

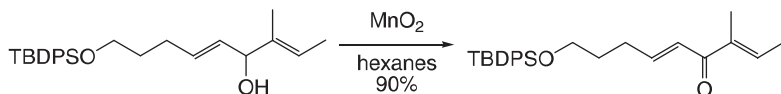
3

Oxidation

3.1 Alcohol to Ketone Oxidation State

3.1.1 Activated Manganese Dioxide Oxidation

Activated manganese dioxide (MnO_2) reliably oxidizes acetylenic, allylic, and benzylic alcohols to aldehydes and ketones. Saturated primary and secondary alcohols are also oxidized, albeit more slowly. The two main concerns are the activity of the manganese dioxide and the slow filtration of salts after the reaction. Activated MnO_2 is available commercially or may be prepared.



To a solution of 15.3 g (37.5 mmol) of the alcohol in 150 mL of hexanes was added 60 g of activated MnO_2 . The reaction mixture was stirred at 22 °C overnight and filtered, and the solid residue was washed with 30% EtOAc in hexanes solution. The combined filtrates were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography on SiO_2 (EtOAc:hexanes, 1:10) to give 13.7 g (90%) of the ketone as a colorless oil.

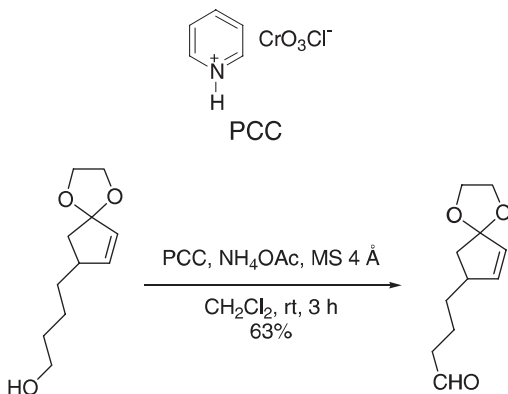
Reference: Wipf, P.; Xu, W. *J. Org. Chem.* **1996**, *61*, 6556–6562.

3.1.2 Chromium-Based Oxidations

Chromium-based oxidations are reliable and well established, but the toxicity associated with chromium salts have meant that they are generally considered the

second choice. For a review of chromium–amine complex oxidations, see Luzzio, F. A. *Org. React.* **1998**, *53*, 1–221.

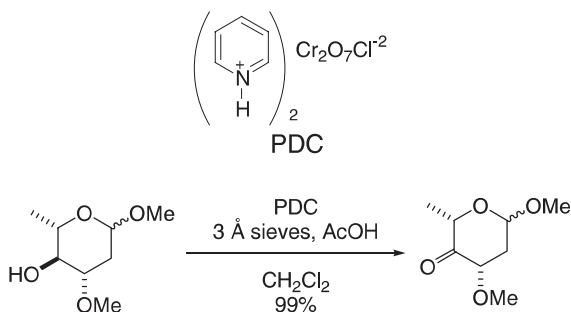
3.1.2.1 Pyridinium Chlorochromate



To a mixture of pyridinium chlorochromate (PCC 339 mg, 1.57 mmol), ammonium acetate (215 mg, 2.62 mmol), and 4 Å molecular sieves (610 mg) in CH_2Cl_2 (33 mL) was added a solution of the alcohol (208 mg, 1.05 mmol) in CH_2Cl_2 (14 mL) under argon at 0 °C over a period of 10 min. After the mixture had been stirred at room temperature for 3 h, diethyl ether (200 mL) was added and the mixture was filtered through a short pad of Florisil. The filtrate was washed successively with water (100 mL) and brine (100 mL), dried with Na_2SO_4 , and concentrated. The residue was purified by chromatography on silica gel (hexane 70%, Et_2O 30%) followed by distillation to give the aldehyde as a colorless oil (132 mg, 63%).

Reference: Ohkita, M.; Kawai, H.; Tsuji, T. *J. Chem. Soc. Perkin. 1*, **2002**, 366–370.

3.1.2.2 Pyridinium Dichromate

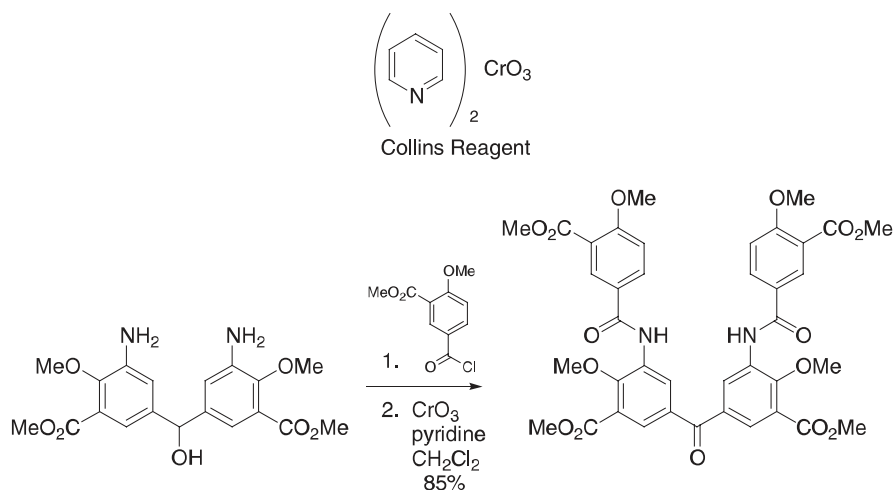


Methyl oleandroside (7.10 g, 40.4 mmol, 1.0 equivalents) in CH_2Cl_2 (200 mL) was treated with 3 Å powdered molecular sieves (20 g) and pyridinium dichromate (PDC 16.7 g, 44.3 mmol, 1.1 equivalents) at 2 °C followed by the addition of AcOH (4.0 mL). The mixture was warmed and stirred for 2 h at 25 °C. The mixture was treated with Celite (20 g), stirred for 30 min, and filtered. The solution was evaporated to a dark oil.

A solution of the oil in EtOAc (50 mL) was filtered through silica gel (50 g, 230–400 mesh) and the eluent was evaporated to give the ketone (7.0 g, 99%) as an oil.

Reference: Loewe, M. F.; Cvetovich, R. J.; DiMichele, L. M.; Shuman, R. F.; Edward J. J.; Grabowski, E. J. *J. Org. Chem.* **1994**, *59*, 7870–7875.

3.1.2.3 Collins Oxidation

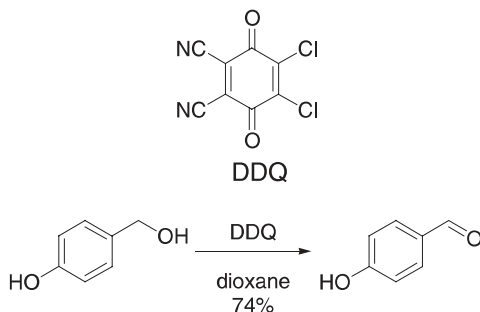


The diamine (0.388 g, 1.0 mmol) and 4-methoxy-3-methoxycarbonylbenzoyl chloride (0.258 g, 2.1 mmol) were stirred in dry pyridine (5 mL) and CH₂Cl₂ (5 mL) overnight under nitrogen. Solid CrO₃ (0.6 g, 6.0 mmol) was added, and the mixture was stirred at 0 °C for 3 h. The CH₂Cl₂ was removed in vacuo and the solution was poured into water (100 mL). The solid produced was filtered and air-dried to give crude the ketone (1.2 g). Purification by silica gel column chromatography (20 g, 230–400 mesh), eluting with EtOAc:hexanes (2:1 v/v), gave the product as an amorphous glass (0.45 g, 85%).

Reference: Ruell, J. A.; De Clercq, E.; Pannecouque, C.; Witvrouw, M.; Stup, T. L.; Turpin, J. A.; Buckheit, Jr., R. W.; Cushman, M. *J. Org. Chem.* **1999**, *64*, 5858–5866.

3.1.3 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone

Most aliphatic alcohols react slowly if at all with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), allowing selective allylic or benzylic alcohol oxidation.



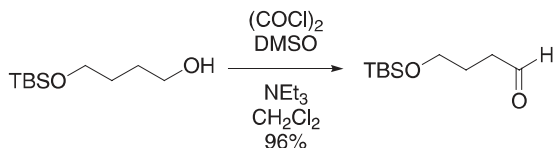
2,3-Dichloro-5,6-dicyano-*p*-benzoquinone (DDQ 908 mg, 4 mmol) was added to a solution of 4-hydroxybenzyl alcohol (496 mg, 4 mmol) in dioxane (24 mL). The reaction mixture immediately turned deep green (exothermic reaction), and DDQH₂ started precipitating within 1 min. Thin layer chromatography (TLC) analysis indicated consumption of starting material after 15 min. The solvent was removed from the yellow reaction mixture in vacuo. Treatment of the residue with CH₂Cl₂ left DDQH₂ undissolved (quantitatively). Filtration followed by evaporation of CH₂Cl₂ gave 4-hydroxybenzaldehyde (74% yield) which was recrystallized from water.

