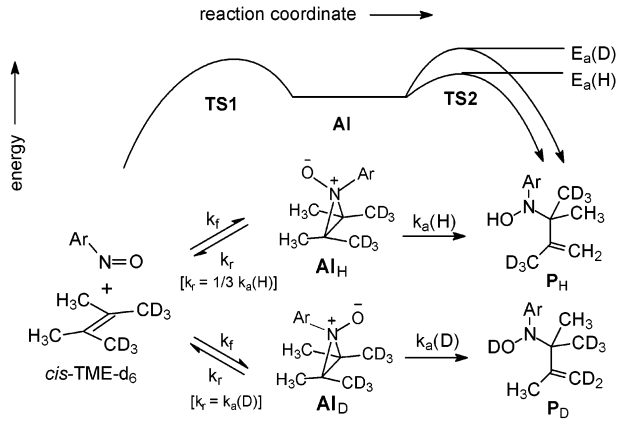
This three-membered-ring intermediate as direct precursor to the ene products was recently questioned by theoretical work.[46,90] Instead, a "polarized diradical" (**PD**) was proposed as the intermediate, and the aziridine *N*-oxide (**AI**) was disposed of as a mere bystander, not responsible for ene product formation (Scheme 11). The observed KIE values were rationalized in terms of hindered rotation around the C−N and the C−C bonds in the diradical, whereas the three-membered-ring intermediate was necessary for the isomerization between **PD** and **PD′** (explains the observed high k_H/k_D values for *gem*-TME-d_6). The hindered rotation in the polarized diradical **PD** (explains the observed small k_H/k_D values for *cis*-

Table 1. Intermolecular and Intramolecular Kinetic Isotope Effects for the Ene Reaction of Tetramethylethylenes (TME) with ArNO (Ar = 4-O_2N-C_6H_4)

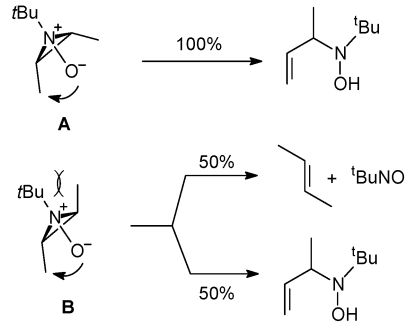
	k_H/k_D values[a]				
	intermolecular		intramolecular		
enophile	versus				
	TME-d_0	TME-d_{12}	*cis*-TME-d_6	*trans*-TME-d_6	*gem*-TME-d_6
4-O_2N-C_6H_4-N=O	2.0		1.5	3.0	4.0

[a] Reference 88.

Scheme 9. Reaction Profile and Relative Extent of Reversibility for the Ene Reaction of ArNO with the *cis*-TME-d_6 Substrate

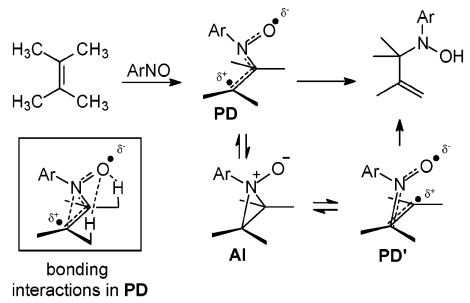


Scheme 10. Steric Inhibition of the Hydrogen Abstraction in the Thermolysis of the Aziridine *N*-Oxides A and B



TME-d_6) was attributed to the favorable orbital interaction between the radical-bearing sp^2 carbon and the π^* orbital of the NO bond of the enophile as well as the coordination of the external oxygen atom with the allylic hydrogen atoms (see the **PD** structure in the inset of Scheme 11). Such a **PD** species may also be viewed as an unsymmetrically bonded three-membered-ring intermediate. Regardless of whether the aziridine *N*-oxide **AI** is a bystander or a direct precursor to the ene products, this three-membered-ring species accounts for the observed isotope effects and regioselectivities (see next section). Thus, we prefer to view the mechanism of the nitroso ene reaction in terms of the established three-membered-ring intermediate[21] and ascribe to the as yet not observed polarized diradical species **PD** a minor role in the interpretation of experimental results.

Scheme 11. Polarized Diradical Intermediate (PD) in the Ene Reaction and the Three-Membered-Ring Species (AI) as Bystander



IV. Regioselectivity

A. Hydrogen Abstraction

The regioselectivity of hydrogen abstraction in the heteroatom ene reaction is a function of the identity of the enophile (Figure 2): Singlet oxygen ($^1O_2$) prefers to abstract allylic hydrogen atoms from the more crowded side of the double bond due to the coordination with the allylic hydrogen atoms (*cis* effect).[16,17] Triazolinedione (TAD) abstracts from the more crowded end due to the steric and electronic effects discussed in section IV.E (*gem* effect).[18] ArNO abstracts both at the more crowded *gem* end and more substituted *cis* side of the double bond, defined as the *twix* position; thus, the combined features of the *gem* and *cis* effects are evident (*skew* effect).[69] Compared to $^1O_2$ and PTAD, the ArNO enophile possesses the higher extent of regioselectivity, which is certainly an advantage for synthetic purposes.

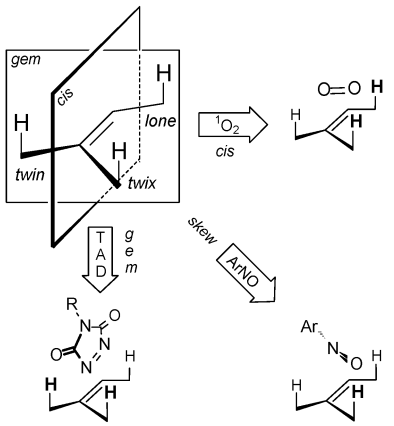


Figure 2. *Skew* regioselectivity in the ene reaction of ArNO, and the *cis* and *gem* regioselectivity of $^1O_2$ and TAD.

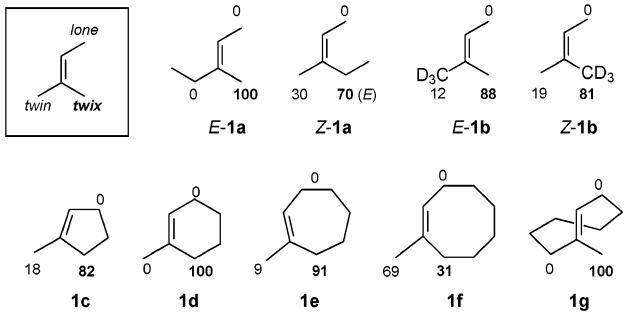
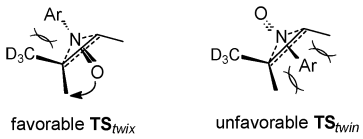


Figure 3. Regioselectivity in the ene reaction of ArNO with various trisubstituted alkenes (refs 69, 83, 91).

This general regiochemical phenomenon of the ArNO ene reaction has been recognized from a comparative study of the enophilic selectivity of various acyclic substrates with different *twix* and *twin* substituents and with 1-methylcycloalkenes (Figure 3). In all cases, except for substrate **1f**, the hydrogen abstraction at the *twix* position is the major pathway and no ene product is observed from *lone* abstraction.

The *skew* effect was rationalized in terms of the steric interactions in the two possible transition states $\mathbf{TS}_{twix}$ and $\mathbf{TS}_{twin}$, which lead to the respective ene products.[69]

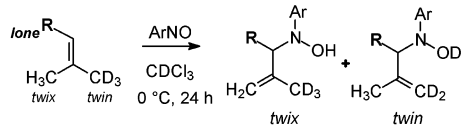


In the $\mathbf{TS}_{twin}$ structure, the aryl substituent of the ArNO enophile is located at the more crowded and, thus, sterically more encumbered side of the alkene, whereas in $\mathbf{TS}_{twix}$, the aryl group points to the unsubstituted corner of the alkene and the steric repulsions are reduced. Consequently, the combined steric repulsions of the aryl group with the *twix* and *lone* substitutents, as well with the *twin* group, forces the ArNO to follow along the *skew* trajectory in the favored $\mathbf{TS}_{twix}$ arrangement. Hydrogen abstraction takes place almost exclusively from the *twix* group, as displayed in the Figures 2 and 3. The differences in the regioselectivities in Figure 3 have been rationalized in terms of the distinct steric hindrance in the attack of the enophile or on account of conformational effects in the hydrogen abstraction (see section IV.C).[83,91]

