Guidelines for Asymmetric Epoxidation
Prepared by O. Andrea Wong 2009


I. Catalyst Selection

1a. Substrate Scope of Ketone 1

<table>
<thead>
<tr>
<th>Substrate Type</th>
<th>Ketone 1 Structure</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-olefins</td>
<td><img src="image" alt="trans-olefins" /></td>
<td>85%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>54%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>54%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>94%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>74%</td>
<td>94%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>71%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>66%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>82%</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>87%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>77%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>82%</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="trans-olefins" /></td>
<td>78%</td>
<td>93%</td>
</tr>
</tbody>
</table>


1b. Synthesis of Ketone 1 and ent-1


1c. Commercial Sources of Ketone 1 (CAS #18422-53-2)

a. Alfar Aesar (1 g, 5 g)
b. Aldrich (5g)
1d. Representative Epoxidation Procedure (small-scale, Oxone/K₂CO₃, see Figures 1 and 2)

trans-β-Methylstyrene (0.118 g, 1 mmol) was dissolved in acetonitrile-DMM (15 mL, 1:2 v/v). Buffer (10 mL, 0.05 M solution of Na₂B₄O₇·10H₂O in 4 x 10⁻⁴ M aqueous Na₂EDTA, tetrabutylammonium hydrogen sulfate (15 mg, 0.04 mmol), and ketone 1 (0.0774 g, 0.3 mmol) were added with stirring. The mixture was cooled to about –10 °C (inside) (bath temperature was about –12 to –15 °C) using an NaCl-ice bath. A solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na₂EDTA (4 x 10⁻⁴, 6.5 mL) and a solution of K₂CO₃ (0.8 g, 5.8 mmol) in water (6.5 mL) were added dropwise separately over a period of 2 h (via syringe pump). At this point, the reaction was immediately quenched by the addition of pentane and water. The mixture was extracted with pentane (3 x 30 mL), washed with brine, dried over Na₂SO₄, purified by flash column chromatography [the silica gel was buffered with 1% Et₃N in pentane; pentane-ether (1:0 to 50:1 v/v) was used as eluent] to afford trans-β-methylstyrene oxide as a colorless liquid (0.126 g, 94% yield, 95.5% ee). Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. J. Am. Chem. Soc. 1997, 119, 11224. See Section VI for general tips and troubleshooting information.

Note:
(a) 0.05 M Na₂B₄O₇·10H₂O solution can be replaced by K₂CO₃-AcOH (pH = 9.3) buffer, see Section III for buffer preparation procedures. References: (a) Cao, G-A.; Wang, Z-X.; Tu, Y.; Shi, Y. Tetrahedron Lett. 1998, 39, 4425. (b) Wang, Z-X.; Cao, G-A; Shi, Y. J. Org. Chem. 1999, 64, 7646.

1e. Representative Epoxidation Procedure (large-scale, Oxone/KOH or Oxone/K₂CO₃, see Figures 3, 4, and 5)

A 2L, three-necked, round-bottomed flask equipped with a 5-cm, egg-shaped, Teflon-coated magnetic 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), 500 mL of a 2:1 mixture of DMM:MeCN, 300 mL of K₂CO₃-AcOH buffer solution (the buffer solution is prepared by adding 4.5 mL of glacial acetic acid to 1 L of a 0.1 M solution of K₂CO₃), tetrabutylammonium hydrogen sulfate (0.375 g, 1.1 mmol), and ketone 1 (4.52 g, 17.5 mmol, 35 mol%). 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 Na₂EDTA solution and the other addition funnel is charged with 170 mL of 1.47 M aqueous 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. 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 Na₂SO₄, filtered, and concentrated at 0 °C. The resulting oil is loaded onto 50 g of Whatman 60 Å (230-400 mesh) silica gel packed in a 5-cm diameter column. The silica gel is first washed with 200 mL of hexanes 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. Wang, Z-X.; Shu, L.; Frohn, M.; Tu, Y.; Shi, Y. Org. Synth. 2003, 80, 9. See Section VI for general tips and troubleshooting information.

Note:

(a) In principle, the Oxone/KOH solutions can be replaced by solutions of Oxone (42.5 g, 69 mmol, 325 mL) and K₂CO₃ (40.0 g, 290 mmol, 325 mL).

