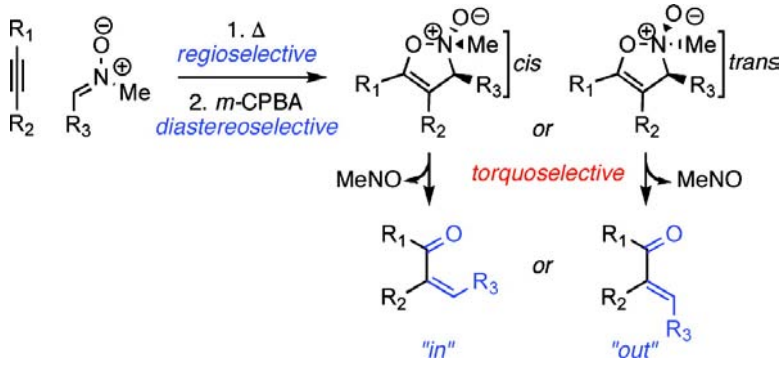
Letter

Origins of Stereoselectivity in the Oxido-Alkylidenation of Alkynes

Daniel P. Canterbury, Alison J. Frontier, Joann M. Um, Paul H.-Y. Cheong, Dahlia A. Goldfeld, Richard A. Huhn, and K. N. Houk

Org. Lett., **2008**, 10 (20), 4597-4600• DOI: 10.1021/ol8019154 • Publication Date (Web): 18 September 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 1 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

ORGANIC LETTERS

2008
Vol. 10, No. 20
4597−4600

Origins of Stereoselectivity in the Oxido-Alkylidenation of Alkynes

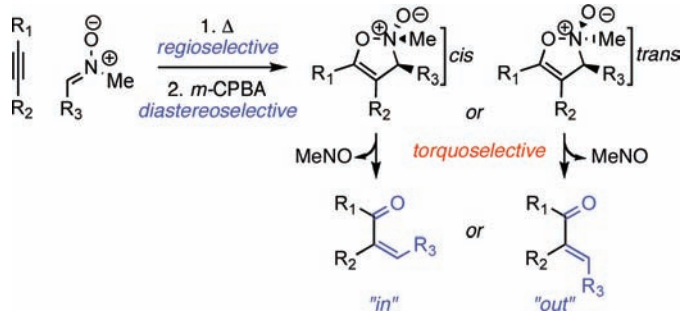
Daniel P. Canterbury,[†] Alison J. Frontier,*[,†] Joann M. Um,[‡] Paul H.-Y. Cheong,[‡] Dahlia A. Goldfeld,[‡] Richard A. Huhn,[‡] and K. N. Houk*[,‡]

Department of Chemistry, University of Rochester, Rochester, New York, 14627-0216, and Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

frontier@chem.rochester.edu; houk@chem.ucla.edu

Received August 15, 2008

ABSTRACT



A mild, convenient oxido-alkylidenation of alkynes is described. The three-step sequence involves the 1,3-dipolar cycloaddition of a nitrone and an alkynoate, oxidation of the resulting isoxazoline, and stereoselective extrusion of nitrosomethane. Quantum mechanical calculations identified the interactions of R_3 with the oxidant and the preferred conformation of a diradical intermediate as major factors controlling the stereoselectivity of the oxidation and torquoselectivity of the extrusion.

We report the origins of selectivity in the oxido-alkylidenation of alkynes involving a reaction sequence which exploits a regioselective 1,3-dipolar cycloaddition, stereoselective *N*-oxidation, and spontaneous torquoselective cheletropic extrusion (Scheme 1). The sequence provides a facile entry to the preparation of alkylidene β-ketoesters, which prove to be useful precursors to the divinyl ketones of value in the Nazarov cyclization.[1] Padwa first reported examples of these reactions but did not provide unequivocal evidence for the alkene geometries or a rationale for the origins of selectivity.[2]

We have now found that a variety of propiolates and nitrones react with highly HOMO−LUMO-controlled regioselectivity[3] to give isoxazoline intermediate **1**. Upon treatment with *m*-CPBA, the ring nitrogen of **1** is thought to undergo oxidation to give intermediate **2**, which cannot be isolated or even observed by NMR spectroscopy. Instead, immediate cheletropic extrusion of nitrosomethane occurs at low temperature to yield trisubstituted alkenes **3** and **4** in high yield (Table 1). Assignment of *E* and *Z* isomers was accomplished by analysis of $^3J_{C,H}$ coupling constants. For most substrates, the extrusion was highly stereoselective, favoring alkene diastereomer **3** (termed the "in" isomer because the torquoselective rotation of R_3 occurs in an "inward" fashion, Scheme 2). In a few cases, alkene **4** (the "out" isomer) dominated (entries 9−12). We and others have shown that stereoelectronic effects control the torquoselec-

[†] University of Rochester.
[‡] University of California.