B. Control by the *Lone* Substituent

The extent of the ArNO regioselectivity has been assessed from a detailed study of simple trisubstituted alkenes with a variety of *lone* substituents. Evidently, both steric and electronic interactions with the *lone* substituent control the regioselectivity. Thus, for a wide selection of primary and secondary *lone* alkyl-substituted substrates, it was found that the *twix*/*twin* regioselectivity is constant at about 85:15. In contrast, for the *lone tert*-butyl group, exclusively the *twix* regioisomer is obtained (Table 2).[44] These unusual results are mechanistically rationalized in terms of the steric effects shown in Figure 4. For all substrates **2a**−**f**, the steric interactions in the *syn*-configured transition structure $\mathbf{TS}_{twix}$ are less severe than in the *anti*-configured $\mathbf{TS}_{twin}$; consequently, the *twix* regioisomers are formed as major ene products. The fact that about the same (ca. 85:15) *twix*/*twin* ratio is observed for the **2a**−**e** substrates may be accounted for in terms of the favored conformations that the *lone* substituent may acquire, which minimize the steric interactions with the aryl group of the enophile in the $\mathbf{TS}_{twin}$ structure. Evidently, for the primary and secondary *lone* substituents in the substrates **2a**−**f** (Table 2, entries 1−5), the hydrogen atom may assume the favorable (minimal 1,3-allylic strain) *inside* conformation in $\mathbf{TS}_{twin}$ whereas the remaining R^1 and R^2 groups are located at the periphery, as displayed in Figure 4 (central structure). Since in the $\mathbf{TS}_{twin}$ structure the R^1 and R^2 groups at the *lone* substituent for the substrates **2a**−**e** are pointing away from the aryl group of the enophile, insignificant differences are encountered in the steric interaction between the alkene and the enophile; consequently, similar *twix*/*twin* ratios are obtained. In contrast, for the substrate **2f** with the tertiary *lone* substituent, namely, the *tert*-butyl group, irrespective of which rotational isomer is considered, no conformational arrangement is possible in which a methyl group does not collide with the aryl substituent. Thus, for substrate **2f**, the $\mathbf{TS}_{twin}$ encounter is sterically prohibitive and the *twix* regioisomer is formed exclusively.

Table 2. Regioselectivity in the Ene Reaction of 4-Nitronitrosobenzene (ArNO) with the *Twin* Deuterium-Labeled, Trisubstituted Alkenes 2



alkene 2[a]	a	b	c	d	e	f	g-j
R_{lone}	Et				^{i}Pr	^{t}Bu	 -X: -H -OCH$_3$ -CH$_3$ -CF$_3$
twin	17	17	14	14	17	< 5	< 5
twix	83	83	86	86	83	> 95	> 95

[a] Reference 83.

In the reaction of the styrenes with *lone* aryl substitutents **2g**−**j**, only the *twix* regioisomer is formed (Table 2, last column). The *lone* aryl group acquires a partial positive charge during the enophilic attack of the conjugated double bond. This foments additional coordination through the elec-

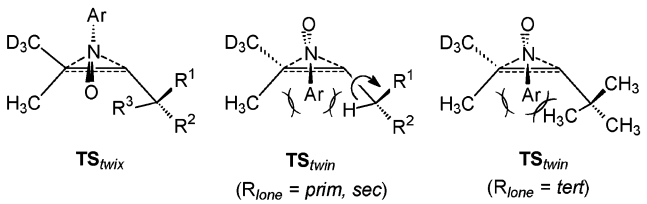


Figure 4. Steric interactions of the *lone* substituent in the transition structures $\mathbf{TS}_{twix}$ and $\mathbf{TS}_{twin}$ for the ArNO ene reaction with the alkenes **2a**−**f**.

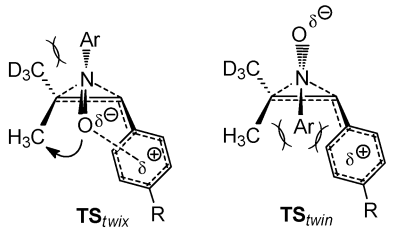


Figure 5. Transition structures $\mathbf{TS}_{twix}$ and $\mathbf{TS}_{twin}$ in the ArNO ene reaction with substituted styrenes (**2g**−**j**; R = H, Me, OMe, F_3C).

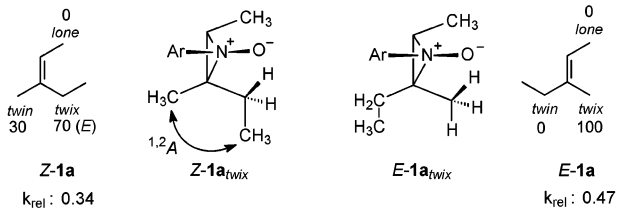


Figure 6. Dependence of the reactivity and the *twix*/*twin* regioselectivity on 1,2-allylic strain ($^{1,2}A$) through hindered hydrogen abstraction.

tronic attraction between the negatively charged oxygen atom of the enophile with the positively charged aryl ring in $\mathbf{TS}_{twix}$, which controls the regioselectivity (Figure 5).

C. Conformational Effects in the Hydrogen Abstraction

The differing *twix*/*twin* regioselectivity with the alkenes *E*-**1a** and *Z*-**1a** (Figure 3) cannot be explained alone in terms of the steric interactions of the alkene substituents with the aryl group of the enophile (*skew* effect). An additional effect must operate, namely, unfavorable 1,2-allylic strain builds up during the hydrogen abstraction at the methylene groups in Z-$\mathbf{1a}_{twix}$ and E-$\mathbf{1a}_{twin}$, which decreases the formation of the corresponding regioisomeric ene products (Figure 6). Since the reversal of the intermediate (see section III) competes with ene product formation for substrates in which hydrogen abstraction at the *twix* (*twin*) substituents is hindered, more of the *twin* (*twix*) regioisomer is formed. Of course, the steric effects in the first reaction step, outlined in section IV.A, are still more pronounced.

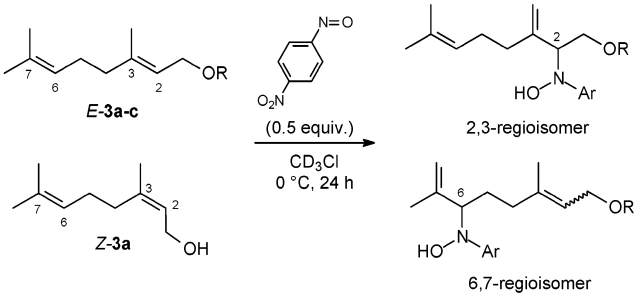
For the *Z*-**1a** substrate, *twix* hydrogen abstraction, which represents the major reaction pathway, is hindered. Consequently, the relative rate (k_{rel}) of *Z*-**1a** is slightly decreased compared to the *E*-**1a** substrate, for which only the minor *twin* pathway is hindered. This feature also plays an important role in the control of the double-bond selectivity, which is described in the next section.

D. Double-Bond Selectivity

The regioselective choice between two double bonds in a substrate depends on their respective reactivity, which was already discussed for the relative rates of intermolecular cases. This *locoselectivity* was determined for geraniol (*E*-**3a**), its derivatives **3b** and **3c**, as well as nerol (*Z*-**3a**), and the results are collected in Table 3.[83]

For all substrates **3a**−**c**, the 6,7 double bond is favored, since the allylic oxygen functionalities electronically deactivate (−I effect) the 2,3 double bond. In geraniol (*E*-**3a**) and nerol (*Z*-**3a**), the coordination of the enophile by hydrogen bonding with the allylic hydroxy group counteracts the electronic deactivation and, thus, the regioselectivity for the 2,3 double bond is slightly increased.

