Control of Regioselectivity by the *lone* Substituent through Steric and Electronic Effects in the Nitrosoarene Ene Reaction of Deuterium-Labeled Trisubstituted Alkenes

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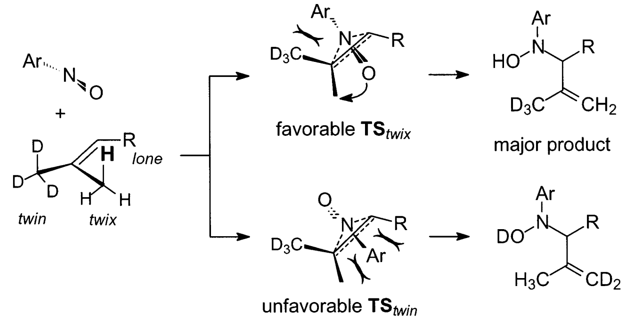
For the ene reaction of 4-nitronitrosobenzene (ArNO) with a variety of primary and secondary *lone* alkyl-substituted substrates, the *twix*/*twin* regioselectivity is constant at about 85:15. In contrast, for the *lone tert*-butyl group and for *lone* aryl substituents, the *twix* regioisomer is obtained exclusively. These regioselectivities have been rationalized in terms of steric interactions and coordination between the enophile and the substrates in the transition states of the first reaction step.

Introduction

Experimental work on the deuterium isotope effects in the ene reaction of nitrosoarene (ArNO) with tetramethylethylene disclosed that the same mechanism operates as in the ene reaction of singlet oxygen ($^1O_2$) and triazolinedione (TAD), namely, through a three-membered-ring intermediate, for ArNO, the aziridine *N*-oxide.[1] Nevertheless, the regioselectivity of these three isoelectronic enophiles shows large differences. Whereas $^1O_2$ favors hydrogen abstraction on the more crowded side of the olefin (*cis* effect)[2] and triazolinedione (TAD) prefers to react at the more crowded end (*gem* effect),[3] the enophile 4-nitronitrosobenzene (ArNO) undergoes the recently discovered highly regioselective ene reaction at the *twix* position (*skew* effect) of the olefin (Scheme 1).[4,5]

To distinguish between *twix* and *twin* hydrogen abstraction in the ene products, one of the methyl groups must be deuterium-labeled (Scheme 1). No significant kinetic isotope effects have been observed, and the regioselectivity is, within the error range (5%), the same for *twix* and *twin* labeled olefins.[4a] The hydrogen abstraction at the *twin* position is small, and no ene product is observed from *lone* abstraction. The *skew* effect was rationalized in terms of steric interactions in the transition states $\mathbf{TS}_{twix}$ and $\mathbf{TS}_{twin}$, which lead to the respective ene products along the enophilic trajectory.[4] In the $\mathbf{TS}_{twin}$ structure, the aryl substituent of the ArNO enophile is located at the more crowded and, thus, the sterically more encumbered side of the alkene, whereas in $\mathbf{TS}_{twix}$, the aryl group points to the free corner of the alkene and the steric repulsions are reduced (*skew* attack). Consequently, hydrogen abstraction takes place preferentially from the *twix* substituent, as shown in Scheme 1.

SCHEME 1. Transition States $\mathbf{TS}_{twix}$ and $\mathbf{TS}_{twin}$ for Formation of the Aziridine *N*-Oxide Intermediate in the Nitrosoarene Ene Reaction with Deuterium-Stereolabeled Trisubstituted Alkenes



To determine the influence of *lone* substitution on the reactivity of the double bond, the relative rate constants (k_{rel}) were determined by means of intermolecular competition experiments for a variety of *lone*-substituted 2-methyl-2-butenes (Figure 1).[4c] An ethyl group at the *lone* site accelerates the reaction rate, but a bulky substituent such as the *tert*-butyl group decreases the ene reactivity significantly.

To probe whether steric interactions of *lone* substituents control the *twix*/*twin* regioselectivity of the nitrosoarene ene reaction, it was decided to use an assort-

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(5) For the differentiation of the regioisomeric ene products derived from *twix* and *twin* hydrogen abstraction, deuterium-labeling of one of the positions is necessary, unless the substrate bears different substituents.