Reference: Becker, H.-D.; Bjork, A.; Alder, E. *J. Org. Chem.* **1980**, *45*, 1596–1600.

3.1.4 Dimethylsulfoxide-Based Oxidations

“Those who’ve learned use the Swern” (John L. Wood). The Swern oxidation is a very reliable oxidation, and is likely the oxidation of choice when the temperature can be carefully controlled (see Tidwell, T. T. *Org. React.* **1990**, *39*, 297–572). However, the active chlorosulfonium intermediate decomposes above approximately –60 °C. Therefore, alternative dehydrating agents have been used (for useful reviews see Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165; Lee, T. V. Oxidation Adjacent to Oxygen of Alcohols by Activated DMSO Methods. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, 291–304). A representative list is shown below.

3.1.4.1 With Oxalyl Chloride (Swern)

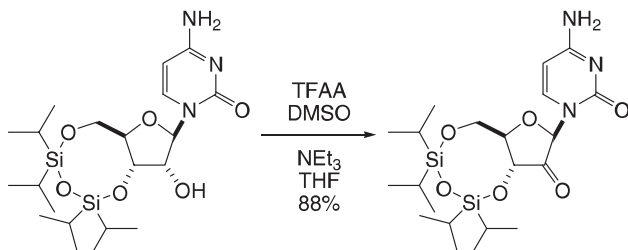


To a solution of oxalyl chloride (2.1 mL, 24 mmol, 1.2 equivalents) in CH₂Cl₂ (30 mL) cooled at –78 °C was added dropwise a solution of dimethylsulfoxide (DMSO 3.3 mL, 21 mmol, 1.1 equivalents) in CH₂Cl₂ (32 mL). After 5 min, a solution of 4-(*tert*-butyldimethylsilyloxy)butan-1-ol (4.0 g, 20 mmol, 1.0 equivalents) in CH₂Cl₂ (26 mL) was added. The reaction mixture was then stirred for 15 min at –78 °C and triethylamine (14.0 mL, 100 mmol, 5.00 equivalents) was added in 1 portion. After 10 min at –78 °C, the mixture was allowed to warm to room temperature and diluted with CH₂Cl₂ (140 mL). The organic layer was successively washed with a saturated aqueous solution of NH₄Cl (30 mL) and brine (2 × 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc: 90/10) afforded 3.88 g (96% yield) of the aldehyde as a colorless oil.

Reference: Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097–2108.

Reference: Ripin, D. H. B.; Abele, S.; Cai, W.; Blumenkopf, T.; Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J.; Teixeira, J.; Vries, T.; Whipple, D. A.; Wilcox, G. *Org. Process Res. Dev.* **2003**, *7*, 115–120.

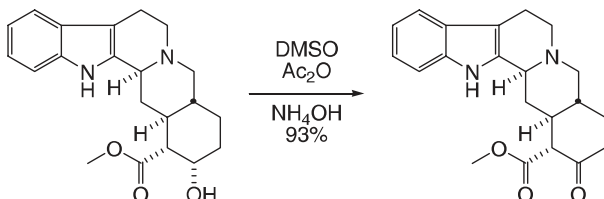
3.1.4.4 With Trifluoroacetic Anhydride



The crude alcohol (5.283 g, 94 area% pure by high performance liquid chromatography, 10.22 mmol) was suspended in dry tetrahydrofuran (24.39 g). Dry DMSO was added dropwise until a homogeneous solution was achieved (4.261 g, 54.6 mmol), and the resulting solution was cooled to $-15\text{ }^{\circ}\text{C}$. Trifluoroacetic anhydride (3.450 g, 16.43 mmol) was added dropwise over 0.25 h. No significant heat liberation was noted. The colorless, homogeneous solution was stirred at $-15\text{ }^{\circ}\text{C}$ for 0.5 h after which dry triethylamine (4.44 g, 43.9 mmol) was added over 0.1 h. During this addition, the reaction temperature increased from $-15\text{ }^{\circ}\text{C}$ to $-10\text{ }^{\circ}\text{C}$. The pale yellow reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was then slowly added to cold water (100 mL) with vigorous stirring. The resulting precipitate was collected by suction filtration, and the filter cake was thoroughly washed with water (50 mL). The filter cake was dried in vacuo leaving a tan, free-flowing powder (4.35 g, 88%).

Reference: Appell, R. B.; Duguid, R. J. *Org. Process Res. Dev.* **2000**, *4*, 172–174.

3.1.4.5 With Acetic Anhydride

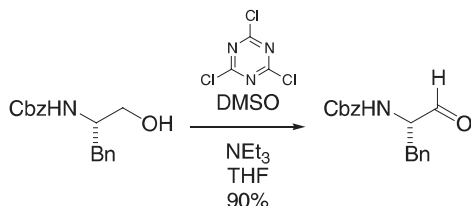


To a mixture of alcohol (886 g, 1.0 equivalents, 2.5 mol) and DMSO (7.55 L) was added acetic anhydride (5.05 L, 21.4 equivalents, 53.4 mol). The mixture was stirred at room temperature for 18 h. The mixture was diluted with ethanol (16.8 L), stirred for 1 h, and diluted with water (4.2 L). Ammonium hydroxide (11 L) was added

while maintaining the temperature at 15–30 °C by cooling and the mixture was then diluted with water (16.8 L). Filtration gave a solid which was washed with water and dried to give the ketone (818 g, 93%) as a tan solid.

Reference: Albright, J. D.; Goldman, L. *J. Org. Chem.* **1967**, 89, 2416–2423.

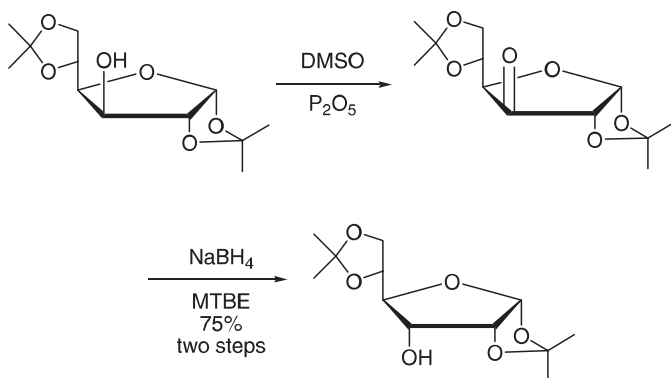
3.1.4.6 With 2,4,6-Trichloro-[1,3,5]-triazine



Dimethylsulfoxide (1.25 mL, 17.6 mmol) was added to a solution of 2,4,6-trichloro-[1,3,5]-triazine (TCT, 0.66 g, 3.6 mmol) in THF (20 mL), stirred, and maintained at –30 °C. After 30 min, *N*-benzyloxycarbonyl-2-amino-3-phenylpropan-1-ol, (0.86 g, 3 mmol) in THF (10 mL) was added slowly at –30 °C with stirring, and after an additional 30 min, NEt₃ (2 mL, 14.3 mmol) was added. After 15 min, the mixture was warmed to room temperature, the solvent evaporated in vacuo, and Et₂O (50 mL) added to the resulting solid. The mixture was quenched with 1 N HCl, and the organic phase washed with 15 mL of a saturated solution of NaHCO₃, followed by brine. The organic layer was dried (Na₂SO₄) and the solvent evaporated to yield pure *N*-benzyloxycarbonyl-2-amino-3-phenylpropionaldehyde (0.77 g, 90%).

Reference: De Luca, L.; Giacomelli, G.; Porcheddu, A. *J. Org. Chem.* **2001**, 66, 7907–7909.

