JOC Note

Variable Markovnikov Orientation and "cis Effect" in Ene Reactions of Nitrosocarbonyl Intermediates

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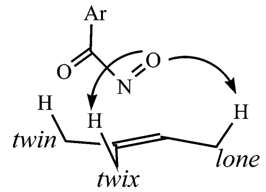
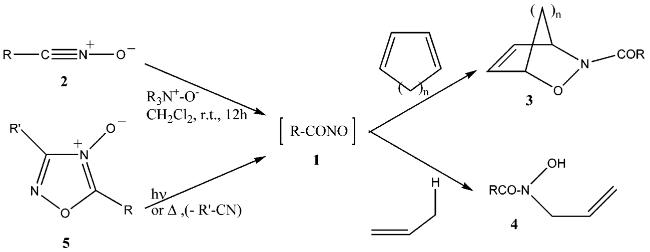


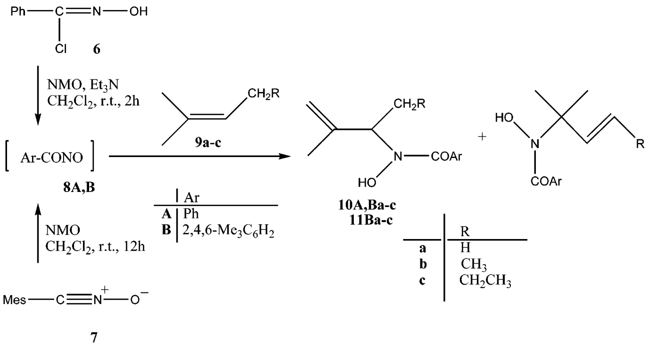
Nitrosocarbonyl intermediates, generated at room temperature by the mild oxidation of nitrile oxides, undergo clean ene reactions with trisubstituted olefins. Allylic hydrogens on the more congested side of the alkene are exclusively abstracted (the "cis effect"), thus resembling singlet oxygen behavior. Nitrosocarbonyl benzene follows a Markovnikov orientation and abstracts preferentially the twix hydrogens over the lone ones. With the more sterically demanding nitrosocarbonyl mesitylene, the Markovnikov directing effect is relieved, and comparable twix and lone abstraction are observed.

Nitrosocarbonyl intermediates **1** (RCONO) are highly reactive species discovered by Kirby and usually generated by periodate oxidation of hydroxamic acids.[1] Recently we have proposed a mild alternative for their generation through the oxidation of nitrile oxides **2** with tertiary amine *N*-oxides,[2] which easily lead to a variety of aromatic and aliphatic nitrosocarbonyls. These fleeting intermediates can be trapped with dienes to afford the corresponding hetero Diels–Alder (HDA) cycloadducts **3** in high yields (Scheme 1). Nitrosocarbonyls **1** also behave as "super enophiles" in ene processes[3] with a variety of olefins, affording the ene adducts **4**. The ene adducts are unstable under the periodate oxidative conditions but stable under the milder oxidation of nitrile oxides and were obtained in excellent yields with tri- and tetra-substituted olefins. With less substituted ethylenes the ene pathway is still active, but the oxidation step of the nitrile oxides competes with the cycloadditions to the olefins. To avoid this competition, nitrosocarbonyls **1** can be generated by clean photochemical[4] fragmentation of 1,2,4-oxadiazole-4-oxides **5**, which represents the softest way for the nitrosocarbonyl generation.

SCHEME 1



SCHEME 2



On pursuing our investigations on the ene reactions of nitrosocarbonyls generated through the mild oxidation of nitrile oxides, we wish to report here the intriguing changes in the regioselectivity of the ene reactions of trisubstituted olefins upon variation of the nitrosocarbonyl substituent, as well as the remarkable "cis" selectivity of these ene reactions.