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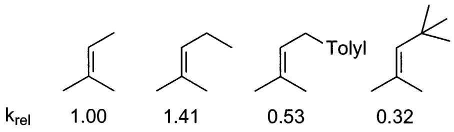


FIGURE 1. Relative ene reactivity of *lone*-substituted 2-methyl-2-butenes with nitrosoarene.

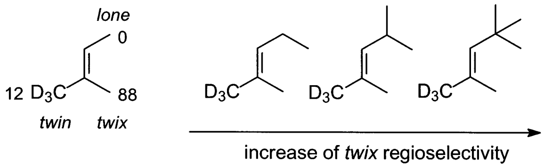
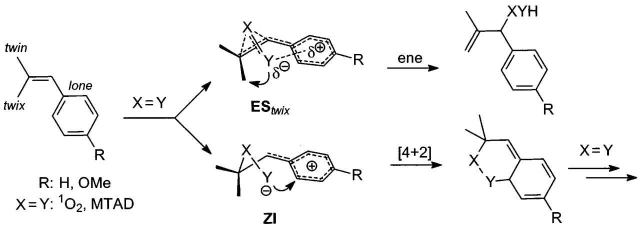


FIGURE 2. Expected steric influence of the *lone* substituent on *twix*/*twin* regioselectivity in the ArNO ene reaction with trisubstituted alkenes.

SCHEME 2. Coordination Effects in $^{1}O_2$ and MTAD Ene Reactions of Alkenes with Aryl Substituents at the *Lone* Position

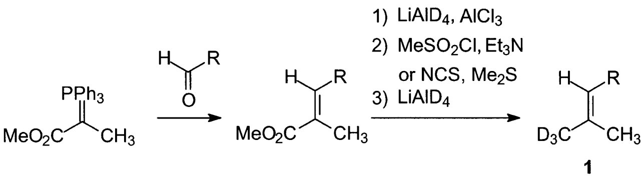


ment of *twin* deuterium-labeled alkenes with different *lone* substituents (Figure 2). Compared to the parent 2-methyl-2-butene substrate, enhanced *twix* regioselectivity is expected as a result of steric obstruction by the *lone* group along the $\mathbf{TS}_{twin}$ approach.

Generally, in contrast to the ArNO enophile, a lower regioselectivity is observed in the ene reaction of $^{1}O_2$ and TAD with simple alkenes.[2,6] However, in the case of styrenes with the aryl group at the *lone* position, enhanced *twix* regioselectivity was reported.[7] This observation was rationalized in terms of coordination between the enophile and the incipient delocalized positive charge of the *lone* aryl group in $\mathbf{TS}_{twix}$, which promotes *twix* hydrogen abstraction (Scheme 2). Moreover, some [4 + 2] cycloaddition occurs with these styrenes,[7,8] which is the consequence of the delocalized positive charge in the *lone* aryl group of the zwitterionic intermediates (**ZI**), especially when stabilized by electron-rich aryl groups (Scheme 2, R = OMe). Such zwitterionic intermediates have been proposed to be responsible for the loss of stereoselectivity in the [4 + 2] cycloaddition of MTAD to the *twix*-CD_3-labeled β,β-dimethyl-(*p*-methoxy)styrene (R = OMe).[7b]

Of mechanistic interest was the assessment of the mode selectivity (ene reaction versus [4 + 2] cycloaddition) and regioselectivity (*twix* versus *twin*) in the reaction of ArNO with styrenes that bear *lone* aryl substituents. Since the nitrosoarene enophile is more prone to steric and electronic control than $^{1}O_2$ and TAD, a highly selective process might be anticipated for ArNO. The results of the *lone*-substituent influence in the ene reaction of ArNO with the deuterium-labeled alkenes **1** are reported here, and their mechanistic consequences presented.

