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Asymmetric Epoxidation Catalyzed by α,α-Dimethylmorpholinone Ketone. Methyl Group Effect on Spiro and Planar Transition States

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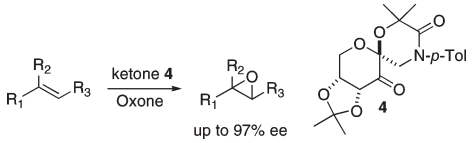

Asymmetric epoxidation of olefins by using an α,α-dimethylmorpholinone-containing chiral ketone catalyst (**4**) has been investigated. This ketone, which has the combined features of several previously studied catalysts, is an effective catalyst for *trans*- and trisubstituted olefins, and up to 97% ee has been achieved. The α,α-dimethyl group has significant impact on spiro and planar transition states.

Chiral dioxirane-mediated epoxidation is a very useful method to synthesize chiral epoxides. A variety of different ketones have been investigated in various research groups.[1] In our laboratory, we found that fructose-derived ketone **1** is a very effective catalyst for the epoxidation of *trans*- and trisubstituted olefins,[2] and oxazolidinone-containing ketones **2** are effective catalysts for a wide variety of conjugated *cis*-olefins,[3a,3c−3e,3g,3k,3l] styrenes,[3b−3d,3f] and certain trisubstituted[3h,3j] and tetrasubstituted olefins[3i,3j] (Figure 1). Subsequently, we have also found that morpholinone-containing

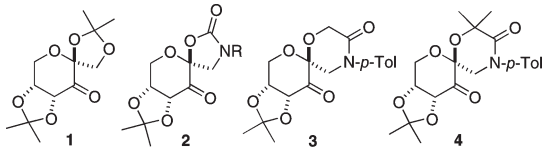

FIGURE 1. Ketones **1**−**4**.

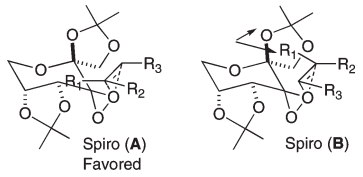

FIGURE 2. Proposed competing transition states for the epoxidation of *trans*- and trisubstituted olefins with ketone **1**.

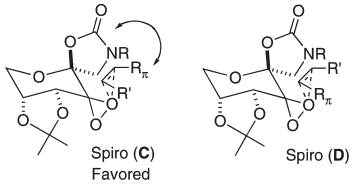

FIGURE 3. Proposed competing transition states for the epoxidation of *cis*-olefins with ketone **2**.

ketone **3** provides encouragingly high enantioselectivity for 1,1-disubstituted and *cis*-olefins.[4]

The enantioselectivity for the epoxidation with ketone **1** is largely due to the steric effect. Spiro **A** is likely to be the major transition state, and transition states such as spiro **B** are disfavored by the steric repulsion between the dimethyl ketal group of the catalyst and the substituent on the reacting olefin (Figure 2). Earlier studies showed that the methyl groups on the spiro ketal ring of ketone **1** are crucial to the high enantioselectivity obtained for *trans*- and trisubstituted olefins.[5]

For the epoxidation of *cis*-olefins with ketone **2**, the stereodifferentiation likely originates from the apparent attraction between the R_π substituent and the oxazolidinone moiety of the ketone catalyst, causing spiro **C** to be favored over spiro **D** (Figure 3). In the case of *trans*-olefins, ketone **2** lacks dimethyl groups on its oxazolidinone moiety and is thus less effective in stereodifferentiating spiro **E** and **F** via the steric repulsion, resulting in more competition from **F** (Figure 4) and giving lower enantioselectivity than ketone **1**.[3a,3c,5,6]

Ketone **3** provides similar enantioselectivity for *cis*-olefins such as *cis*-β-methylstyrene (85% ee) and 6-cyano-2,2-dimethylchromene (84% ee) to ketone **2**, indicating that

(1) For leading reviews, 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. (e) Wong, O. A.; Shi, Y. *Chem. Rev.* **2008**, *108*, 3958.