The ene reaction of nitrosocarbonyl benzene **8A** with 2-methyl-2-butene **9a** (trimethylethylene) afforded a single ene adduct in an almost quantitative yield.[3] A few other isopentenyl derivatives have been tested in the ene reaction with the nitrosocarbonyl benzene **8A**, and the results are reported in Scheme 2. Addition of benzhydroximoyl chloride **6** to a stirred CH_2Cl_2 solution of *N*-methylmorpholine *N*-oxide (NMO, 1.2 equiv), triethylamine (1.1 equiv), and an excess of the olefins **9a–c** (10 equiv) at room temperature afforded, after 2 h of stirring, the ene adducts **10Aa–c** in excellent yields (Table 1).

The structures of all of the isolated ene adducts rely upon the corresponding analytical and spectroscopic data that show the presence of an olefinic methylene. Compounds **10Aa–c** derive from the addition of nitrosocarbonyl **8A** to the less substituted carbon atom of the double bond, in full accordance with a prevailing $HOMO_{(olefin)}-LUMO_{(nitrosocarbonyl)}$ interaction that orientates the addition of the nitrosocarbonyl electrophilic nitrogen to the alkene in a Markovnikov (M) fashion.[3]

We have extended our investigations to nitrosocarbonyl mesitylene, which is generated under simple and clean experimental conditions. Mesitonitrile oxide **7** was added to a stirred CH_2Cl_2 solution of NMO (1.2 equiv) and an excess of olefins **9a–c** (10 equiv) at room temperature. After stirring overnight

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(1) (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1–24. (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348.

(2) (a) Quadrelli, P.; Gamba Invernizzi, A.; Caramella, P. *Tetrahedron Lett.* **1996**, *37*, 1909–1912. (b) Quadrelli, P.; Mella, M.; Gamba Invernizzi, A.; Caramella, P. *Tetrahedron* **1999**, *55*, 10497–10510.

(3) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*, 3233–3236.

(4) (a) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1999**, *40*, 797–800. (b) Quadrelli, P.; Scrocchi, R.; Piccanello, A.; Caramella, P. *J. Comb. Chem.* **2005**, *7*, 887–892.

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TABLE 1. Yields of Adducts in the Reactions of Nitrosocarbonyls 8A,B with Alkenes 9a−c and E,Z-12

Ar-CONO	alkene	**10**	**11**	
8A	**9a**	95		
	9b	94		
	9c	96		
8B	**9a**	43	54	
	9b	44	53	
	9c	45	52	
		13	**14**	**15**
8A	**12 E**	73	3	
	12 Z		10	67
8B	**12 E**	63	29	
	12 Z		54	41

and column chromatographic separation, comparable amounts of the M adducts **10Ba−c** and the anti-Markovnikov (AM) adducts **11Ba−c** were isolated. As shown in Table 1, the Markovnikov selectivity is fully relieved and even slightly reversed in the ene additions of mesityl nitrosocarbonyl **8B**. The structures of the AM adducts rely upon the spectroscopic data that show the presence of a vinyl substituent in **11Ba** and two vicinal olefinic protons in a trans arrangement in **11Bb,c**. In the AM additions to **9b,c** only the (*E*) stereoisomers **11Bb,c** were formed owing to the severe A(1,3) strain[5] involved in the formation of the (*Z*) stereoisomers.

To gain further insights on the origin of this variable Markovnikov selectivity, we have investigated the ene reactions with the stereoisomeric (*E*)- and (*Z*)-3-methyl-2-pentenes **12E** and **12Z**.

These stereoisomeric enes have been extensively used in the investigations of ene reactions because they allow for fully defining the stereochemical paths and assessing the intriguing phenomenon known as the "cis effect".[6] The cis effect typically occurs in singlet oxygen ene reactions and refers to the neat preference of singlet oxygen for the abstraction of the twix and lone[7] allylic hydrogens from the more congested side of an olefin (Figure 1). Other enes display different selectivities. Aromatic nitroso compounds (Ar-NOs)[8] and triazolinediones (TADs)[9] favor the M "end" selectivity but differ in the "cis" preferences. The Ar-NOs maintain some "cis" selectivity favoring the twix over the twin abstraction, whereas TADs do not discriminate between the two sites.