3.1.4.7 With P₂O₅



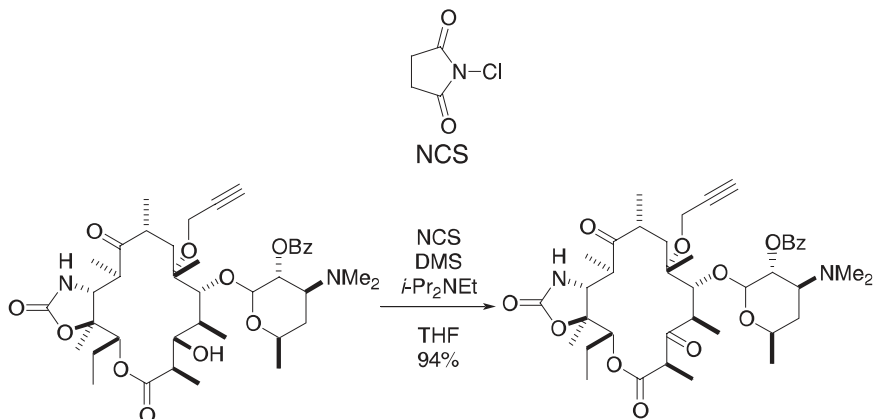
Anhydrous DMSO (650 mL) was cooled to 18–20 °C under nitrogen in a 3-L round-bottomed glass flask. DMSO solidifies at 18 °C and therefore it is important to keep the reaction mixture just above freezing point. To this cold solution was added P₂O₅ (142 g, 1.0 mol, 1 equivalent) in 3 portions under a N₂ atmosphere. The addition of P₂O₅

to DMSO is exothermic, and if the mass temperature exceeds 28 °C, the color darkens and the product will be of inferior quality. The mixture was cooled to 18–20 °C between each addition. After addition of P₂O₅ was completed, the mixture was stirred at 18–25 °C for 10–15 min. 1,2:5,6-Di-*O*-isopropylidene-*D*-glucofuranose (260 g, 1.0 mol) was dissolved in anhydrous DMSO (1.3 L) and added over 30 min (maintaining the temperature at 18–25 °C) to the stirred solution of P₂O₅ in DMSO under a N₂ atmosphere. The resulting solution was heated to 50–55 °C for 3 h. TLC (eluent: CH₂Cl₂:MeOH, 95:5) shows complete conversion of glucofuranose (*R*_f = 0.68) to ulose (*R*_f = 0.81). The reaction mixture was allowed to reach 25–30 °C and was extracted twice with methyl *tert*-butyl ether (MTBE 1.5 and 1 L) in a 6-L separation funnel. The combined MTBE layer (~4 L) was concentrated in vacuo (water-bath temperature set to 40 °C) to approximately 2 L and allowed to reach 25–30 °C. NaBH₄ (24 g, 0.63 mol) was dissolved in water (1 L, 55.6 mol) at 0–10 °C, and the concentrated MTBE layer was added to the aqueous layer over 30 min to keep the temperature at 0–10 °C. TLC (eluent: EtOAc/heptane, 6:4) after 30 min shows full conversion of ulose (*R*_f = 0.53) to 1,2:5,6-di-*O*-isopropylidene-*D*-allofuranose (*R*_f = 0.39). The reaction mixture was allowed to reach 25–30 °C. CH₂Cl₂ (1 L) and water (500 mL) were added, and the layers were separated. The aqueous layer was extracted once more with CH₂Cl₂ (500 mL). The combined organic layers were concentrated in vacuo to an oil which was subsequently dissolved in MTBE (300 mL) and extracted with water (3 × 500 mL). The combined aqueous layers were extracted with CH₂Cl₂ (3 × 500 mL). The combined CH₂Cl₂ layers were dried (Na₂SO₄, 100 g), filtered, and concentrated in vacuo to provide the crude oil. Crystallization from cyclohexane (500 mL), washing of crystals with cold *n*-pentane, and drying hereof in vacuo afforded analytically pure 1,2:5,6-di-*O*-isopropylidene-*D*-allofuranose (191 g, 73%).

Reference: Christensen, S. M.; Hansen, H. F.; Koch, T. *Org. Proc. Res. Dev.* **2004**, 8, 777–780.

3.1.4.8 With *N*-Chlorosuccinimide (Corey–Kim)

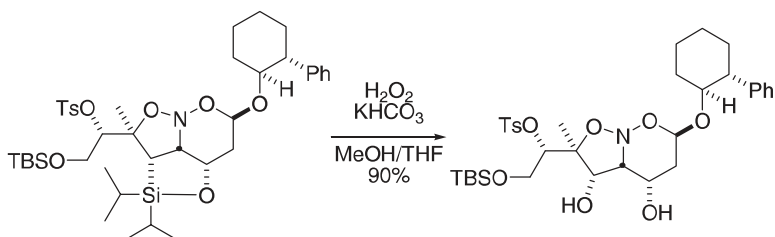
The Corey–Kim reaction is different from DMSO-based oxidations in that the first step is an oxidation of dimethyl sulfide, rather than activation of DMSO. The active oxidizing agent, however, is the chlorosulfonium ion analogous to the Swern oxidation.



The alcohol (1.5 L, 208 g, 280 mmol) in THF is charged to a jacketed flask followed by dimethyl sulfide (37 g, 590 mmol) and diisopropylethylamine (47 g, 364 mmol). The solution is cooled to approximately $-13\text{ }^{\circ}\text{C}$. *N*-Chlorosuccinimide (NCC 71 g, 532 mmol) is dissolved in THF (240 mL) and added to the flask at a rate so as to maintain the internal temperature at -11 to $-13\text{ }^{\circ}\text{C}$. The mixture is then stirred at $-15 \pm 5\text{ }^{\circ}\text{C}$ for 3 h. Isopropyl acetate (3 L) is added followed by 0.5 N NaOH (1.2 L). The mixture is warmed to room temperature and stirred for 1 h. The organic layer is washed with 5% NaCl ($2 \times 600\text{ mL}$) and brine ($2 \times 600\text{ mL}$). The product layer is concentrated under vacuum to obtain, at first, a yellow amorphous solid which when dried under high vacuum turns into a white foam. Slurrying the solid in warm water followed by filtration and drying afforded 196 g (94%) of the 3-ketomacrolide as a white solid after trituration with 10% EtOAc/heptane.

Reference: Kerdesky, F. A. J.; Premchandran, R.; Wayne, G. S.; Chang, S.-J.; Pease, J. P.; Bhagavatula, L.; Lallaman, J. E.; Arnold, W. H.; Morton, H. E.; King, S. A. *Org. Proc. Res. Dev.* **2002**, 6, 869–875.

3.1.5 Fleming Oxidation



To a suspension of the siloxane (760.3 mg, 1.0 mmol) and KHCO_3 (300.2 mg, 3.0 mmol) in a 1:1 mixture of MeOH:THF (10 mL) was added H_2O_2 (0.76 mL, 30% aqueous, 5 mmol). After being heated to $53\text{ }^{\circ}\text{C}$, the mixture was cooled to $0\text{ }^{\circ}\text{C}$ (ice bath), and $\text{Na}_2\text{S}_2\text{O}_3$ (2.80 g, 17.7 mmol, 17.7 equiv) was added in 4 portions over 40 minutes. The mixture was then allowed to warm to room temperature for 2 h until H_2O_2 could not be detected by iodine/starch test paper. The inorganic salts were removed by filtration (Celite) and were washed with ether (25 mL). Removal of the solvent in vacuo provided a colorless oil which was purified twice by column chromatography (SiO_2 , hexane/EtOAc 4/1 \rightarrow 1/1; then hexane/EtOAc 1/2) to provide the diol (595.8 mg, 90%) as a colorless viscous oil.

Reference: Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, 66, 4276–4284.

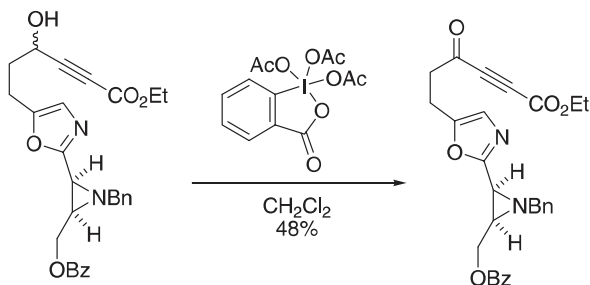
3.1.6 Iodosobenzene-Based Oxidations

3.1.6.1 Dess–Martin periodinane

The Dess–Martin (D–M) oxidation is the method of choice for the oxidation of alcohols bearing sensitive functional groups to the corresponding carbonyl compounds.

The reagent that accomplishes this oxidation is 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one or simply the Dess–Martin periodinane (DMP). Several reviews have been written (see Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273–418; De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272–9279). The preferred preparation of DMP is found in Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

3.1.6.1.1 Standard



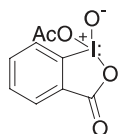
Dess–Martin periodinane (579 mg, 1.37 mmol, for preparation see chapter 1) was added to a solution of oxazole alkyne (214 mg, 0.44 mmol) in 25 mL of CH_2Cl_2 . After 30 min, saturated aqueous NaHCO_3 and excess $\text{Na}_2\text{S}_2\text{O}_3$ were added to the reaction mixture. After the solids were dissolved, the mixture was extracted with CH_2Cl_2 . The combined organic layers were washed with saturated aqueous NaHCO_3 , dried (MgSO_4), and filtered. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (13 mm \times 20 cm) using 2:3 EtOAc/hexane as the eluent, to afford 102 mg (48%) of the ketone as an oil.