Table 3. Locoselectivities for the Ene Reaction of 4-Nitronitrosobenzene with Geraniol (*E*-3a), Its Derivatives 3b and 3c, and Nerol (*Z*-3a)



olefin	R	regioselectivity[a] 6,7:2,3
E-**3a**	H	77:23[b]
E-**3b**	Me	>95:<5
E-**3c**	Ac	>95:<5
Z-**3a**	H	90:10[c]

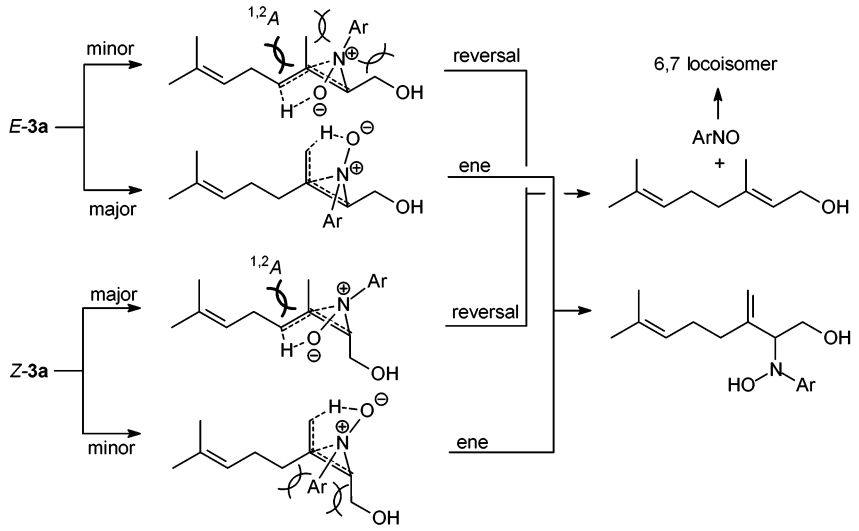
[a] Reference 83. [b] *Twix* abstraction. [c] *Twin* abstraction.

This hydrogen-bonding effect is more pronounced for geraniol (*E*-**3a**), since here the *twix* hydrogen abstraction at the 2,3 double bond is not hindered. This difference in 2,3 versus 6,7 locoselectivity between geraniol (23:77) and nerol (10:90) confirms that the reactivity of the double bond depends on whether hydrogen abstraction is hindered. Note that the 2,3 locoisomer of geraniol (*E*-**3a**) results only from *twix*, in nerol (*Z*-**3a**) exclusively from the *twin* hydrogen abstraction. In the nerol case, the 2,3 locoisomer is formed to a lesser extent than for geraniol, since formation of the aziridine *N*-oxide intermediate for *twin* abstraction is more difficult due to the more severe interactions along the trajectory opposite of the *skew* direction (section IV.A) and lack of hydrogen bonding with the hydroxy group (see section V.A). For both substrates, hydrogen abstraction at the 2,3 double bond from the alkyl chain is not observed, irrespective of whether it is the *twin* group in geraniol or the *twix* group in nerol. This is rationalized in terms of unfavorable 1,2-allylic strain ($^{1,2}A$), which builds up during the abstraction of the coplanar allylic hydrogen atom from this alkyl chain (see Figure 6) and promotes reversal of the aziridine *N*-oxide intermediate to the starting partners (Scheme 12).[92]

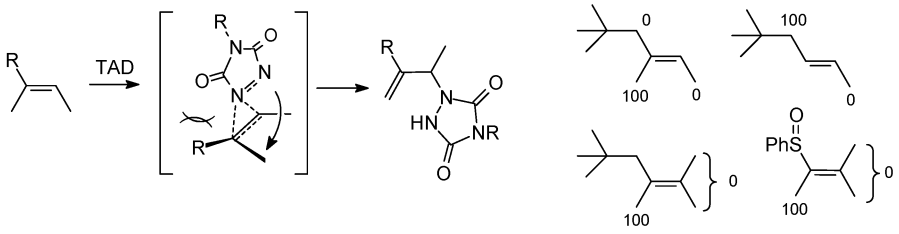
E. "*Skew* Effect" in the Ene Reactions of Singlet Oxygen and Triazolinedione

The steric interactions in the enophilic trajectory, which control the regioselectivity for the ene reaction of ArNO, are also encountered for the isoelectronic enophiles singlet oxygen ($^1O_2$) and triazolinedione (TAD). The general *gem* regioselectivity in the ene reaction of TAD[18,93] with trisubstituted alkenes (see section IV.A) is rationalized by the steric repulsion

Scheme 12. Hindrance of Hydrogen Abstraction by 1,2-Allylic Strain ($^{1,2}A$) and Intermediate Reversal in the Ene Reaction of Geraniol (*E*-3a) and Nerol (*Z*-3a)



Scheme 13. "Geminal" Regioselectivity in the Ene Reaction of TAD

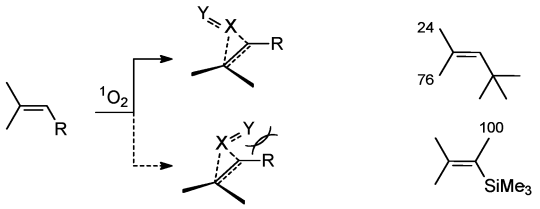


with the *twin* substituent, and thus, *lone* hydrogen abstraction is not observed (Scheme 13). This *gem* effect for TAD may be explained in terms of formation of the more stabilized radical or cation intermediate by opening of the three-membered ring in the hydrogen-abstracting step; however, the same sterically controlled regioselectivity trend is evident for di- and tetrasubstituted alkenes, in which the ring opening is equally stabilized at both ends of the double bond and only steric effects operate. Thus, the repulsion of the enophile by the *twin* substituent, as observed in the hydrogen abstraction for the ArNO enophile (*skew* effect), also plays its role in the TAD ene reaction.

For $^1O_2$, usually the *cis* effect operates in the perepoxide-like transition structure since this enophile is coordinated by the allylic hydrogen atoms, which are to be abstracted (see section IV.A).[16,17] But when the *cis* side is sterically hindered, such substrates are obliged to form the perepoxide-like intermediate from the less encumbered trans side and the regioselectivity is contrary to the usual *cis* effect. Such an anti-*cis* effect is displayed in Scheme 14.[93,94] This steric repulsion is analogous to that between the aryl group of the ArNO enophile and the allylic *twix* and *lone* substituents in the first reaction step, the so-called *skew* effect discussed in section IV.A.

In this context, also the *gem* and *large-group-nonbonding* effects in the ene reaction of $^1O_2$ are related to the ArNO regioselectivity in both reaction steps (Scheme 15).[95,96] In the first step, the side selectivity is ruled by the anti-*cis* effect (see above), and in the hydrogen-abstracting second step the same *gem* selectivity applies as already presented

Scheme 14. Anti-*cis* Effect in the Ene Reaction of $^1O_2$

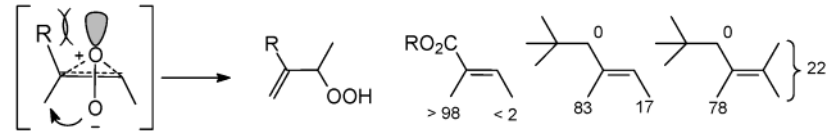


above in this section for TAD. Again, this applies to substrates which are sterically hindered such that the *skew* trajectory is followed to afford as the major ene product hydrogen abstraction geminal to the largest substituent, namely, at the *twix* position in a trisubstituted substrate (Scheme 15).

V. Stereoselectivity

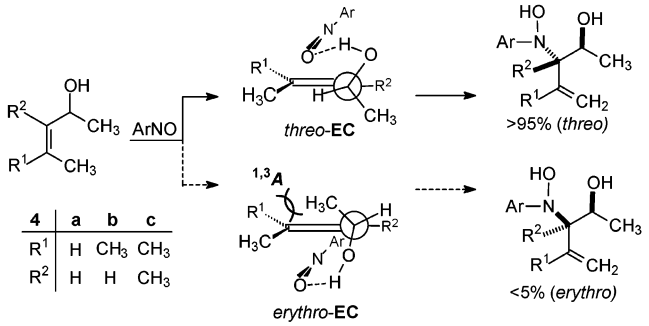
In general, the diastereoselectivity of the ene reaction may be controlled by steric or electrostatic shielding of one π face of the double bond or by the use of chiral enophiles. Some examples for synthetic applications shall be given in section V.B. Additionally, since heteroatom enophiles always bear free electron pairs, they may be coordinated by hydrogen bonding with a protic functionality (OH, NH_2) in the substrate. By the design of appropriate substrates, in which such a protic functionality is available only at one π face of the double bond, high diastereoselectivity may be induced. This concept of diastereoselective control we shall elaborate in the next section for the nitroso ene reaction with allylic alcohols.

Scheme 15. *Gem* and *Large-Group-Nonbonding* Effects in the $^1O_2$ Ene Reaction



R = carbonyl, sulfinyl... (electrostatic repulsion), alkyl, aryl... (steric repulsion).

