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Enantioselective Epoxidation of Conjugated *cis*-Enynes by Chiral Dioxirane

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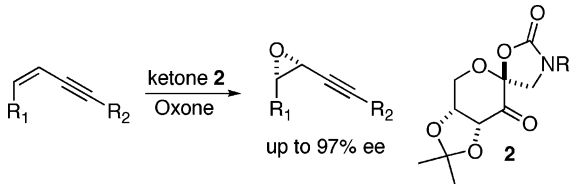
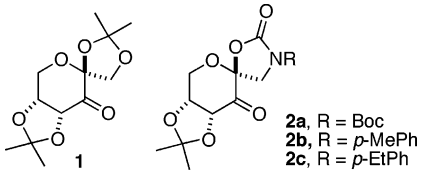


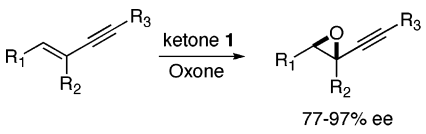
This paper describes a highly chemo- and enantioselective epoxidation of conjugated *cis*-enynes using readily available glucose-derived ketone **2** as catalyst and Oxone as oxidant to form *cis*-propargyl epoxides in high ee's. The interaction between the alkyne group of the substrate and the oxazolidinone moiety of the ketone catalyst as well as the interactions between the substituents on enynes and the oxazolidinone moiety of the ketone catalyst are important for the stereodifferentiation.

Introduction

Chiral propargyl epoxides are very useful synthetic intermediates which can undergo a variety of synthetic transformations,[1] and enantioselective epoxidation of enynes provides a direct approach to these epoxides.[2,3] Enantioselective epoxidation of conjugated *cis*-enynes using chiral (salen)Mn catalysts has been shown to form *trans*-propargyl epoxides as major products in high ee's.[3a−e] Recently, it also has been reported that *cis*-1-phenylpent-3-en-1-yne can be epoxidized stereospecifically using chiral (salan)Ti catalysts, giving the *cis*-epoxide in high ee.[3f,g] Previously, we reported that fructose-derived ketone **1** provides high ee's for a wide variety of *trans*- and trisubstituted olefins (Scheme 1).[4,5] Conjugated *trans*- and trisubstituted enynes have also been found to be effective substrates for this ketone, giving *trans*-propargyl epoxides in high ee's (eq 1).[6]

SCHEME 1





(**1**)

However, generally speaking, an efficient synthesis of optically active *cis*-propargyl epoxides is still challenging and highly desirable.

* Corresponding author. Phone: 970-491-7424. Fax: 970-491-1801.

(1) For some examples of synthetic applications of propargyl epoxides, see: (a) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677. (b) Marshall, J. A.; DuBay, W. J. *J. Am. Chem. Soc*. **1992**, *114*, 1450. (c) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180. (d) Marshall, J. A.; Tang, Y. *J. Org. Chem.* **1994**, *59*, 1457. (e) Mukai, C.; Sugimoto, Y-i.; Ikeda, Y.; Hanaoka, M. *Tetrahedron Lett.* **1994**, *35*, 2183. (f) Aurrecoechea, J. M.; Solay, M. *Tetrahedron Lett.* **1995**, *36*, 2501. (g) Piotti, M. E.; Alper, H. *J. Org. Chem.* **1997**, *62*, 8484. (h) Aurrecoechea, J. M.; Alonso, E.; Solay, M. *Tetrahedron* **1998**, *54*, 3833. (i) Aurrecoechea, J. M.; Solay, M. *Tetrahedron* **1998**, *54*, 3851. (j) Bernard, N.; Chemla, F.; Normant, J. F. *Tetrahedron Lett.* **1998**, *39*, 6715. (k) Klein, S.; Zhang, J. H.; Holler, M.; Weibel, J-M.; Pale, P. *Tetrahedron* **2003**, *59*, 9793.

(2) For leading references on asymmetric epoxidation 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.