(2) (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) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

(3) (a) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551. (b) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929. (c) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435. (d) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293. (e) Shu, L.; Shi, Y. *Tetrahedron Lett.* **2004**, *45*, 8115. (f) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715. (g) Wong, O. A.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 3973. (h) Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 1429. (i) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. (j) Wang, B.; Shen, Y.-M.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 9519. (k) Burke, C. P.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4475. (l) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 4093. (m) Burke, C. P.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 6320.

(4) Wang, B.; Wong, O. A.; Zhao, M.-X.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 9539.

(5) Crane, Z.; Goeddel, D.; Gan, Y.; Shi, Y. *Tetrahedron* **2005**, *61*, 6409.

(6) *trans*-7-Tetradecene was epoxidized in 44% yield and 62% ee with ketone **2** (R = *p*-Tol) [reaction conditions: olefin (0.5 mmol), ketone **2** (0.15 mmol), tetrabutylammonium hydrogen sulfate (0.003 mmol), Oxone (1.32 mmol, 0.20 M), K_2CO_3 (5.29 mmol, 0.84 M) in CH_3CN−DMM (1:2, v/v) (7.5 mL) and buffer (0.1 M K_2CO_3−AcOH, pH 9.3) (5.0 mL) at 0 °C for 3.5 h].

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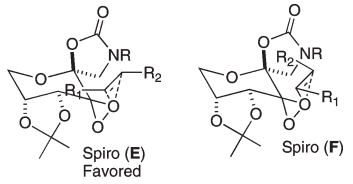


FIGURE 4. Proposed competing transition states for the epoxidation of *trans*-olefins with ketone **2**.

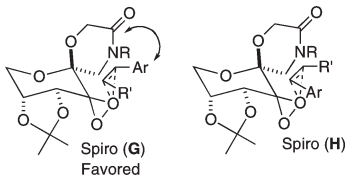


FIGURE 5. Proposed competing transition states for the epoxidation of *cis*-olefins with ketone **3**.

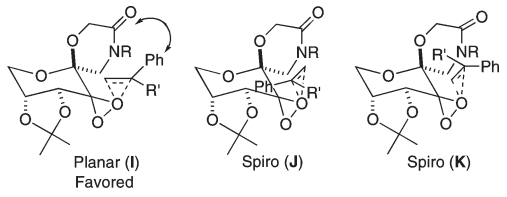


FIGURE 6. Proposed competing transition states for the epoxidation of 1,1-disubstituted olefins with ketone **3**.

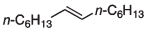
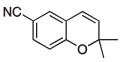
the aforementioned electronic attraction also exists between the morpholinone moiety and the phenyl group of the olefin in spiro transition state **G**, causing spiro **G** to be favored over spiro **H** (Figure 5).[4] The six-membered morpholinone moiety of ketone **3** appears to be more favorable for such attraction in the planar transition state as compared to the five-membered oxazolidinone moiety of ketones **2**. As a result, ketone **3** gives higher ee values for 1,1-disubstituted terminal olefins (up to 88% ee) than ketone **2**, with planar **I** being a possible favored transition state (Figure 6).[4]

In our continuing efforts to study the structural effect of ketone catalysts on asymmetric epoxidation and develop ketone catalysts with a broad substrate scope, we synthesized ketone **4** to combine the steric and electronic features of ketones **1** and **3** (Figure 1) with the aim to investigate whether the dimethylmorpholinone moiety of ketone **4** would provide a steric environment similar to that of the spiro ketal of ketone **1** to provide high enantioselectivity for *trans*- and trisubstituted olefins in a manner similar to ketone **1**, and whether the dimethylmorpholinone moiety would also interact with the Ar group of the olefin in a manner similar to ketone **3**, thus giving good enantioselectivity for *cis*- and 1,1-disubstituted olefins as well. Herein we wish to report our studies on this subject.

The synthesis of ketone **4** is outlined in Scheme 1. Known amino diol **5**, prepared from D-glucose by Amadori rearrangement and ketalization,[3d,7] was converted to ketone **4** by the formation of six-membered morpholinone and subsequent PDC oxidation (for the X-ray structure of ketone **4**, see the Supporting Information).