Scheme 16. Efficient Control of the Diastereoselectivity in the Ene Reaction of ArNO with the Chiral Allylic Alcohols 4a−c through Hydrogen Bonding



A. Chiral Allylic Alcohols (The Hydroxy-Directive Effect)

The ene reaction of 4-nitronitrosobenzene (ArNO) with 1,3-allylically strained chiral allylic alcohols leads to the *threo*-configured ene product in high diastereoselectivity,[62,97] a consequence of the hydroxy-group directivity.[92] Due to 1,3-allylic strain,[92,98] the hydroxy group is conformationally aligned toward the *threo* face of the double bond. Effective hydrogen bonding with the incoming enophile leads, therefore, preferably to the *threo*-configured ene product (Scheme 16).

To shed light on the mechanism of this diastereoselective control during the enophilic attack, it has been instructive to assess the interdependence of the diastereoselectivity and regioselectivity for the ene reactions of the nitrosoarene with the deuterium-labeled allylic alcohols *Z*-**4b**-d_3 and *Z*-**4c**-d_3 (Figure 7).[97] From this interdependence, the diastereoselectivity for the individual regioisomers has been assessed as well as the extent to which the regioselectivity is steered by the hydroxy-group directive effect. Mechanistically significant, not only is absolute *threo* diastereoselectivity observed for the nitrosoarene ene reaction with these stereolabeled substrates, but also absolute *twix* regioselectivity (Figure 7).

In methanol as protic solvent, the *threo*/*erythro* diastereoselectivity (88:12) and the *twix*/*twin* regioselectivity (73:27) are lowered for the *Z*-**4c**-d_3 allylic alcohol. This demonstrates that both the diastereoselectivity and regioselectivity are controlled by the hydroxy-group directive effect. Thus, the enophile is coordinated through hydrogen bonding with the allylic hydroxy group on the *threo* π face to form the *threo*-configured encounter complex *threo*-**EC** (Scheme 17). Subsequent penetration of the ArNO enophile into the π system may lead to the two possible transition structures *syn*-**TS** and *anti*-**TS** for allylic hydrogen abstraction. Of these two transition states, the *syn*-**TS** to afford the *twix* ene product is favored, since the assistance through hydrogen bonding persists. Moreover, for the *anti*-**TS** that leads to the *twin* ene product, the steric repulsions between the aryl group of the enophile and the substrate substituents is more severe, especially for trisubstituted allylic alcohols (R^2 = H). Consequently, a high *threo* diastereoselectivity coupled with high *twix* regioselectivity has been achieved.

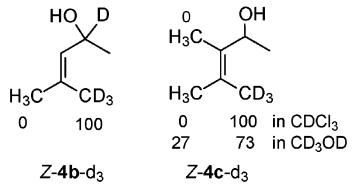
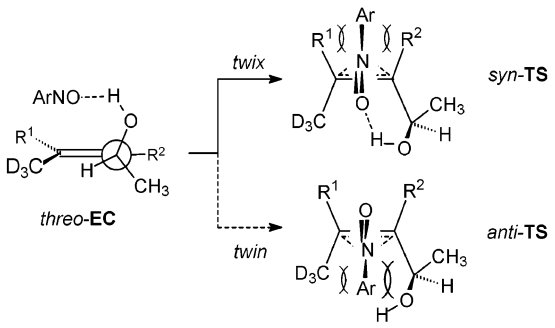


Figure 7. Regioselectivity in the ene reaction of ArNO with the *twix* deuterium-labeled allylic alcohols *Z*-**4b**-d_3 and *Z*-**4c**-d_3 (>95% *threo* diastereoselectivity, see Scheme 16).

Scheme 17. Hydroxy-Group Coordination in the Ene Reaction of ArNO with the Chiral Allylic Alcohols *Z*-4b-d_4 and *Z*-4c-d_3; Control of the Diastereoselectivity in the *threo*-EC Encounter Complex and of the Regioselectivity in the *syn*-TS Transition Structure



B. Synthetic Applications

Chiral nitroso compounds have been successfully employed in the diastereoselective [4+2] cycloaddition[38,42,43] and nitroso aldol reaction[25a,b] (see section II.A); a few chiral nitroso compounds are shown in Figure 8. Similarly, α-chloronitrososo sugar derivatives were also used for the nitroso ene reaction, which undergo a highly enantioselective transforma-

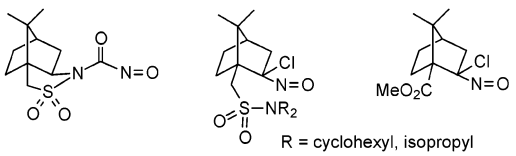
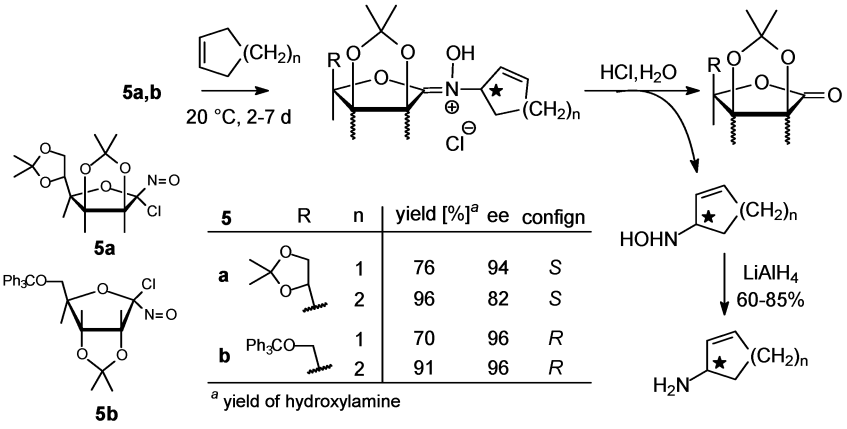
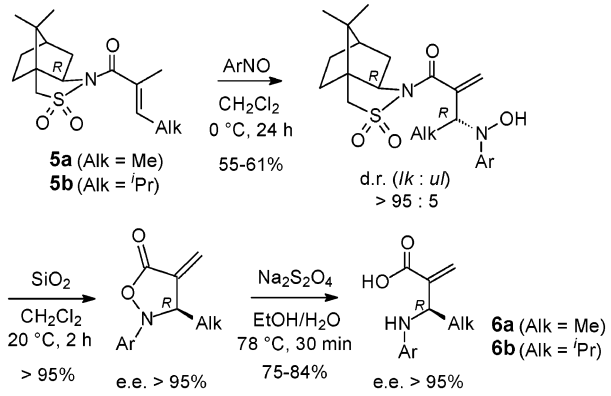


Figure 8. Chiral nitroso compounds employed in cycloadditions and aldol reactions.

Scheme 18. Diastereoselective Ene Reaction of the Chiral Sugar-Derived α-Chloronitroso Enophiles



Scheme 19. Chiral-Auxiliary-Controlled Ene Reaction of ArNO with the Tiglic Amides 5, Silica-Gel-Mediated Cyclization of the Ene Products, and Selective Reduction to the Respective α-Methylene *β*-Amino Acid Derivatives.

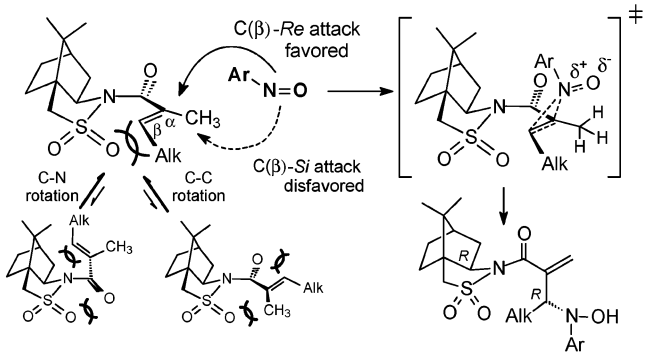


tion with simple alkenes (Scheme 18).[64] As outlined in section II.B (Scheme 4), the initial nitroso ene product leads to a nitrone hydrochloric-acid salt, which is readily hydrolyzed to the primary hydroxylamine. Reduction of the latter by $LiAlH_4$, $TiCl_3$, or $LiBH_4/Me_3SiCl$ affords the optically active primary amines in high enantioselectivity. When the mannose derivative **5a** is employed, *S*-configured amines are obtained, whereas **5b** leads to *R*-configured ene products.

The efficient and economical preparation of enantiomerically pure *β*-amino acids has become a worthwhile goal and challenge, since these substances are of biological and pharmaceutical interest.[99−102] In this respect, the ene reaction of ArNO with optically active tiglic acid derivatives, equipped with Oppolzer's bornane sultam as chiral auxiliary, affords the respective ene products regioselectively, in excellent diastereoselectivity, and in good yields (Scheme 19).[103] The ene products may be transformed in two steps into the respective *β*-amino acid derivatives: Silica gel promotes the cyclization (nucleophilic attack of the hydroxylamine at the carbonyl group) and extrusion of the auxiliary; subsequently, the resulting heterocycle may be selectively reduced by sodium dithionite to the corresponding *β*-amino acid.