(3) For leading references on asymmetric epoxidations of *cis*-enynes using chiral salen-type catalysts, see: (a) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (b) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378. (c) Hamada, T.; Irie, R.; Katsuki, T. *Synlett* **1994**, 479. (d) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827. (e) Hamada, T.; Daikai, K.; Irie, R.; Katsuki, T. *Synlett* **1995**, 407. (f) Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem., Int. Ed.* **2005**, *44*, *4935*. (g) Sawada, Y.; Matsumoto, K.; Kondo, S.; Watanabe, H.; Ozawa, T.; Suzuki, K.; Saito, B.; Katsuki, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3478.

(4) For leading reviews on chiral ketone catalyzed asymmetric epoxidations, see: (a) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Shi, Y. *Acc. Chem. Res*. **2004**, *37*, 488. (d) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497.

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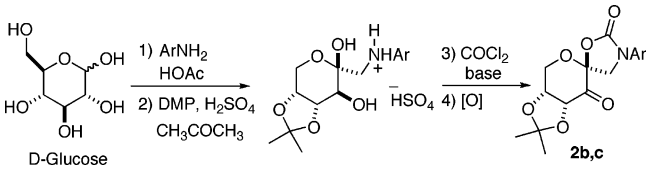
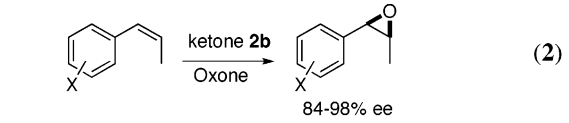
SCHEME 2

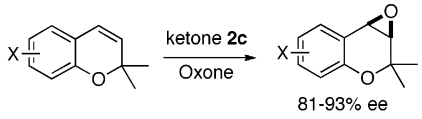


Recently, we found that oxazolidinone-containing ketones **2** can provide high ee's for substrates which are not effective with ketone **1** (Scheme 1).[7] *N*-Aryl substituted oxazolidinone-containing ketones such as **2b** and **2c**, readily prepared in large quantities from D-glucose and anilines in four steps (Scheme 2),[8] are particularly promising for practical use. Studies have shown that ketone **2** can give high ee's for olefins such as conjugated aromatic *cis*-olefins (eqs 2 and 3),[9a,b] styrenes (eq 4),[8b] certain trisubstituted and tetrasubstituted olefins (eqs 5 and 6)[9c,d,e] and conjugated *cis*-dienes (eq 7).[9f]

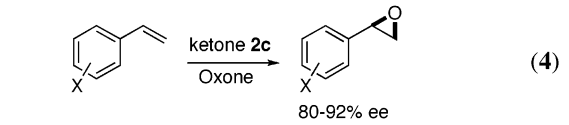
The origin of enantioselectivity of ketone **2** appears to arise from an attraction between the R_π group and the oxazolidinone moiety of the ketone catalyst, causing spiro transition state **A** to be favored over spiro **B** (Scheme 3),[7,8,10] To further understand the factors influencing the enantioselectivity of the epoxidation and expand the scope of the reaction, we decided to explore the epoxidation of conjugated *cis*-enynes with readily available ketones **2b** and **2c**.[8] Herein we wish to report our efforts on this subject.[11]



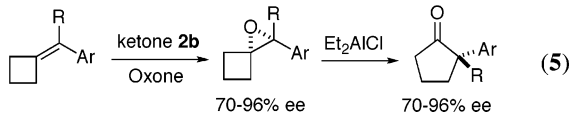
(**2**)



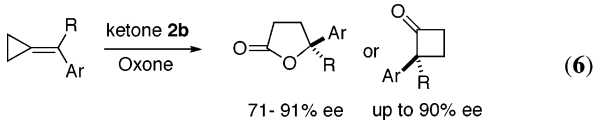
(**3**)



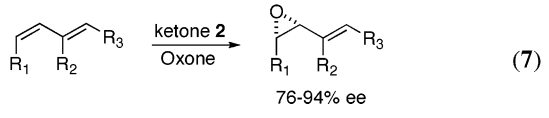
(**4**)