(7) Zhao, M.-X.; Goeddel, D.; Li, K.; Shi, Y. *Tetrahedron* **2006**, *62*, 8064.
(8) Zhu, Y.; Shu, L.; Tu, Y.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 1818.

TABLE 1. Asymmetric Epoxidation with Ketones 3 and 4[a]

entry	substrate	ketone (eq.)	T (°C)	t (h)	yield (%)[d]	ee (%)	config.[i]
1		**3** (0.30)	0	4	82	83[e]	(+)-(*R*,*R*)[2b]
2		**4** (0.30)	0	4	67	97[e]	(+)-(*R*,*R*)[2b]
3		**3** (0.15)	0	8	70	33[f]	(+)-(*R*,*R*)[2b]
4		**4** (0.15)	0	8	81	90[f]	(+)-(*R*,*R*)[2b]
5		**3** (0.15)	0	8	40	35[g]	(+)-(*R*,*R*)[2b]
6		**4** (0.15)	0	8	67	83[g]	(+)-(*R*,*R*)[2b]
7		**3** (0.15)	0	8	64	62[e]	(+)-(*R*,*R*)[2b]
8		**4** (0.15)	0	8	67	89[e]	(+)-(*R*,*R*)[2b]
9		**3** (0.15)	0	8	73	34[h]	(+)-(*R*,*R*)[8]
10		**4** (0.15)	0	8	83	90[h]	(+)-(*R*,*R*)[8]
11[b]		**3** (0.20)	-10	4	89	80[f]	(-)-(*S*,*S*)[j,2a]
12[b]		**4** (0.20)	-10	4	80	87[f]	(+)-(*R*,*R*)[2a]
13[c]		**3** (0.30)	-10	2	71	84[f]	(+)-(*S*)[j,k]
14[c]		**4** (0.30)	-10	2	89	45[f]	(-)-(*R*)[k]
15[b]		**3** (0.20)	-10	4	85	85[f]	(-)-(1*R*,2*S*)[3c]
16[b]		**4** (0.20)	-10	4	71	63[f]	(-)-(1*R*,2*S*)[3c]
17[b]		**3** (0.20)	0	12	87	84[e]	(+)-(3*R*,4*R*)[j,3g]
18[b]		**4** (0.20)	0	12	61	81[e]	(+)-(3*R*,4*R*)[3g]

[a]All reactions were carried out with olefin (0.2 mmol), ketone (0.03−0.06 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.01 mmol), Oxone (0.26 mmol, 0.20 M), K_2CO_3 (1.16 mmol, 0.89 M) in CH_3CN−DMM (1:2 v/v) (3 mL), and buffer (0.1 M K_2CO_3−AcOH, pH 9.3) (2 mL) for the indicated time and at the indicated temperature unless otherwise stated. [b]0.32 mmol of Oxone (0.20 M) and 1.34 mmol of K_2CO_3 (0.84 M) were used, and DME−DMM (3:1) was used as the organic solvent. [c]0.32 mmol of Oxone (0.20 M) and 1.34 mmol of K_2CO_3 (0.84 M) were used, and 1,4-dioxane was used as the organic solvent. [d]Isolated yield. [e]The ee was determined by chiral HPLC (Chiralcel OD column). [f]The ee was determined by GC (Chiraldex B-DM). [g]The epoxide was opened with NaOMe−MeOH, the resulting alcohol was converted to its benzoate, and the ee was determined by chiral HPLC (Chiralcel OD-H). [h]The ee was determined by chiral HPLC (Chiralpak AD-H column). [i]The absolute configurations were determined by comparing the measured optical rotations, GC trace, and HPLC trace with reported ones. [j]This result was previously reported in ref 4. [k]The configuration was assigned by analogy based on the mechanistic model described in ref 4.