(1) (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278 Correction: *J. Am. Chem. Soc.* **2004**, *126*, 10493. (b) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (c) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.

(2) (a) Padwa, A.; Kline, D. N.; Perumattam, J. *Tetrahedron Lett.* **1987**, *28*, 913. (b) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1988**, *58*, 2238.

(3) (a) Houk, K. N.; Sims, J.; Duke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. (b) Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301. (c) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798.

10.1021/ol8019154 CCC: $40.75
Published on Web 09/18/2008

Scheme 1

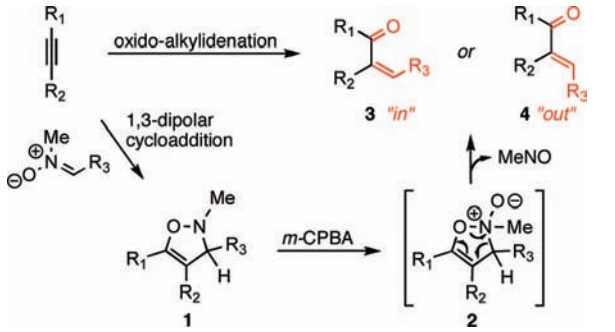
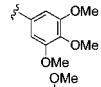
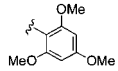
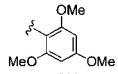
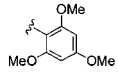


Table 1. Oxido-Alkylidenation Results[a]

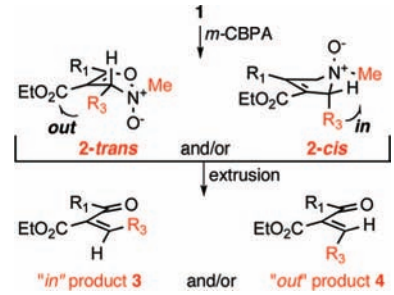
entry	R_1	R_3	% yield of **1**[b]	% yield of **3**+**4**[c]	ratio (**3** : **4**)
1		Ph	88	94	>15:1
2		Ph	61	85	8:1
3		Ph	89	64	>15:1
4		Ph	85	93	>15:1
5			96	92	12:1
6			86	93	>15:1
7		^{n}Bu	72	95	12:1
8			70	85	15:1
9			72	94	1:2
10			38	89	<1:15
11			49	96	1:12
12			67	96	1:2.6

[a] $R_2 = CO_2Et$ for all entries. [b] Reaction conditions: alkyne (1.0 equiv), nitrone (1.3 equiv), toluene, 50 °C, 12 h. [c] Reaction conditions: isoxazoline (1.0 equiv), *m*-CPBA (1.5 equiv), CH_2Cl_2, 0 °C, 5 min.

tivity of numerous pericyclic reaction types,[4−7] but only one group of related torquoselective extrusions has been reported, involving an achiral nitrogen center.[8]

Quantum mechanical calculations were performed to identify the factors controlling the stereoselectivity of the oxidation and extrusion steps. All structures were computed using UB3LYP[9] density functional theory as implemented in Gaussian 03.[10] The structures and energies reported in Schemes 5 and 6 were calculated with the 6-31+G(d)[11] basis set. Because calculations at the UB3LYP/6-31G(d)[12] level resulted in virtually no geometry or energy change, the remaining structures are calculated at this level of theory. All stationary points were verified as minima or first-order

Scheme 2. Extrusion of Diastereomeric Isoxazoline *N*-Oxides



saddle points by vibrational frequency analysis. All free energies are reported in kcal·mol^{-1}.

Performic acid was used to model the oxidant and isoxazoline **1a** (Scheme 3) was used to model Table 1, entry 4 as a typical "in"-yielding isoxazoline. Although isoxazoline conformation **1a-*trans*** is more stable than **1a-*cis***, oxidation of **1a** is selective for *N*-oxide diastereomer **2a-*cis*** due to an unfavorable interaction between the oxidant and phenyl π system in **TS1a-*trans***.