(**5**)



(**6**)

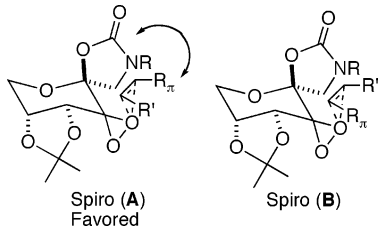


(**7**)

Results and Discussion

The enyne substrates were generally readily prepared from vinyl halides and alkynes via Sonogashira coupling (see Supporting Information for details). The epoxidation of enynes was carried out using ketones **2b** or **2c** as catalyst and Oxone as oxidant. As shown in Table 1, a variety of enyne substrates

SCHEME 3



can be effectively epoxidized with high enantioselectivities (80−97% ee). The reactions were generally clean, as judged by the ^1H NMR spectra of the crude reaction mixtures.[12] The reactions were stereospecific in that *cis*-olefins yielded only *cis*-epoxides with no isomerization observed. Among the solvents screened, DME gave the best combination of ee and conversion. Very nonpolar substrates show markedly decreased reactivity presumably due to poor solubility in the reaction mixture (e.g., Table 1, entry 5). For these substrates, dioxane was used as solvent, which has the effect of raising conversion while slightly lowering ee's with respect to DME. For these and other less reactive substrates, conversion can also usually be improved with a slower addition of Oxone and/or higher reaction temperature (0 °C). The slow addition of Oxone lowers its concentration in solution, thus reducing the undesired reaction processes such as Oxone self-decomposition (pathway **e**), consumption of the dioxirane by Oxone (pathway **h**), and racemic epoxidation of olefin by Oxone itself (pathway **i**) (Scheme 4).[13]

As shown in Table 1, the ee's are highly dependent upon the substituents on the olefin and alkyne (R_1 and R_2). This could

(5) For examples of asymmetric epoxidation mediated by fructose-derived ketone **1**, see: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (c) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (d) Wang, Z-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. (e) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. (f) Frohn, M.; Zhou, X.; Zhang, J-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718−7719. (g) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818. (h) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213. (i) Tu, Y.; Frohn, M.; Wang, Z-X.; Shi, Y. *Org. Synth.* **2003**, *80*, 1. (j) Wang, Z-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. *Org. Synth.* **2003**, *80*, 9. (k) Lorenz, J. C.; Frohn, M.; Zhou, X.; Zhang, J-R.; Tang, Y.; Burke, C.; Shi, Y. *J. Org. Chem.* **2005**, *70*, 2904.

(6) (a) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (b) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646.

(7) For asymmetric epoxidation with ketone **2a**, see: (a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435.

(8) (a) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (b) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. (c) Zhao, M.-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.

(9) (a) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115. (b) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973. (c) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (d) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (e) Wang, B.; Shen, Y-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519. (f) Burke, C.P.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4475.

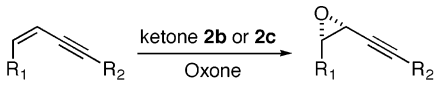
(10) (a) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (b) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5794.

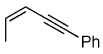
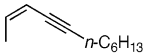
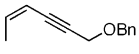
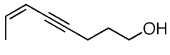
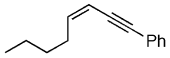
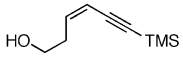
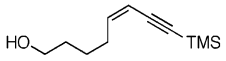
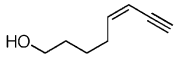
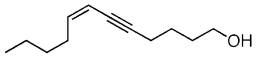
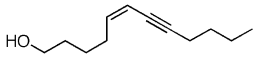
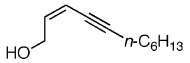
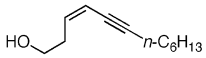
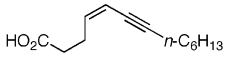
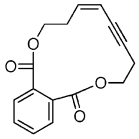
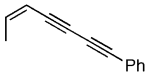
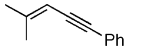
(11) Two examples of conjugated *cis*-enynes (*cis*-1-phenyl-3-penten-1-yne and *cis*-2-undecen-4-yne) were previously examined with ketone **2a** (91% and 87% ee obtained repectively) (ref 7).