SCHEME 3. Synthesis of *twin* Deuterium-Stereolabeled Alkenes 1



Results

The *twin* deuterium-stereolabeled alkenes with various *lone* substituents were prepared by stereoselective Wittig coupling between methyl 2-triphenylphosphoranylidenepropanoate and the appropriate aldehydes, followed by reduction of the *E*-configured esters with $LiAlD_4$ (Scheme 3).[9] The resulting alcohols were mesylated[7b] or, in the case of the styrenes, transformed into the corresponding chlorides[7b] for the subsequent reduction with $LiAlD_4$ to the *twin* deuterium-labeled alkenes **1**.

The ene reaction of 4-nitronitrosobenzene with the *twin* deuterium-labeled *lone* alkyl- and aryl-substituted alkenes **1** gave the expected regioisomeric ene products from *twix* and *twin* hydrogen abstraction, which were identified and quantified by means of ^{1}H NMR spectroscopy (Table 1). To confirm the authenticity of the ene products, the ene reaction with the unlabeled alkenes **1-$\boldsymbol{d_0}$** was conducted on the preparative scale and the unlabeled ene products were isolated and fully characterized (see Supporting Information).

For the *lone* alkyl-substituted alkenes **1a**−**f** (entries 1−6), the *twix* selectivity is quite constant at about 85 ± 3%, while for the *tert*-butyl derivative **1g** (entry 7), the *twix* regioisomer is heavily favored (> 95%). For the ethyl substrate **1b** (entry 2), about 16% of the ene product (hydroxylamine) is oxidized in situ by the enophile to the corresponding nitrone and hydrolyzed to its ketone.[10] Fortunately, the regioselectivity is not affected by this side reaction, since the two regioisomeric ene products are equally likely oxidized by the nitroso enophile. This was confirmed by a control experiment for the regioisomeric ene products derived from the ene reaction of *E*- and *Z*-3-methyl-2-pentene.[11]

For the styrenes **1h**−**k** with *lone* aryl substituents, *twix* selectivity is also exclusive (>95%). Since the reactivity of the aryl conjugated double bond in styrenes **1h**−**k** is lower, their conversion is less than for the alkyl-substituted cases **1a**−**g**. For all of these alkenes, only the

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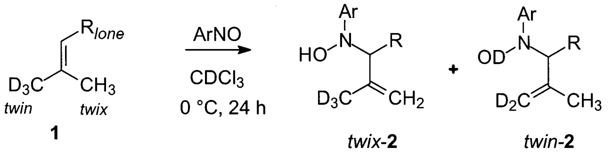
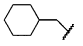
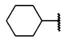
TABLE 1. Regioselectivity in the Ene Reaction of 4-Nitronitrosobenzene (ArNO) with Trisubstituted Alkenes 1



entry	R	alkene (equiv.)	convn[a,b] [%]	regioselectivity[b] *twix*	regioselectivity[b] *twin*
1	Me[c]	**1a** (1.7)	71	88	12
2	Et	**1b** (1.3)	87	83	17
3	PhCH$_2$	**1c** (1.5)	77	86[d]	14
4		**1d** (1.5)	86	83[d]	17
5	^{i}Pr	**1e** (1.3)	78	83	17
6		**1f** (1.5)	87	86[d]	14
7	^{t}Bu	**1g**[e] (1.2)	90	> 95[d,e]	< 5[e]
8	4-MeO-C$_6$H$_4$	**1h** (3.0)	57	> 95	< 5
9	4-Me-C$_6$H$_4$	**1i** (3.0)	26	> 95	< 5
10	Ph	**1j** (3.0)	18	> 95	< 5
11	4-F$_3$C-C$_6$H$_4$	**1k** (3.0)	11	> 95	< 5

[a] Normalized to 1 equiv of alkene. [b] Determined by ^{1}H NMR spectroscopy; error ca. 5% of the stated value, mass balance > 95%. [c] Taken from ref 4a. [d] Values corrected for the stereochemical purity of the alkenes (see Supporting Information). [e] The *E*/*Z* ratio of **1g** was 85:15 (±5%) and the observed *twix*/*twin* product ratio was 85/15 (±5%).

ene reaction is observed; no [4 + 2] cycloaddition occurs, as in the reaction of these styrenes with TAD and $^1O_2$.[7,8]