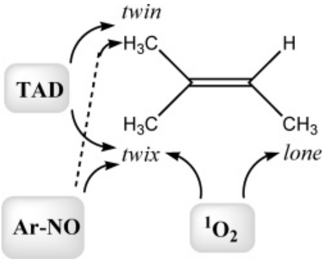
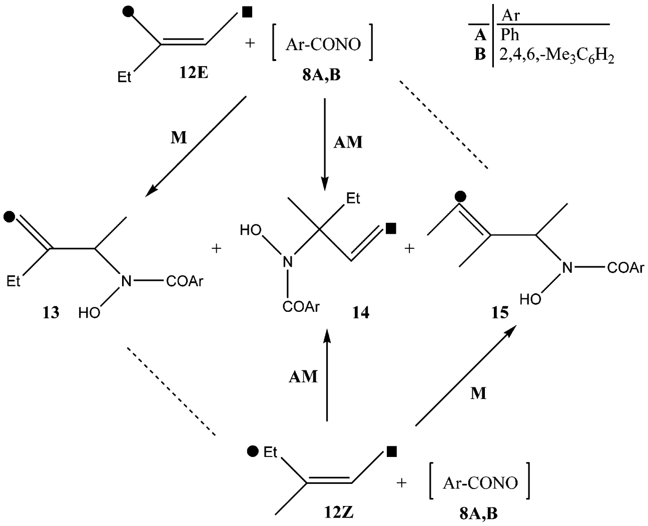


FIGURE 1. Sites of hydrogen abstraction in ene reactions of trimethyl ethylene. Arrows indicate the preferred sites of H abstraction of the different enes.

SCHEME 3. Full Arrows Indicate the M and AM "cis" Paths; Dashed Lines Specify the Not Observed "trans" M Paths



Addition of benzhydroximoyl chloride **6** to a stirred CH_2Cl_2 solution of NMO (1.2 equiv), Et_3N (1.1 equiv), and excess of olefins **12E,Z** (10 equiv) at room temperature afforded exclusively the "cis" ene adducts with a less strict M control with respect to the analogous addition to olefins **9a−c** (Scheme 3). The M adducts **13A** (from (*E*)-**12**) and **15A** (from (*Z*)-**12**) were predominantly formed besides minor amounts of the (identical) AM adducts **14A** (Table 1). The structures of the adducts **13−5A** rely upon the spectroscopic data that show the presence of an olefinic methylene, a vinyl moiety, and a single olefinic proton, respectively. The major adducts derive from the M coupling of the nitrogen atom of the nitrosocarbonyl **8A** to the less substituted carbon of the olefin with abstraction of the twix hydrogens (dots). In the case of **12Z**, the twix abstraction from the ethyl group takes place selectively affording the (*E*) adduct **15A** by avoidance of the A(1,3) strain as observed in the related cases of aromatic nitroso compounds.[7,8] The minor adducts derive instead from an AM coupling of the nitrogen with abstraction of the lone hydrogens (squares). Thus, subtle differences between nitrosocarbonyls and Ar-NO compounds begin to emerge. The dominating path involves twix abstraction in both cases while the minor products derive from different paths, nitrosocarbonyls being inclined to the AM lone route and Ar-NOs to the M twin route.

The experiments performed with nitrosocarbonyl mesitylene **8B** and olefins **12E,Z** confirm the neat cis effect, as well as the relief of M control observed in the addition of **8B** to enes **9a−c** (Table 1). In the case of the ene reaction with olefin **12Z** the major AM ene adduct **14B** is slightly prevalent over the (*E*) M adduct **15B**, whereas the ene reaction of olefin **12E** affords instead the prevailing M adduct **13B** along with the AM adduct **14B**. We trace this slight preference for the M path to the geminal group effect[6c] attributable to some steric hindrance in the AM path because of the approach of the bulkier mesitoyl and ethyl groups.

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(5) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(6) (a) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419−425. (b) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151−9179. (c) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615. (d) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, 1243−1255. (e) Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319−1328.

(7) For definition, see: Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791−6792.