The catalytic property of ketone **4** was evaluated with various olefins. A comparison of the epoxidation results of ketones **3** and **4** is presented in Table 1. In contrast to ketone **3**, ketone **4** gave generally high enantioselectivities for the epoxidation of *trans*- and trisubstituted olefins (Table 1, entries 2, 4, 6, 8, and 10). For example, 90% ee was obtained for *trans*-β-methylstyrene with ketone **4** (Table 1, entry 4) while only 33% ee was obtained with ketone **3** (Table 1, entry 3). Interestingly, the epoxidation of 1-phenylcyclohexene with ketone **4** produced the (+)-(*R*,*R*) epoxide in 87% ee (Table 1, entry 12). The configuration of the resulting epoxide is opposite to that of the epoxide produced from the epoxidation

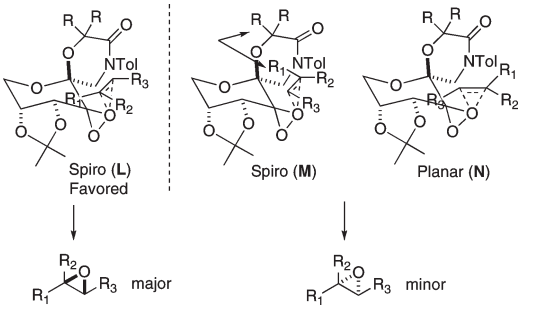


FIGURE 7. Proposed competing transition states for the epoxidation of *trans*- and trisubstituted olefins with ketones **3** and **4**.

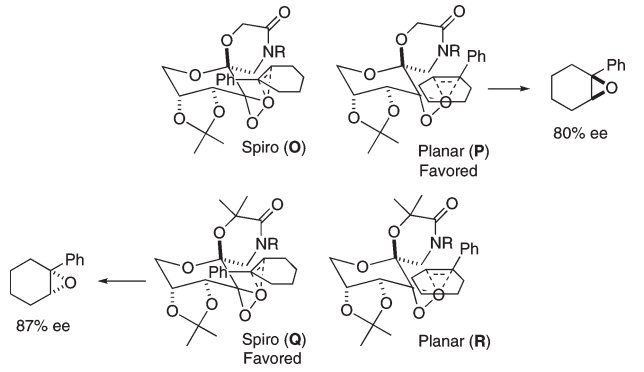
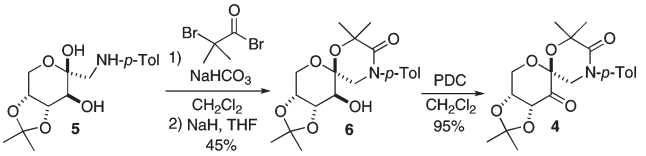


FIGURE 8. Proposed competing transition states for the epoxidation of 1-phenylcyclohexene with ketones **3** and **4**.

SCHEME 1



with ketone **3** (Table 1, entry 11) but the same as that of the epoxide produced from the epoxidation with ketone **1**.[2a] The epoxidation of α-isopropylstyrene with ketones **3** and **4** also gave opposite enantiomers (Table 1, entries 13 and 14). The epoxidation of *cis*-olefins with ketone **4** is somewhat less enantioselective compared to that with ketone **3** (Table 1, entries 15−18).

An overlay of ketones **1** and **4** shows that the two methyl groups at the α-position of the lactam of ketone **4** are very close to the methyl groups on the spiro ketal of ketone **1** (for the structure overlay of ketones **1** and **4**, see the Supporting Information). The dimethyl group on the six-membered morpholinone of **4** thus reduces the competition from transition states such as spiro **M** via the greater steric repulsion as compared to ketone **3** (R = H) (Figure 7), consequently increasing the enantioselectivity for the epoxidation.

In the case of 1-phenylcyclohexene, the attraction between the morpholinone moiety of ketone **3** and the phenyl ring of the olefin favors planar transition state **P** (Figure 8).[4] As a result, the (*S*,*S*) epoxide is obtained in 80% ee (Table 1, entry 11). However, the dimethyl group on the morpholinone moiety of ketone **4** disfavors the corresponding planar transition state **R**,

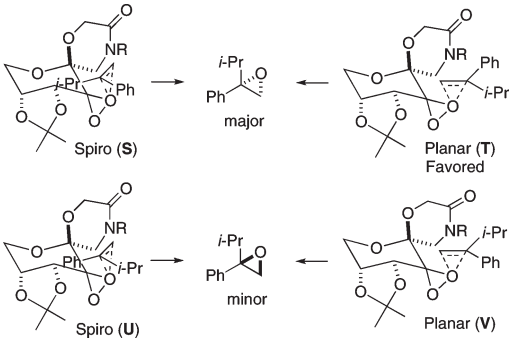


FIGURE 9. Proposed competing transition states for the epoxidation of α-isopropylstyrene with ketone **3**.