(12) For the substrates with a TMS group on the alkyne (Table 1, entries 6 and 7), some cleavage of the TMS group occurred during the reaction.

(13) For a detailed discussion, see: ref 4b.

TABLE 1. Asymmetric Epoxidation of Enynes by Ketones 2b and 2c[a]

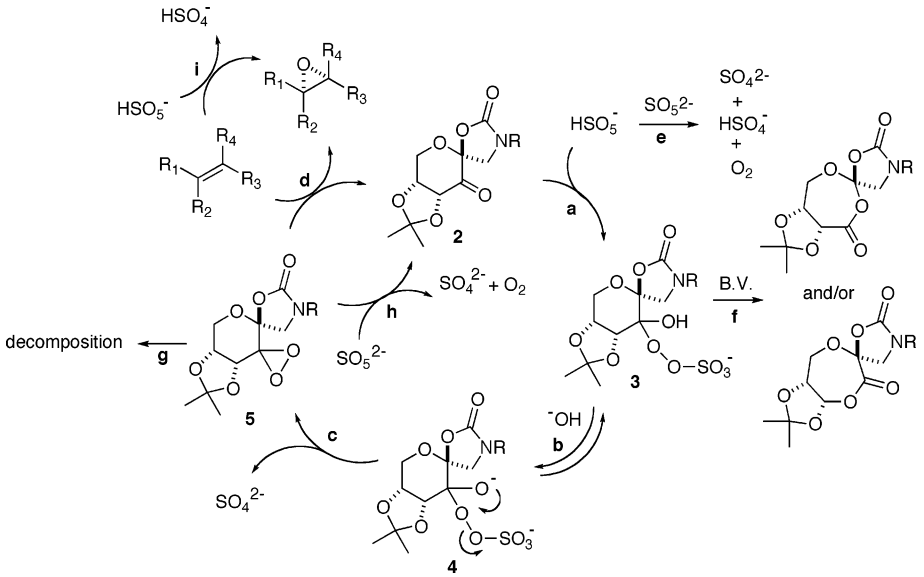


Entry	Enyne	Ketone	T (°C)	t (h)	Yield (conv.) (%)[b]	ee (%)
1		**2c**	-10	8	78 (100)[c,d]	93[h,3a,d,f,g,7]
2		**2c**	0	12	84 (95)[e,f,g]	90[i,3a,7]
3		**2c**	0	12	67 (91)	92[i]
4		**2b**	-10	8	83 (100)	88[j]
5		**2b**	0	12	52 (70)[e,f,g]	84[i]
6		**2c**	0	4	46 (80)[e,f]	94[i,17]
7		**2b**	0	4	52 (82)[e,f]	87[i]
8		**2b**	0	8	59 (92)	80[k]
9		**2b**	-10	8	64 (100)[c]	80[h]
10		**2b**	-10	8	70 (97)	90[l]
11		**2c**	-10	8	68 (92)	97[i]
12		**2c**	-10	8	66 (96)	97[i]
13		**2c**	0	12[m]	61 (nd)	96[n]
14		**2c**	0	12	54 (100)[c,e,f,o]	87[h]
15		**2b**	0	8	76 (86)[c,f,o,p]	93[h]
16		**2c**	-10	8	71 (88)	94[i,18]