Discussion

Analogous to the previously studied trisubstituted alkenes,[4] the nitrosoarene ene reaction displays a high *twix* selectivity for all *lone*-substituted derivatives **1**. For the alkyl-substituted cases **1a**–**f** (the *tert*-butyl derivative **1g** falls out of line, since the *twix* regioisomer is exclusively produced, which provides valuable mechanistic details as we shall see later on), the *twix* ene products is the main regioisomer (85 ± 3%), whereas for the *lone* aryl-substituted styrenes **1h**–**k** only *twix* ene product is obtained. This implies that different steering mechanisms apply in these two types of substrates: While only steric effects dictate the *twix* regioselectivity (85 ± 3%) for the *lone* alkyl-substituted substrates **1a**–**f**, for the aryl-substituted derivatives **1h**–**k** additional coordination of the enophile by the *lone* aryl ring enhances *twix* selectivity (>95%). This becomes apparent on comparing the substrates **1f** (R$_{lone}$ = cyclohexyl) and **1j** (R$_{lone}$ = phenyl), which possess similar steric but different electronic properties and exhibit different efficiencies in the regiochemical control (Table 1, entries 6 and 10). The mechanistic features of the two sets of *lone*-substituted alkenes shall be discussed separately.

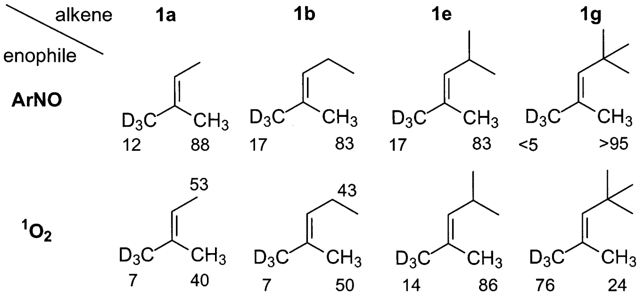


FIGURE 3. Regioselectivities for the ene reaction of ArNO and $^1O_2$ with trisubstituted alkenes.

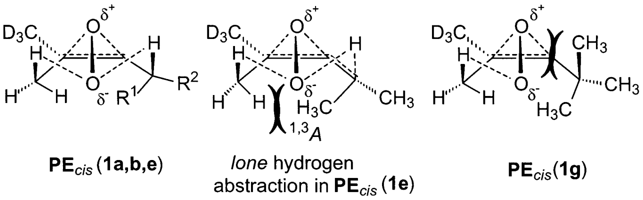


FIGURE 4. Steric interactions in the *cis*-configured perepoxide-like structures **PE**$_{cis}$ of the $^1O_2$ ene reaction.

Regioselectivity in the Nitrosoarene Ene Reaction with Alkyl-Substituted Alkenes 1a–g. For ease of comparison, a structural overview of the *twin*/*twix* regioselectivity is given for the ArNO ene reaction with the simple *lone* alkyl groups Me (**1a**), Et (**1b**), *i*-Pr (**1e**), and *t*-Bu (**1g**), together with the reported data of $^1O_2$ (Figure 3).[2a,4,12]

It is mechanistically instructive to consider first the $^1O_2$ enophile, for which a regular regiochemical trend is noted. With increasing steric demand of the *lone* substituent, the *cis* (*twix* + *lone*) selectivity decreases. The very high *cis* (*twix* + *lone*) regioselectivity (*cis* effect)[2a,12a] for **1a** and **1b** has been attributed to the coordination of the enophile with the allylic hydrogens in the *cis*-configured perepoxide-like structure **PE**$_{cis}$ (Figure 4).[13a]

In substrate **1e**, hydrogen abstraction at the *lone* isopropyl group is hindered, since unfavorable 1,3-allylic strain ($^{1,3}A$) builds up during the hydrogen abstraction step in **PE**$_{cis}$ and, thus, the *lone* selectivity is diminished. For the reaction of $^1O_2$ with substrate **1g**, the sterically obstructing *lone tert*-butyl group forces hydrogen abstraction at the *twin* side, i.e., the "anti-*cis* effect"[12c] operates. Steric encumbrance by the *lone tert*-butyl group on the *cis* side hinders the formation of **PE**$_{cis}$ for the **1g** substrate (Figure 4) and *twin* reactivity dominates (Figure 4).

