Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds
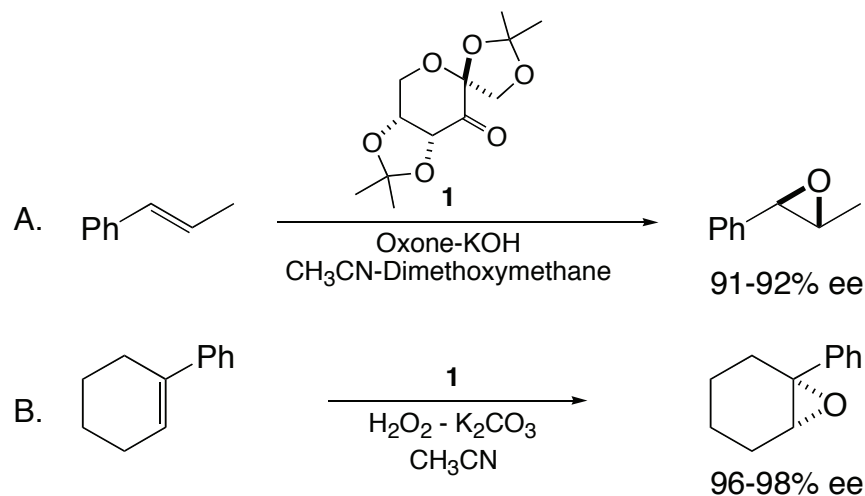
Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

ASYMMETRIC EPOXIDATION OF *trans*-β-METHYLSTYRENE AND 1-PHENYLCYCLOHEXENE USING A D-FRUCTOSE-DERIVED KETONE: (*R,R*)-*trans*-β-METHYLSTYRENE OXIDE AND (*R,R*)-1-PHENYLCYCLOHEXENE OXIDE
[(Oxirane, 2-methyl-3-phenyl-, (2*R*,3*R*)- and 7-Oxabicyclo[4.1.0]heptane,1-phenyl-)]

A.

Ph ⟶ (Oxone-KOH, CH₃CN-Dimethoxymethane) ⟶ Ph epoxide

91-92% ee

B.

Ph-cyclohexene ⟶ (1, H₂O₂ - K₂CO₃, CH₃CN) ⟶ Ph-cyclohexene oxide

96-98% ee

Submitted by Zhi-Xian Wang, Lianhe Shu, Michael Frohn, Yong Tu, and Yian Shi.[1]
Checked by Jason M. Diffendal and Rick L. Danheiser.

Discussion Addendum *Org. Synth.* **2012**, *89*, 350

1. Procedure

A. (R,R)-trans-β-Methylstyrene oxide.[2] A 2-L, three-necked, round-bottomed flask (Note 1) equipped with a 5-cm, egg-shaped, Teflon-coated stir bar and two addition funnels is cooled in an ice-bath. The flask is charged with *trans*-β-methylstyrene (5.91 g, 50.0 mmol) (Note 2), 500 mL of a 2:1 mixture of dimethoxymethane (Note 2) and acetonitrile (CH₃CN) (Note 2), 300 mL of potassium carbonate-acetic acid buffer solution (Note 3), tetrabutylammonium hydrogen sulfate (0.375 g, 1.1 mmol), and the chiral ketone **1** (4.52 g, 17.5 mmol, 35 mol%) (Note 4). One addition funnel is charged with a solution of Oxone (46.1 g, 75.0 mmol) in 170 mL of aqueous 4×10^{-4}M disodium ethylenediaminetetraacetate (Na₂EDTA) solution (Note 5) and the other addition funnel is charged with 170 mL of 1.47M aqueous potassium hydroxide (KOH) solution. The two solutions in the addition funnels are added dropwise at the same rate over 2.5 h to the cooled reaction mixture which is stirred vigorously at 0 °C (Notes 6, 7). The resulting

suspension is stirred at 0 °C for an additional hour and then 250 mL of pentane is added. The aqueous phase is separated and extracted with two 250-mL portions of pentane, and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated by rotary evaporation at 0 °C (Note 8). The resulting oil is loaded onto 50 g of Whatman 60 Å (230-400 mesh) silica gel (Note 9) packed in a 5-cm diameter column. The silica gel is first washed with 200 mL of hexane to remove trace amounts of unreacted olefin, then the product is eluted with 200 mL of 10:1 hexane:ether to afford 6.02-6.31 g (90-94%) of *trans*-β-methylstyrene oxide (Notes 10-12).

