Diastereoselective Epoxidation of Cyclohexene Derivatives by Dioxiranes Generated in Situ. Importance of Steric and Field Effects

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In this paper, diastereoselective epoxidation of substituted cyclohexenes (substrates **1**−**7**) by dioxiranes generated in situ from ketones and Oxone was systematically investigated. The results revealed that the diastereoselectivity was determined by the steric and field effects of both dioxiranes and substrates, and high diastereoselectivity can be achieved by tuning the ketone structure. Among the ketones tested, **12** and **19** gave the best diastereoselectivities.

Introduction

Dioxiranes[1] are synthetically useful oxidants for epoxidation of olefins.[2] While significant progress has been made in enantioselective epoxidation by chiral dioxiranes,[3−8] highly diastereoselective epoxidation remains a challenge for organic synthesis. Several studies have been carried out on diastereoselective epoxidation[9−16] with isolated dimethyldioxirane and methyl(trifluoromethyl)dioxirane,[17] and the diastereoselectivity was found to be determined by steric effects,[9a,10c,e,11a,12] hydrogen-bonding,[9,10b−d,f,11b,12,15] dipole−dipole interactions,[9a,10c,e,14] torsional effects,[13,16] and solvent effects.[9,10b−d,f,11b,12] For epoxidation of a given olefin substrate, the convenient method of generating dioxiranes in situ from ketones and Oxone[18−24] makes it possible to screen as many dioxiranes as needed in order to achieve high diastereoselectivity. Therefore, it becomes important to understand how the nature of dioxiranes controls the diastereoselectivity of epoxidation.[20,22] We have systematically examined the effect of ketone structures as well as the nature of substrates on the diastereoselectivity of in situ dioxirane epoxidation reactions. The detailed results are reported herein.

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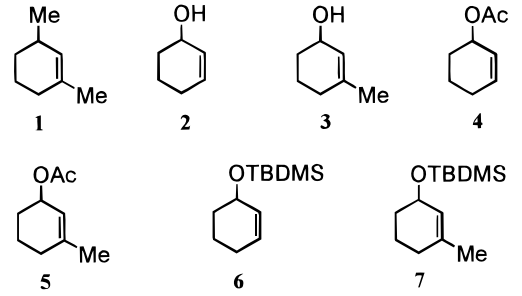
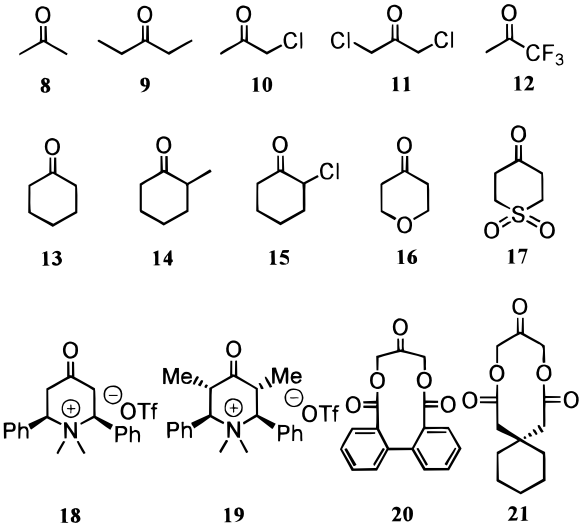
Chart 1

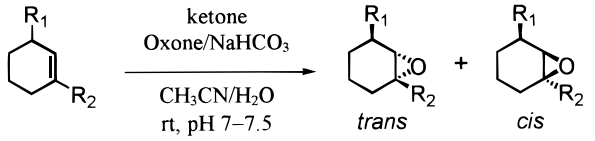
substrates:



ketones:



Scheme 1



Results

Since cyclohexene ring is widely found in biologically important natural products and has well defined conformations,[25] cyclohexene derivatives **1**−**7** bearing allylic substituents (CH_3, OH, OAc, and OTBDMS) were chosen as substrates, which are expected to have distinct steric and electronic interactions with dioxiranes (Chart 1). Acyclic ketones **8**−**12** and cyclic ketones **13**−**21**[26] were employed as catalysts for in situ epoxidation of those substrates. Ketone pairs, such as **8** and **9**, **13** and **14**, **18** and **19**, which differ in the steric bulkiness at α-positions, were selected to probe the steric effect of dioxiranes on diastereoselectivity, whereas ketones **10**−**12** and **15**−**21** were employed to study the electronic effect. All epoxidation reactions were carried out under our previously reported in situ reaction conditions (Scheme 1).[24] To minimize the background epoxidation mediated by Oxone,[22a] only one equivalent of Oxone was used, and the epoxidation reactions were quenched in a short period of time (10 min for substrates **1**−**3**, and 1 h for substrates **4**−**7**). The conversion was generally high (>85%). Epoxidation using *m*-CPBA was also performed for comparison. The results are summarized in Table 1.

Table 1. Diastereoselective Epoxidation of Cyclohexene Derivatives by Dioxiranes Generated *in situ*[a]

		diastereoselectivity (ratio of *trans*/*cis* epoxides)[b,c]						
entry	ketone	**1**[d]	**2**[d,e]	**3**[d,e]	**4**[f]	**5**[f]	**6**[f]	**7**[f]
1	**8**[g]	3.7/1	1.2/1	1.4/1	2.2/1	5.9/1	4.8/1	13.6/1
2	**9**[g]	–[h]	–[h]	–[h]	2.7/1[i]	8.5/1[i]	6.3/1[i]	14.1/1[i]
3	**10**	4.7/1	2.0/1	3.5/1	2.2/1	4.8/1	4.2/1	7.4/1
4	**11**	5.4/1	2.7/1	5.2/1	1.7/1	3.5/1	3.3/1	4.5/1
5	**12**[g,j]	8.4/1	3.3/1	9.1/1	1.9/1	6.1/1	5.6/1	19.3/1
6	**13**[g]	4.4/1	1.3/1	2.0/1	2.3/1	6.6/1	5.6/1	14.2/1
7	**14**[g]	–[h]	–[h]	–[h]	2.8/1[i]	7.8/1[i]	7.0/1[i]	16.7/1[i]
8	**15**	5.4/1	2.1/1	3.9/1	2.7/1	7.7/1	6.9/1	16.6/1
9	**16**	4.4/1	1.6/1	3.3/1	2.1/1	5.0/1	4.6/1	10.4/1
10	**17**[k]	4.7/1	1.9/1	3.7/1	2.0/1	4.7/1	3.7/1	6.3/1
11	**18**	3.8/1	1.9/1	4.4/1	1.5/1	3.4/1	2.8/1	4.3/1
12	**19**	18.7/1	5.9/1	8.9/1	2.4/1	15.1/1	4.6/1	19.7/1
13	**20**[k]	4.7/1	1.7/1	2.9/1	1.6/1	3.0/1	2.1/1	4.3/1
14	**21**[k]	6.3/1	1.9/1	3.5/1	1.4/1	2.9/1	3.1/1	6.4/1
15	Oxone	2.1/1[l]	1/2.5[l]	1/2.7[l]	–[m]	–[m]	–[m]	–[m]
16	*m*-CPBA	1.2/1	1/7.5	1/10.3	1.7/1	2.7/1	4.7/1	7.5/1

[a] Unless otherwise stated, the reaction conditions were as follows: room temperature, 0.1 mmol of substrate, 0.1 mmol of ketone, 0.1 mmol of Oxone, 0.31 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] The ratio of epoxide diastereomers was determined by GC analysis (error ± 2 % of the stated values) and ^1H NMR spectroscopy. [c] Unless otherwise noted, conversion > 85%. [d] Epoxidation reaction was quenched after 10 min. [e] Trace amount of the corresponding enone was detected. [f] Epoxidation reaction was quenched after 1 h. [g] 1 mmol of ketone. [h] The epoxidation reaction was too slow to provide a reliable result. [i] Conversion 20–30%. [j] The epoxidation reaction was carried out at 0–1 °C. [k] 0.01 mmol of ketone. [l] Conversion < 5%. [m] No epoxide was detected.