In contrast to $^1O_2$ (*cis* effect),[12a] for the sterically more encumbered ArNO enophile (*skew* effect),[4] the aryl group is sterically more demanding than the terminal oxygen atom of the nitroso group. Thus, for all of the substrates **1a**–**g**, the steric interactions in the *cis*-configured transition structure **TS**$_{twix}$ are less severe than in the *trans*-configured **TS**$_{twin}$ (Figure 5); consequently, the *twix* regioisomers are formed as major ene products.

The fact that about the same (ca. 85:15) *twix*/*twin* ratio for the **1a**–**f** substrates is observed may be rationalized

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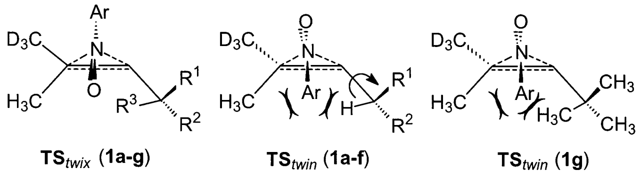


FIGURE 5. Steric interactions of the *lone* substituent in the transition structures **TS**$_{twix}$ and **TS**$_{twin}$ for the ArNO ene reaction

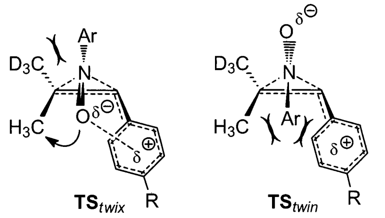
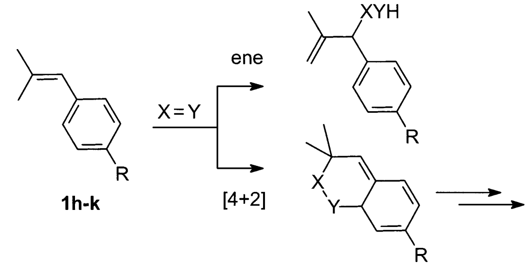


FIGURE 6. Enophile/substrate transition structures **TS**$_{twix}$ and **TS**$_{twin}$ in the ArNO ene reaction with the styrenes **1h**−**k**.

in terms of favored conformations that the *lone* substituent may acquire, which minimize steric interaction with the aryl group of the enophile in **TS**$_{twin}$. For the primary and secondary *lone* substituents in the substrates **1a**−**f** (Table 1, entries 1−6), the hydrogen atom may assume the favorable (minimal 1,3-allylic strain) *inside* conformation in **TS**$_{twin}$, whereas the remaining R^1 and R^2 groups are located at the periphery, as displayed in Figure 5. Since the R^1 and R^2 groups at the *lone* substituent are at the periphery in the **TS**$_{twin}$ structure for the substrates **1a**−**f**, insignificant differences are encountered in the steric interaction between the alkene and the enophile, and consequently, similar *twix*/*twin* ratios are obtained. In contrast, for the substrate **1g** with the tertiary *lone* substituent, namely, the *tert*-butyl group, no conformational arrangement is possible in which the methyl groups at the *lone* substituent avoid 1,3-allylic strain (one methyl group is always *inside*!). Thus, for substrate **1g**, the **TS**$_{twin}$ encounter is sterically prohibitive and the *twix* regioisomer is formed exclusively (Table 1, entry 7).

Regioselectivity in the Nitrosoarene Ene Reaction with Styrenes 1h−k. In the ene reaction between ArNO and the styrenes **1h**−**k** with the *lone* aryl substitutents, the *twix* regioisomer is formed exclusively (Table 1). In contrast to the nitrosoarene ene reaction with the *lone* alkyl-substituted alkenes **1a**−**g**, an additional coordination of the enophile with the *lone* aryl group may be controlling the regioselectivity of the aryl-substituted substrate **1h**−**k**. In analogy to the ene reactions of $^1O_2$ and TAD with these substrates, the aryl group acquires a partial positive charge during the enophilic attack of the conjugated double bond. This positively charged ring coordinates effectively with the negatively charged terminal oxygen atom of the ArNO enophile, and hence, the *cis*-configured transition structure **TS**$_{twix}$ for *twix* hydrogen abstraction is stabilized (Figure 6). Additionally, the **TS**$_{twin}$ species is sterically disfavored, as discussed above for the alkenes **1a**−**g**. In the case of the styrenes **1h**−**k** this applies all the more, because the aryl group in **TS**$_{twin}$ tends to be coplanar with the double bond for optimal conjugation, which increases the steric obstruction on the *cis* side.