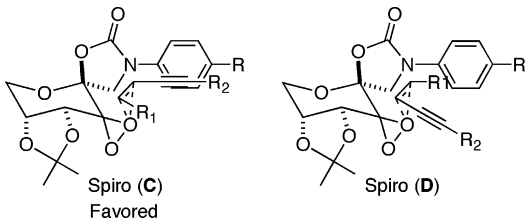
[a] Unless stated otherwise, all reactions were carried out with enyne (1.0 eq.), catalyst (0.25 eq.), Oxone (1.6 eq.), and K_2CO_3 (6.7 eq.) in DME and buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} aq EDTA, pH 9.3) (1.5:1, v/v). Oxone and K_2CO_3 were added separately and simultaneously over the time and temperature specified. [b] Unless stated otherwise, the conversion was determined by GC of the crude reaction mixture. [c] The conversion was determined by ^{1}H NMR of the crude reaction mixture. [d] 0.20 equiv catalyst used. [e] Dioxane used as solvent. [f] Solvent-buffer (2:1, v/v). [g] 2.4 equiv Oxone/10.1 equiv. K_2CO_3 were used. [h] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). [i] Enantioselectivity was determined by Chiral GC (Chiraldex B-DM column). [j] Enantioselectivity was determined using the corresponding benzoate by chiral HPLC (Chiralpak AD column). [k] Enantioselectivity was determined using the corresponding acetate by Chiral GC (Chiraldex B-DM column). [l] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ column). [m] Oxone was added over 8 h, and then the mixture was allowed to stir for an additional 4 h at 0 °C. [n] Enantioselectivity was determined using the corresponding benzoate by chiral HPLC (Chiralcel OD column). [o] 0.30 equiv. catalyst used. [p] With DME/dioxane (1:1) as solvent.

be rationalized by spiro transition states **C** and **D** (Scheme 5). Spiro **C** should be favored due to the apparent attractive interaction between the alkyne group and the oxazolidinone moiety of the catalyst. Moreover, it appears that there exist

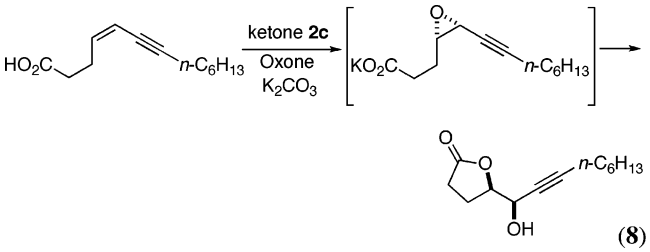
SCHEME 4



SCHEME 5

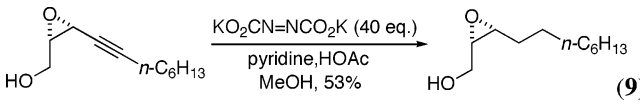


additional interactions such as hydrophobic interactions between the R_1 and R_2 groups of the substrate and the oxazolidinone moiety of the catalyst (possibly the *N*-aryl group). Thus, the competition between spiro **C** and **D** is significantly influenced by the nature of the R_1 and R_2 groups. Generally, increasing the hydrophobicity of R_1 group will enhance the competition of spiro **D**, thus lowering ee's (entry 5 vs entry 1, entry 7 vs entry 6). Favorable substrates have more polar R_1 groups and less polar R_2 groups (entries 11 and 12). Likewise, unfavorable substrates contain less polar R_1 groups and more polar R_2 groups (entry 9 vs entry 10). For entry 13, the lactone resulting from the opening of the epoxide was obtained (eq 8). Further studies have shown that a *cis*-endiyne is also an effective substrate (Table 1, entry 15). This transformation is potentially useful since several of this type of epoxides have been shown to be biologically active compounds.[14]



(**8**)

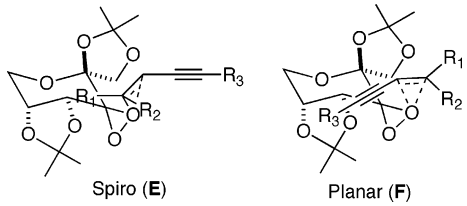
The absolute configurations of the epoxides in entries 1 and 2 were determined by comparing the optical rotations with those previously determined. For entry 11, the configuration was determined by reducing the alkyne with excess diimide[15] to the known saturated compound and comparing the optical rotation with the reported one (eq 9).[16] In all these cases, the obtained configurations are consistent with spiro transition state **C** being favored. The stereochemistry of the remaining epoxides in Table 1 is tentatively assigned based on this model.



