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Chemo- and Enantioselective Epoxidation of Enynes

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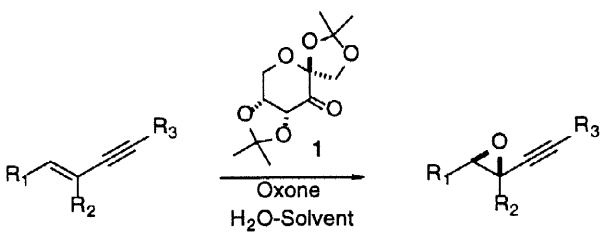
Abstract: High chemo- and enantioselectivity have been obtained for asymmetric epoxidation of conjugated enynes using a fructose-derived chiral ketone as catalyst and Oxone as oxidant.

Introducing an epoxide α to an alkyne further enhances the synthetic utility of the epoxide. The alkynyl group provides a controlling group for regioselective opening of the epoxide and the C-C triple bond itself is a synthetically versatile functional group.[1] In addition, some natural products contain alkynyloxiranes (for example, the antitumor agent neocarzinostatin[2]). Enantioselective epoxidation of enynes would provide a direct approach to alkynyloxiranes.[3,4] Recently we reported a highly enantioselective epoxidation method for *trans*- and trisubstituted olefins using a fructose-derived ketone **1** as catalyst and Oxone as oxidant.[5] In an effort to expand the scope of this epoxidation, we have been investigating the feasibility of chemo- and enantioselective epoxidation of enynes with this catalyst (Scheme 1). Although dioxiranes are known to be able to epoxidize C-C triple bonds,[6] chemoselective epoxidation of the enynes using dimethyldioxirane has been observed.[7] Herein we wish to report our studies on the asymmetric epoxidation of enynes using ketone **1** as catalyst and Oxone as oxidant.



Scheme 1

Our investigation started with 1-ethynylcyclohexene as the test substrate (Table 1, entry 1). Subjecting this enyne to the epoxidation conditions gave a chemoselective epoxidation of the double bond. The analysis of the epoxide using chiral GC (Chiraldex B-TA column) showed 93% ee. Further studies demonstrated that the acetylene could bear a variety of substituents such as alkyl, TMS, and ester groups (Table 1, entries 3-5). To further explore

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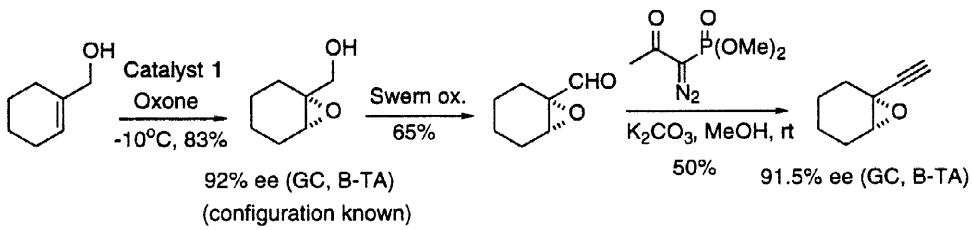
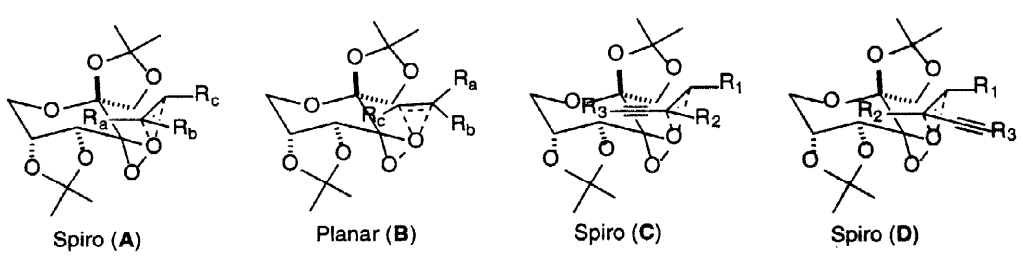
the generality of these substrates, a variety of enynes were prepared[8] and epoxidized. The ^1H NMR spectra of the reaction mixtures in all cases were very clean, and showed that the epoxidations chemoselectively occurred at the olefins. The enantioselectivities for the substrates studied are also generally high (Table 1). In contrast to certain isolated trisubstituted olefins,[5c] the enantioselectivity for the trisubstitued enynes is noticeably high, which indicates that the alkyne groups are beneficial for these substrates.

