ORGANIC LETTERS

2008
Vol. 10, No. 4
661−663

Reactive Intermediates from DMDO Oxidation of Ynamides. Trapping of a de novo Chiral Push–Pull Carbene via Cyclopropanation

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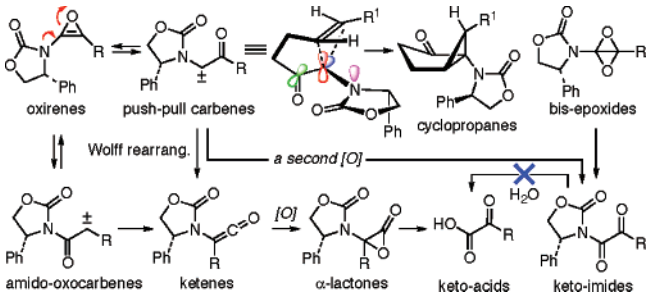
Received December 21, 2007

ABSTRACT



The reaction profile of DMDO oxidations of ynamides is described. This work illustrates the first examples of highly diastereoselective intramolecular cyclopropanations of a push–pull carbene derived from alkyne oxidation. In addition, the ynamide oxidation provides facile access to ketoimides and reveals mechanistic insights into the chemistry of electronically biased oxirenes.

Oxocarbene intermediates derived from epoxidations of alkynes have been strongly suggested to arise from the rearrangement of oxirenes.[1] Subsequent transformations of the oxocarbenes include Wolff rearrangement and further reaction of the resultant ketene, C−H insertion, hydrogen or alkyl migration, secondary oxidation, and formation of stable metalla-keto carbene complexes.[2] Despite unleashing a remarkable array of transformations through a simple π-bond oxidation, little has been reported on engaging this potential toward precise ends.[1] Ynamides,[3] a class of electron-rich and electronically biased alkynes, are uniquely positioned for the tuning of such reactivity.

The postulated oxirenes **2** derived from an oxidation of ynamides **1**[4] could rearrange to amido-oxocarbene **3** or push−pull carbene **4**, the latter experiencing dual stabilization[5] (Scheme 1). While amido-oxocarbenes **3** have been represented by related diazo compound decomposition reactions,[6] push−pull carbenes **4** represent a novel species that is intriguing both in reactivity and in synthetic potential.[7]

(1) For reviews on oxirenes, see: (a) Zeller, K. P. *Sci. Synth.* **2002**, *9*, 19. (b) Lewars, E. G. *Chem. Rev.* **1983**, *83*, 519. (c) Torre, M.; Lown, E. M.; Gunning, H. E.; Strauzz, O. P. *Pure Appl. Chem.* **1980**, *52*, 1623.

(2) For an example of metal keto carbenoid formation by DMDO oxidation of alkynes, see: Sun, S.; Edwards, J. O.; Sweigart, D. A.; D'Accolti, L.; Curci, R. *Organometallics* **1995**, *14*, 1545.

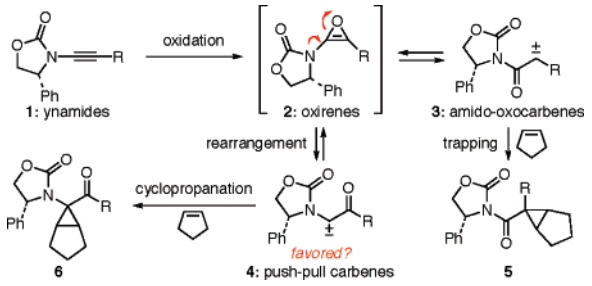
(3) For a review, see: Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575.

(4) For oxidations of ynamines employing ozone and oxygen, see: (a) Foote, C. S.; Lin, J. W.-P. *Tetrahedron Lett.* **1968**, *9*, 3267. (b) Schank, K.; Beck, H.; Himbert, G. *Synthesis* **1998**, 1718. (c) During our submission of this work, an account on epoxidation of ynamides appeared. See: Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, *18*, 2819 (received July 28, 2007). (d) For our preliminary disclosure of this work, see: Al-Rashid, Z. F.; Hsung, R. P.; Antoline, J. E.; Ko, C.; Wei, Y.; Yang, J. 40th ACS National Organic Symposium, Durham, NC, June 3, 2007; Abstract No. A-11.