(8) (a) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131−4146. (b) Leach, A. G.; Houk, K. N. *Org. Biomol. Chem.* **2003**, *1*, 1389−1403. (c) Leach, A. G.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 14821−14822. (d) Adam, W.; Krebs, O.; Orfanopoulos, M.; Stratakis, M.; Vougioukalakis, G. C. *J. Org. Chem.* **2003**, *68*, 2420−2425. (e) See also: Adam, W.; Bottke, N.; Engels, B.; Krebs, O. *J. Am. Chem. Soc.* **2001**, *123*, 5542−5548.

(9) (a) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885−11893. (b) Vougioukalakis, G. C.; Orfanopoulos, M. *Synlett* **2005**, 713−731.

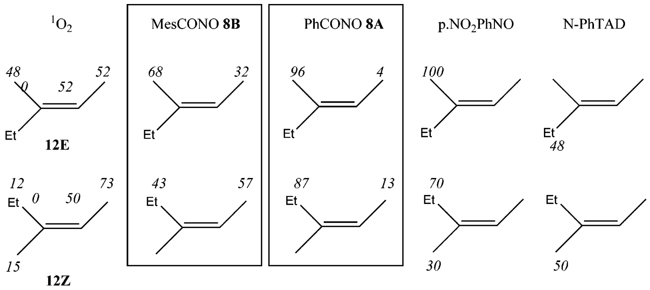
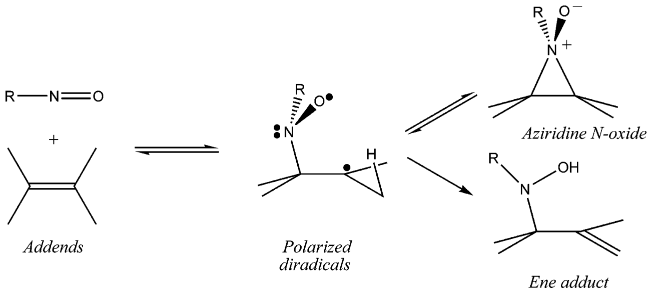


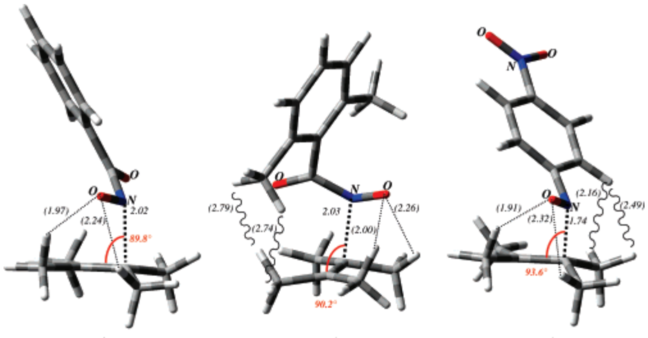
FIGURE 2. Comparison of regioselective outcome in ene reactions of enophiles in the presence of olefins **12E,Z**. Numerical values represent percentage of H abstraction.

SCHEME 4



The results show the remarkable influence of the nitrosocarbonyl substituent on the selectivities in the ene reactions with trisubstituted olefins. The reactions are "cis" specific and differ for the "end" selectivity. Nitrosocarbonyl benzene **8A** gives mainly the M twix adducts, whereas the bulkier nitrosocarbonyl mesitylene **8B** affords mixtures of M twix and AM lone adducts.

Comparing these results with those of other enophiles,[7] such as singlet oxygen, Ar-NOs, and TADs, some similarities and differences can be noted. As far as Markovnikov selectivity is concerned, nitrosocarbonyls locate between the unselective $^1O_2$ and the regiospecific Ar-NO and TAD ene reactions (Figure 2). Detailed mechanistic studies and kinetic isotope effects have provided evidence for the formation of intermediates in the ene reactions of Ar-NOs.[8] The stepwise mechanism involves a side-on attack at the least substituted double bond carbon similar to the nonlinear[10] approach of carbene cycloadditions. The addition leads to unsymmetrical bonded intermediates (the so-called polarized diradicals),[8b,c] which can revert to the addends, rearrange to the ene adducts by H transfer, or cyclize to the aziridine *N*-oxide (Scheme 4). The transition structures (TSs) of the various steps are energetically quite close, and the addition step is mostly reversible in keeping with experiments[8d] and calculations.[8b,c] The regiochemistry depends upon the addition rate and the partitioning of the intermediate among reversion, H-transfer, and cyclization as well.[11] The preference for the twix over the twin abstraction is attributed to the cis effect because of the two favorable allylic CH···O interactions assisting the initial approach of the addends and comparable partitioning of the intermediates.[8b,c] The same mechanism applies to the TAD reactions, which display a rather unselective abstraction of twix and twin hydrogens with no notable cis effect owing to the less favorable CH···N interactions.[9]