Both experimental and theoretic data have shown that the spiro reaction mode is favored for the dioxirane mediated epoxidation and is anticipated for the epoxidation of enynes.[9,5a,5c] The absolute configurations of the epoxides in Table 1 are assigned based on this model. A correlation of one enyne epoxide (Table 1, entry 1) with an authentic sample prepared from an epoxy alcohol with known configuration[10] validates the assignment (Scheme 2).[11]



Scheme 2

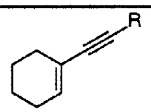
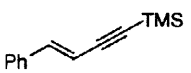
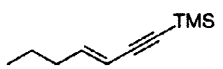
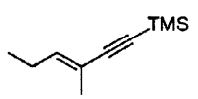
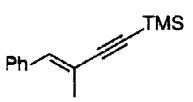
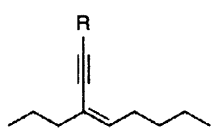
It is widely believed that the favoring of the spiro transition state is due to the stabilizing interaction of an oxygen lone pair of the dioxirane with the π^* orbital of the olefin.[9c,e] One contributing factor for the high enantiomeric excess for the epoxidation of conjugated enynes could be due to the fact that the spiro transition state is further favored by the presence of the alkyne group. Since the conjugation of an alkyne to the olefin lowers the olefin's LUMO, there results an enhanced stabilizing interaction between the dioxirane oxygen's lone pair and the olefin's LUMO. Previously we have shown that the main competing transition state is the planar transition state **B** in using this catalyst system (Scheme 3).[5c] The competition between spiro **A** and planar **B** is affected by the steric bulk of substituents on the olefin. Higher ee could be obtained by decreasing the size of R_a (favoring spiro **A**) and increasing the size of R_c (disfavoring planar **B**). The epoxidation of the enynes in Table 1 is expected to proceed via spiro transition states **C** and **D**. The sterically less demanding acetylene groups should favor the spiro transition states particularly spiro **C**.



Scheme 3

In summary, we have found that the epoxidation of conjugated enynes is highly chemo-, enantioselective, and stereospecific. The alkyne groups are beneficial for the enantioselectivity due to both electronic and steric effects. The availability of these enantiomerically enriched enyne epoxides provides opportunities for potential synthetic applications. Such studies are currently under way.

Table 1. Asymmetric Epoxidation of Enynes Catalyzed by Ketone **1** & **ent-1**[a]

Entry	Substrate	T (°C)	t (h)	Yield (%)[c]	ee (%)	Config.
						
1[4b]	R = H	-10	3	78	93[d]	(R,R)[h]
2	R = H (**ent-1**)	-10	3	75	94[d]	(S,S)[i]
3	R = CH_3	-10	3	88	90[d]	(R,R)[i]
4	R = TMS	-10	3	86	94[e]	(R,R)[i]
5	R = CO_2Et	0	2	71	93[f]	(R,R)[i]
6[b,4a]		0	4	59	96[g]	(R,R)[i]
7		-10	4	71	89[g]	(R,R)[i]
8		-10	3	84	95[g]	(R,R)[i]
9		0	2	64	94[g]	(R,R)[i]
						
10	R = H	-10	3	60	93[f]	(R,R)[i]
11	R = TMS	-10	3	83	97[g]	(R,R)[i]

[a] All reactions except entry 6 were carried out with substrate (1 eq.), ketone (0.3 eq.), Oxone (1.38 eq.), and K_2CO_3 (5.8 eq.) in CH_3CN-DMM-aqueous K_2CO_3/AcOH solution (prepared by adding 0.5 mL of AcOH to 100 mL of 0.1 M aqueous K_2CO_3, pH 9.3) (1:2:2, v/v). [b] Ketone (0.5 eq.), Oxone (2.07 eq.), and K_2CO_3 (8.7 eq.) in CH_3CN-DMM-aqueous K_2CO_3/AcOH solution (1:2:2, v/v). [c] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [d] Enantioselectivity was determined by chiral GC (Chiraldex B-TA column). [e] Enantioselectivity was determined by chiral GC (Chiraldex B-TA column) after desilylation. [f] Enantioselectivity was determined by ^1H NMR shift analysis of the epoxide products directly with Eu(hfc)$_3$. [g] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [h] The absolute configuration was determined by a correlation of the epoxide with a prepared authentic sample (see text). [i] The absolute configuration was tentatively assumed by analogy based on the spiro reaction mode.