1f. Representative Epoxidation Procedure (MeCN/H₂O₂, see Figure 6)

To a solution of trans-stilbene (0.180 g, 1.0 mmol) and ketone 1 (0.0774 g, 0.30 mmol) in MeCN-DMM (1:2 v/v) (6.0 mL) was added a solution of 2.0 M K₂CO₃ in 4 × 10⁻⁴ M Na₂EDTA (1.5 mL) followed by H₂O₂ (30%, 0.4 mL, 4 mmol) at 0 °C. Upon stirring at 0 °C for 10 h and at rt for 14 h, the reaction mixture was extracted with hexanes, washed
with 1 M aqueous Na$_2$S$_2$O$_3$ and brine, dried (Na$_2$SO$_4$), filtered, concentrated, and purified by chromatography (silica gel was buffered with 1% Et$_3$N in hexanes, using hexanes/ether 50/1 as eluent) to afford trans-stilbene oxide as a white solid (0.151 g, 77 % yield, 99% ee). Shu, L.; Shi, Y. *Tetrahedron* **2001**, 57, 5213. See Section VI for general tips and troubleshooting information.

**Note:**

(a) Vigorous stirring is crucial for epoxidation efficiency in the H$_2$O$_2$ epoxidation, particularly for less reactive (i.e. nonpolar) substrates.

(b) Mixed solvent systems such as MeCN-EtOH-DCM, MeCN-nPrOH-DCM, MeCN-nPrOH-PhCH$_3$, and MeCN-nPrOH-PhH are beneficial for olefins with poor solubility.

(c) The quality of H$_2$O$_2$ is important. Old or contaminated H$_2$O$_2$ cannot provide maximum conversion.


**1g. Examples of Synthetic Applications of Ketone 1**

![Diagram of synthetic application of ketone 1](attachment:image.png)


2a. Substrate Scope of Ketone 2


### 2b. Synthesis of Ketone 2

![Chemical structure diagram of the synthesis of Ketone 2]

D-glucose $\xrightarrow{Bn_2NH, HOAc}$

$\xrightarrow{H_2, Pd/C, HOAc}$

$\xrightarrow{NH_2OAc}$

$\xrightarrow{COCl_2, NaHCO_3}$

$\xrightarrow{PDC}$

$\xrightarrow{(Boc)_2O, DMAP}$


### 2c. Representative Epoxidation Procedure (small-scale, Oxone/K$_2$CO$_3$, see Figures 1 and 2)

To a solution of cis-$\beta$-methylstylene (0.059 g, 0.5 mmol) and ketone 2 (0.026 g, 0.075 mmol) in DME-DMM (3:1, v/v) (7.5 mL) were added buffer (0.2 M K$_2$CO$_3$-AcOH in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA, buffer pH = 8.0) (5 mL) and Bu$_4$NHSO$_4$ (0.0075 g, 0.02 mmol) with stirring. After the mixture was cooled to about –10 °C (bath temperature) using an NaCl-ice bath, a solution of Oxone (0.21 M in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA, 4.2 mL) (0.548 g 0.89 mmol) and K$_2$CO$_3$ (0.48 M in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA, 4.2 mL) (0.278 g, 2.01 mmol) were added dropwise separately over a period of 3.5 h via syringe pump. The reaction was then quenched with the addition of pentane and...
extracted with pentane. The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et₃N in pentane; pentane-ether (1/0 to 50/1) was used as eluent] to give cis-β-methylstyrene oxide as a colorless liquid (0.058 g, 87% yield, 91% ee). Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. J. Am. Chem. Soc. 2000, 122, 11551. See Section VI for general tips and troubleshooting information.

3a. Substrate Scope of Ketones 3


3b. Synthesis of Ketones 3


3c. Commercial Sources of Ketone 3a (CAS #403501-30-4)

Aldrich (100 mg, 500 mg)

3d. Representative Epoxidation Procedure (small-scale, Oxone/K$_2$CO$_3$, see Figures 1 and 2)

To a mixture of 2,2-dimethylchromone (0.4 mmol), Bu$_4$NHSO$_4$ (0.001 g, 0.003 mmol), and ketone 3b (0.028 g, 0.08 mmol) was added DME/DMM (v/v 3:1) (6.0 mL). After the mixture was stirred at rt for 20 min, buffer (0.1 M K$_2$CO$_3$-AcOH in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA, pH 9.3) (4.0 mL) was added. After being stirred at rt for 10 additional min, the mixture was cooled using an ice bath (0 °C). Oxone (5.04 mL, 0.212 M in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA) and K$_2$CO$_3$ (5.04 mL, 0.84 M in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA) were added simultaneously and separately via syringe pump over 6 hours. The reaction was quenched by the addition of diethyl ether and extracted with diethyl ether. The
combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% NEt$_3$) to afford the corresponding epoxide. Wong, O.A.; Shi, Y. J. Org. Chem. 2006, 71, 3973. See Section VI for general tips and troubleshooting information.

