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Notes

An Efficient Ketone-Catalyzed Epoxidation Using Hydrogen Peroxide as Oxidant

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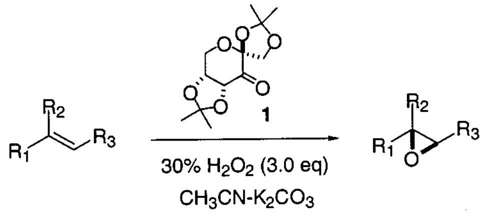
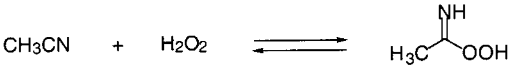
Epoxides are very important building blocks in organic synthesis.[1] Dioxiranes, either isolated or generated in situ, have been shown to be extremely versatile epoxidation reagents.[2−6] In nearly every case, the generation of dioxiranes uses potassium peroxomonosulfate ($KHSO_5$) as oxidant (Scheme 1).[7,8] During our recent study on asymmetric epoxidation using the fructose-derived ketone (**1**), we found that hydrogen peroxide (H_2O_2) could be used as primary oxidant in combination with acetonitrile (eq 1).[6l] High yields and ee's were obtained for a number of olefins. In this epoxidation, peroxyimidic acid **2** is likely to be the active oxidant for the formation of the dioxirane (eq 2).[9,10] The epoxidation requires substantially less solvent and salts compared to the procedure using Oxone, along with being operationally simple. To further extend this oxidant system ($H_2O_2-CH_3CN$) to the dioxirane-mediated epoxidation, we have tested a variety of achiral ketones as possible catalysts. Among those tested, trifluoroacetone (CF_3COCH_3) was found to be a particularly active catalyst. Herein we wish to report our recent studies in this area.



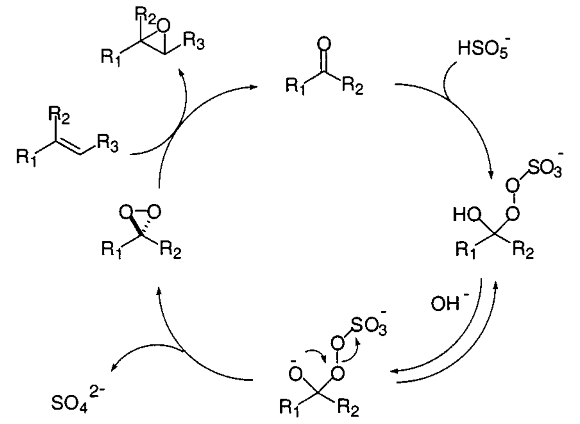
(eq. 1)



$$CH_3CN + H_2O_2 \rightleftharpoons H_3C\overset{NH}{C}OOH \quad \textbf{(eq. 2)}$$

2

Scheme 1



In our previous studies of the asymmetric epoxidations with Oxone as oxidant, it has been found that the pH of reaction mixture is a very important factor to the efficiency of the epoxidation reactions. Higher pH is usually beneficial to both the conversion and ee's.[6b−c] A similar phenomenon was also observed in the asymmetric epoxidation when H_2O_2 was used as the oxidant.[6l] In current studies, the pH effect was further investigated using trifluoroacetone (CF_3COCH_3) and tetrahydropyran-4-one as catalyst. The reaction was run in a 1:1 mixture of CH_3CN and aqueous EDTA solution (4×10^{-4} M) using *trans-β*-methylstyrene as substrate. The reaction pH was

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(1) For reviews, see: (a) Gorzynski Smith, J. *Synthesis* **1984**, 629. (b) Besse, P.; Veschambre, H. *Tetrahedron* **1994**, *50*, 8885.

(2) For general leading references on dioxiranes, see: (a) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (c) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure & Appl. Chem.* **1995**, *67*, 811. (d) Clennan, E. L. *Trends Org. Chem.* **1995**, *5*, 231. (e) Adam, W.; Smerz, A. K. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581. (f) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.

(3) Murray, R. W.; Singh, S. *Org. Synth.* **1996**, *74*, 91.