Reference: Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498–5505.*

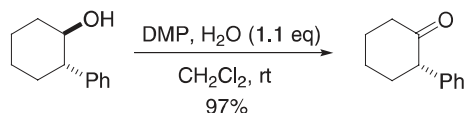
*For substrates with simpler functionalities, the yields are generally in the range of > 90%.

3.1.6.1.2 Schreiber–Meyer Modification

The Dess–Martin oxidation reaction rate is significantly accelerated in the presence of 1.1 equivalents of water (see table below). In addition, excess reagent and water do not appear to increase the reaction rate. In the presence of a controlled amount of water, the Dess–Martin reagent is partially hydrolyzed to an acetoxyiodinane oxide, which is a more reactive oxidant than DMP, thus an increase in the reaction rate is seen. To obtain reproducible results, the DMP should be of high purity prior to the addition of water.



acetoxyiodinane oxide

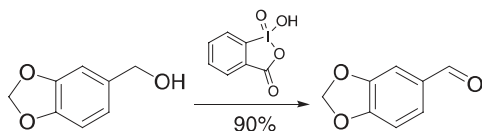


DMP (eq)	H ₂ O (eq)	reaction time (h)	Yield
1.5	0	14	97%
1.5	1.1	0.5	97%
4.9	excess	1.2	98%

Water (10 mL, 0.55 mmol) was solvated in CH₂Cl₂ (10 mL) by drawing the solvent mixture into and expelling it from a disposable pipette several times. The wet CH₂Cl₂ was added slowly via a dropping funnel to a vigorously stirring solution of *trans*-2-phenylcyclohexanol (88.4 mg, 0.502 mmol) and DMP (321 mg, 0.502 mmol) in dry CH₂Cl₂ (3 mL). The clear solution grew cloudy toward the end of the wet CH₂Cl₂ addition, which required 30 min. The mixture was diluted with ether and then concentrated into a few milliliters of solvent by rotary evaporator. The residue was taken up in ether and then washed with a mixture of 10% Na₂S₂O₃ and saturated aqueous NaHCO₃ (1:1, 15 mL), followed by water (10 mL) and brine (10 mL). The aqueous washes were back-extracted with ether (20 mL), and this organic layer was washed with water and brine. The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The crude product was purified by flash chromatography eluting with hexane:EtOAc (20:1 to 10:1) to provide 84.7 mg (97%) of 2-phenylcyclohexanone as a crystalline solid.

Reference: Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

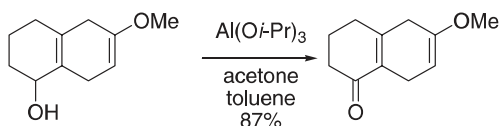
3.1.6.2. 1-Hydroxy-1,2,benziodoxol-3(1H)-one Oxidation



Piperonyl alcohol (0.15 g, 1.00 mmol) was dissolved in EtOAc (7 mL, 0.14 M final concentration), and 1-hydroxy-1,2,benziodoxol-3(1H)-one (IBX 0.84 g, 3.00 mmol) was added. The resulting suspension was immersed in an oil bath set to 80 °C and stirred vigorously open to the atmosphere. After 3.25 h (TLC monitoring), the reaction was cooled to room temperature and filtered through a medium glass frit. The filter cake was washed with 3 × 2 mL of EtOAc, and the combined filtrates were concentrated to yield 0.14 g (90%, > 95% pure by ¹H NMR) of piperonal as a waxy solid.

Reference: More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.

3.1.7 Oppenauer Oxidation

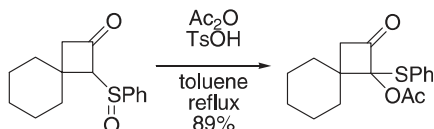


A solution of the alcohol (40.1 g, 0.23 mol) in toluene (180 mL) and acetone (105 mL) containing aluminum isopropoxide (7.7 g, 0.038 mol) was heated to reflux (87 °C) under argon for 4.5 h. The cooled solution was then treated with water (77 mL) and filtered. The aqueous layer was extracted with ether (3 × 250 mL) and the organic layers were combined, washed with water (250 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting oil can be distilled under reduced pressure, but can also be crystallized directly in the refrigerator under argon after addition of petroleum ether (40–60, 50 mL) to give the ketone (34.0 g, 87%) as a white solid.

Reference: Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R.; Cowley, A. *Org. Lett.* **2003**, *5*, 3049–3052.

3.1.8 Pummerer Rearrangement

The Pummerer rearrangement is similar mechanistically to a DMSO-based oxidation, transferring oxidation from a sulfur to a carbon, in this case intramolecularly. Reviews of the Pummerer rearrangement and its variants have been written: (a) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432. (b) Padwa, A.; Waterson, A. G. *Curr. Org. Chem.* **2000**, *4*, 175–203. (c) Padwa, A.; Gunn, Jr., D. E.; Osterhout, M. H. *Synthesis* **1997**, 1353–1377. (d) DeLucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157–405.



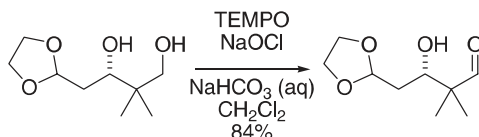
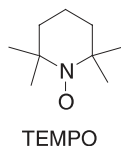
A 10-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the sulfoxide (91 mg, 0.35 mmol) in 3 mL of toluene. Acetic anhydride (0.164 mL, 0.177 g, 1.74 mmol) and *p*-toluenesulfonic acid (2 mg, 0.001 mmol) were added, and the flask was fitted with a reflux condenser and heated at reflux for 1 h. The resulting mixture was cooled to 25 °C and concentrated to afford 113 mg of an oil. Column chromatography on silica gel (gradient elution with 5–10% ethyl acetate–hexane) provided the mixed acetal (94 mg, 89%) as a colorless oil.

Reference: Lawlor, M. D.; Lee, T. W.; Danheiser, R. L. *J. Org. Chem.* **2000**, *65*, 4375–4384.

3.1.9 2,2,6,6-Tetramethylpiperidine 1-oxyl-Catalyzed Oxidation

There are a variety of stoichiometric oxidants that can be used in conjunction with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), including TCCA, iodobenzene diacetate, *meta*-chloroperbenzoic acid (*m*-CPBA), sodium bromite, sodium hypochlorite, and *N*-chlorosuccinimide. TEMPO can be used to oxidize primary alcohols to aldehydes or carboxylic acids, based on reaction conditions. A particularly attractive feature is that the product is usually isolated quite pure after concentration of the organic layer.

The following is typical—the aldehyde is used crude, and therefore the yield for the TEMPO oxidation is combined with the yield in the next step.

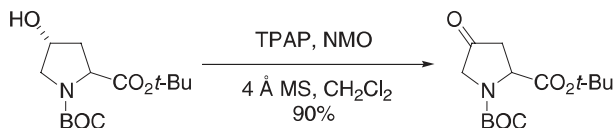


To the diol (735 mg, 3.93 mmol) in CH_2Cl_2 (35 mL) at 0°C was added TEMPO (13 mg, 0.080 mmol) and KBr (47 mg, 0.39 mmol). The mixture was vigorously stirred and NaOCl (approximately 1.5 M in H_2O , 4.0 mL, 5.9 mmol) in 25-mL pH 8.6 buffer (0.5 M NaHCO_3 /0.05 M Na_2CO_3) was added in portions. Additional NaOCl solution was added in portions until the reaction maintained a dark color and TLC analysis indicated the complete consumption of the starting material. The reaction was quenched by addition of MeOH (1 mL) and the aqueous phase extracted with CH_2Cl_2 (3×30 mL). The combined organic solutions were washed with brine (60 mL), dried over Na_2SO_4 , and concentrated under reduced pressure to provide the aldehyde which was used without further purification. The yield for the aldehyde formation and next step (oxime formation) was 84%.

Reference: Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410–6424.

3.1.10 Tetrapropylammonium Perruthenate oxidation

Discovered in 1987, the tetra-*n*-propylammonium perruthenate (TPAP) oxidation is straightforward to run. The reagent is expensive and thus it is used in catalytic amounts and becomes re-oxidized by *N*-methyl morpholine-*N*-oxide. For a review see Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.