3e. Representative Epoxidation Procedure (MeCN/H$_2$O$_2$, see Figure 6)
A mixture of 2-methyl-1-phenyl-1-propene (0.135 g, 1.00 mmol) and ketone 3b (0.051 g, 0.15 mmol) in n-BuOH (3.0 mL) was cooled to 0 °C with an ice bath. CH$_3$CN (0.20 mL, 3.8 mmol) and 0.30 M K$_2$CO$_3$ in 4 x 10$^{-4}$ M aqueous Na$_2$EDTA (3.0 mL) were then added, followed by H$_2$O$_2$ (30%, 0.30 mL, 3.0 mmol) with vigorous stirring at 0 °C. The mixture was stirred at 0 °C for 24 h and was then poured into petroleum ether and extracted with petroleum ether. The combined organic layers were washed with water and saturated aqueous Na$_2$S$_2$O$_3$, dried (Na$_2$SO$_4$), filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et$_3$N in petroleum ether; petroleum ether was used as eluent) to give 2,2-dimethyl-3-phenyloxirane as a colorless oil (0.121 g, 82% yield, 92% ee). Burke, C.P.; Shu, L.; Shi, Y. J. Org. Chem. 2007, 72, 6320. See Section VI for general tips and troubleshooting information.

Notes:

a) The quality of the ketone catalyst is very important when H$_2$O$_2$ is used as the oxidant. For example, it was observed that lower conversions were obtained with the ketones 3a-c prepared from the TEMPO-bleach oxidation of the alcohol precursor. It appears that some residual impurities from TEMPO-bleach oxidation somehow affect the epoxidation.

b) Vigorous stirring is crucial for epoxidation efficiency in the H$_2$O$_2$ epoxidation, particularly for less reactive (i.e. nonpolar) substrates.

c) The quality of H$_2$O$_2$ is important. Old or contaminated H$_2$O$_2$ cannot provide maximum conversion.
4a. Substrate Scope of Ketone 4

**trans and trisubstituted olefins**
- Ph
  - 63% yield, 93% ee
- OAc
  - 97% yield, 95% ee

**trans and trisubstituted olefins**
- Ph
  - 78% yield, 86% ee
- nBu
  - 95% yield, 75% ee

**cis-olefins**
- Ph
  - 75% yield, 88% ee
- nBu
  - 73% conv., 90% ee

**α,β-unsaturated esters**
- Ph
  - 73% yield, 96% ee
- CO₂Et
  - 57% yield, 90% ee
- Ph
  - 93% yield, 96% ee
- F
  - 86% yield, 91% ee

**fluoroolefins**
- Ph
  - 77% yield, 93% ee
- CO₂Et
  - 96% yield, 94% ee
- Ph
  - 64% yield, 82% ee
- F
  - 68% yield, 92% ee
- Ph
  - 77% yield, 91% ee
- n-Bu
  - 60% yield, 90% ee


**Fluoroolefins:** Wong, O.A.; Shi, Y. *J. Org. Chem.*, **2009**, 74, 8377-8380
4b. Synthesis of Ketone 4 (hydrate of ketone 4, 4\(^\cdot\)H\(_2\)O, can be used in place of ketone 4)


4c. Representative Epoxidation Procedure (small-scale, Oxone/K\(_2\)CO\(_3\), see Figures 1 and 2)

To a solution of trans-\(\beta\)-methylstyrene (0.059 g, 0.5 mmol), ketone 4\(\cdot\)H\(_2\)O (0.015 g, 0.046 mmol), and tetrabutylammonium hydrogen sulfate (0.01 g, 0.03 mmol) in MeCN-DMM (v/v, 1/2) (9 mL) was added buffer (0.05 M aq Na\(_2\)HPO\(_4\)-0.05 M aq KH\(_2\)PO\(_4\), pH 7.0) (3 mL) with stirring. Upon cooling to 0 °C, a solution of Oxone (0.212 M in 4 x 10\(^{-4}\) M aq Na\(_2\)EDTA, 4.8 mL) and a solution of K\(_2\)CO\(_3\) (0.42 M in 4 x 10\(^{-4}\) M aq Na\(_2\)EDTA, 4.8 mL) were added dropwise simultaneously and separately over 8 h via syringe pump. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et\(_3\)N in organic solvent, first pentane, then pentane/Et\(_2\)O = 20/1) to give the epoxide as a colorless oil (0.054 g, 81% yield, 86% ee). Wang, B.; Wu, X.-Y.; Wong, O.A.; Nettles, B.; Zhao, M.-X.; Chen, D.; Shi, Y. J. Org. Chem. 2009, 74, 3986. See Section VI for general tips and troubleshooting information.
4d. Representative Epoxidation Procedure (NaHCO₃/Oxone, see Figure 7)