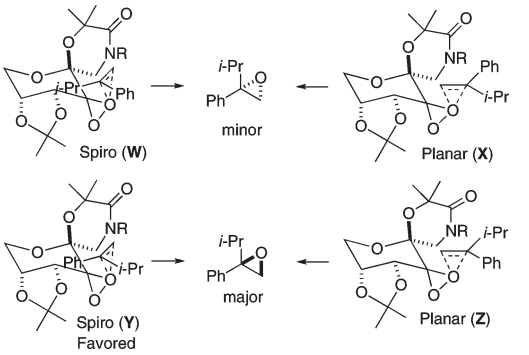


FIGURE 10. Proposed competing transition states for the epoxidation of α-isopropylstyrene with ketone **4**.

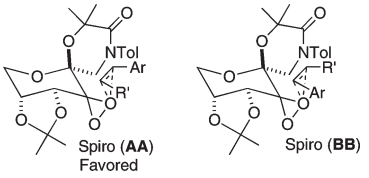


FIGURE 11. Proposed competing transition states for the epoxidation of *cis*-olefins with ketone **4**.

thus giving the (*R*,*R*) epoxide in 87% ee via spiro transition state **Q** (Table 1, entry 12, Figure 8).

α-Isopropylstyrene is another case where the dimethyl group in ketone **4** disfavors the planar transition state. Planar **T** is favored when ketone **3** is used for the epoxidation, resulting in the (+) epoxide in 84% ee (Table 1, entry 13, Figure 9). However, when ketone **4** is used as the catalyst, spiro **Y** may become the major transition state, providing the (−) epoxide in 45% ee (Table 1, entry 14, Figure 10).

The epoxidation of *cis*-olefins with ketone **3** and **4** both provided the same enantiomer for both *cis*-β-methylstyrene (Table 1, entries 15 and 16) and 6-cyano-2,2-dimethylchromene (Table 1, entries 17 and 18), indicating there also exists an attraction between the morpholinone moiety of the catalyst and the aromatic substituent of the olefin in spiro transition state **AA** of ketone **4** (Figure 11). The attraction in spiro **AA** may have been weakened by the dimethyl group as compared to spiro **G** of ketone **3** (Figure 5), thus giving lower enantioselectivity for the epoxidation compared to that of ketone **3**.

In conclusion, a ketone (**4**) that possesses the features of fructose-derived ketone **1** and glucose-derived ketone **3** has been synthesized and investigated for asymmetric epoxidation. Ketone **4** has proven to be a highly effective catalyst for the epoxidation of *trans*- and trisubstituted olefins. The addition of the dimethyl group onto the morpholinone of ketone **3** increased the enantioselectivity for *trans*- and trisubstituted olefins, presumably by inhibiting competing transition state(s) via the steric repulsion between the dimethyl group of the catalyst and the olefin substituent. However, the addition of the dimethyl group onto ketone **3** decreased the epoxidation enantioselectivity of 1,1-disubstituted and *cis*-olefins. The apparent attraction between the aromatic group and the morpholinone moiety, particularly in planar transition states, is decreased by the addition of the dimethyl group, thus reducing the enantioselectivity or even giving the opposite enantiomer in some cases. The information gained in this study will be helpful for the future design of new catalysts with a broader substrate scope.