The results shown in Table 1 revealed that in situ dioxirane epoxidation exhibited *trans*-selectivity for all substrates tested including allylic alcohols **2** and **3**, and the epoxide diastereomeric ratios are dependent on the structures of both the alkene substrates and ketone catalysts. In general, epoxidation of substrates **1** and **4**−**7** by dioxiranes generated in situ from ketones **8**−**21** and Oxone provided higher *trans*-selectivity than that by *m*-CPBA. As reported in the literature,[27] for epoxidation of allylic alcohols **2** and **3**, *m*-CPBA and Oxone gave mainly *cis*-epoxides.

Concerning the substrate features, three important trends were observed. (a) Substrates with $R_2 = CH_3$ gave much higher *trans*/*cis* epoxide ratios than the corresponding substrates with $R_2 = H$ (substrates **2** vs **3**, **4** vs **5**, and **6** vs **7**). This is in accord with the observations by Murray and co-workers using isolated dimethyldioxirane.[9a] (b) In addition, as the size of allylic substituent R_1 of substrates increased from OAc to OTBDMS, the *trans*-selectivity of epoxidation increased dramatically (substrates **4** vs **6**, and **5** vs **7**). (c) Among those substrates screened, *tert*-butyldimethyl[(3-methyl-2-cyclohexen-1-yl)oxy]silane (substrate **7**) showed the highest *trans*-selectivity.

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As to the effect of ketone structures, several interesting trends were observed. (a) For all of the substrates tested, epoxidations catalyzed by ketones of more steric hindrance at α-positions generally gave higher *trans*-selectivity (ketones **8** vs **9** and **12**; **13** vs **14** and **15**; **18** vs **19**). (b) For epoxidation of substrate **1** carrying the nonpolar allylic methyl group, ketones **10**−**12**, **15**, **20**, and **21** with electron-withdrawing substituents at α-positions gave higher *trans*-selectivity than ketone **8**, while electron-withdrawing substituents at the remote positions of ketones **16**−**18** had little effect on *trans*-selectivity. (c) In contrast, for epoxidation of substrates **4**−**7** bearing the allylic OAc or OTBDMS group, ketones **10**, **11**, **16**−**18**, **20**, and **21**, substituted by electron-withdrawing groups at α-positions or more remote sites, provided lower *trans*-selectivity than ketone **8** (see boxes in Table 1). (d) Ketones **12** and **19** gave the best *trans*-selectivities among the ketones tested.

Discussion

Steric Effect. Generally speaking, diastereoselective epoxidation with dioxiranes is more sensitive to the steric bulkiness of substrates than that with *m*-CPBA,[9a,10c,e,11a,12] which is in agreement with our data in Table 1. However, the effect of dioxirane structures on diastereoselectivity is still under debate.[10e,20,22] For example, Kurihara et al.[22] found that α-substituents of the dioxiranes generated in situ had a pronounced effect on diastereoselectivity in epoxidation of substrates **1**, **2**, **6**, and acyclic allylic silyl ethers in CH_2Cl_2−MeOH−phosphate buffer solvent system at pH 11; but Marples et al.[20] only observed very small steric influence of dioxiranes generated in situ for epoxidaton of steroids in CH_2Cl_2−phosphate buffer solvent system at pH 7.5. Adam and co-workers[10e] also claimed that no dramatic steric effect was observed in epoxidation of 2-menthene and substrate **1** using isolated dioxiranes in the corresponding ketone solutions. Our results shown in Table 1 reveal that steric interactions between the substrates and dioxiranes significantly affected the diastereoselectivity of dioxirane epoxidation in the homogeneous CH_3CN-H_2O solvent system at pH 7.0−7.5.