(4) For examples of in situ generation of dioxiranes, see: (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol.* **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758. (c) Gallopo, A. R.; Edwards J. O. *J. Org. Chem.* **1981**, *46*, 1684. (d) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670. (e) Corey, P. F.; Ward, F. E. *J. Org. Chem.* **1986**, *51*, 1925. (f) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* **1991**, *124*, 227. (g) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett.* **1994**, *35*, 1577. (h) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391 (i) Yang, D.; Wong, M. K.; Yip, Y. C. *J. Org. Chem.* **1995**, *60*, 3887. (j) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (k) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964. (l) Boehlow, T. R.; Buxton, P. C.; Grocock, E. L.; Marples, B. A.; Waddington, V. L. *Tetrahedron Lett.* **1998**, *39*, 1839. (m) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1998**, *63*, 2810. (n) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. (o) Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem.* **1998**, *63*, 8952. (p) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, *63*, 9888.

(5) For leading references on asymmetric epoxidation mediated in situ by chiral ketones, see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett.* **1995**, *36*, 5831. (c) Reference 4h. (d) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L *Tetrahedron* **1995**, *51*, 3587. (e) Yang, D.; Yip, Y. C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (f) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (g) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymmetry* **1997**, *8*, 2921. (h) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (i) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (j) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622. (k) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (l) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (m) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (n) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. (o) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 6443. (p) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett.* **1999**, *40*, 8029. (q) Armstrong, A.; Hayter, B. R. *Tetrahedron* **1999**, *55*, 11119.

10.1021/jo001180y CCC: $19.00

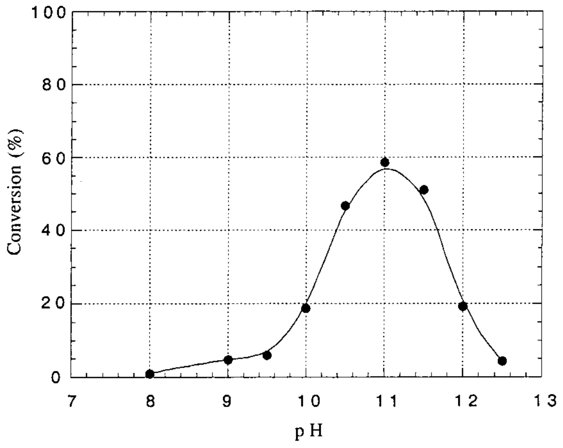
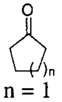
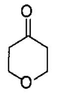
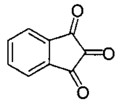
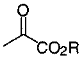
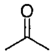
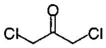
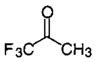


Figure 1. Plot of the conversion of *trans*-β-methylstyrene against pH using CF_3COCH_3 as catalyst (5 mol %). Reactions were carried out with *trans*-β-methylstyrene (1 mmol), ketone (0.05 mmol), and H_2O_2 (4 mmol) in CH_3CN (1.5 mL) and aqueous EDTA (4×10^{-4} M) (1.5 mL) at 0 °C for 10 h. Conversions were determined by GC.

adjusted by adding K_2CO_3 or AcOH and monitored by a pH meter. It was found that both ketones gave the best conversions at pH around 11.0 while trifluoroacetone showed much higher activity (the pH effect of trifluoroacetone is shown in Figure 1).[11]

Table 1. Epoxidation of *trans*-β-Methylstyrene Using Different Ketones[a]

Entry	Ketone	Cat (eq.)	T(°C)	t (h)	Conv. (%)
					
1	n = 1	0.3	0	10	5
2	n = 2	0.3	0	10	20
3	n = 3	0.3	0	10	2
4		0.3	0	10	15
5		0.3	0	10	8
					
6	R = Me	0.3	0	10	1
7	R = Na	0.3	0	10	8
8		0.3	0	10	<1
9		0.3	0	10	46
10		0.3	0	10	100

[a] All reactions were carried out with *trans*-β-methylstyrene (1 mmol), ketone (0.3 mmol), and H_2O_2 (4 mmol) in CH_3CN (1.5 mL) and aqueous K_2CO_3 solution (1.5 M in 4×10^{-4} M EDTA) (1.5 mL) at 0 °C for 10 h. Conversions were determined by GC.