The decomposition of intermediate **2** can occur via a concerted or stepwise sequence (Scheme 4). The barrier for the concerted pathway was calculated to be 6 kcal·mol^{-1} higher than that of the stepwise. Reactions that preferentially

(4) Electrocyclic reactions: (a) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (b) Evanseck, J. D.; Thomas, B. E., IV; Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1995**, *60*, 7134. (c) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471. (d) Luo, L.; Bartberger, M. D.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 12366. (e) Walker, M. J.; Hietbrink, B. N.; Thomas, B. E., IV; Nakamura, K.; Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 6669. (f) Ikeda, H.; Kato, T.; Inagaki, S. *Chem. Lett.* **2001**, *3*, 270. (g) Murakami, M.; Miyamoto, Y.; Ito, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 189. (h) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072.

(5) Nazarov-type cyclizations: (a) Dieker, J.; Froehlich, R.; Wuerthwein, E.-U. *Eur. J. Org. Chem.* **2006**, *23*, 5339. (b) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A.; Occhiato, E. G. *Chem. Eur. J.* **2006**, *12*, 2836. (c) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J. Am. Chem. Soc.* **2004**, *126*, 10954. (d) Faza, O. N.; Lopez, C. S.; Alvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324. (e) Lopez, C. S.; Faza, O. N.; York, D. M.; de Lera, A. R. *J. Org. Chem.* **2004**, *69*, 3635.

(6) Sigmatropic shift: Faza, O. N.; Lopez, C. S.; de Lera, A. R. *J. Org. Chem.* **2007**, *72*, 2617.

(7) Cope rearrangement: Zhao, Y.-L.; Suhrada, C. P.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 11106.

(8) (a) Chiacchio, U.; Liguori, A.; Rescifina, A. *Tetrahedron* **1992**, *48*, 123. (b) Chiacchio, U.; Casuscelli, F.; Liguori, A.; Romeo, G.; Sindona, G.; Uccella, N. *Heterocycles* **1993**, *36*, 585. (c) Casuscelli, F.; Chiacchio, U.; Rescifina, A.; Romeo, R.; Romeo, G.; Tommasini, S.; Uccella, N. *Tetrahedron* **1995**, *51*, 2979.

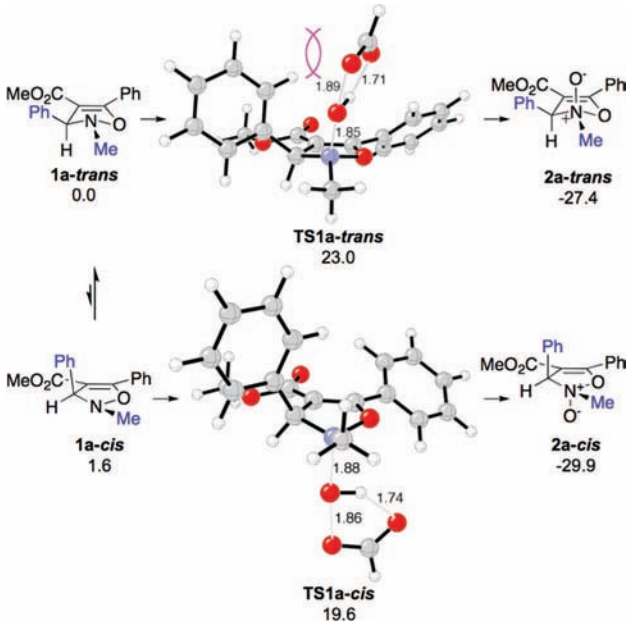
(9) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5468. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *98*, 785.

(10) Frisch, M. J. et al. *Gaussian 03*, revision C.02; 2004. See the Supporting Information for a full reference.

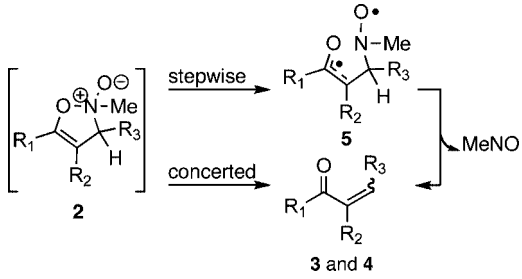
(11) (a) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265. (c) Latajka, Z.; Scheiner, S. *Chem. Phys. Lett.* **1984**, *105*, 435.

(12) (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.