Experimental[4b−d,5a,c,e,28] and theoretical studies[29−31] have established a concerted spiro transition state for dioxirane epoxidation. In diastereoselective epoxidation of allylically substituted cyclohexenes, dioxiranes can transfer an oxygen atom to the C=C double bond of substrates from both faces, so there are two possible spiro transition states based on steric considerations (Figure 1). In the favored TS leading to *trans*-epoxides, there is little or no steric interactions between the R group of dioxiranes and the allylic hydrogen of substrates. However, severe steric interaction between the R group of dioxiranes and the allylic R_1 group of substrates are expected in the disfavored TS, giving rise to *cis*-epoxides. The free energy difference between the favored and disfavored TS determines the diastereoselectivity. This explains why *trans*-epoxides are obtained as the major isomers in dioxirane epoxidation of all substrates tested. For a given dioxirane, when the allylic R_1 group of substrates becomes larger, leading to more steric interactions between the R_1 and R groups in the disfavored TS, more *trans*-epoxides are expected. This is why an OTBDMS group at the allylic position of substrates gave higher *trans*-selectivity than an OAc group. Similarly, for a given substrate, when the R group of dioxiranes becomes larger (i.e., ketone catalysts become sterically bulkier at α-positions), higher *trans*-selectivity should be obtained. This is especially true for epoxidation of substrate **1** with a nonpolar allylic CH_3 substituent, where only the steric effect is involved. The similar trend was observed for epoxidation of substrates **2**−**7**.

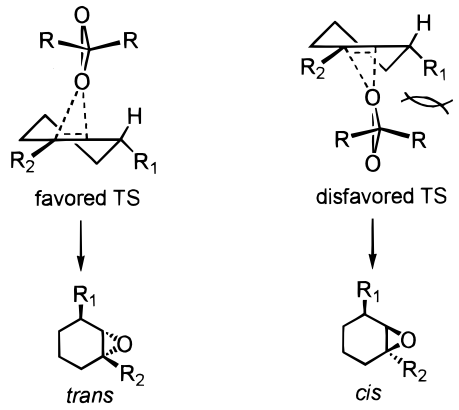

Figure 1.

Theoretical studies showed that epoxidation of ethylene by unsubstituted dioxirane should have a synchronous spiro transition state, i.e., equal C−O bond formation.[29−31] But substitution of ethylene by methoxy, methyl, vinyl, and cyano groups changes the transition state geometry toward asynchronous spiro structures with the longer C−O bond formation for the carbon carrying the substituent.[30a] In epoxidation of substituted cyclohexenes with $R_2 = CH_3$, the methyl group pushes the approaching dioxiranes closer to the allylic hydrogen or the allylic R_1 group of substrates, which intensifies the steric interaction between the R_1 and R groups in the disfavored TS. As a result, higher *trans*-selectivities were observed for epoxidation of substrates with $R_2 = CH_3$ than those with $R_2 = H$.

Electronic Effect. In addition to the steric effect, we also observed a significant electronic effect in diastereoselective epoxidation. As shown in the boxes of Table 1, compared with ketone **8**, ketone catalysts **10**, **11**, **16**−**18**, **20**, and **21** with polar substituents such as Cl, ester group, O, SO_2, or $^{\oplus}NMe_2$ gave lower *trans*-selectivity in epoxidation of substrates **4**−**7**. In the earlier reports,[9a,10c,e,14] the electronic effect on diastereoselective epoxidation of olefins bearing polar substituents by isolated dimethyldioxirane was rationalized by invoking the dipole−dipole interactions between the dioxirane and the polar substituents of substrates.[32] We consider it applicable to explain our observation that the polar substituents at α-positions of dioxiranes gave lower *trans*-selectivities.