The high diastereoselectivity of the above ene reaction is rationalized in terms of the proper conformational alignment of the substrate (Scheme

Scheme 20. Preferred Conformation of the CC-Double-Bond Functionality in the *π*-Facial Enophilic Attack of ArNO on the Chiral Tiglic Amides.

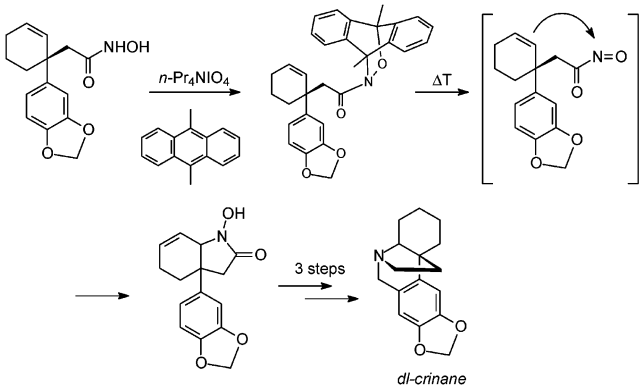


20).[104] Steric effects oblige the enophilic attack to be preferred from the C(*β*)-*Re* face [Since only one stereogenic center is formed in these ene reactions, namely, at the *β* position of the CC double bond, the descriptor for the *π*-face attack refers to the *β*-carbon atom] of the double bond since the C(*β*)-*Si* face is efficiently shielded by the sulfonyl oxygen atoms.[105]

For preparative or pharmaceutical applications of these optically active *β*-amino acids as chiral building blocks, the aryl group at the nitrogen functionality must be removed to release the primary amino group. Since reductive dearylation or nucleophilic aromatic substitution is not tolerated by the other functional groups present in the ene product, oxidative dearylation is the method of choice to remove the 4-nitrophenyl group; however, this has proved to be exceedingly difficult in practice. Since the electron-rich 4-methoxyphenyl group may be readily eliminated from an amino group by oxidation with cerium ammonium nitrate (CAN)[85,86] or by silver(I)-catalyzed oxidation with persulfates,[87] such nitroso enophiles would be advantageous; unfortunately, the corresponding 4-methoxynitrosobenzene enophile does not undergo a clean ene reaction.[49] The problematic side reactions (see section II.B) may be avoided by employing the catalytic amination method (see section VI) or, alternatively, heteroatom-substituted nitroso enophiles (see Perspectives, section VIII).

An impressive application is the stereoselective construction of the perhydroindole skeleton of the *Amaryllis* and *Sceletium* alkaloids, a widespread and

Scheme 21. Synthesis of DL-*Crinane* by the Acylnitroso Ene Reaction



intensively studied class of nitrogen-containing natural products. These are readily obtained by the intramolecular nitroso ene reaction of the acylnitroso functionality, as illustrated in the synthesis of DL-*crinane* (Scheme 21),[106] DL-*mesembrine*, and DL-*dihydromaritidine*.[107] To avoid destruction of the hydroxylamine ene products through the oxidation by periodate (see section II.B), the nitroso species is first trapped by [4+2] cycloaddition with DMA. For the intramolecular ene reaction, the nitroso compound is released from the [4+2] adduct by subsequent thermolysis. The resulting allylic hydroxylamines are readily converted to the desired alkaloids.

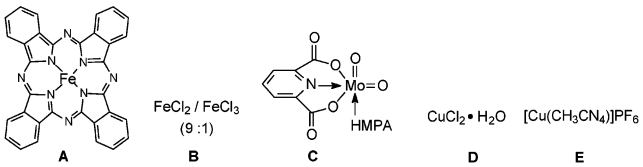
VI. Metal Catalysis

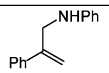
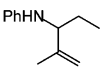
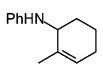
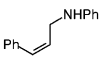
In addition to the ene reaction, in which the nitroso enophile is employed stoichiometrically, various metal-activated allylic aminations have been developed with catalytically generated nitrosoarenes. In the latter process, the enophile is often not involved as a free species but coordinated and activated by the metal catalyst. Two different methodologies have been worked out for such metal-catalyzed nitroso ene reactions: (i) In the oxidative catalytic amination, a hydroxylamine is in-situ oxidized by the catalyst to the nitrosoarene and the catalyst is regenerated by oxidation with the initial ene product; (ii) in the reductive catalytic amination, a nitroarene is reduced by the catalyst and the catalyst is regenerated by reduction with carbon monoxide. The first methodology has been extensively studied; the second one is quite novel and presumably advantageous; very little is known about its mechanism and applications.

A. Oxidative Catalytic Amination by Employing a Hydroxylamine as Nitroso Source

The metal-catalyzed "nitroso ene reaction" is an efficient method for the allylic amination of a variety of alkenes (Table 4).[4,108−115] Molybdenum, iron, and copper catalysts oxidize the phenylhydroxylamine to the required nitrosobenzene, which reacts with alkenes to the initial hydroxylamine ene products. The latter are in-situ reduced to the corresponding amines simultaneously with regeneration of the catalytic oxidant, which is essential for maintenance of the catalytic cycle.

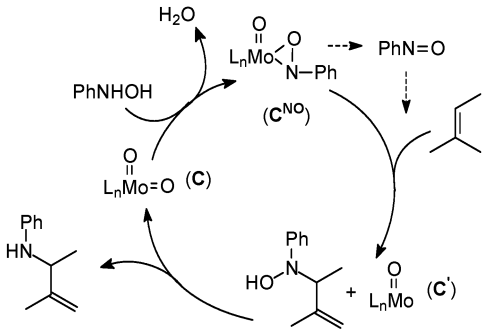
Table 4. Molybdenum, Iron, and Copper Complexes/ Salts as Catalysts in the Nitroso Ene Reaction with Diverse Alkenes



entry	alkene	ene product	yield [%] A[a]	B[b]	C[c]	D[d]	E[e]
1			76	41	42	30	40
2			-	72	52	38	-
3			22	13	-	10	9
4			30	22	11	-	-

[a] References108 and 109. [b] References 110 and 111. [c] References 112 and 113. [d] Reference 114. [e] References 115.

Scheme 22. Catalytic Cycle for the Molybdenum-Catalyzed Nitroso Ene Reaction with Phenyl Hydroxylamine as Nitroso Source and the Molybdenum Complex C as Catalyst

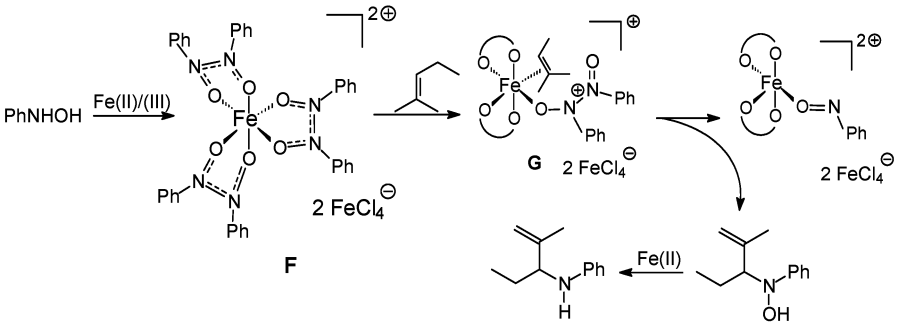


The copper-catalyzed nitroso ene reaction, for which free nitrosobenzene was detected by trapping with 2,3-dimethylbutadiene, suggests that this is an *off*-metal process. In contrast, the iron and copper catalysts do not solely act as redox shuttles but also coordinate the generated nitroso species and activate it for the ene reaction (*on*-metal process).

In Scheme 22, the catalytic cycle for the molybdenum complex **C** is shown.[112] The dioxo complex **C** condenses with phenylhydroxylamine to form the active catalytic species $\mathbf{C}^{NO}$, which transfers the nitroso enophile to the alkene. The initial hydroxylamine ene product regenerates the **C** complex from **C′** by reduction to the amine.