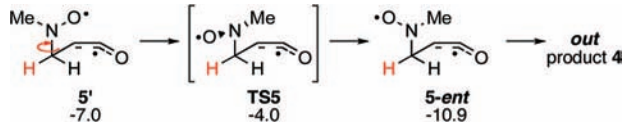
Scheme 3. Oxidation Stereoselectivity



Scheme 4. Possible Decomposition Mechanisms of **2**



Scheme 5



proceed through low energy diradical NO intermediates such as **5** are not uncommon.[13]

To explain the torquoselectivity, the "inward" and "outward" decompositions of unsubstituted **2** ($R_1 = R_2 = R_3 =$ H) were investigated (Scheme 6). The N−O bonds of **2**, bearing a pseudoaxial oxygen, and **2′**, bearing a pseudoequatorial oxygen, readily cleave to form "in" and "out" diradicals **5** and **5′**, respectively. While the *N*-oxide exhibits a modest selectivity for *outward* ring-opening, the resulting **5′** is 3.9 kcal·mol^{-1} less stable than "in" diradical **5** due to repulsion between the oxygen lone pairs in **5′**. Diradical **5′** undergoes a nearly barrierless rotation via **TS4** to the more stable **5**, which then extrudes nitrosomethane to yield "in" alkene **3**. The rotational barrier for the C−N bond of **5′** (**TS5**, Scheme 5), which would give the more stable conformation **5-*ent*** and subsequently "out" alkene **4**, is 2.6 kcal·mol^{-1} higher in energy than **TS4**.

Having established that the relative energies of **TS3** and **TS3′** (C−N bond cleavage of **5** and **5′**) determines the alkene ratio, these transition structures were located for the "in" and "out" diradicals resulting from decomposition of substituted *N*-oxide **2a-*cis***. Consistent with experimental results the "in" alkene was calculated to be favored by 3.0 kcal·mol^{-1} (Figure 1).

To explain "out" product **4**, entry 10 of Table 1 was modeled by **1b** (Figure 2). The oxidation selectivity was calculated to be similar to that of "in"-yielding isoxazoline **1a**, with a 3.6 kcal·mol^{-1} preference for **TS1b-*cis*** over **TS1b-*trans***. These results show that formation of **4** is not due to a change in the oxidation selectivity.

The stereochemistry-determining C−N bond cleavage transition state was next investigated (Figure 3). In agreement with experimental results, decomposition to "out" alkene **4b** was calculated to be favored by 0.8 kcal·mol^{-1}. The reversal

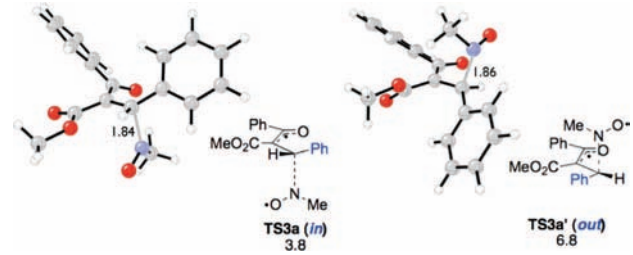


Figure 1. Model MeNO extrusion TSs; Table 1, entry 4.