(5) For push−pull carbene stability and reactivity, see: (a) Buron, C.; Gornitzka, H.; Romanenko, V.; Bertrand, G. *Science* **2000**, *288*, 834. (b) Moss, R. A.; Zdrojewski, T.; Ho, G.-J. *J. Chem. Soc., Chem. Commun.* **1991**, 946. For elegant work on donor−acceptor metal carbenoids, see: (c) Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davis, H. M. L. *J. Org. Chem.* **2006**, *71*, 5349. (d) Davis, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109.

10.1021/ol703083k CCC: $40.75
Published on Web 01/17/2008

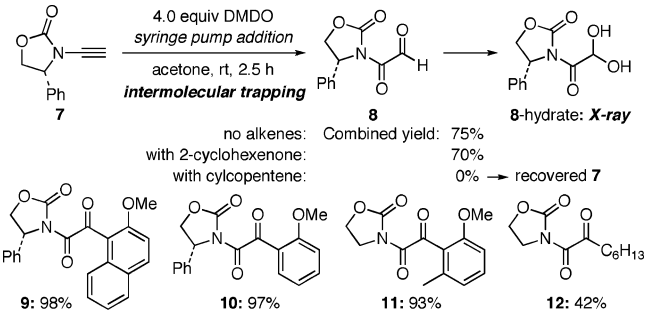
Scheme 1



Were such a carbene to arise, one may expect promiscuity with respect to the reactive partners it may choose (electron-rich versus electron-deficient).[5b] We report here the first epoxidation of ynamides **1** and trapping of novel chiral push−pull carbenes **4** via intramolecular cyclopropanations.[8]

Our efforts commenced with dimethyldioxirane (DMDO) oxidation of terminally unsubstituted ynamide **7** (Scheme 2).

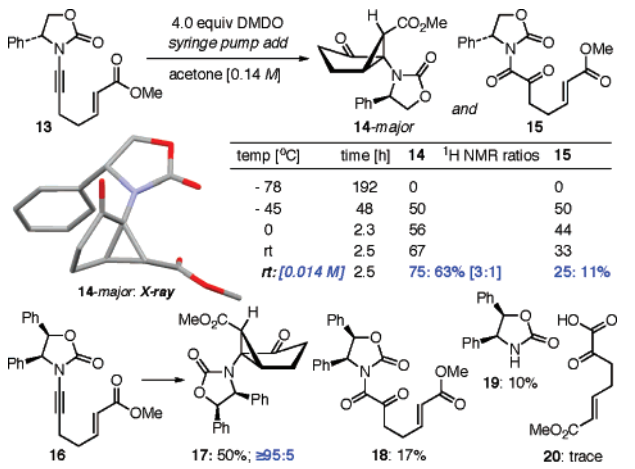
Scheme 2



While initial reaction analysis was complicated by partitioning of the resulting amidoglyoxal **8**[9] with its hydrate (confirmed by X-ray), it became clear that (1) ynamide oxidation could be achieved and is relatively faster than reported alkyne oxidations;[10] (2) oxidation of the proposed oxocarbenes proceeded at a faster rate than cyclopropanation of cyclohexenone, even when DMDO concentrations were limited by syringe pump addition; (3) electron-rich olefin cyclopentene out competed the ynamide for DMDO. While not informative concerning the parent carbenes, amidoglyoxal **8** and ketoimides **9**−**12** could be obtained in good yields and represent potentially useful synthons.[11]

To continue probing for the proposed oxocarbenes, we examined intramolecular systems. As shown in Scheme 3,

Scheme 3



temp [°C]	time [h]	14	^{1}H NMR ratios	15
- 78	192	0		0
- 45	48	50		50
0	2.3	56		44
rt	2.5	67		33
rt: [0.014 M]	2.5	75: 63% [3:1]		25: 11%

oxidation of ynamide **13** provided amido-cyclopropane **14** in a 3:1 isomeric ratio with **14**-*major* being confirmed by X-ray crystal analysis. Ketoimide **15** was also obtained, but its formation appears to decrease at elevated temperatures. The competing intermolecular DMDO oxidation of the proposed oxocarbenes was further suppressed by dilution. Oxidation of 4,5-diphenyl oxazolidinone-substituted ynamide **16** provided amido-cyclopropane **17** as a single diastereomer. The respective ketoimide **18**, free auxiliary **19**, and ketoacid **20** were also identified. The formations of **19** and **20** are likely mutually related.