In case of the iron catalysis, no definitive catalytic cycle has been postulated; however, the triazodioxide complex **F** was confirmed to be the active species (Scheme 23). It was proposed that metal coordination of the alkene and subsequent intramolecular ene reaction (structure **G**) leads to the ene product, but alternative pathways were also given.[111] As in the molybdenum-catalyzed reactions, the initial hydroxylamine ene product is reduced to the amine in the

Scheme 23. Iron-Catalyzed Nitroso Ene Reaction with the Triazodioxide Complex F as Active Catalytic Species



oxidative step, regenerating the active catalytic species.

This latter step was observed to be the crucial one for most catalytic systems. The usual side reactions of the nitroso ene processes, which have been addressed in section II.B, are also observed in the metal-catalyzed process. The regioselectivity is controlled by the same factors as already divulged for the nitrosoarene ene reaction without metal catalysis (see section IV).

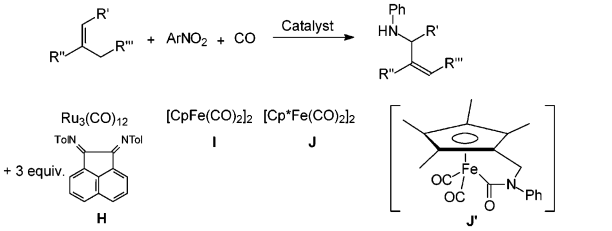
B. Reductive Catalytic Amination by Employing Carbon Monoxide as Reducing Agent and a Nitroarene as Nitroso Source

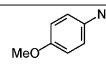
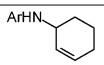
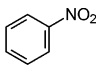
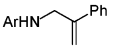
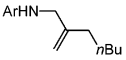
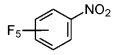
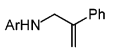
Reductive allylic amination with nitroarenes as nitroso source and carbon monoxide as reducing agent represents a remarkable synthetic advance in metal-catalyzed nitroso ene reactions. The undesirable subsequent in-situ transformation of the initial hydroxylamine ene products are avoided by efficient in-situ reduction with carbon monoxide. Additionally, in contrast to the above metal-catalyzed nitroso ene reactions, in which a hydroxylamine is employed, the regeneration of the catalyst is straightforward, since in this step the reduction with carbon monoxide takes place and not oxidation by hydroxylamine ene product. Various nitroarenes, metal catalysts, olefinic substrates, and reaction conditions have been employed in this novel methodology (Table 5).

The ruthenium complex derived from $Ru_3(CO)_{12}$ and a diimide ligand **H** were first employed under these conditions.[116] Later, Nicholas et al. found that $[CpFe(CO)_2]_2$ and $[Cp^*Fe(CO)_2]_2$ are superior catalysts.[117,118] For $[Cp^*Fe(CO)_2]_2$, the cyclic carbamoyl complex **J′** was isolated as the resting state after completion of the amination reaction. The thermal catalytic amination with the iron complex **J** (160 °C, 800 psi CO pressure) was improved through the development of a photoassisted variant, which proceeds under milder conditions [100 °C, 100 psi CO pressure, $h\nu > 300$ nm].[119]

This metal-mediated methodology offers promising future opportunities to achieve the synthetic goal of catalytically rather than stoichiometrically preparing allylic amines by means of the nitroso ene reaction. For example, in the novel work by Nicholas et al., 2,4-dinitrophenylhydroxylamine was employed as nitroso source in the $FeCl_2/FeCl_3$-catalyzed ene reaction.[120] The encouraging breakthrough is the fact that the resulting ene products may be dearylated by

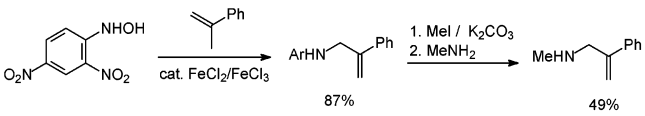
Table 5. Reductive Metal-Catalyzed Amination with Nitroarenes as Nitroso Source and Carbon Monoxide as Reducing Agent



entry	nitro-arene	alkene	ene product	yield [%] H[a]	I[b]	J[c,d]
1				26		
2				59		
3					92/12[d]	85/63[d]
4					10	80/73[d]
5					27	16/1[d]
6					57	100[d]

[a] Reference 116. [b] Reference 117. [c] Reference 118. [d] Photoassisted amination, ref 119.

Scheme 24. Catalytic Allylic Amination of α-Methylstyrene with 2,4-Dinitrophenyl-hydroxylamine and Dearylation of the Ene Product



nucleophilic aromatic substitution with $MeNH_2$, after protection of the amino functionality with methyl iodide (Scheme 24).

When 1-methoxy-4-nitrosobenzene is used as the nitroso enophile in the reductive catalytic amination (Table 5, entry 1), the respective 4-methoxyphenyl-substituted amine is obtained, which may be readily dearylated by oxidation with cerium ammonium nitrate or persulfates.[85−87] This is remarkable when it is recalled that the 1-methoxy-4-nitrosobenzene

under stoichiometric conditions does not give a clean ene reaction (see section II.B).[49]

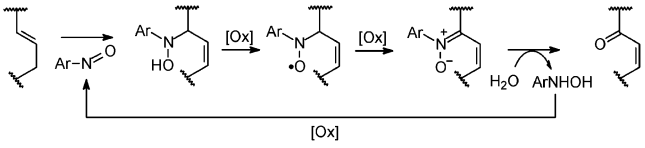
VII. Biological Relevance

Nitrosoarenes, cytotoxic substances and well-known cancer promoters, are the in-vivo metabolites of aromatic amines through their oxidation by cytochrome P450 or by environmental pollutants (e.g., smoking).[121−124] This is a serious health problem, especially since aromatic amines are ubiquitous environmental chemical substances which result from combustion, manufacture of dyestuffs, medicaments, plastics, and pesticides.

For the cancer-promoting effect of nitrosoarenes, two general mechanisms have been established: (i) The nitroso functionality may act as direct growth promoter for neoplastically changed cells by interaction with specific receptors, which lead to an overexpression of cancer-promoting enzymes,[125] a process in which the nitroso ene reaction might be involved; (ii) the toxic nitroso compounds destroy healthy cells, whereas the resistant heptatocytes are only stimulated, and thus, they possess a selective growth benefit.[126]

It should be evident that the nitroso ene reaction may play an important role in such deleterious processes. For example, the ene reaction of nitroso compounds with unsaturated lipids leads to hydroxylamines and their further oxidation to nitroxide radicals.[127] For example, nitrosofluorene, an active metabolite of the complete carcinogen acetaminofluorene, acts as redox-cycling agent in the mitochondrial membrane.[124,128] Reduction of the nitrosofluorene to its nitroxide and reoxidation by molecular oxygen results in superoxide, which is well-known to cause oxidative stress and cell damage. The nitroso ene reaction with cell nutrients and further oxidation to the corresponding nitrones (see section II.B) may lead to hydroxylamines on hydrolysis. The latter are oxidized to their nitroso compound, which therefore becomes available for subsequent ene reaction (Scheme 25).

Scheme 25. In-vivo Ene Reaction of Nitrosoarenes, Followed by Oxidation of the Ene Products and Regeneration of the Nitroso Enophile



Recently, the ene reaction of 2-nitrosoadenosin was also reported.[129] Consequently, the nitroso ene reaction might also be involved in the direct damage of DNA.

VIII. Perspectives and Challenges

The mechanism, reactivity, and selectivity as well as the synthetic applications, catalytic modifications, and biological relevance of the nitroso ene reaction each offer interesting perspectives and formidable challenges for future consideration.

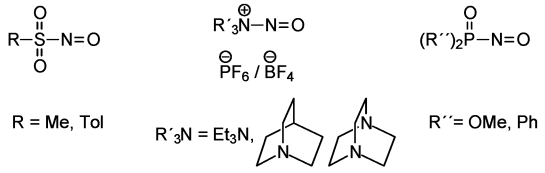


Figure 9. Promising heteroatom-substituted nitroso enophiles

For example, as outlined in the last section, it would be instructive to detect the nitroso ene reaction as an important component of the cytotoxic and cancer-promoting effects of nitroso compounds under in-vivo conditions.

The further mechanistic elucidation of the nitroso ene reaction is advisable, since the structure of the intermediate and the factors which control reactivity and selectivity still are not fully understood. For example, the synthesis of genuine aziridine *N*-oxides derived from alkenes with diverse substitution patterns (section III) and their thermolysis may provide product distributions, which on comparison with the nitroso ene reaction would allow assignment of the proposed three-membered ring as an authentic intermediate.