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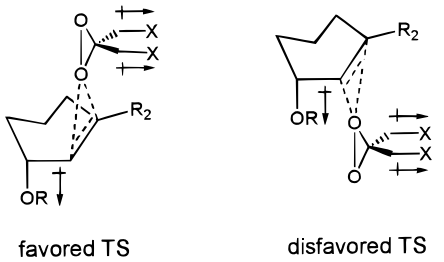

Figure 2.

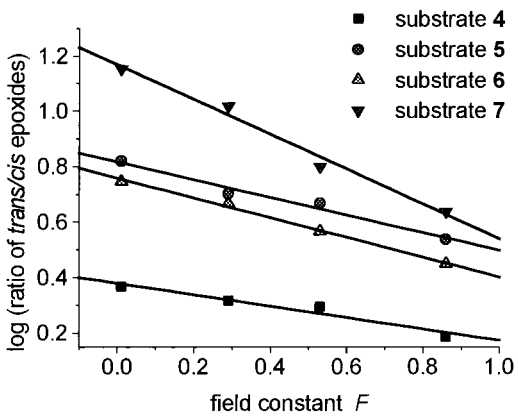

Figure 3. Hammett plots of the logarithm of ratios of *trans*/*cis* epoxides against the field constants *F* of remote substituents of ketones **13** and **16**−**18** ($\rho = -0.206$, $r = 0.974$ for substrate **4**; $\rho = -0.319$, $r = 0.987$ for substrate **5**; $\rho = -0.357$, $r = 0.998$ for substrate **6**; $\rho = -0.629$, $r = 0.992$ for substrate **7**).

As shown in Figure 2, the dipole of the C−X bonds (X is an electron-withdrawing group) of dioxiranes can interact with the dipole of substrates, thus stabilizing the disfavored TS and destabilizing the favored TS. Therefore, lower *trans*-selectivity was obtained.

Recently, significant field effect[33] of nonconjugated remote substituents of dioxiranes on enantioselectivity was reported by our group[4d] in chiral dioxirane epoxidation in the CH_3CN-H_2O solvent system. It would be interesting to explore the field effect in diastereoselective dioxirane epoxidation. Indeed, we found that, for epoxidation of substrates **4**−**7** by dioxiranes generated in situ from ketones **13** and **16**−**18** (with similar steric environment at α-positions yet different remote substituents), the more polar the remote substituent of dioxiranes was, the less *trans*-epoxide isomer was formed. And the linear Hammett plots of the logarithm of *trans*/*cis* epoxide ratios against the field constants *F* of those remote substituents[34,35] of ketones **13** and **16**−**18** were obtained ($\rho = -0.206$, $r = 0.974$ for **4**; $\rho = -0.319$, $r = 0.987$ for **5**; $\rho = -0.357$, $r = 0.998$ for **6**; $\rho = -0.629$, $r = 0.992$ for **7**) (Figure 3). The excellent correlations suggest that the through-space electrostatic effect, i.e., field effect, plays an important role in determining the diastereoselectivity of dioxirane epoxidation.

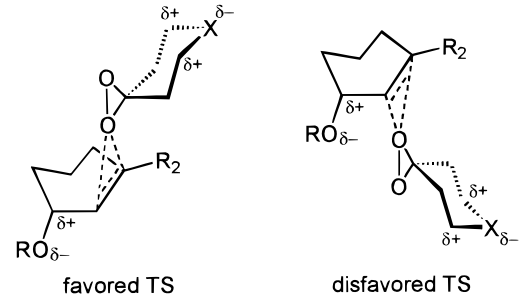

Figure 4.