Tetrapropylammonium perruthenate (TPAP 63 mg) was added in 1 portion to a stirred mixture of *N*^α-Boc-4-*trans*-hydroxy-*L*-proline (1 g, 3.47 mmol), *N*-methylmorpholine *N*-oxide (0.62 g, 15.6 mmol), and powdered molecular sieves (4 Å, 1.78 g) in CH_2Cl_2 (7 mL) at room temperature under argon. The mixture was stirred for 3 h, filtered, and evaporated in vacuo to give a black residue. The product was purified by

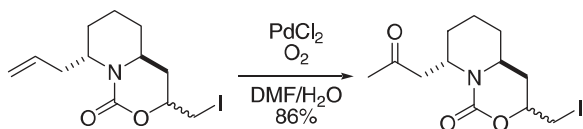
flash column chromatography on silica gel (CH_2Cl_2 :EtOAc = 1:1, v/v) and recrystallized from ether and hexane to give the corresponding ketone (0.9 g, 90%).

Reference: Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66*, 3593–3599.

3.1.11 Wacker Oxidation

The Wacker oxidation oxidizes a terminal olefin to a methyl ketone.

Review: Takars, J. M.; Jiang, X.-t. *Curr. Org. Chem.* **2003**, *7*, 369–396.



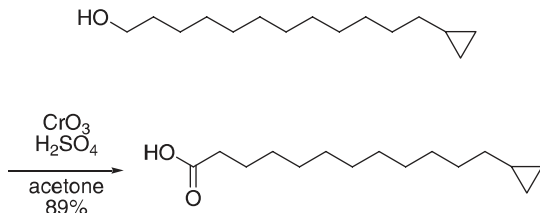
A suspension of PdCl_2 (4 mg, 23.6 μmol) and CuCl (23 mg, 0.23 mmol) in a mixture of DMF and H_2O (7:1, 0.3 mL) was stirred under oxygen atmosphere at room temperature for 1 h. A solution of the olefin (79 mg, 0.24 mmol) in DMF and H_2O (7:1, 0.1 mL) was added to the reaction mixture. After being stirred at room temperature overnight, the mixture was quenched with 20% KHSO_4 and extracted with Et_2O three times. The extracts were successively washed with saturated NaHCO_3 and brine, dried, and evaporated. The residue was purified with chromatography using *n*-hexane:EtOAc (3:1) as eluent to yield the ketone (71 mg, 86%).

Reference: Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459–3462.

3.2 Alcohol to Acid Oxidation State

For a review of chromium–amine complex oxidations, see Luzzio, F. A. *Org. React.* **1998**, *53*, 1–221.

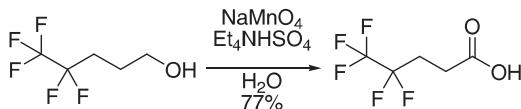
3.2.1 Jones Oxidation



To a stirred solution of the alcohol in acetone (~ 0.1 M) at 0 °C was added Jones reagent (8 N, see chapter 1 for the preparation of this reagent) until the solution remained orange. The reaction was left to stir for 10 min before water (40 mL) was added, and the aqueous layer was extracted with hexanes (4 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO_4 , and concentrated in vacuo to afford the acid at 89% yield.

Reference: Cryle, M. J.; Ortiz de Montellano, P. R.; De Voss, J. J. *J. Org. Chem.* **2005**, *70*, 2455–2469.

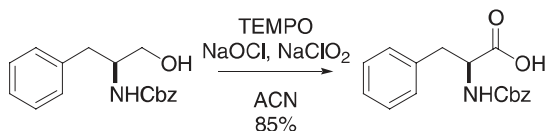
3.2.2 Permanganate Oxidation



4,4,5,5,5-Pentafluoropentanol (1.8 kg, 10.1 mol), tetraethylammonium hydrogen sulfate (18.1 g, 0.08 mole), and water (10.8 L) were added to a 50 L QVF vessel and heated with stirring to 70 °C. Sodium permanganate monohydrate (2.33 kg, 14.14 mol) was dissolved at 20 °C in water (10.8 L) and transferred to a measure vessel. Aqueous sodium permanganate was added in aliquots (approximately 10% at a time) to the stirred aqueous solution of pentafluoropentanol and tetraethylammonium hydrogen sulfate maintaining a temperature of 65–75 °C by the additions of permanganate. The total time taken to add the aqueous permanganate was 2 h 30 min. The reaction was stirred at 70 °C for 4 h when gas chromatography (GC) analysis showed conversion of pentafluoropentanol to pentafluoropentanoic acid to be complete. The reaction mixture was allowed to cool to ambient temperature overnight and screened through a Celite filter aid (500 g) to remove precipitated manganese dioxide. The isolated manganese dioxide was washed with hot water (60 °C, 18 L). The combined aqueous layers were extracted with methyl *tert*-butyl ether (5.4 L), and the upper organic layer was discarded. The aqueous layer was acidified with concentrated sulfuric acid (320 mL) to pH 1. The *lower* organic layer which separated was retained. The aqueous layer was extracted with methyl *tert*-butyl ether (2 × 5.4 L), and the upper organic layers were combined with the initial, lower organic layer. The combined organic layers were washed with water (5.4 L) and dried with anhydrous sodium sulfate. The organic solvent was removed in vacuo at 50 °C and the residue distilled to give the acid as a pale pink, low-melting solid (1.49 kg, 77%).

Reference: Mahmood, A.; Robinson, G. E.; Powell, L. *Org. Proc. Res. Dev.* **1999**, *3*, 363–364.

3.2.3 2,2,6,6-Tetramethylpiperidine 1-oxyl-Catalyzed Oxidation



A mixture of the alcohol (11.4g, 40 mmol), TEMPO (436 mg, 2.8 mmol), MeCN (200 mL), and sodium phosphate buffer (150 mL, 0.67 M, pH = 6.7) is heated to 35 °C. Sodium chlorite (NaClO₂, 9.14 g 80%, 80.0 mmol in 40 mL water) and dilute bleach (1.06 mL 5.25% NaOCl diluted into 20 mL, 2.0 mol %) are then added

simultaneously over 2 h. (Caution! Do not mix bleach and NaClO_2 before being added to the reaction mixture.) The mixture is stirred at $35\text{ }^\circ\text{C}$ until the reaction is complete and then cooled to room temperature. Water (300 mL) is added, and the pH is adjusted to 8.0 with 2.0 N NaOH (48 mL). The reaction is quenched by pouring into cold ($0\text{ }^\circ\text{C}$) Na_2SO_3 solution (12.2 g in 200 mL water) maintained at $< 20\text{ }^\circ\text{C}$. The pH of the aqueous layer should be 8.5–9.0. After stirring for 0.5 h at room temperature, MTBE (200 mL) is added. The organic layer is separated and discarded. More MTBE (300 mL) is added, and the aqueous layer is acidified with 2.0 N HCl (100 mL) to pH 3–4. The organic layer is separated, washed with water ($2 \times 100\text{ mL}$) and brine (150 mL), and then concentrated to give the crude Cbz-phenylalanine (10.2 g, 85%) with no detectable racemization.

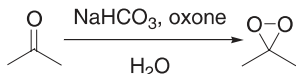
Reference: Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschäen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.

3.3 Olefin to Diol

3.3.1 Dimethyl Dioxirane

Caution: Dioxiranes are usually volatile peroxides and thus should be handled with care by observing all safety measures. The preparations and oxidations should be carried out in a hood with good ventilation. *Inhalation and direct exposure to skin must be avoided!* There is an excellent review of dioxirane (DMDO) chemistry in Adam, W.; Saha-Möller, C. R.; Zhao, C.-G. *Org. React.* **2002**, *61*, 219–516.

Preparation of Dimethyl Dioxirane

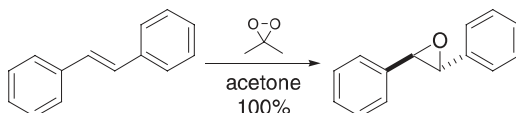


A 2-L, three-necked, round-bottomed flask containing a mixture of water (80 mL), acetone (50 mL, 0.68 mol), and sodium bicarbonate (96 g) is equipped with a magnetic stir bar and a pressure equalizing addition funnel containing water (60 mL) and acetone (60 mL, 0.82 mol). A solid addition flask containing Oxone (180 g, 0.29 mol) is attached to the reaction vessel via a rubber tube. An air condenser (20 cm length) loosely packed with glass wool is attached to the reaction vessel. The outlet of the air condenser is connected to a 75×350 -mm Dewar condenser filled with dry ice–acetone that is connected to a receiving flask (100 mL) cooled in a dry ice–acetone bath. The receiving flask is also connected in series to a second dry ice–acetone cold trap, a trap containing a potassium iodide solution, and a drying tube. A gas inlet tube is connected to the reaction flask and a stream of nitrogen gas is bubbled through the reaction mixture. The Oxone is added in portions (10–15 g) while the acetone–water mixture is simultaneously added dropwise. The reaction mixture is stirred vigorously throughout the addition of reagents (approximately 30 min). A yellow solution of dimethyldioxirane in acetone collects in the receiving flask. Vigorous stirring is continued for an additional 15 min while a slight vacuum (about 30 mm, water aspirator) is applied to the cold trap. The yellow dioxirane solution (62–76 mL) is dried

over sodium sulfate (Na_2SO_4), filtered, and stored in the freezer (-25°C) over Na_2SO_4 . The dioxirane content of the solution is assayed using phenyl methyl sulfide and the gas-liquid chromatography (GLC) method. Generally, concentrations in the range of 0.07–0.09 M are obtained.