16A (ΔH‡ 4.8) **16B'** (ΔH‡ 5.7) **17** (ΔH‡ 14.8)

FIGURE 3. Side view of the B3LYP/6-31G* TSs **16A**,**B′** and **17** for the ene reactions of TME with **8A**, **8B′** (where the mesityl was replaced by 2,6-dimethylphenyl in the calculations) and *p*-NO$_2$Ph-NO. Activation enthalpies $\Delta H^\ddagger$ are given in kcal/mol. Bond distances are in Å; the CH···O contacts (dotted) and steric clashes (wavy lines) are shown in parentheses. The attacking NCC angles are shown in red.

The selectivity of $^1O_2$ arises instead because of a different approach of the addends. In the ene reaction with tetra- and trimethylethylene, $^1O_2$ adopts a perepoxide-like TS[6e] involving the linear attack of oxygen at the center of the double bond and almost symmetrical contacts of the outer oxygen with the twix and lone allylic hydrogens. The H transfer takes place in the subsequent fly through a valley-ridge inflection point with no intermediates. In frontier orbital terms the Stephenson/Fukui model[6a] accounts well for the features of the perepoxide-like TS. Nitrosocarbonyl benzene **8A** closely approaches the main pNO$_2$Ph-NO selectivity, but **8B** diverges remarkably. How to account for the convergence of the selectivities of nitrosocarbonyl **8B** and $^1O_2$?

Model calculations on the reaction of **8A,B′** with tetramethylethylene (TME) shed light on the factors involved in the varying selectivities (Figure 3). The lowest B3LYP/6-31G*[12] transition structures (TSs) **16A,B′** of the initial addition step show in both cases the typical side-on attack at a double bond carbon and the two favorable CH···O contacts. TS **16B′** displays however the usual twisting of the 2,6-dimethylphenyl ring out of the nitrosocarbonyl plane causing visible steric crowding[13] with the methyl group attached to the distal olefinic carbon and lying on the opposite side of the nitroso oxygen. This hindrance should affect and raise energetically the M twix path in the reaction of trimethylethylene, too.

For comparison the TS **17** of the ene reaction of *p*-NO$_2$Ph-NO with TME is also given in Figure 3. TS **17** is later and its

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(10) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970; pp 152−163. (b) Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 1475−1485. (c) Keating, A. E.; Merrigan, S. R.; Singleton, D. A.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 3933−3938 and references therein.

(11) (a) In the simpler case of consecutive first-step reversible reactions, the rate depends upon the partitioning of the intermediate according to the familiar steady-state expressions:[11b,c]

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} C \xrightarrow{k_2} D \qquad k_{obs} = k_1 \frac{k_2}{k_2 + k_{-1}}$$

In other words the reversibility of the addition step decreases the reaction rate with respect to the addition rate k_1, and only a fraction of diradicals enter the H-abstraction channel. (b) Gellene, G. I. *J. Chem. Ed.* **1995**, *72*, 196−9. (c) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2000, Part A, pp 192−204.

(12) Frisch, M. J. et al. *Gaussian 98*, Revision A.9; Gaussian, Inc.: Pittsburgh PA, 1998; *Gaussian 03*, revision B. 02; Gaussian, Inc.: Pittsburgh, PA, 2003.

(13) Steric crowding raises the energy of the TS since the two methyls involved adopt higher energy conformations to minimize steric clashes thereby increasing the distortion energy of the addends. An energetic evalution of the steric hindrance in the case at hand (1.6 kcal/mol) is detailed in Supporting Information.