TABLE 2. Mode Selectivity (Ene versus [4 + 2]) and Regioselectivity (*twix* versus *twin*) in the Ene Reaction of ArNO, ^{1}O$_2$, and MTAD with Styrenes 1h−k

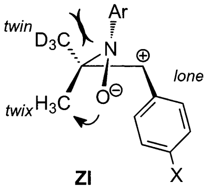


enophile X = Y	styrene	R	selectivity mode ene	[4 + 2]^d	regio twix	twin
$^1O_2$^{a}	**1j**	H	34	66	63	37
MTAD^b	**1h**	MeO	60	40	>95	<5
ArNO^c	**1h**−**k**	all	>95	<5	>95	<5

[a] Reference 7a, 8. [b] Reference 7b. [c] This work. [d] The cycloadducts undergo a second addition of the enophile ([4 + 2] for $^1O_2$, mainly ene for MTAD).

Also remarkable for the ArNO ene reaction with these substrates **1h**−**k** is the absence of [4 + 2] cycloaddition, especially for the electron-rich (R = OMe) derivative **1h** (Table 1, entry 8). In contrast, a low mode selectivity (ene reaction versus [4 + 2] cycloaddition) is observed in the reaction of $^1O_2$ with the **1j** and MTAD with the **1h** substrates, since considerable amounts of [4 + 2] cycloadducts are formed (Table 2).[7]

Responsible for the [4 + 2] cycloaddition is the zwitterionic intermediate **ZI** (see also Scheme 2), which is stabilized by aryl conjugation. That no [4 + 2] cycloaddition is observed for ArNO is presumably due to steric interactions between the aryl group of the enophile and the *twin* substituent of the styrene (*skew* effect), as shown in the zwitterionic intermediate (**ZI**) for the ArNO ene reaction. The *twin* substituent pushes the aryl group to the unsubstituted corner of the double bond, such that *twix* hydrogen abstraction dominates along the *skew* trajectory of the enophile.



In summary, for all of the *lone* alkyl-substituted (**1a**−**g**) and the *lone* aryl-substituted (**1h**−**k**) substrates, the ArNO results only in ene reaction. For the styrenes **1h**−**k** this exclusive mode selectivity is in contrast to $^1O_2$ and TAD, for which both ene reaction and [4 + 2] cycloaddition are observed. Also the regioselectivity of these *lone* aryl-substituted substrates with ArNO contrasts that of $^1O_2$ and TAD, since for ArNO the twix regioisomer is obtained exclusively. This has been rationalized in terms of cooperative effects between the steric and electronic interactions of the ArNO enophile with the *lone* aryl group, which favor the *skew* arrangement for exclusive *twix* hydrogen abstraction. Coordination with the *lone* substituent is absent in the alkyl-substituted substrates

1a–**g** and as much as about 15% *twin* hydrogen abstraction is observed, except in the case of the *tert*-butyl derivative **1g**, for which again *twix* abstraction is exclusive. The constancy of the *twix*/*twin* ratio (ca. 85:15) for the diverse primary and secondary *lone* substituents is interpreted in terms of the favorable *inside* conformation for minimal 1,3-allylic strain that the allylic *lone* hydrogen atom(s) may assume, such that the remaining groups of the *lone* substituent are located at the periphery and do not exert significantly different steric effects on the attacking enophile. For the substrate **1g** with the lone *tert*-butyl group, the exclusive *twix* regioselectivity is due to the fact that the *inside* conformational arrangement is not possible and the massive steric obstruction by the *lone* substituent forces the enophile to attack exclusively along the *skew* trajectory. Comparison of the regioselectivities for *lone*-substituted substrates has been instructive to draw a detailed mechanistic picture for heteroatom ene reactions.

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

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