As shown in Figure 4, the polar nature of the allylic C−O bond of substrates **4**−**7** makes the O atom bearing δ^- charges and the allylic C atom bearing δ^+ charges; and the electron-withdrawing substituent X (O, SO_2, or $^{\oplus}NMe_2$) of dioxiranes imparts δ^+ charges to the two adjacent C atoms. By through-space electrostatic interactions, the remote polar substituent X of dioxiranes will stabilize the disfavored TS and destabilize the favored TS, thus providing lower *trans*-selectivity. This explains why the slopes of the Hammett plots shown in Figure 3 are all negative. In addition, the substrates with $R_2 = CH_3$ should make dioxiranes closer to the allylic C−O bond in the transition states than those with $R_2 = H$; consequently, a more significant electronic effect is expected in epoxidation of substrates **5** and **7** than that of corresponding substrates **4** and **6**. This is corroborated by the observation that the slope of the Hammett plot of substrate **5** or **7** is more negative than that of substrate **4** or **6**, respectively.

Solvent Effect. Epoxidation of allylic alcohols by many oxidants such as *m*-CPBA,[27] perbenzimidic acid,[36] organo sulfonic peracids,[37] hydroperoxyphosphinic acid,[38] CF_3CO_3H,[39] isolated dimethyldioxirane,[9,10b−d] and methyl(trifluoromethyl)dioxirane[10c,f] generally shows *cis*-selectivity in nonpolar solvents due to hydrogen-bonding between the allylic OH group of substrates and the oxidants. However, in the homogeneous CH_3CN-H_2O solvent system employed in our study, such hydrogen-bonding is disrupted due to the presence of a significant amount of water. *Trans*-epoxides were obtained as the major isomers for epoxidation of substrates **2** and **3** by dioxiranes generated in situ, which reflects mainly the steric effect of substrates.

Conclusion

Our results clearly indicated that the steric and electronic properties of ketones can significantly influence the diastereoselectivity in epoxidation of cyclohexene derivatives. While it was known that the presence of electron-withdrawing substituents at α-positions or more remote sites leads to increased activity of ketones,[4a,26] our data showed that those substitutions might not have beneficial effect on diastereoselectivity in epoxidation of substrates bearing polar allylic substituents. On the other hand, bulky groups at α-positions rendered ketones less reactive catalysts[4a] but gave higher diastereoselectivity.

(33) For a recent review of field effects on chemical reactivity in organic reactions, see: Bowden, K.; Grubbs, E. J. *Chem. Soc. Rev.* **1996**, 171.

(34) The field constants of substituents at the 1-position of 4-heterocyclohexanones were approximated by those of CH_3, OCH_3, SO_2CH_3, and $^{\oplus}N(CH_3)_3$ groups. See: Conroy, J. L.; Sanders, T. C.; Seto, C. T. *J. Am. Chem. Soc.* **1997**, *119*, 4285.

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Therefore, to achieve high reactivity and diastereoselectivity, it is important to fine-tune the ketone structures by introducing substituents of appropriate steric sizes and electronic properties. Ketones **12** and **19** gave similarly high diastereoselectivities in dioxirane epoxidation. But ketone **12** has to be used in large excess[24] and is not readily recyclable owing to its volatility. Ketone **19**, a good epoxidation catalyst (normally 10−20 mol % loading),[26a] should be an ideal choice for diastereoselective epoxidation. Our work provides useful insights on the design of new ketone catalysts for stereoselective epoxidation of olefins as well as kinetic resolution of racemic olefins.

Experimental Section

General. Product analysis was performed on a HP-5890 capillary gas chromatography using a flame ionization detector (FID), a 25 m × 0.32 mm × 0.52 μm HP-Ultra 1 (cross-linked methyl silicone gum) capillary column, or a 30 m × 0.32 mm × 0.50 μm HP−INNOWAX (cross-linked poly(ethylene glycol)) capillary column, and helium as the carrier gas. Ketones **8**−**16** and Oxone were purchased from Aldrich Chemical Co. and used without further purification. Preparation of substrates **1**,[40] **2**−**3**,[41] **4**−**5**,[42] **6**−**7**,[43] and ketones **17**−**21**[26] was carried out according to the literature procedures. The epoxides of substrates **1**−**5**[9a] and **6**[22a] were identified by comparison of their spectral data with those reported in the literatures.