Currently there is a high demand for selective and catalytic nitrogen functionalizations in organic synthesis. In that regard, use of chiral metal complexes in the catalytic allylic aminations should open up an effective pathway to valuable, optically active amines from readily available olefins.

In this context, it is crucial to release the primary amine from the nitroso ene product. For the metal-catalyzed process, the promising 4-methoxynitrosobenzene and 2,4-dinitronitrosobenzene enophiles have already been employed (section VI) to give ene products, which could be readily dearylated. Development of new reactive heteroatom-substituted nitroso compounds that can be readily converted to the primary amines is a high priority in both stoichiometric and metal-catalyzed reactions. Promising examples are sulfonic-acid nitrites,[130−132] nitrosoammonium salts,[133,134] and nitrosophosphonates[135] (Figure 9); the latter have already been successfully employed in the nitroso [4+2] cycloaddition. The heteroatom substituent in the resulting ene products might be removed under mild reductive conditions (e.g., sodium amalgam for the sulfonyl group)[136] or by nucleophilic substitution (e.g., tetrabutylammonium fluoride for the phosphinyl or phosphonyl group).[137]

The chiral acyl nitroso compounds (section II.B), employed in [4+2] cycloadditions (section V.B, Figure 8), might afford valuable optically active amides through their ene reaction. The problematic in-situ decomposition of such acyl nitroso enophiles to the acid anhydride and dinitrogen oxide gas (Scheme 6) might be avoided by employing metal catalysis or high-pressure conditions.

The search for more reactive α-chloronitroso enophiles (sections II.B and V) is also a worthwhile synthetic goal. Their ene reaction may lead to optically active primary amines, and the enophile may be readily regenerated. The factors which control the reactivity of α-chloronitroso enophiles are not fully

understood, and a detailed study might help circumvent the very long reaction times encountered in these reactions.

In conclusion, the nitroso ene reaction serves as a mild and selective method for the direct allylic nitrogen functionalization of alkenes. The incentive of this review has been to kindle interest among chemists to become more active in this promising field, both mechanistically and synthetically.

IX. Acknowledgments

We thank the "Deutsche Forschungsgemeinschaft" and the "Fonds der Chemischen Industrie" for generous financial support. We dedicate this review to F. D. Greene, whose mechanistic pioneering work on the nitroso ene reaction has stimulated us and others to revisit this fascinating transformation and exploit it for synthetic purposes.

X. References

(1) Richter-Addo, G. B., Legzdins, P., Burstyn, J., Eds. Thematic issue: Nitric Oxide Chemistry. *Chem. Rev.* **2002**, *102*.
(2) Banks, R. E.; Barlow, M. G.; Haszeldine, R. N. *J. Chem. Soc.* **1965**, 4714.
(3) Knight, G. T. *J. Chem. Soc., Chem. Commun.* **1970**, 1016.
(4) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.
(5) Brennan, R. J.; Schiestl, R. H. *Mutagenesis* **1997**, *12*, 215.
(6) Khan M. F.; Wu X.; Ansari G. A. *J. Toxicol. Environ. Health, Part A* **2000**, *60*, 263 (CAN 133:160655).
(7) Magee, P. N.; Swann, P. F. *Br. Med. Bull.* **1969**, *25*, 240.
(8) Baker, C. S. L.; Barnard, D. *Polym. Prepr.* **1985**, *26*, 29 (CAN 104:90192).
(9) Magnus, P.; Lacour, J.; Goldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087.
(10) Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
(11) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(12) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1.
(13) Burgess, K.; Liu, L.; Pal, B. *J. Org. Chem.* **1993**, *58*, 4758.
(14) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
(15) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419.
(16) Orfanopoulos, M.; Stratakis, M. *Tetrahedron* **2000**, *56*, 1595.
(17) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151.
(18) Cheng, C. C.; Seymour, C. A.; Petty, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910.
(19) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885.
(20) Stratakis, M.; Hatzimarinaki, M.; Froudakis, G. E.; Orfanopoulos, M. *J. Org. Chem.* **2001**, *66*, 3682.
(21) Seymour, C. A.; Greene, F. D. *J. Org. Chem.* **1982**, *47*, 5226.
(22) Greene, F. D. In *Stereochemistry and Reactivity of Systems Containing p-Electrons*; Watson, W. H., Ed.; Verlag Chemie: Deersfield Beach, FL, 1983; p 197.
(23) Boyer, J. H. In *The Chemistry of the Nitro and Nitroso Groups, Part 1*; Patai, S., Ed.; Interscience Publishers: New York, 1969; Chapter 5.
(24) Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621.
(25) Oppolzer, W.; Tamura, O. *Tetrahedron Lett.* **1990**, *31*, 991.
(26) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900.
(27) Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579.
(28) Goelitz, P.; Meijere, A. *Angew. Chem.* **1977**, *89*, 892.
(29) Aston, A.; Menard, M *J. Am. Chem. Soc.* **1935**, *57*, 1922.
(30) Forrester, A. R.; Hepburn, S. P. *J. Chem. Soc. C* **1971**, 3322.
(31) Goldman, J. *Tetrahedron* **1973**, *29*, 3833.
(32) Druellinger, M. L. *J. Heterocycl. Chem.* **1976**, *13*, 1001.
(33) Adam, W.; Bottle, S. E.; Peters, K. *Tetrahedron Lett.* **1991**, *32*, 4283.
(34) Torssell, K. *Tetrahedron* **1970**, *26*, 2759.
(35) Forrester, A. R.; Henderson, J.; Reid, K. *Tetrahedron Lett.* **1983**, *24*, 5547.
(36) Ginsburg, V. A. *J. Org. Chem. USSR* (*Engl. Trans.*) **1974**, *10*, 1427.
(37) Barr, A.; Hazeldine, R. N. *J. Chem. Soc.* **1955**, 1881.
(38) Lin, C.-T.; Hsu, W.-J. *Can. J. Chem.* **1989**, *67*, 2153.
(39) Viehe, H. G.; Merenyi, R.; Francotte, E.; Van Meerssche, M.; Germain, G.; Declercq, J. P.; Bodart-Gilmont, J. *J. Am. Chem. Soc.* **1977**, *99*, 2340.
(40) Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron Asymmetry* **1991**, *12*, 1173.
(41) Christie, C. C.; Kirby, G. W.; McGuian, H.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin. Trans. 1* **1985**, *11*, 1972.
(42) Gouverneur, V.; McCarthy, S. J.; Mineur, C.; Belotti, D.; Dive, G.; Ghosez, L. *Tetrahedron* **1998**, *54*, 10537.
(43) Elango, S.; Wang, Y.-C.; Cheng, C.-K.; Yan, T.-H. *Tetrahedron Lett.* **2002**, *43*, 3757.
(44) Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M. *J. Org. Chem.* **2002**, *67*, 8395.
(45) Adam, W.; Griesbeck, A.; El-Idreesy, T.; Krebs, O. In *CRC Handbook of Organic Photochemistry and Photobiology, 2nd ed.;* Horspool, W. M., Song, P.-S., Eds.; CRC Press: Boca Raton, 2003.
(46) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, *12*, 1243.
(47) Knight, G. T.; Pepper, B. *Tetrahedron* **1971**, *27*, 6201.
(48) Knight, G. T.; Loadman, M. J. R. *J. Chem. Soc., B* **1971**, 2107.
(49) Knight, G. T.; Pepper, B. *Chem. Commun.* **1971**, 1507.
(50) Renner, G. Z. *Anal. Chem.* **1963**, *193*, 92.
(51) Utzinger, G. E.; Regenass, F. A. *Helv. Chim. Acta* **1954**, *37*, 1885.
(52) Abramovitch, R. A.; Challand, S. R.; Yamada, Y. *J. Org. Chem.* **1975**, *40*, 1541.
(53) Ehrlich, P.; Sachs, F. *Chem. Ber.* **1899**, *32*, 2341.
(54) Sullivan, A. B. *J. Org. Chem.* **1966**, *41*, 2811.
(55) Mulvey, D.; Waters, W. A. *J. Chem. Soc., Perkin. Trans. 2* **1978**, 1059.
(56) Knight, G. T. *Chem. Commun.* **1970**, 1016.
(57) Chatgilialoglu, C.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 4833.
(58) Kliegel, W. *Tetrahedron Lett.* **1969**, *31*, 2627.
(59) Huisgen, R. *Angew. Chem.* **1963**, *13*, 602.
(60) Banks, R. E.; Haszeldine, R. N.; Miller, P. J. *Tetrahedron Lett.* **1970**, *50*, 4417.
(61) Krebs, O. *Diplomarbeit*, Würzburg, 2000.
(62) Adam, W.; Bottke, N. *J. Am. Chem. Soc.* **2000**, *122*, 9846.
(63) Schenk, C.; de Boer, T. J. *Tetrahedron* **1979**, *35*, 147.
(64) Kreβe, G.; Vasella, A.; Felber, H.; Ritter, A.; Ascherl, B. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 295.
(65) Braun, H.; Felber, H.; Kreβe, G.; Ritter, A.; Schmidtchen, F. P.; Schneider, A. *Tetrahedron* **1991**, *47*, 3313.
(66) Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007.
(67) Adam, W.; Bottke, N.; Krebs, O.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **1999**, 1963.
(68) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*, 3233.
(69) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791.
(70) Oppholzer, W.; Tamura O. *Tetrahedron Lett.* **1990**, *31*, 991.
(71) Trepalin, S. V.; Yarkov, A. V.; Sokolov, V. B.; Ivanov, A. N.; Aksineko, N. A.; FetisovV. I. *Bull. Acad. Sci. USSR Div. Chem. Sci.* (*Engl. Trans.*) **1989**, *38*, 2326.
(72) Wieland, M. *Chem. Ber.* **1907**, *40*, 1677.
(73) Kupfer, R.; Nagel, M. *Chem. Ber.* **1985**, *118*, 3089.
(74) Felber, H.; Kresze, G.; Prewo, R.; Vasella A. *Helv. Chim. Acta* **1986**, *69*, 1137.
(75) Kirby, G. W. *Chem. Soc. Rev.* **1977**, 1.
(76) Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 883.
(77) Kirby, G. W.; McGuigan, H.; McLean, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1961.
(78) Quadrelli, P.; Mella, M.; Invernizzi, A. G.; Caramella, P. *Tetrahedron* **1999**, *55*, 10497.
(79) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1999**, *40*, 797.
(80) Quadrelli, P.; Campari, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **2000**, *41*, 2019.
(81) Bamberger, E.; Hübner, R. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 3803.
(82) Krebs, O. Dissertation, Würzburg, 2002, (available at http://www.bibliothek.uni-wuerzburg.de from the OPUS server).
(83) Adam, W.; Bottke, N.; Krebs, O.; Engels, B. *J. Am. Chem. Soc.* **2001**, *123*, 5542.
(84) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585.
(85) Adam, W.; Groer, P.; Humpf, H.-U.; Saha-Möller, C. R. *J. Org. Chem.* **2000**, *65*, 4919.
(86) Gordon, K. H.; Balasubramanian, S. *Org. Lett.* **2001**, *3*, 53.
(87) Bhattarai, K.; Cainelli, G.; Panunzio, M. *Synlett* **1990**, *4*, 229.
(88) Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M.; Vougioukalakis, G. C. *J. Org. Chem.* **2003**, *68*, 2420.
(89) Baldwin, J. E.; Bhantnagar, A. K.; Choi, S. C.; Shortridge, T. J. *J. Am. Chem. Soc.* **1971**, *93*, 4082.
(90) Leach, A. G.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 14820.
(91) Adam, W.; Bottke, N.; Krebs, O. *Org. Lett.* **2000**, *2*, 3293.
(92) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.
(93) Stratakis, M.; Orfanopoulos, M.; Elemes, Y. *J. Am. Chem. Soc.* **1991**, *113*, 3180.