Upon the determination of the optimal reaction pH, a number of ketones were then investigated as epoxidation catalyst using *trans*-β-methylstyrene as substrate. In all cases, the ketone was used in 30 mol % and the reactions were stopped after 10 h. As shown in Table 1, among these ketones tested, trifluoroacetone (CF_3COCH_3) showed the highest activity.[12] A complete conversion of substrate was obtained under the reaction conditions. The high efficiency displayed by this $CF_3COCH_3-H_2O_2-CH_3CN$ system suggested that this would provide a valuable epoxidation procedure. We therefore decided to test various olefins to ascertain the generality of the reaction.

The epoxidation was carried out at apparent pH around 11.0, which could be easily obtained by using a 1.5 M K_2CO_3 aqueous solution. The reaction was run at 0 °C to slow the decomposition of H_2O_2 and the peroxyimidic intermediate. As shown in Table 2, a variety of terminal, cyclic, acyclic, *trans*-, *cis*-, and trisubstituted olefins have been epoxidized with good yields. Functional groups such as hydroxy, TMS, ester, and alkynes can be tolerated under this reaction condition. For those more reactive substrates, the epoxidation was completed using 10 mol % ketone within 4 h. For those less reactive substrates, 30 mol % ketone was required to gain a high conversion. For substrates such as *trans*-stilbene and *trans*-7-tetradecene with poor solubility (Table 2, entries 2 and 6), the epoxidation did not give a reasonably high conversion when CH_3CN was used as the organic solvent. However, a good conversion could be obtained by running the epoxidation in a mixed solvent of $CH_3CN-DMM$ (1:2, v/v).[13] Under this mixed solvent system, the decomposition of H_2O_2 or the peroxyimidic intermediate might become slow, and the epoxidation could be carried out at room temperature. To further illustrate the usefulness

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(6) For examples of asymmetric epoxidation mediated in situ by fructose-derived ketones, see: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948. (e) Wang, Z.-X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 3099. (f) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (g) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (h) Tu, Y.; Wang, Z−X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475. (i) Wang, Z−X.; Cao, G−A.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7646. (j) Warren, J. D.; Shi, Y. *J. Org. Chem.* **1999**, *64*, 7675. (k) Frohn, M.; Zhou, X.; Zhang, J−R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc.* **1999**, *121*, 7718. (l) Shu, L.; Shi. Y. *Tetrahedron Lett.* **1999**, *40*, 8721.

(7) Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is currently the common source of potassium peroxomonosulfate ($KHSO_5$).

(8) As close analogues of potassium peroxomonosulfate, arenesulfonic peracids generated from (arenesulfonyl)imidazole/H_2O_2/NaOH have also been shown to produce dioxiranes from acetone and trifluoroacetone as illustrated by ^{18}O-labeling experiments see: Schulz, M.; Liebsch, S.; Kluge, R.; Adam, W. *J. Org. Chem.* **1997**, *62*, 188.

(9) For leading references on epoxidation using H_2O_2 and RCN, see: (a) Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. Chem.* **1961**, *26*, 659. (b) Payne, G. B. *Tetrahedron* **1962**, *18*, 763. (c) McIsaac, J. E. Jr.; Ball, R. E.; Behrman, E. J. *J. Org. Chem.* **1971**, *36*, 3048. (d) Bach, R. D.; Knight, J. W. *Org. Synth.* **1981**, *60*, 63. (e) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.

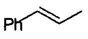
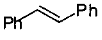
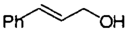
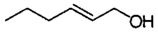
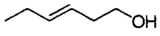
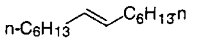
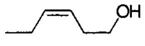
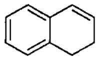
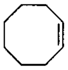
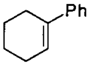
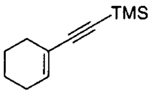
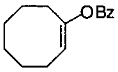
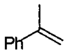
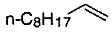
(10) For a general reference on hydrogen peroxide see: Strukul, G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer Academic Publishers: New York, 1992.

(11) In the absence of ketone catalyst, the epoxidation was minimal at high pH both at 0 °C and room temperature. However, at low pH (8−9) a substantial amount of epoxidation occurred at room temperature but not at 0 °C.