Aqueous Na₂(EDTA) (1×10⁻⁴ M, 2.5 mL) and a catalytic amount of tetrabutylammonium hydrogen sulfate (0.010 g, 0.03 mmol) were added to a solution of ethyl trans-4-methylcinnamate (0.095 g, 0.5 mmol) in CH₃CN (2.5 mL) with vigorous stirring at 0 °C. A mixture of Oxone (1.537 g, 2.5 mmol) and NaHCO₃ (0.651 g, 7.75 mmol) was pulverized, and a small portion of this mixture was added to the reaction mixture to bring pH to >7.0. Then a solution of ketone 4 (0.038 g, 0.125 mmol) in CH₃CN (1.25 mL) was added. The remainder of the Oxone and NaHCO₃ was added to the reaction mixture portionwise over a period of 4.5 h. Upon stirring for an additional 7.5 h at 0 °C and 12 h at rt, the resulting mixture was diluted with water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried over Na₂SO₄, filtered, concentrated, and purified by flash chromatography (silica gel, hexane/EtOAc = 1/0 to 95/5) to give the epoxide as a colorless oil (0.094 g, 91% yield, 97% ee). Wu, X-Y.; She, X.; Shi, Y. J. Am. Chem. Soc. 2002, 124, 8792. See Section VI for general tips and troubleshooting information.
5a. Substrate Scope of Ketone 5

1,1-disubstituted olefins

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>Ph</td>
<td>62%</td>
<td>77%</td>
</tr>
<tr>
<td>Ph</td>
<td>43%</td>
<td>86%</td>
</tr>
<tr>
<td>F</td>
<td>72%</td>
<td>88%</td>
</tr>
<tr>
<td>Ph, OH</td>
<td>93%</td>
<td>77%</td>
</tr>
<tr>
<td>Ph, Me, Me</td>
<td>76%</td>
<td>87%</td>
</tr>
<tr>
<td>Ph, Me, Me</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>nC6H13, OH</td>
<td>78%</td>
<td>60%</td>
</tr>
</tbody>
</table>

cis-olefins

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph, NC</td>
<td>60%</td>
<td>85%</td>
</tr>
<tr>
<td>Ph, Ph</td>
<td>87%</td>
<td>84%</td>
</tr>
<tr>
<td>Ph</td>
<td>89%</td>
<td>80%</td>
</tr>
<tr>
<td>Ph</td>
<td>56%</td>
<td>90%</td>
</tr>
</tbody>
</table>

5b. Synthesis of Ketone 5

D-Glucose

OH OH OH

\[ \text{p-Toluidine} \]

OH OH OH

H^+

OH OH OH

Me_2C(OMe)\_2

acetone

H_2SO_4

5c. Representative Epoxidation Procedure (small-scale, Oxone/K\_2CO\_3, see Figures 1 and 2)

To a solution of α-methylstyrene (0.024 g, 0.20 mmol), tetrabutylammonium hydrogen sulfate (0.0038 g, 0.010 mmol), and ketone 5 (0.0208 g, 0.06 mmol) in dioxane (3 mL) was added buffer (0.1 M K\_2CO\_3-AcOH in 4 x 10^{-4} M aqueous Na\_2EDTA, pH = 9.3; 2 mL) with stirring. After the mixture was cooled to -10 °C (bath temperature), a solution of Oxone (0.20 M in 4 x 10^{-4} M aqueous Na\_2EDTA, 1.6 mL) (0.197 g, 0.32 mmol) and a solution of K\_2CO\_3 (0.84 M in 4 x 10^{-4} M aqueous Na\_2EDTA, 1.6 mL) (0.185 g, 1.344 mmol) were added separately and simultaneously via syringe pump over a period of 2 h. The reaction mixture was quenched with hexane, extracted with EtOAc, dried over Na\_2SO\_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% Et\_3N in organic solvent) to give α-methylstyrene oxide (60% yield, 62% ee). Wang, B.; Wong, O.A.; Zhao, M.-X.; Shi, Y. J. Org. Chem. 2008, 73, 9539. See Section VI for general tips and troubleshooting information.
II. General Guidelines for Epoxidation Setup