(**9**)

Besides *cis*-enynes, ketone **2** also gave higher ee's than ketone **1** for certain trisubstituted enynes. For example, 94% ee was obtained for 4-methyl-1-phenyl-3-penten-1-yne (Table 1, entry 16) as compared to 55% ee with ketone **1**. The low ee's obtained for this class of enyne with ketone **1** is likely due to a significant competition from planar transition state **F** because the acetylene group is a sterically small group (Scheme 6).[5b] On the other hand, the desired spiro transition state **G** for ketone **2** is further favored over the competing planar transition state such as **H** due to the attractive interaction between the alkyne group of the olefin and the oxazolidinone moiety of the ketone catalyst (Scheme 7),[7,8,9,10] thus giving higher enantioselectivities.

SCHEME 6



In summary, we report an effective method for the asymmetric epoxidation of conjugated *cis*-enynes with readily available

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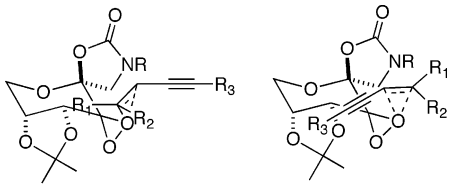
SCHEME 7



chiral ketones **2b** and **2c** as catalyst and Oxone as oxidant. The reactions are highly chemo- and enantioselective and are stereospecific, allowing exclusive formation of *cis*-propargyl epoxides from *cis*-enynes in high ee's. This method should provide a valuable route to this useful class of compounds. Studies have shown that while the interaction between the alkyne group of the substrate and the oxazolidinone moiety of the ketone catalyst plays an important role in stereodifferentiation, the interactions (likely hydrophobic) between the substituents on the enyne and the oxazolidinone moiety of the ketone catalyst (possibly *N*-aryl group) also significantly influence the enantioselectivity. The information obtained will be useful for the prediction of the stereochemical outcome for a given substrate and the design of more effective catalysts in the future.

Experimental Section

Representative procedure for asymmetric epoxidation (Table 1, entry 1). To a solution of *cis*-1-phenyl-3-penten-1-yne (0.071 g, 0.5 mmol) and ketone **2c** (0.035 g, 0.10 mmol) in DME (7.5 mL) were added buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aqueous EDTA, pH = 9.3) (5.0 mL) and Bu_4NHSO_4 (0.0075 g, 0.02 mmol) with stirring (in order to maximize the conversion, efficient stirring is required, but excessive splashing of the reaction mixture should be avoided). After the mixture was cooled to −10 °C (bath temperature) via NaCl-ice bath, solutions of Oxone (0.20 M in 4×10^{-4} M aqueous EDTA, 4 mL) (0.49 g, 0.80 mmol) and K_2CO_3 (0.84 M in 4×10^{-4} M aqueous EDTA, 4 mL) (0.46 g, 3.36 mmol) were added dropwise separately and simultaneously over a period of 8 h via syringe pump. The reaction was then quenched with the addition of petroleum ether and extracted with petroleum ether. The combined organic layers were washed with water, brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in petroleum ether; petroleum ether was used as eluent] to give the *cis*-epoxide as a colorless oil (0.062 g, 78% yield, 93% ee).

Acknowledgment. We are grateful to the generous financial support from the General Medical Sciences of the National Institutes of Health (GM59705-08).

Supporting Information Available: Synthesis and characterization of conjugated *cis*-enynes and epoxides as well as the data for the determination of the enantiomeric excess of the epoxides and the NMR spectra of selected epoxides. This material is available free of charge via the Internet at http://pubs.acs.org.

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