Experimental Section

Synthesis and Characterization of Ketone 4. To a slurry of **5** (3.09 g, 10.0 mmol) (prepared from D-glucose in two steps)[3d,7] and $NaHCO_3$ (1.68 g, 20.0 mmol) in DCM (400 mL) was added 2-bromo-2-methylpropanoyl bromide (2.76 g, 1.48 mL, 12.0 mmol) dropwise at rt. The resulting mixture was stirred at rt for 16 h to form a brown slurry (monitored by TLC until no starting material remained, the product and the starting material have similar R_f values, but can be differentiated by color with anisaldehyde stain). The reaction was quenched by addition of 0.1 M aqueous K_2CO_3 solution (50 mL), and the layers were separated. The organic layer was dried (Na_2SO_4), filtered, concentrated, and dried under vacuum for 3 h to give crude brown syrup (this intermediate is unstable and should be used without delay), which was dissolved in THF (200 mL). Upon addition of NaH (60%, 0.8 g, 20.0 mmol), the resulting mixture was stirred at rt for 0.5 h, quenched with water (0.2 mL), filtered, concentrated, and purified by flash chromatography (silica gel, hexanes/EtOAc = 1/1) to give alcohol **6** as a light yellow syrup (1.70 g, 45% yield). $[\alpha]^{25}_D$ −54.4 (*c* 1.0, $CHCl_3$); IR (film) 3431, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−7.16 (m, 4H), 4.30−4.23 (m, 2H), 4.19 (d, J = 12.9 Hz, 1H), 4.13 (dd, J = 13.2, 1.8 Hz, 1H), 4.00 (d, J = 13.2 Hz, 1H), 3.71 (d, J = 12.9 Hz, 1H), 3.63−3.61 (m, 1H), 2.34 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 139.6, 137.0, 130.0, 125.8, 109.7, 95.7, 77.3, 76.0, 73.3, 71.7, 60.7, 55.8, 28.3, 27.8, 27.0, 25.9, 21.3; HRMS calcd for $C_{20}H_{28}NO_6$ (M + 1) 378.1917, found 378.1907.

To a slurry of alcohol **6** (1.70 g, 4.5 mmol), PDC (5.12 g, 13.6 mmol), and 3 Å MS (3.3 g) in DCM (50 mL) was added 2 drops of AcOH. The resulting mixture was stirred at rt for 3 d (monitored by TLC until no alcohol remained), filtered through a pad of silica gel, washed with EtOAc, concentrated, and purified by flash chromatography (silica gel, hexanes/EtOAc = 2/1) to give ketone **4** as a white solid (1.60 g, 95% yield). Mp 118−119 °C; $[\alpha]^{25}_D$ −96.9 (*c* 1.2, $CHCl_3$); IR (film) 1751, 1677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.17 (m, 4H), 4.86 (d, J = 5.7 Hz, 1H), 4.61 (dd, J = 5.7, 1.5 Hz, 1H), 4.46 (dd, J = 13.5, 2.4 Hz, 1H), 4.39 (d, J = 13.8 Hz, 1H), 4.18 (d, J = 13.5 Hz, 1H), 3.78 (d, J = 13.8 Hz, 1H), 2.35 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 170.8, 139.2, 137.1, 129.9, 125.7, 110.8, 96.5, 78.6, 78.4, 75.7, 59.6, 52.0, 27.7, 27.3, 26.6, 26.3, 21.3. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 63.75; H, 6.89.

Representative Epoxidation Procedure (Table 1, Entry 4). To a solution of *trans*-β-methylstyrene (0.024 g, 0.026 mL, 0.2 mmol), tetrabutylammonium hydrogen sulfate (0.004 g, 0.012 mmol), and ketone **4** (0.011 g, 0.03 mmol) in CH_3CN−DMM (v/v, 1:2) (3.0 mL) was added buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (2.0 mL) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.20 M, in 4×10^{-4} M aqueous Na_2(EDTA), 1.3 mL) and a solution of K_2CO_3 (0.89 M in 4×10^{-4} M aqueous Na_2(EDTA), 1.3 mL) were added separately and simultaneously with a syringe pump over a period of 8 h at 0 °C. The reaction mixture was quenched with hexanes, extracted with hexanes, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in organic solvent; hexanes/Et_2O = 50/1 was used as eluent] to give the epoxide as a colorless oil (0.022 g, 81% yield, 90% ee).

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Supporting Information Available: The characterization of epoxides, the X-ray structure of ketone **4**, the structure overlay of ketones **1** and **4**, the NMR spectra of compound **6** and ketone **4**, and the data for the determination of the enantiomeric excess of the epoxides obtained with ketone **4**. This material is available free of charge via the Internet at http://pubs.acs.org.