To account for all the observed products, a comprehensive reaction profile for the oxidation of ynamides is shown in Figure 1. Amido-cyclopropanes **14** and **17** unambiguously confirm the presence of push−pull carbenes **4**. The major stereoisomer is likely derived from cyclopropanations of oxocarbenes **4** assuming a conformation that accommodates both the nitrogen electron pair donation (pink) to the carbene empty p-orbital (red) and delocalization of the carbene electron pair into the keto carbonyl group (green), while the oxazolidinone carbonyl is *anti* to the carbene lone pair.

Ketoimide formation can be rationalized through a second DMDO oxidation of oxocarbene intermediates **4** (or **3**),[10a] although a pathway involving dioxabicyclobutane **21** cannot be ruled out. The stability of ketoimides **15** in acetone/water suggests ketoacids **20** do not arise simply by hydrolysis.

(6) (a) Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* **1985**, *50*, 1663. (b) Doyle, M. P.; Kalinin, A. V. *Synlett* **1995**, 1075. (c) Jiang, N.; Ma, Z.; Qu, Z.; Xing, X.; Xie, L.; Wang, J. *J. Org. Chem.* **2003**, *68*, 893.

(7) For some examples of related α-azacarbenoids, see: (a) Schöllkopf, U.; Hauptreif, M.; Dippel, J.; Nieger, M.; Egert, E. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 192. (b) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 2473. (c) Wurz, R. P.; Charette, A. B. *J. Org. Chem.* **2004**, *69*, 1262. (d) Bégis, G.; Sheppard, T. D.; Cladingboel, D. E.; Motherwell, W. B.; Tocher, D. A. *Synthesis* **2005** 3186. For elegant examples of α-azametallo-carbenoids, see: (e) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105. (f) Hegedus, L. S.; Lastra, E.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1992**, *114*, 2991. (g) Powers, T. S.; Wulff, W. D.; Quinn, J.; Shi, Y.; Jiang, W. Q.; Hsung, R. P.; Parisi, M.; Rahm, A.; Jiang, X. W.; Yap, G. A.; Rheingold, A. L. *J. Organomet. Chem.* **2001**, *617*, 182.

(8) For leading reviews, see: (a) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (b) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603.

(9) See Supporting Information.

(10) For DMDO oxidation of alkynes, see: (a) Zeller, K.-P.; Kowallik, M.; Haiss, P. *Org. Biomol. Chem.* **2005**, *3*, 2310. (b) Murray, R. W.; Singh, M. *J. Org. Chem.* **1993**, *58*, 5076. (c) Curci, R.; Fiorentino, M.; Fusco, C.; Mello, R.; Ballistreri, F. P.; Failla, S.; Tommaselli, G. A. *Tetrahedron Lett.* **1992**, *33*, 7929.

(11) For some examples, see: (a) Kim, S. M.; Byun, I. S.; Kim, Y. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 728. (b) Corey, E. J.; McCaully, R. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1970**, *92*, 2476.

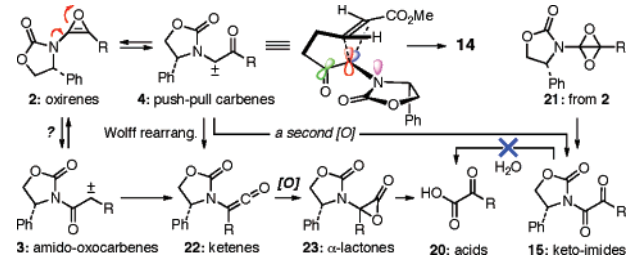
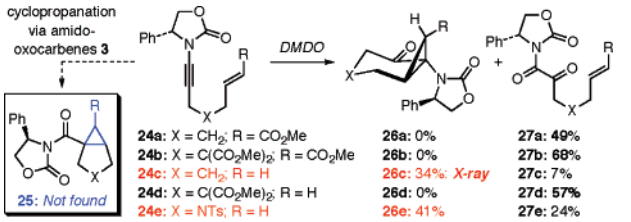


Figure 1. A mechanistic overview.