(12) It follows that electron-withdrawing groups such as CF_3 are highly beneficial for the reactivity of a ketone catalyst. For some less active ketones, higher conversions could be obtained by using more ketone and prolonged reaction times. For example, an 80% yield of 1-phenylcyclohexene oxide was obtained when the epoxidation was carried out using 27 equiv of acetone for 24 h.

(13) The epoxidation also proceeded using CH_3CN as a reagent in other solvents. For example, an 84% yield was obtained for β-methylstyrene oxide when the epoxidation was carried out using 4 equiv of CH_3CN in butanol. However, for most substrates, the epoxidations were much slower using butanol as solvent instead of CH_3CN.

Table 2. Epoxidations of Olefins Using H_2O_2 as Oxidant and CF_3COCH_3 as Catalyst[a]

Entry	Substrate	Cat. (mol%)	Time (h)	Yield (%)[b]
1		10	4	93[6c]
2[c]		30	6	89[6c]
3		30	5	84[6b]
4		10	10	64[6e]
5		10	10	70[6e]
6[d]		30	5	94[6c]
7		30	4	76[4n]
8		10	4	83[6c]
9		10	4	70[9d]
10		10	4	86[6c]
11		10	4	81[6f]
12		10	4	80[6g]
13		10	3	80[6c]
14		30	8	89[6c]

[a] All reactions were carried out with olefin (1 mmol), CF_3COCH_3 (0.1−0.3 mmol), and H_2O_2 (4 mmol) in CH_3CN (1.5 mL) and aqueous K_2CO_3 solution (1.5 M in 4×10^{-4} M EDTA) (1.5 mL) at 0 °C unless otherwise noted. [b] Isolated yield. [c] The reaction was carried out with CH_3CN−DMM (1/2) (8.5 mL) and aqueous K_2CO_3 solution (1.5 M in 4×10^{-4} M EDTA) (1.5 mL) at 0 °C for 1 h and at room temperature for 5 h. [d] The reaction was carried out with CH_3CN−DMM (1/2) (5.5 mL) and aqueous K_2CO_3 solution (1.5 M in 4×10^{-4} M EDTA) (1.5 mL) at 0 °C for 1 h and at room temperature for 4 h.

of this epoxidation, the epoxidations of two selected olefins (α-methylstyrene and *trans*-stilbene) were carried out on a 100 mmol scale (see the Experimental Section). The epoxidation worked well in each case.

Trifluoroacetone (CF_3COCH_3) has been shown to be a very active promoter for in situ epoxidation using Oxone as oxidant at neutral reaction conditions (pH 7−7.5) with stoichiometric amount of ketone.[4i,14] Our observation that CF_3COCH_3 could be used in a catalytic amount when the epoxidation was carried out at high pH using H_2O_2 as oxidant suggested that this ketone could also be catalytically active at high pH with Oxone. To this end, a pH effect of CF_3COCH_3 using Oxone was then carried out (Figure 2). Indeed, the pH has a large effect on the epoxidation. At pH 10.0, an 80% conversion of *trans*-β-methylstyrene was obtained using a catalytic amount of ketone (5 mol %). With 10 mol % CF_3COCH_3, *trans*-β-methylstyrene and 1,2-dihydronaphthalene could be epoxidized in 82% and 92% yield, respectively.

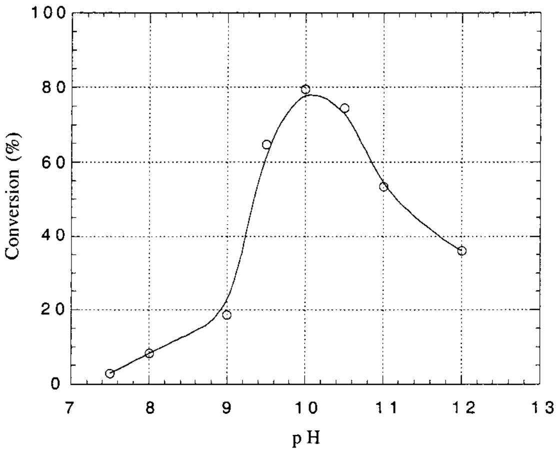


Figure 2. Plot of the conversion of *trans*-β-methylstyrene against pH using CF_3COCH_3 as catalyst and Oxone as oxidant. Reactions were carried out with *trans*-β-methylstyrene (1 mmol), ketone (0.05 mmol) in CH_3CN−DMM (1/2) (15 mL), and aqueous EDTA (4×10^{-4} M) (10 mL) at 0 °C. Oxone (1.38 mmol in 6.5 mL of 4×10^{-4} M EDTA) was added via syringe pump over 1.5 h. The pH of the reaction mixture was adjusted by adding K_2CO_3 or AcOH and monitored by a pH meter. Conversion was determined by GC.