*Small-scale epoxidation set up (Figures 1 and 2)*

**Figure 1. Epoxidation using Oxone/K$_2$CO$_3$ (syringe)**

![](image1)

- a) Fill with Oxone dissolved in 4x10$^{-4}$ M aq. Na$_2$EDTA
- b) Fill with K$_2$CO$_3$ dissolved in 4x10$^{-4}$ M aq. Na$_2$EDTA
- c) Syringes are taped together for stability.
- d) Rubber tubing and plastic tip, do not use metal.
- e) Holes are spaced to prevent mixing at the tube tips and to prevent the solutions from dripping down the side of the flasks where they freeze.

**Figure 2. Epoxidation using Oxone/K$_2$CO$_3$**

![](image2)

- a) Syringe pump. Oxone and K$_2$CO$_3$ should be added at a constant rate over the desired reaction time. Air at the tip of
the syringe should be pushed out to ensure the simultaneous addition of Oxone and K$_2$CO$_3$ as pH control is important for the epoxidation reactions. It has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches.

b) Reaction flask is suspended into Dewar with a clamp. All glassware should be washed with soap to be free of any trace metals, which catalyze the decomposition of Oxone. Cap should not be airtight.

c) Dewar flask. For $-10 \, ^\circ C$ epoxidations, bath temperature should not be below $-15 \, ^\circ C$ which will freeze the reaction. Low conversions will result from frozen reactions.

d) Stir plate. Stirring should be vigorous but without splashing.

Large-scale epoxidation set up (Figures 3-5)

Figure 3. Epoxidation using Oxone/ K$_2$CO$_3$

a) Fill with Oxone dissolved in $4\times10^{-4}$ M aq. Na$_2$EDTA
b) Fill with K$_2$CO$_3$ dissolved in $4\times10^{-4}$ M aq. Na$_2$EDTA
c) Ice bath. For $-10 \, ^\circ C$ epoxidations, bath temperature should not be below $-15 \, ^\circ C$ which will freeze the reaction. Low conversions will result from frozen reactions.

d) Stir plate. Stirring should be vigorous but without splashing.
Figure 4. Epoxidation using Oxone/ K₂CO₃ or Oxone/ KOH

- a) Fill with Oxone dissolved in 4x10⁻⁴ M aq. Na₂EDTA
- b) Fill with KOH or K₂CO₃ dissolved in 4x10⁻⁴ M aq. Na₂EDTA
- c) Ice bath. For –10 °C epoxidations, bath temperature should not be below –15 °C which will freeze the reaction. Low conversions will result from frozen reactions.
- d) Stir plate. Stirring should be vigorous but without splashing.
Figure 5. Epoxidation using Oxone/ $K_2CO_3$ or Oxone/ KOH (addition funnel)

![Figure 5](image)

a) Addition funnel equipped with needle stopcock is preferred for precise addition-rate control.

Figure 6. Epoxidation using MeCN/H$_2$O$_2$

![Figure 6](image)

a) The ketones 3a-c used in the $H_2O_2$ epoxidation were synthesized by the PDC oxidation. It was observed that lower conversions were obtained with the ketones prepared from the TEMPO-bleach oxidation of the alcohol precursor. It appears that some residual impurities from TEMPO-bleach oxidation somehow affect the epoxidation.
b) Vigorous stirring is crucial for epoxidation efficiency in the H₂O₂ epoxidation, particularly for less reactive (i.e. nonpolar) substrates.

\[ \text{c) For the } \text{H}_2\text{O}_2 \text{ epoxidation with ketone 1, a mixed solvent such as MeCN-EtOH-DCM is beneficial for olefins with poor solubility.} \]

**Figure 7. Epoxidation using Oxone/NaHCO₃ (solid mixture)**

- a) Oxone needs to be pulverized before use.
- b) The pH of the reaction mixture needs to be >7 before adding ketone.
- c) For substrates with poor solubility, the amount of organic solvent used can be doubled.
### III. Buffer Preparations