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References

(1) For some leading references see: (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *Tetrahedron* **1991**, *47*, 1677-1696. (b) Marshall J.A.; DuBay, W.J. *J. Am. Chem. Soc.* **1992**, *114*, 1450-1456. (c) Marshall J.A.; Pinney, K.G. *J. Org. Chem.* **1993**, *58*, 7180-7184. (d) Marshall J.A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457-1464. (e) Mukai, C.; Sugimoto, Y-i.; Ikeda, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2183-2186. (f) Aurrecoechea, J.M.; Solay, M. *Tetrahedron Lett.* **1995**, *36*, 2501-2504. (g) McDonald, F.E.; Gleason, M.M. *J. Am. Chem. Soc.* **1996**, *118*, 6648-6659. (h) Piotti, M.E.; Alper, H. *J. Org. Chem.* **1997**, *62*, 8484-8489.

(2) For a leading reference see: Myers, A.G.; Hammond, M.; Wu, Y.; Xiang, J-N.; Harrington, P.M.; Kuo, E.Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006-10007.

(3) For leading references on asymmetric epoxidations of enynes directed by hydroxyl groups see: (a) Johnson, R.A.; Sharpless, K.B. In *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH: New York, 1993; Chapter 4.1. (b) Katsuki, T.; Martin, V.S. *Org. React.* **1996**, *48*, 1-299.

(4) For leading references on asymmetric epoxidations of enynes using (salen)Mn(III) see: (a) Lee, N.H.; Jacobsen, E.N. *Tetrahedron Lett.* **1991**, *32*, 6533-6536. (b) Brandes, B.D.; Jacobsen, E.N. *J. Org. Chem.* **1994**, *59*, 4378-4380. (c) Hamada, T.; Irie, R.; Katsuki, T. *Synlett*, **1994**, 479-481. (d) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827-11838. (e) Hamada, T.; Daikai, K.; Irie, R.; Katsuki, T. *Synlett* **1995**, 407-408.

(5) (a) Tu, Y.; Wang, Z-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806-9807. (b) Wang, Z-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328-2329. (c) Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224-11235.

(6) (a) Curci, R.; Fiorentino, M.; Fusco, C.; Mello, R. *Tetrahedron Lett.* **1992**, *33*, 7929-7932. (b) Murray, R.W.; Singh, M. *J. Org. Chem.* **1993**, *58*, 5076-5080.

(7) Wang, X.; Ramos, B.; Rodriguez, A. *Tetrahedron Lett.* **1994**, *35*, 6977-6980.

(8) Corey, E.J.; Fuchs, P.L. *Tetrahedron Lett.* **1972**, 3769-3772.

(9) For leading references on the transition states of the dioxirane-mediated epoxidation see: (a) Baumstark, A.L.; McCloskey, C.J. *Tetrahedron Lett.* **1987**, *28*, 3311-3314. (b) Baumstark, A.L.; Vasquez, P.C. *J. Org. Chem.* **1988**, *53*, 3437-3439. (c) Bach, R.D.; Andres, J.L.; Owensby, A.L.; Schlegel, H.B.; McDouall, J.J.W. *J. Am. Chem. Soc.* **1992**, *114*, 7207-7217. (d) Yang, D.; Wang, X-C.; Wong, M-K.; Yip, Y-C.; Tang, M-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311-11312. (e) Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* **1997**, *119*, 10147-10152. (f) Jenson, C.; Liu, J.; Houk, K.N.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1997**, *119*, 12982-12983.

(10) (a) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780. (b) Wang, Z-X.; Shi, Y. *J. Org. Chem.* in press

(11) Müller, S.; Liepold, B.; Roth, G.J.; Bestmann, H.J. *Synlett* **1996**, 521-522.