In summary, we report an efficient trifluoroacetone (CF_3COCH_3)-catalyzed epoxidation using hydrogen peroxide (H_2O_2) as primary oxidant at high pH. The ketone can be used in a catalytic amount. The reaction is mild and gives good yields for a number of olefin substrates. The usage of H_2O_2 as oxidant significantly reduces the amount of the solvent and salt introduced. We believe that this procedure is operationally simple and will provide a valuable epoxidation method.

Experimental Section

The general experimental information is similar to those recently described.[6c] Hydrogen peroxide (H_2O_2) is potentially explosive. Although no incidents occurred by our experience, care must be taken in handling this compound. In the epoxidation reaction, EDTA is used to minimize the decomposition of H_2O_2 catalyzed by any trace metals. All the epoxides in Table 2 are known compounds and give satisfactory spectroscopic characterization. The corresponding references for these epoxides are included in Table 2.

General Epoxidation Procedure for Table 2. To a mixture of an olefin (1 mmol) and CF_3COCH_3 (0.1−0.3 mmol) in CH_3CN (1.5 mL) and aqueous K_2CO_3 (1.5 M in 4×10^{-4} M EDTA, 1.5 mL) was added H_2O_2 (30%, 0.4 mL, 4 mmol) at 0 °C. Upon stirring at 0 °C over the indicated time,[15] the reaction mixture was extracted with hexane or ether, washed with aqueous $Na_2S_2O_3$ (1 M) and brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (buffered with 1% NEt_3) to give the pure epoxide product.

α-Methylstyrene Oxide.[6c] To a mixture of α-methylstyrene (11.8 g, 0.1 mol) and CF_3COCH_3 (1.12 g, 0.01 mol) in CH_3CN (150 mL) and aqueous K_2CO_3 (1.5 M in 4×10^{-4} M EDTA, 150 mL) was added H_2O_2 (30%, 40 mL, 0.4 mol) at 0 °C. Upon stirring at 0 °C for 3 h, the reaction mixture was extracted with hexane (3 × 300 mL). The combined organic layers were washed with aqueous $Na_2S_2O_3$ (1 M) (3 × 50 mL) and brine (100 mL), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (buffered with 1% NEt_3) using hexanes−ether (1/0−10/1) as eluent to give α-methylstyrene as a colorless

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(14) For epoxidation promoted by the acyclic analogues of trifluoroacetone, see ref 5i.

(15) Efficient stirring is important to the epoxidation. Poor stirring frequently leads to lower conversions and requires longer reaction times.

liquid (10.8 g, 80.6%): ^{1}H NMR δ 7.40−7.25 (m, 5H), 2.98 (d, J = 5.4 Hz, 1H), 2.81 (d, J = 5.4 Hz, 1H), 1.72 (s, 3H).

***trans*-Stilbene Oxide.**[6c] To a mixture of a suspension of *trans*-stilbene (18.02 g, 0.1 mol) and CF_3COCH_3 (3.36 g, 0.03 mol) in CH_3CN−DMM (1/2 v/v, 750 mL) and aqueous K_2CO_3 (1.5 M in 4 × 10^{-4} M EDTA, 150 mL) was added H_2O_2 (30%, 40 mL, 0.4 mol) at 0 °C. Upon stirring at 0 °C for 1 h and at room temperature for 5 h, the reaction mixture was extracted with hexane (3 × 500 mL). The combined organic layers were washed with aqueous $Na_2S_2O_3$ (1 M) (3 × 50 mL) and brine (100 mL), dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography on silica gel (buffered with 1% NEt_3) using hexanes−ether (1/0−100/1) as eluent to give *trans*-stilbene oxide as a white solid (18.3 g, 93.3%): ^{1}H NMR δ 7.40−7.15 (m, 10H), 3.88 (s, 2H).

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