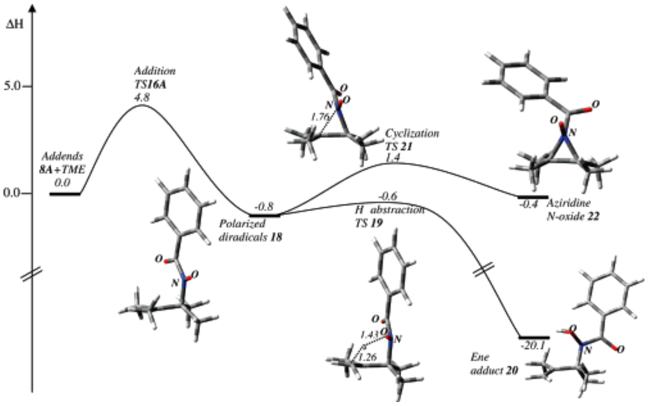

FIGURE 4. Enthalpic profile of the reaction of nitrosocarbonyl benzene **8A** and TME. Numbers are enthalpic differences in kcal/mol. The key distances in TS **19** and **21** are given in Å.

activation enthalpy higher than those of TSs **16A,B** in keeping with the increased stability of the Ar-NOs. A remarkable steric hindrance shows up between an aromatic proton and the methyl group attached to the olefinic carbon undergoing attack and lying on the opposite side of the nitroso oxygen. This hindrance should raise energetically the AM approaches in the cases of trimethylethylene thus favoring M selectivity as observed.

The enthalpic profile of the reaction of **8A** with TME is given in Figure 4. At variance with the case of the Ar-NOs,[14] the TSs of the various steps are well spaced. The profile points out that the addition is not reversible and the addition step is either rate- and product-determining. The addition step leads (IRC)[12] to the polarized diradical **18**, which readily undergoes H abstraction through TS **19** to yield the ene adduct **20**.

The polarized diradical **18** is also connected through a cyclization TS **21** to the aziridine *N*-oxide **22**, but cyclization is more difficult than H-transfer presumably because the *N*-acyl substituent substantially destabilizes the aziridine *N*-oxide, which carries a positive charge on nitrogen. As already noted in the case of Ar-NOs,[8b,c] restricted and unrestricted calculations yield identical structures for all species except for the diradical itself. Spin unrestricted calculations give a diradical with $<S^2 = 0.49>$, whereas the restricted ones afford a slightly different structure that lies 0.2 kcal/mol above the unrestricted diradical.

In summary, the results point out that the ene reactions of nitrosocarbonyls follow a nonlinear "cis" path because of the two favorable CH···O interactions assisting the twix and lone approach. In the reactions of trimethylethylenes the Markovnikov twix path is favored in the case of nitrosocarbonyl benzene **8A**, whereas steric hindrance in the twix approach of **8B** compensates somewhat its electronic preference and mixtures of twix and lone adducts are formed. Conversely in the ene reaction of *p*-NO_2Ph-NO steric hindrance disfavors AM approaches enhancing M selectivity. The formal closeness of the selectivities of $^1O_2$ and **8B** rests therefore on different grounds. At variance with the $^1O_2$ case, nitrosocarbonyls adopt side-on approaches like Ar-NOs and TADs and ordinary steric effects modulate the Markovnikov bias.

Nitrosocarbonyls are versatile synthetic tools in allylic amination[15] and the knowledge of the factors determining their selectivities should increase the potentialities and synthetic use of these fleeting intermediates.