B. *(R,R)-1-Phenylcyclohexene oxide*.[3] A 250-mL, round-bottomed flask (Note 1) equipped with a 4.5-cm, egg-shaped Teflon-coated magnetic stir bar is charged with 1-phenylcyclohexene (7.91 g, 50.0 mmol) (Note 2) and the chiral ketone **1** (1.29 g, 5.00 mmol, 10 mol%) (Note 4). The flask is cooled in an ice-bath, and 75 mL of CH_3CN and 75 mL of a solution which is 2.0M potassium carbonate and $4 \times 10^{-4}M$ EDTA are added. The reaction mixture is cooled to 0 °C, and 20 mL (200 mmol) of 30% hydrogen peroxide (H_2O_2) is added. The resulting mixture is vigorously stirred at 0 °C for 6 h (Note 13), then diluted with 50 mL of hexane. The aqueous phase is separated and extracted with three 200-mL portions of hexane, and the combined organic phases are washed with two 50-mL portions of 1M aqueous sodium thiosulfate solution and 100 mL of brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation at 0 °C. The resulting oil is applied to 180 g of Whatman 60 Å (230-400 mesh) silica gel (Note 9) packed in a 5-cm diameter column, then the product is eluted with 600 mL of hexane and finally 1 L of 20:1 hexane:Et_2O to afford 6.88-8.01 g (79-92%) of *(R,R)*-1-phenylcyclohexene oxide as a colorless oil (Notes 14, 15).

2. Notes

1. All glassware used for the epoxidation reaction is carefully washed to remove trace metals, which may catalyze the decomposition of Oxone and H_2O_2. The checkers used Alconox, followed by water, and then acetone.

2. β-Methylstyrene (99%) and dimethoxymethane (99%) were obtained from Aldrich Chemical Company, Inc. and used as received. ACS grade acetonitrile and 30% H_2O_2 were purchased from Fisher Scientific and

10

used as received. 1-Phenylcyclohexene (99%) was obtained from Alfa Aesar.

3. The buffer solution is prepared by adding 4.5 mL of glacial acetic acid (Fisher Scientific) to 1 L of a 0.1M solution of K_2CO_3 (Fisher Scientific).

4. The chiral ketone **1** was prepared as described in *Org. Synth.* **2003**, *80*, 1.

5. Oxone was obtained from the Aldrich Chemical Company, Inc. The activity of commercial Oxone in oxidation reactions occasionally varies with different batches. Na_2EDTA was purchased from Fisher Scientific.

6. The concentration of Oxone in the reaction mixture and the reaction pH are very important factors in determining the epoxidation efficiency. Both the Oxone and KOH solutions must be added to the reaction mixture in a steady, uniform manner over 2.5 h.

7. As the reaction progresses, the organic and aqueous phases separate. Salts precipitate during the first 10-20 min of addition. Vigorous stirring is required to sufficiently mix the two phases; however, excessive splashing of the reaction mixture must be avoided in order to maximize conversion.

8. The epoxide product is volatile. Care should be taken to minimize the loss of the epoxide during concentration.

9. The silica gel is buffered by packing the column with hexane containing 1% triethylamine.

10. The product exhibits the following physical and spectral properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (d, 3 H, $J = 5.1$), 3.03 (qd, 1 H, $J = 5.1, 2.1$), 3.57 (d, 1 H, $J = 2.1$), 7.20-7.40 (m, 5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.1, 59.2, 59.7, 125.7, 128.2, 128.6, 137.9; Anal. Calcd C, 80.56; H, 7.51. Found: C, 80.39; H, 7.37; $[\alpha]_D^{25}$ +45.3 ($CHCl_3$, c 1.84).