Reference: Murray, R. W.; Singh M. *Org. Syn.* **1998**, *Coll. Vol. IX*, 288–293.

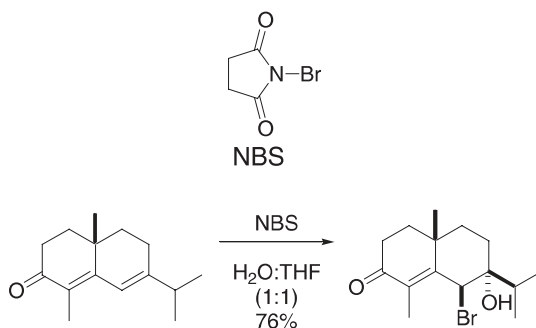
Epoxidation with Dimethyl Dioxirane



To a magnetically stirred solution of *trans*-stilbene (0.724 g, 4.02 mmol) in 5 mL of acetone in a 125-mL stoppered Erlenmeyer flask was added a solution of DMDO in acetone (0.062 M, 66 mL, 4.09 mmol) at room temperature (about 20°C). The progress of the reaction was followed by GLC analysis, which indicated that *trans*-stilbene was converted into the oxide in 6 h. Removal of the excess acetone on a rotary evaporator (20°C , 15 mm Hg) afforded a white crystalline solid. The solid was dissolved in CH_2Cl_2 (30 mL) and dried over anhydrous Na_2SO_4 . The drying agent was removed by filtration and washed with CH_2Cl_2 . The solution was concentrated on a rotary evaporator, and the remaining solvent was removed (20°C , 15 mmHg) to give an analytically pure sample of the oxide (0.788 g, 100%).

Reference: Murray, R. W.; Singh M. *Org. Syn.* **1998**, *Collective Volume 9*, 288–293.

3.3.2 Halogenation with *N*-bromosuccinimide

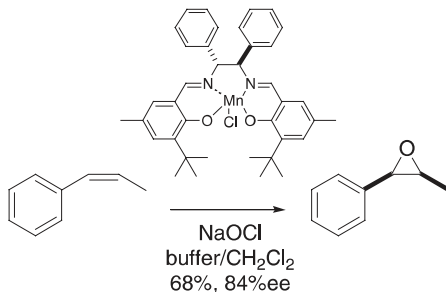


To a solution of the olefin (500 mg, 2.29 mmol, 1.0 equivalents) in THF and water (50 mL, 1:1 v:v) was added *N*-bromosuccinimide (NBS 2 g, 28.1 mmol, 12.3 equivalents) at room temperature and the mixture was stirred for 22 h. The reaction mixture was diluted with water (50 mL) and extracted with Et_2O (2×100 mL), and the organic layer was washed with water (3×50 mL), dried (MgSO_4), and concentrated. Crystallization of the residue from ether/petroleum ether gave the bromohydrin as colorless crystals (550 mg, 76%).

Reference: Kutney, J. P.; Singh, A. K. *Can. J. Chem.* **1982**, *60*, 1842–1846.

3.3.3 Jacobsen–Katsuki Epoxidation

Jacobsen–Katsuki epoxidation works best with *cis*-styrene type olefins.

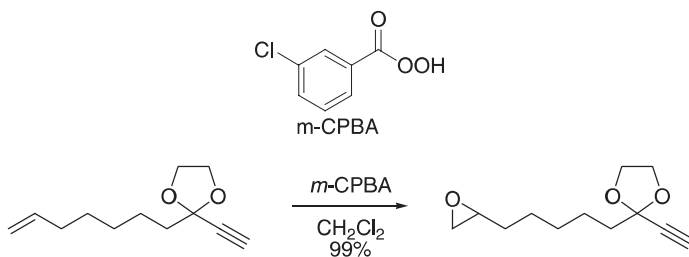


A solution of 0.05 M Na_2HPO_4 (10.0 mL) was added to a 25-mL solution of undiluted commercial household bleach (Clorox). The pH of the resulting buffered solution (0.55 M in NaOCl) was adjusted to pH 11.3 by addition of a few drops of 1 M NaOH solution. This solution was cooled to 0 °C and then added at once to a 0 °C solution of the manganese catalyst (260 mg, 0.4 mmol) and *cis*-*o*-methylstyrene (1.18 g, 10 mmol) in 10 mL of CH_2Cl_2 . The two-phase mixture was stirred at room temperature, and the reaction progress was monitored by TLC. After 3 h, 100 mL of hexane was added to the mixture and the brown organic phase was separated, washed twice with 100 mL of H_2O and once with 100 mL of saturated NaCl solution, and then dried (Na_2SO_4). After solvent removal, the residue was purified by flash chromatography on silica gel to afford the epoxide (0.912 g, 68%). The *ee* of the epoxide was determined to be 84% by ^1H NMR analysis in the presence of $\text{Eu}(\text{hfc})_3$.

Reference: Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296–2298.

3.3.4 Oxidation of Olefin with *meta*-Chloroperbenzoic Acid

meta-Chloroperbenzoic acid (*m*-CPBA) is known to decompose at elevated temperatures (starting at approximately 97 °C) and therefore reactions with *m*-CPBA should be run below 50 °C (see Kubota, A; Takeuchi, H. *Org. Proc. Res. Dev.* **2004**, *8*, 1076–1078).



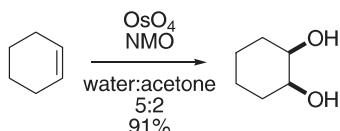
A solution of *m*-CPBA (10.4 g, 70%, 42.3 mmol) in CH_2Cl_2 (80 mL) was added to a solution of the olefin (3.73 g, 19.2 mmol) in CH_2Cl_2 (40 mL). The reaction was stirred for 12 h and cooled to 0 °C. 2-Methyl-2-butene (8.1 mL, 76.9 mmol) was

added (to quench the reaction) and the resulting mixture was slowly warmed to 25 °C and stirred for 4 h to consume excess *m*-CPBA. The mixture was diluted with saturated NaHCO₃ and extracted by CH₂Cl₂. The combined CH₂Cl₂ extracts were washed with saturated Na₂SO₃ (30 mL), 5% NaOH (2 × 30 mL), and water (2 × 30 mL), dried (MgSO₄), and concentrated to afford the crude epoxide. Flash chromatography on silica gel (10:1 hexanes/EtOAc) yielded 4.03 g (99%) of pure epoxide as a colorless oil.

Reference: Snider, B. B.; Zhou, J. *Org. Lett.* **2006**, 8, 1283–1286.

3.3.5 Osmium Tetroxide Dihydroxylation

Osmium tetroxide is a highly toxic reagent. It is volatile and can cause blindness.

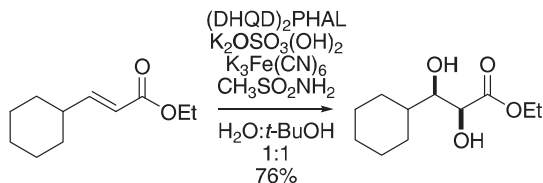


To a mixture of *N*-methylmorpholine-*N*-oxide·2H₂O (18.2 g, 155 mmol), water (50 mL), acetone (20 mL), and osmium tetroxide (80 mg) in *t*-butanol (8 mL) was added distilled cyclohexene (10.1 mL, 100 mmol). The reaction was slightly exothermic initially and was maintained at room temperature with a water bath. The reaction was complete after stirring overnight at room temperature under nitrogen. A slurry of 1 g of sodium hydrosulfite, 12 g of magnesium silicate (magnesol), and 80 ml of water was added, and the magnesol was filtered. The filtrate was neutralized to pH 7 with 1 N H₂SO₄, the acetone was evaporated under vacuum, and the pH was further adjusted to pH 2. The solution was saturated with NaCl and extracted with EtOAc. The aqueous phase was concentrated by azeotroping with *n*-butanol and further extracted with ethyl acetate. The combined ethyl acetate layers were dried and evaporated, yielding 11.2 g (96.6%) of crystalline solid. Recrystallization from ether provided 10.6 g (91%) of *cis*-1,2-cyclohexanediol, mp 95–97°C.