(94) Stratakis, M.; Orfanopoulos, M. *Tetrahedron Lett.* **1995**, *36*, 4291.
(95) Stratakis, M.; Orfanopoulos, M.; Elemes, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6417.
(96) Stratakis, M.; Orfanopoulos, M.; Elemes, Y. *Tetrahedron Lett.* **1990**, *40*, 5775.
(97) Adam, W.; Bottke, N.; Krebs, O.; Lykakis, I.; Orfanopoulos, M.; Stratakis, M. *J. Am. Chem. Soc.* **2002**, *124*, 14403.
(98) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(99) Seebach, D.; Overhand, M.; Kühnle F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
(100) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
(101) Gademann, K.; Seebach, D. *Helv. Chim. Acta* **2001**, *84*, 2924.
(102) Ziegelbauer, K.; Babczinski, P.; Schonfeld, W. *Antimicrob. Agents Chemother.* **1998**, *42*, 2197.
(103) Adam, W.; Degen, H.-G.; Krebs, O.; Saha-Möller, C. R. *J. Am. Chem. Soc.* **2002**, *124*, 12938.
(104) Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559.
(105) Curran, D. P.; Kim, B. H.; Daugherty, J.; Heffner, T. A. *Tetrahedron Lett.* **1988**, *29*, 3555.
(106) Keck, G. E.; Webb, R. R. *J. Org. Chem.* **1982**, *47*, 1302.
(107) Keck, G. E.; Webb, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3173.
(108) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1994**, *59*, 214.
(109) Johannsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5979.
(110) Srivastava, R. S.; Nicholas, K. M. *J. Am. Chem. Soc.* **1996**, *118*, 3311.
(111) Srivastava, R. S.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 3302.
(112) Srivastava, R. S.; Nicholas, K. M. *J. Org. Chem.* **1994**, *59*, 5365.
(113) Møller, E. R.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11814.
(114) Ho, C.-M.; Lau, T.-C. *Chem. Commun.* **2000**, *24*, 859.
(115) Hogan, G. A.; Gallo, A. A.; Nicholas, K. M.; Srivastava, R. S. *Tetrahedron Lett.* **2002**, *43*, 9505.
(116) Cenini, S. Ragaini, F.; Tollari, S.; Paone D. *J. Am. Chem. Soc.* **1996**, *118*, 11964.
(117) Srivastava, R. S.; Nicholas, K. M. *Chem. Commun.* **1998**, 2705.
(118) Kolel-Veetil, M. K.; Khan, M. A.; Nicholas, K. M. *Organometallics* **2000**, *19*, 3754.
(119) Srivastava, R. S.; Kolel-Veetil, M. K.; Nicholas, K. M. *Tetrahedron Lett.* **2002**, *43*, 931.
(120) Singh, S.; Nicholas, K. M. *Synth. Commun.* **2001**, *31*, 3087.
(121) Kadlubar, F. F.; Butler, M. A.; Kaderlik, K. R.; Chou, H. C.; Lang, N. P. *Environ. Health Perspect.* **1992**, *98*, 69.
(122) Hammons, G. J.; Guengerich, F. P.; Weis, C. C.; Beland, F. A.; Kadlubar, F. F. *Cancer Res.* **1985**, *45*, 3578.
(123) Kiese, M.; Renner, G. *Nauyn-Schmiedebergs Arch. Pharmacol.* **1963**, *246*, 163.
(124) Klöhn, P. C.; Massalha, H.; Neumann, H. G. *Biochim. Biophys. Acta* **1995**, *1229*, 363.
(125) Gerlyng, P.; Seglen, P. O. *Bull. Cancer* **1990**, *77*, 461.
(126) Farber, E.; Solt, D.; Cameron, R.; Laishes, B.; Ogawa, K.; Medline, A. *Am. J. Pathol.* **1977**, *89*, 477.
(127) Raleigh, J. A.; Shum, F. Y.; Liu, S. F. *Biochem. Pharmacol.* **1981**, *30*, 2921.
(128) Bitsch, A.; Fecher, J.; Jost, M.; Klohn, P. C.; Neumann, H. G. *Recent Results Cancer Res.* **1997**, *143*, 2209.
(129) Wanner, M. J.; Koomen, G.-J. *J. Chem. Soc., Perkin Trans 1* **2001**, 1908.
(130) Oae, S.; Shinhama, K.; Fujimori, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 775.
(131) Street, G. B.; Gill, W. D.; Heiss, R. H.; Greene, R. L. *J. Chem. Soc., Chem. Commun.* **1977**, 407.
(132) Briganti, F.; Pieratelli, R.; Scozzafava, A.; Supuran, C. T. *Eur. J. Med. Chem.* **1996**, *31*, 1001.
(133) Garcia-Rio, L.; Iglesias, E.; Leis, J. R.; Pena, M. E.; Rios, A. *J. Chem. Soc., Perkin Trans. 2* **1993**, 29.
(134) Castro, A.; Leis, J. R.; Pena, M. E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1861.
(135) Ware, R. W.; King, S. B. *J. Org. Chem.* **2000**, *65*, 8725.
(136) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Exeter, 1993.
(137) Capozzi, G.; Menichetti, S.; Neri, S.; Skowronska, A. *Synlett* **1994**, *4*, 267.

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