Experimental Section

General Procedure for Ene Reactions of Nitrosocarbonyl Benzene 8A. A solution of 1.56 g (10 mmol) of benzhydroximoyl chloride **6** in 30 mL of CH_2Cl_2 was added dropwise to a stirred solution of *N*-methylmorpholine *N*-oxide (NMO, 1.2 equiv), triethylamine (1.1 equiv) and an excess of the olefins **9a**−**c** and **12E,Z** (10 equiv) in 100 mL of CH_2Cl_2 and allowed to react at room temperature for 2 h. The reaction mixtures were washed twice with water (2 × 50 mL), and the organic phases were dried on Na_2SO_4. The residues, collected upon evaporation of the solvent, were crystallized to afford the ene adducts **10Aa**−**c** (see Supporting Information) or submitted to chromatographic separation to yield the ene adducts **13**−**15A**, which were isolated and crystallized. **13A**: colorless crystals, mp 95−96 °C from *i*-Pr_2O. IR: ν_{max} 3123, 1590 cm^{-1}. ^1H NMR (DMSO): δ 1.00 (t, 3H, *J* 7 Hz); 1.31 (d, 3H, *J* 7 Hz); 2.06 (m, 2H); 4.94 and 4.97 (bs, 1H + 1H); 5.00 (b, 1H); 7.3−7.7 (m, 5H); 9.41 (s, 1H). Anal. Calcd for $C_{13}H_{17}NO_2$ (MW 219.27): C, 71.20; H, 7.82; N, 6.39. Found: C, 71.28; H, 7.81; N, 6.30. **14A**: colorless crystals, mp 91−93 °C from *i*-Pr_2O. IR: ν_{max} 3135, 1597 cm^{-1}. ^1H NMR (DMSO): δ 0.89 (t, 3H, *J* 7 Hz); 1.42 (s, 3H); 1.94 (m, 2H); 5.02 (bd, 1H, *J* 11 Hz); 5.08 (bd, 1H, *J* 17 Hz); 6.16 (dd, 1H, *J* 17, 11 Hz); 7.3−7.7 (m, 5H); 9.52 (s, 1H). Anal. Calcd for $C_{13}H_{17}NO_2$ (MW 219.27): C, 71.20; H, 7.82; N, 6.39. Found: C, 71.14; H, 7.74; N, 6.46. **15A**: colorless crystals, mp 62−64 °C from *i*-Pr_2O. IR: ν_{max} 3180, 1596 cm^{-1}. ^1H NMR (DMSO): δ 1.25 (d, 3H, *J* 7 Hz); 1.59 (d, 3H, *J* 6 Hz); 1.61 (s, 3H); 4.88 (q, 1H, *J* 7 Hz); 5.41 (q, 1H, *J* 7 Hz); 7.3−7.7 (m, 5H); 9.32 (s, 1H). The *E* configuration was assigned through a NOESY experiment, which showed cross-peaks between the vinyl and the CH−N protons. Anal. Calcd for $C_{13}H_{17}NO_2$ (MW 219.27): C, 71.20; H, 7.82; N, 6.39. Found: C, 71.29; H, 7.81; N, 6.30.

General Procedure for Ene Reactions of Nitrosocarbonyl Mesitylene 8B. A solution of 1.61 g (10 mmol) of mesitonitrile oxide **7** in 30 mL of CH_2Cl_2 was added dropwise to a stirred solution of NMO (1.2 equiv) and an excess of olefins **9a**−**c** and **12E,Z** (10 equiv) in 100 mL of CH_2Cl_2 at room temperature. After stirring overnight the reaction mixtures were washed twice with water (2 × 50 mL), and the organic phases were dried on Na_2SO_4. Column chromatographic separations afforded the ene adducts **10** and **11Ba**−**c** and **13**−**15B**, which were isolated and crystallized (see Supporting Informations).

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Supporting Information Available: Physical and spectral characterization data for all new compounds, Cartesian coordinates and thermodynamic data of reactants and TSs, full quotation of ref 12, steric hindrance in TS **16B′**, and profile of the ene reaction of *p*-NO_2Ph-NO with TME. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) In the ene reaction of the Ar-NOs the TSs of the various steps are mostly energetically quite close.[8b,c] The profile of the ene reaction of *p*-NO_2-Ph-NO with TME conforms to the trend and is given in Supporting Information.

(15) (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (b) Matunas, R.; Lai, A.; Lee, C. *Tetrahedron* **2005**, *61*, 6298−6308. (c) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164−5173. (d) Srivastava, R. S.; Nicholas, K. M. *Organometallics* **2005**, *24*, 1563−1568.