Instead, a sequence of Wolff rearrangement of **4** (or **3**) follow by oxidation of the resulting ketene **22**[12a] has been proposed as the major pathway en route to **20** via α-lactones **23**.[10a]

In the context of ynamides **13** and **16**, the involvement of amido-oxocarbenes **3** in cyclopropanation is less likely given the concomitant cyclobutane formation. To probe for **3**, we examined oxidations of homologous ynamides **24a**−**e** (Scheme 4) because cyclopropanations of the respective olefin in

Scheme 4



24a−**e** through the amido-oxocarbene intermediate **3** would lead to bicyclo[3.1.0]hexanes **25**. To our surprise, the epoxidation of the acrylate containing ynamide **24a** gave neither cyclopropanes **25** nor **26a** but only ketoimide **27a**. This outcome was unaltered by inclusion of a buttressing moiety in the tether (see **24b**).[13]

Reasoning that the respective amido-oxocarbene **3** could prefer electron-rich olefins, we prepared ynamide **24c**. Although the olefin of **24c** was not entirely stable to oxidation conditions,[12b] a single isomer of amido-cyclopropane **26c** was obtained, thereby confirming the promiscuity of push−pull carbenes **4**. Attempting to again enhance the cyclopropanation pathway, we examined the oxidation of ynamide **24d** only to find ketoimide **27d** as the sole product.[13] A tether dependence reported in enyne cycloisomerizations[14] prompted our investigation of the oxidation of nitrogen-tethered ynamide **24e**. In this case, amido-cyclopropane **26e** was isolated in 41% along with ketoimide **27e** with no traces of bicyclo[3.1.0]hexane **25**.

While amido-oxocarbenes **3** cannot be ruled out, these experiments further demonstrated the tendency for ynamide oxidation to yield cyclopropane products exclusively arising from push−pull carbenes **4**, thereby suggesting either a strong bias in the rearrangement of oxirenes **2** or a pathway that does not involve an oxirene. Electrophilic substitution of ynamides **28** could occur preferentially at the β-position,[3a] as is conveyed by the electronic distribution in resonance structure **29** (Figure 2). This in turn could lead to the

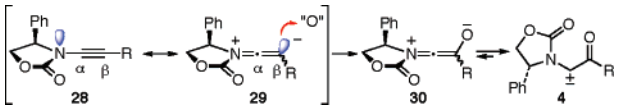


Figure 2. An alternative pathway to push−pull carbenes **4**.

oxyketene iminium ion **30** giving rise to push−pull carbenes **4**.

We have described here a mechanistic profile of DMDO oxidation of ynamides that led to the first examples of stereoselective intramolecular cyclopropanations of a chiral push−pull carbene derived from alkyne oxidation, a facile access to ketoimides, and insights in the chemistry of electronically biased oxirenes. Further investigations into reactivities and applications are underway.

Acknowledgment. We thank NIH (GM066055) for funding. We thank Dr. Vic Young and Ben Kucera at University of Minnesota for solving X-ray structures.

Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectral and characterizations are available for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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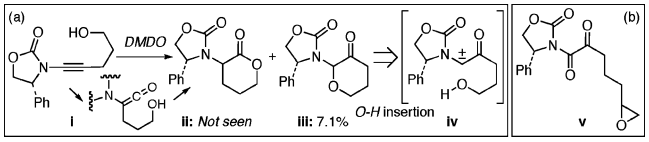
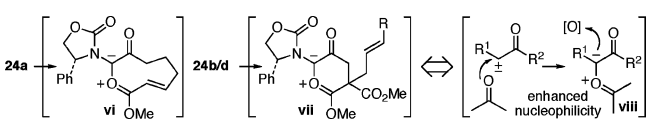
(12) (a) Attempts at trapping this ketene afforded ketoaminal **iii** accompanied by free auxiliary. The formation of **iii** suggests the interception of oxocarbene **iv**. (b) Ketoimide **v** was isolated in 8% yield.



(13) We attributed this observation as a result of the complexation of the ester carbonyl oxygen with carbene intermediates derived from **24a** and **24b** (or **24d**), leading to carbonyl ylides **vi** and **vii**, respectively, with an enhanced nucleophilicity favoring the second electrophilic addition of DMDO over cyclopropanation. Related discussions were reported (ref 10a) where the solvent acetone (see **viii**) was observed to facilitate the double oxidation.



(14) (a) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (b) Nieto-Oberhuber, C.; López, S.; Jiménez-Núñez, E.; Echavarren, A. M. *Chem.*−*Eur. J.* **2006**, *12*, 5916.