<table>
<thead>
<tr>
<th>Buffer solution</th>
<th>Ratio of components</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 9.3 buffer (0.05 M Na₂B₂O₇·10H₂O)</td>
<td>1.907 g Na₂B₂O₇·10H₂O, 100 mL 4 x 10⁻³ M aq Na₂(EDTA) solution</td>
</tr>
<tr>
<td>pH 9.3 buffer (0.1 M K₂CO₃·AcOH)</td>
<td>13.82 g K₂CO₃ and 4.80 mL AcOH in 1L H₂O</td>
</tr>
<tr>
<td>pH 8.0 buffer (0.1 M K₂CO₃·AcOH)</td>
<td>13.82 g K₂CO₃ and 5.96 mL AcOH in 1L H₂O</td>
</tr>
<tr>
<td>pH 7.0 buffer</td>
<td>7.1 g Na₂HPO₄, 6.8 g KH₂PO₄ in 1L H₂O</td>
</tr>
</tbody>
</table>

### IV. K₂CO₃ Concentration Chart (Oxone concentration = 0.21 M)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>K₂CO₃ Concentration (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.89</td>
</tr>
<tr>
<td>2</td>
<td>0.48</td>
</tr>
<tr>
<td>3a-c</td>
<td>0.84</td>
</tr>
<tr>
<td>4·H₂O</td>
<td>0.42</td>
</tr>
<tr>
<td>5</td>
<td>0.84</td>
</tr>
</tbody>
</table>
V. Preparation of Buffers for pH Study

<table>
<thead>
<tr>
<th>Buffer solution</th>
<th>Ratio of components</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 8.0 buffer</td>
<td>13.82 g K₂CO₃ and 5.96 mL AcOH in 1 L H₂O</td>
</tr>
<tr>
<td>pH 8.5 buffer</td>
<td>13.82 g K₂CO₃ and 5.70 mL AcOH in 1 L H₂O</td>
</tr>
<tr>
<td>pH 9.0 buffer</td>
<td>13.82 g K₂CO₃ and 5.30 mL AcOH in 1 L H₂O</td>
</tr>
<tr>
<td>pH 9.3 buffer</td>
<td>13.82 g K₂CO₃ and 4.80 mL AcOH in 1 L H₂O</td>
</tr>
<tr>
<td>pH 9.5 buffer</td>
<td>13.82 g K₂CO₃ and 4.40 mL AcOH in 1 L H₂O</td>
</tr>
<tr>
<td>pH 10.0 buffer</td>
<td>13.82 g K₂CO₃ and 2.80 mL AcOH in 1 L H₂O</td>
</tr>
</tbody>
</table>
VI. General Tips and Troubleshooting Information

a) Oxone and K$_2$CO$_3$ should be added at a constant rate over the desired reaction time. Air at the tip of the syringe should be pushed out to ensure the simultaneous addition of Oxone and K$_2$CO$_3$ as pH control is important for the epoxidation reactions. It has been found that the oxidation activity of the purchased Oxone occasionally varies with different batches.

b) Reaction flask is suspended into Dewar with a clamp. All glassware should be washed with soap to be free of any trace metals, which catalyze the decomposition of Oxone. Avoid using metal needles for the addition of aqueous Oxone solution.

c) For –10 °C epoxidations, bath temperature should not be below –15 °C which will freeze the reaction. Even momentary freezing will result in low conversions.

d) Stirring should be vigorous but without splashing.

e) Relatively insoluble substrates should be stirred in only organic solvent at room temperature for about 20-30 min before adding buffer and cooling to ensure maximum conversion.

f) For less reactive substrates, conversion can also usually be improved with a slower addition of Oxone and/or higher reaction temperature (0 °C or rt). However, a decrease of ee may result from higher reaction temperature.

g) Purification columns are usually performed with solvents buffered with 1% Et$_3$N as the epoxides are acid-sensitive. However, it was found that certain epoxides decompose in the presence of Et$_3$N (e.g. Fluoroepoxides: Wong, O. A.; Shi, Y. J. Org. Chem., 2009, 74, 8377-8380). Moreover, Et$_3$N maybe difficult to completely remove for extremely volatile epoxides.

h) The quality of H$_2$O$_2$ is important in the case where H$_2$O$_2$ is used as the oxidant. Old or contaminated H$_2$O$_2$ cannot provide maximum conversion.

i) The quality of the ketone catalyst is very important when H$_2$O$_2$ is used as the oxidant. For example, it was observed that lower conversions were obtained with the ketones 3a-c prepared from the TEMPO-bleach oxidation of the alcohol.
precursor. It appears that some residual impurities from TEMPO-bleach oxidation somehow affect the epoxidation.

j) Certain reactive olefins may contain racemic epoxide resulting from oxidation during storage. To ensure maximum enantioselectivities, those olefins should be purified before asymmetric epoxidation.