11. The submitters obtained the product in 91-92% ee as determined by chiral GC with a Chiraldex G-TA column (25 μm × 30 m) (oven temperature: 80 °C; head pressure: 20 psi; retention time: minor isomer at 11.8 min, major isomer at 15.8 min). The checkers obtained epoxide with 89% ee.

12. The submitters report that the ee can be increased to 94% if the epoxidation is carried out at −8 to −10 °C.

13. The reaction was monitored by TLC and was complete after 6 hr. The reaction rate is affected by the rate of stirring.

14. The product exhibits the following physical and spectral properties: ^{1}H NMR (500 MHz, CDCl$_3$) δ: 1.25-1.65 (m, 4 H), 1.95-2.03 (m, 2 H), 2.12 (dt, 1 H, J = 15.0, 5.1), 2.29 (ddd, 1 H, J = 15.0, 8.4, 5.1), 3.09 (br s, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (125 MHz, CDCl$_3$) δ: 19.8, 20.1, 24.7, 28.9, 60.2, 61.9, 125.3, 127.1, 128.2, 142.5. Anal. Calcd: C, 82.72; H, 8.10. Found: C, 82.76; H, 8.13; [α] $\frac{25}{D}$ +113.0 (benzene, c 0.56).

15. The submitters obtained the product in 96-98% ee as determined by chiral GC with a Chiraldex G-TA column (25 μm × 30 m) (oven temperature: 80 °C; head pressure: 25 psi; retention time: minor isomer at 68.0 min, major isomer at 71.8 min). The checkers obtained the product in 94-95% ee.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.
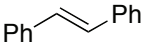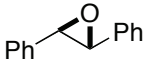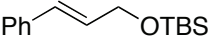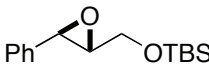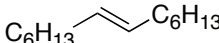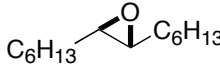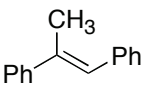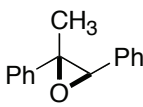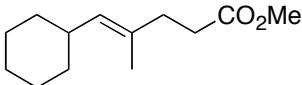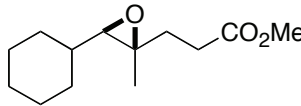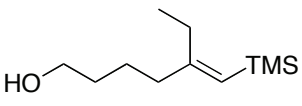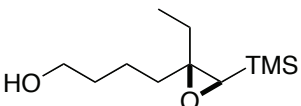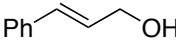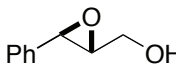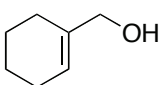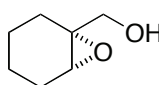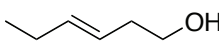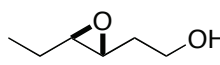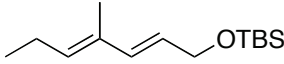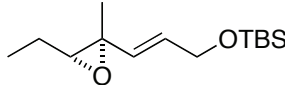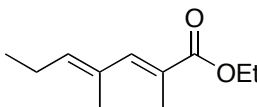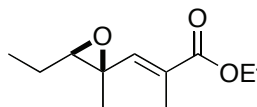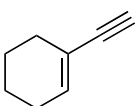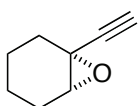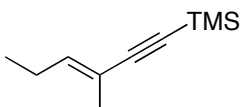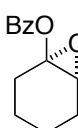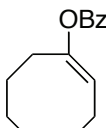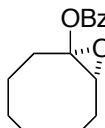
3. Discussion