Reference: Van Rhenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 17, 1973–1976.

3.3.6 Sharpless Asymmetric Dihydroxylation

Commercially available asymmetric dihydroxylation mixtures are AD-mix α (chiral ligand (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, and K₂OsO₄·2H₂O) and AD-mix β (chiral ligand (DHQD)₂PHAL, K₃Fe(CN)₆, K₂CO₃, and K₂OsO₄·2H₂O). Reviews: (a) Noe, M. C.; Letavic, M. A.; Snow, S. L. *Org. React.* **2005**, 66, 109–625. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483–2547.

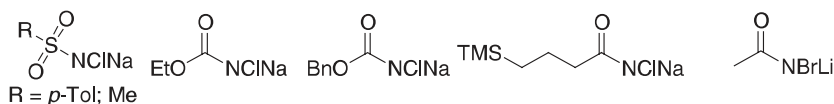


To a mixture of (DHQD)₂PHAL (800 mg, 1.03 mmol), K₃Fe(CN)₆ (101.5 g, 308 mmol), and K₂CO₃ (42.6 g, 308 mmol) in H₂O:*t*-BuOH (1:1, 1000 mL) cooled to 0 °C was added K₂OsO₄(OH)₄ (158 mg, 0.411 mmol) followed by methanesulfonamide (9.8 g, 102.8 mmol). After stirring for 10 min at 0 °C, 3-cyclohexylacrylic acid ethyl ester (18.7 g, 102.8 mmol) was added in 1 portion. The reaction mixture was stirred at 0 °C for 18 h and then quenched with sodium sulfite (154 g). Stirring was continued for 1 h at room temperature and the solution extracted with CH₂Cl₂ (3 × 300 mL). The organic layer was washed with KOH (2 N), dried over MgSO₄, and evaporated to give the diol. Crystallization in heptane afforded 17.0 g (76%) of the diol as a white solid.

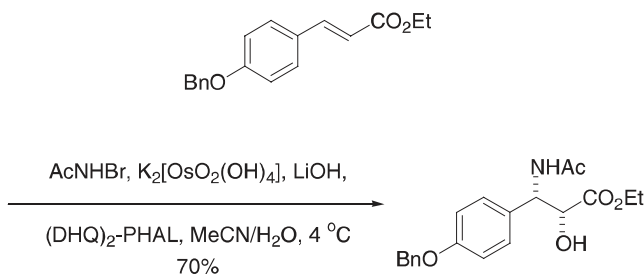
Reference: Alonso, M.; Santacana, F.; Rafecas, L.; Riera, A. *Org. Proc. Res. Dev.* **2005**, 9, 690–693.

3.3.7 Sharpless Asymmetric Aminohydroxylation

The nitrogen sources for the aminohydroxylation are shown below.



Sharpless, along with Noyori and Knowles, won the Nobel Prize in 2001 for his contribution to the field of asymmetric synthesis.



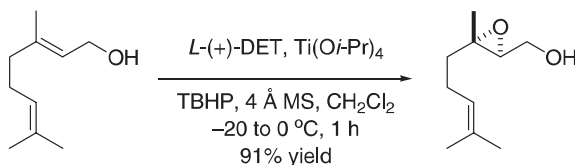
In 335 mL of an aqueous solution of LiOH·H₂O (7.59 g, 181 mmol), K₂[OsO₂(OH)₄] (2.6 g, 7.1 mmol, 4 mol %) was dissolved with stirring. After addition of *t*-BuOH (665 mL), (DHQ)₂PHAL (6.91 g, 8.87 mmol, 5 mol %) was added, and the mixture was stirred for 10 min to give a clear solution. The solution was then diluted with additional water (665 mL) and immersed in a cooling bath set to 0 °C. A solution of the cinnamate (50.0 g, 177 mmol) in acetonitrile (335 mL) was then added to the mixture, followed by addition of *N*-bromoacetamide (26.91 g, 195.1 mmol) in one lot, and the mixture was vigorously stirred between 0 and 5 °C. After stirring for 24 h, the reaction mixture was treated with Na₂SO₃ (89 g) and stirred at room temperature for 30 min, and ethyl acetate (1 L) was added. The organic layer was separated, and the water layer was extracted three times with EtOAc. The combined organic extracts were washed with brine and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the crude product was purified by flash chromatography on silica gel.

Elution with EtOAc:hexane (1:1) afforded 10% of the diol by-product followed by 40 g (70%) of the amino alcohol as a white crystalline solid.

Reference: Reddy, S. H. K.; Lee, S.; Datta, A.; Georg, G. I. *J. Org. Chem.* **2001**, *66*, 8211–8214.

3.3.8 Katsuki–Sharpless Asymmetric Epoxidation

The Katsuki–Sharpless asymmetric epoxidation is one of the first predictably enantioselective oxidations. For reviews see (a) Katsuki, T.; Martin, V. *Org. React.* **1996**, *48*, 1–299. (b) Pfenniger, D. S. *Synthesis* **1986**, 89–116.



L-(+)-DET = *L*-(+)-Diethyl tartrate;

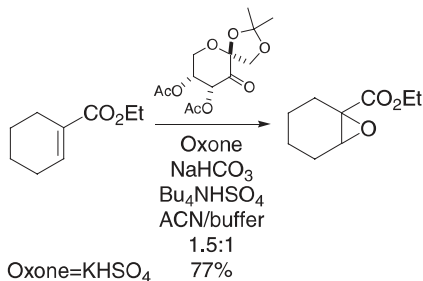
TBHP = *tert*-butylhydroperoxide.

A mixture of activated 4 Å molecular sieves (1.80 g, 15–20 wt% based on geraniol) and CH₂Cl₂ (100 mL) was cooled to –10 °C. *L*-(+)-Diethyl tartrate (1.00 g, 4.8 mmol), titanium(IV) isopropoxide (0.91 g, 3.2 mmol), and *tert*-butylhydroperoxide (19.4 mL, 97 mmol, 5.0 M in CH₂Cl₂) were added sequentially. After 10 min of stirring, the mixture was cooled to –20 °C, and freshly distilled geraniol (10.0 g, 65 mmol, in 10 mL of CH₂Cl₂) was added dropwise over 15 min. After 45 min of stirring at –20 to –15 °C, the mixture was warmed to 0 °C. After an additional 5 min of stirring at 0 °C, the mixture was quenched sequentially with water (20 mL) and 4.5 mL of 30% aqueous NaOH saturated with solid NaCl. After 10 min of vigorous stirring, the reaction mixture was partitioned between CH₂Cl₂ and water. The combined organic extract was dried (MgSO₄) and then filtered through Celite to give a clear colorless solution. Concentration followed by bulb to bulb distillation [bp (bath) = 100 °C at 0.1 mm Hg] gave the epoxide as a colorless oil (10.3 g, 91%).

Reference: Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423–3426.

3.3.9 Shi Epoxidation

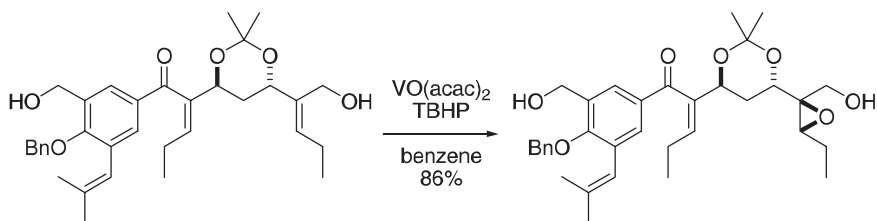
For a review on the scope of this reaction, and impact of reaction conditions on the course of the reaction, see Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496.



Aqueous $\text{Na}_2(\text{EDTA})$ (1×10^{-4} M, 2.5 mL) and Bu_4NHSO_4 (10 mg, 0.03 mmol) were added to a solution of the olefin (77 mg, 0.5 mmol) in acetonitrile (2.5 mL) with vigorous stirring at 0°C . A mixture of oxone (1.5 g, 2.5 mmol) and NaHCO_3 (0.65 g, 7.75 mmol) was pulverized, and a small portion of this mixture was added to the reaction mixture to bring the pH to > 7 . Then a solution of the ketone (38 mg, 0.125 mmol) in ACN (1.25 mL) was added. The rest of the Oxone and NaHCO_3 was added to the reaction mixture portionwise over 4.5 h. On stirring for an additional 7.5 h at 0°C and 12 h at room temperature, the resulting mixture was diluted with water and extracted with EtOAc. The combined extracts were washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography to give the epoxide as a colorless oil (65 mg, 77% yield, 93% *ee* by GC, absolute stereochemistry not determined unambiguously).