General Procedure for Epoxidation of Cyclohexene Derivatives with Dioxiranes Generated in Situ from Ketones 8−21. To an CH_3CN solution (1.5 mL) of substrate (0.1 mmol) and ketone (1 mmol for **8**−**9** and **12**−**14**; 0.1 mmol for **10**−**11**, **15**−**16**, and **18**−**19**; 0.01 mmol for **17** and **20**−**21**) at room temperature (0−1 °C for ketone **12**) was added an aqueous Na_2·EDTA solution (1 mL, 4 × 10^{-4} M). To this mixture was added in portions a mixture of Oxone (61.5 mg, 0.1 mmol) and sodium bicarbonate (26 mg, 0.31 mmol) over the reaction period (10 min for substrates **1**−**3**; 1 h for substrates **4**−**7**). The reaction mixture was diluted by addition of 10 mL of CH_2Cl_2, dried over anhydrous Na_2SO_4 (ca. 3 g), and filtered through a pad of silica gel (Merck, 230−400 mesh). The filtrate was used directly in GC analysis to determine the ratio of epoxide diastereomers and the conversion of the epoxidation reaction. The ratio of epoxide diastereomers was also determined by ^{1}H NMR spectroscopy on the crude products obtained after removal of the solvent under reduced pressure at low temperature. The ratio determined by ^{1}H NMR was comparable to that by GC. The diastereomeric epoxides of substrate **7** can be separated by flash column chromatography, and their purity was determined to be >98% by GC analysis (using HP-Ultra 1 capillary column).

***tert*-Butyldimethyl[(3-methyl-*trans*-2,3-epoxycyclohexan-1-yl)oxy]silane**: a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (dd, J = 8.2, 6.0 Hz, 1H), 2.85 (s, 1H), 1.91−1.84 (m, 1H), 1.80−1.72 (m, 1H), 1.70−1.59 (m, 1H), 1.48−1.39 (m, 1H), 1.33 (s, 3H), 1.30−1.07 (m, 2H), 0.92 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 67.70, 64.18, 58.85, 30.70, 29.61, 25.87, 23.34, 18.22, 15.88, −4.69, −4.87; IR (CH_2Cl_2) 2954, 1472, 838 cm^{-1}; EIMS (70 eV) m/z 242 (3), 227 (2), 185 (70), 75 (100); HRMS for $C_{13}H_{26}O_2Si$ (M^+), calcd 242.1702, found 242.1700.

***tert*-Butyldimethyl[(3-methyl-*cis*-2,3-epoxycyclohexan-1-yl)oxy]silane**: a colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.01 (ddd, J = 8.1, 6.3, 1.9 Hz, 1H), 2.96 (d, J = 1.3 Hz, 1H), 1.82−1.71 (m, 1H), 1.66−1.38 (m, 4H), 1.32 (s, 3H), 1.28−1.12 (m, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 69.63, 63.32, 60.47, 28.03, 27.81, 25.91, 24.20, 20.04, 18.26, −4.46, −4.51; IR (CH_2Cl_2) 2958, 1470, 836 cm^{-1}; EIMS (70 eV) m/z 242 (0.1), 227 (2), 185 (100), 75 (32); HRMS for $C_{13}H_{26}O_2Si$ (M^+), calcd 242.1702, found 242.1695.

Background Epoxidation of Cyclohexene Derivatives with Oxone. The same procedure as above was followed except that no ketone was added.

Epoxidation of Cyclohexene Derivatives with *m*-CPBA. A CH_2Cl_2 solution (5 mL) of substrate (0.1 mmol), *m*-CPBA (0.2 mmol), and sodium bicarbonate (0.4 mmol) was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and filtered through a pad of silica gel (Merck, 230−400 mesh). The product analysis was performed as above.

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JO9821978

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