The epoxidation procedure described herein utilizes the fructose-derived ketone (1) as catalyst and Oxone[4a-j] or H$_2$O$_2$[4k,l] as oxidant. The procedure provides a valuable method for the preparation of enantiomerically-enriched epoxides from *trans*- and trisubstituted olefins. High enantioselectivies have been obtained for a variety of unfunctionalized trans-disubstituted and trisubstituted olefins,[4a-c] vinylsilanes,[4j] hydroxyalkenes,[4e] conjugated dienes,[4d] conjugated enynes,[4f,i] and enol derivatives.[4g] Representative examples are shown in Table I.
Previously, the generation of dioxiranes almost exclusively used potassium peroxomonosulfate (KHSO$_5$) as oxidant.[5,6] Recently, we found that hydrogen peroxide (H$_2$O$_2$) could be used as primary oxidant in combination with a nitrile for the epoxidation catalyzed by **1**.[4k,l] In this epoxidation, the peroxyimidic acid generated from the addition of H$_2$O$_2$ to CH$_3$CN is likely to be the active oxidant for the formation of the dioxirane.[7] The Oxone procedure described herein can be applied to a wide variety of olefins without the need for extensive optimization. T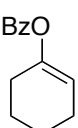he more recent H$_2$O$_2$ procedure uses much less solvent and salts and is operationally simpler. However, this procedure is somewhat sensitive to the reactivity and

solubility of olefins; some optimization (varying catalyst loading, reaction time, reaction temperature, amount of H_2O_2 and solvent) may be required for different substrates.[41]

Table 1. Asymmetric Epoxidation of Representative Olefins by Ketone **1** (0.3 equiv) with Oxone

Entry	Substrate	Product	Yield (%)	ee (%)	Ref.
1.	Ph—=—Ph	Ph epoxide Ph	85	98	4c
2.	Ph—=—OTBS	Ph epoxide OTBS	87	94	4c
3.	C_6H_{13}—=—C_6H_{13}	C_6H_{13} epoxide C_6H_{13}	89	95	4c
4.	CH_3 / Ph—=—Ph	CH_3 / Ph epoxide Ph	89	95	4c
5.	cyclohexyl—=—CO_2Me	cyclohexyl epoxide CO_2Me	89	94	4c
6.	HO— ...—TMS	HO— ...—TMS	71	93	4j
7.	Ph—=—OH	Ph epoxide OH	85	94	4e
8.	cyclohexenyl—OH	cyclohexyl epoxide OH	93	94	4e
9.	—=—OH	—epoxide—OH	82	90	4e
10.	—=—OTBS	—epoxide—OTBS	81	96	4d
11.	—=—OEt	—epoxide—OEt	89	94	4d
12.	cyclohexenyl—=—	cyclohexyl epoxide—=—	78	93	4i
13.	—=—TMS	—epoxide—TMS	84	95	4i
14.	BzO—cyclohexenyl	BzO—cyclohexyl epoxide	82	93	4g
15.	OBz—cyclooctenyl	OBz—cyclooctyl epoxide	82	95	4g

14

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523.

2. Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc*. **1957**, *79*, 197.

3. Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Org. Chem.* **1968**, *33*, 4045.

4. For examples of asymmetric epoxidation mediated 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) Shu, L.; Shi, Y. *Tetrahedron Lett.* **1999**, *40*, 8721; (l) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213.

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

6. 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.

7. 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. Coll. Vol. VII* **1990**, 126; (e) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.

(*R,R*)-*trans*-β-Methylstyrene oxide: Oxirane, 2-methyl-3-phenyl-, (2*R*,3*R*)- (9); (14212-54-5)

trans-β-Methylstyrene: Benzene, (1E)-1-propenyl- (9); (873-66-5)

Dimethoxymethane: Methane, dimethoxy- (8, 9); (109-87-5)

1,2:4,5-Di-*O*-isopropylidene-D-erythro-2,3-hexodiulo-2,6-pyranose: β-Dk-erythro-2,3-Hexodiulo-2,6-pyranose,1,2:4,5-bis-O-(1-methylethylidene)- (9); (18422-53-2)

Tetrabutylammonium hydrogen sulfate: 1-Butanaminium, *N,N,N*-tributyl-, sulfate (1:1) (9); (32503-27-8)

Disodium ethylenediaminetetraacetate: Glycine, N,N'-1,2-ethanediylbis [*N*-(carboxymethyl)-, disodium salt (9); (139-33-3)

(*R,R*)-1-Phenylcyclohexene oxide: 7-Oxabicyclo[4.1.0]heptane, 1-phenyl-, (1R,6R)- (9); (17540-04-4)

Oxone: Peroxymonosulfuric acid, monopotassium salt, mixt. with dipotassium sulfate and potassium hydrogen sulfate (9); (37222-66-5)