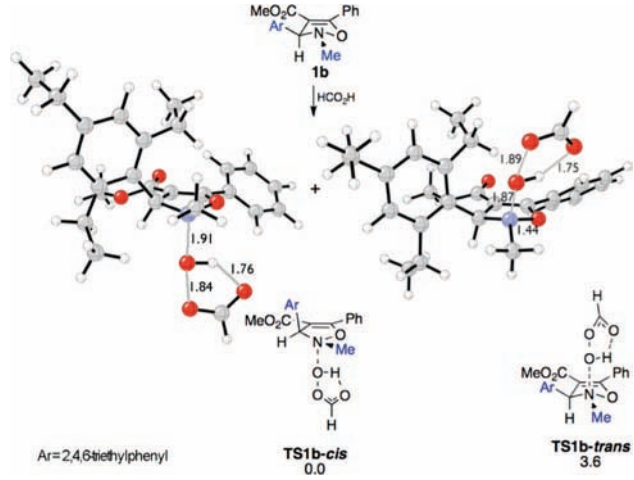
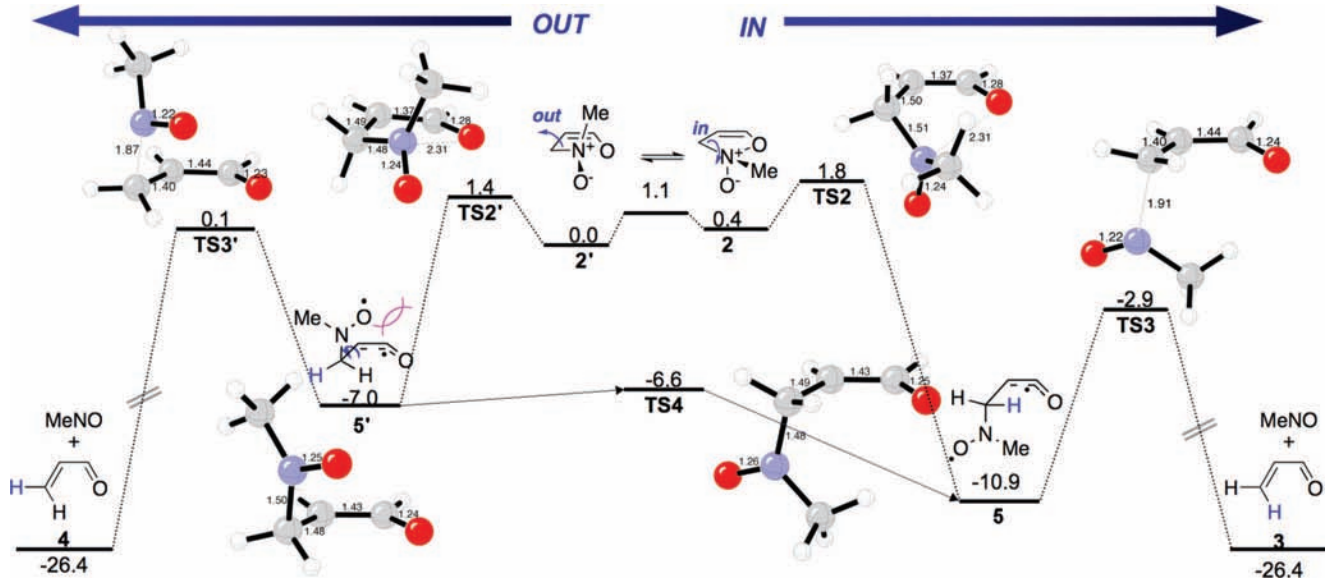


Figure 2. Transition structures for oxidation of **1b**.

(13) (a) Breton, G. W.; Nickerson, J. E.; Greene, A. M.; Oliver, L. H. *Org. Lett.* **2007**, *9*, 3005. (b) Leach, A. G.; Houk, K. N. *Org. Biomol. Chem.* **2003**, *1*, 1389. (c) Leach, A. G.; Houk, K. N. *Chem. Commun.* **2002**, *12*, 1243. (d) Leach, A. G.; Houk, K. N. *J. Am. Chem. Soc.* **2002**, *124*, 14820.

Scheme 6



of torquoselectivity of **1b** is attributed to steric clash between an ortho ethyl group of R_3 and the planar allyl radical in **TS3b**.

In conclusion, stereoselective oxidation of **1** occurs to minimize steric hindrance between the oxidizing agent and substituent alpha to the isoxazoline nitrogen (R_3). A stepwise extrusion that maximizes the distance between the two radical oxygens in the diradical intermediate (e.g., **5** vs **5′**) explains the general formation of "in" alkene **3**. This selectivity is reversed when large ortho substituents on R_3 destabilize the diradical intermediate of type **5**.

Acknowledgment. We are grateful to the University of Rochester and the National Institute of General Medical Sciences, National Institutes of Health (GM 36700) for support of this work. We thank Dr. Alice Bergmann (SUNY-Buffalo) for the collection of high-resolution mass spectra.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. Cartesian coordinates and energies of all reported structures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8019154

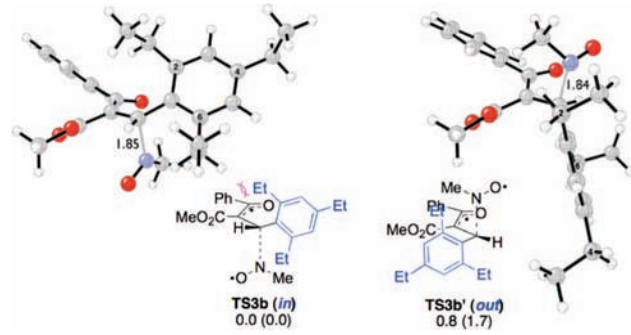


Figure 3. Model MeNO extrusion TSs; Table 1, entry 10 (relative enthalpies in parentheses).