Reference: Wu, X.-Y.; She, X.; Shi Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792–8793.

3.3.10 $\text{VO}(\text{acac})_2$, *t*-BuOOH Oxidation of Allylic Alcohols



To a solution of allylic alcohol (688 mg, 1.05 mmol) in benzene (25 mL) was added vanadyl acetylacetonate (58 mg, 0.22 mmol) and *tert*-butylhydrogenperoxide as a 1.0 M solution in toluene (2.2 mL, 2.2 mmol). The resulting blood-red slurry was stirred rapidly for 2 h, quenched with saturated sodium thiosulfate (25 mL), and the organic layer collected and dried over sodium sulfate. The solvents were removed under reduced pressure and the resulting brown residue was purified by flash chromatography (45% EtOAc/hexanes) to afford the epoxide as a 1.2:1 mixture of diastereomers (605 mg, 86%).

Reference: Shotwell, J. B.; Krygowski, E. S.; Hines, J.; Koh, B.; Huntsman, E. W. D.; Choi, H. W.; Schneekloth, J. S., Jr.; Wood, J. L.; Crews, C. M. *Org. Lett.* **2002**, *4*, 3087–3089.

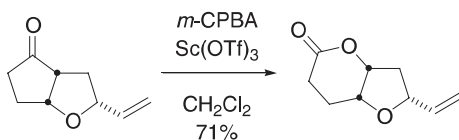
3.4 Aldehyde to Acid Oxidation State

3.4.1 Baeyer–Villiger Oxidation

Reviews: (a) Mihovilovic, M. D.; Rudroff, F.; Grotzl, B. *Curr. Org. Chem.* **2004**, *8*, 1057–1069 (enantioselective). (b) Strukul, G. *Angew. Chem. Int. Ed.* 1998, *37*, 134–142 (enantioselective). (c) Krow, G. R. *Org. React.* **1993**, *43*, 251–798 (traditional).

The reaction has traditionally been run with 90% trifluoroacetic peracid or 90% H_2O_2 , but the explosive nature of these reagents, as well as the availability of safer

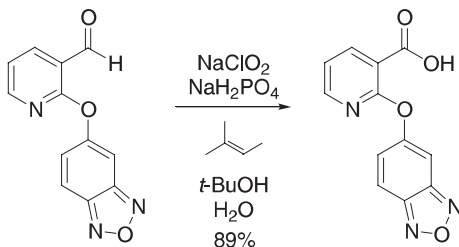
alternatives, makes their use inadvisable. The group better able to stabilize a positive charge will be the group to migrate.



To a stirred solution of the ketone (200 mg, 1.31 mmol, 1 equivalent) in CH_2Cl_2 (10 mL) at room temperature was added scandium triflate (32 mg, 0.066 mmol, 0.05 equivalents). After stirring for 10 min, *m*-chloroperoxybenzoic acid (450 mg, 2.63 mmol, 2 equivalents) was added. The reaction was stirred for 3 h and quenched with Na_2SO_3 -doped saturated NaHCO_3 solution. After stirring for 10 min, the layers were separated and the combined organics were washed with saturated NaCl , dried over MgSO_4 , vacuum filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (30% EtOAc/hexanes) to yield 158 mg (71%) of the lactone as a clear oil.

Reference: Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, 7, 3493–3495.

3.4.2 Sodium Chlorite Oxidation

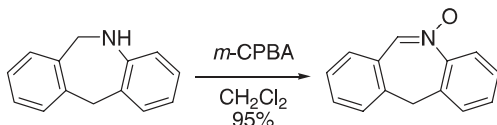


A clean vessel was charged with water (20 gal), sodium hydrogen phosphate (25 kg, 183.5 mol), 5-(2-formyl-pyridin-2-yloxy)-benz[1,2,5]oxadiazole (15 kg, 62 mol), and *tert*-butyl alcohol (99 gal). The mixture was stirred for 1 h, and then a solution of sodium chlorite (34 kg, 379 mol) in water (40 gal) was added at a rate to keep the internal temperature < 35 °C. The reaction was quenched with a solution of sodium bisulfite (90 kg) in water (99 gal) at a rate to keep the temperature < 25 °C. The *tert*-butyl alcohol was stripped at slightly below atmospheric temperature (to control the bisulfite fumes released) until the head temperature was 80 °C. After cooling to 20 °C, the solids were stirred for 5.5 h, filtered, and washed with water (10 gal). The wet cake was reslurried in water (30 gal) for 1 h at 80 °C. After cooling to 20–25 °C, the solids were slurried for 2 h, filtered, and washed with water (5 gal). The solids were dried in a vacuum oven at 45–55 °C until the KF was < 0.5%, yielding 14.3 kg (89%) of the desired product.

Reference: Ruggeri, S. G.; Bill, D. R.; Bourassa, D. E.; Castaldi, M. J.; Houck, T. L.; Ripin, D. H. B.; Wei, L.; Weston, N. *Org. Process Res. Dev.* **2003**, *7*, 1043–1047.

3.5 Heteroatom Oxidations

3.5.1 Amine to Nitron



Solution A: The amine (68.3 g, 0.35 mol) was dissolved in 1750 mL of CH₂Cl₂ and cooled to 5 °C (ice bath).

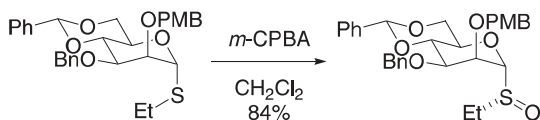
Solution B: *m*-CPBA (175.1 g, 0.7 mol; containing 24 wt % water and 7 wt % 3-Cl-benzoic acid) was dissolved in 1750 mL of CH₂Cl₂ and cooled to 5 °C (ice bath).

Solution B (except for the water) was added dropwise to solution A over a period of 45 min at 5–10 °C. The mixture was stirred for another 30 min at 10–15 °C. The oxidation was considered complete when the amine content was less than 6%. The reaction mixture was washed with 750 mL of a 10% Na₂CO₃ solution. The layers were separated, and the organic phase was vigorously stirred with 280 mL of 10% aqueous Na₂SO₃ solution for 1 h. (*Note: the aqueous layer should be treated with Na₂SO₃ before disposal.*) The organic layer was evaporated to half its volume, and 1050 mL of toluene was added. This mixture was heated to 80 °C while distilling off the remaining CH₂Cl₂. The mixture was kept at 80 °C until the reflux stopped. The resulting toluene solution (HPLC 95.5%) was processed in the cycloaddition step without purification.

Reference: Stappers, F.; Broeckx, R.; Leurs, S.; Van Den Bergh, L.; Agten, J.; Lambrechts, A.; Van den Heuvel, D.; De Smaele, D. *Org. Proc. Res. Dev.* **2002**, *6*, 911–914.

3.5.2 Sulfide to Sulfoxide Oxidation

A variety of reagents will accomplish this oxidation, but the stoichiometry and temperature must be carefully controlled to avoid over-oxidation (see, for example, Uemura, S. Oxidation of Sulfur, Selenium and Tellurium. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 7, 758–769 and Kowalksi, P.; Mitka, K.; Ossowska, K.; Kolarska, Z. *Tetrahedron*, **2005**, *61*, 1933–1953).

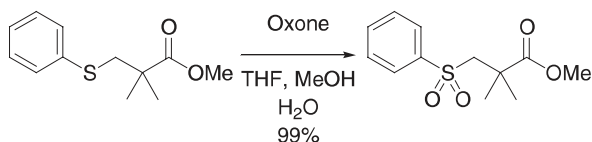


To a stirred solution of the sulfide (8.11 g, 15.5 mmol) in CH_2Cl_2 (150 mL) was added 90% *m*-CPBA (2.97 g, 15.5 mmol) at -78°C . The reaction mixture was stirred at -78°C for 4 h, warmed to -20°C , and quenched with saturated aqueous Na_2CO_3 . The solution was washed with saturated aqueous Na_2CO_3 , brine, and dried over anhydrous Na_2SO_4 . Removal of solvent and recrystallization from EtOAc and hexane gave the sulfoxide (7.00 g, 13.0 mmol, 84%).

Reference: Crich, D.; Banerjee, A.; Yao, Q. *J. Am. Chem. Soc.* **2004**, *126*, 14930–14934.

3.5.3 Sulfide to Sulfone Oxidation

Similar conditions can be used to oxidize sulfoxides to sulfones.

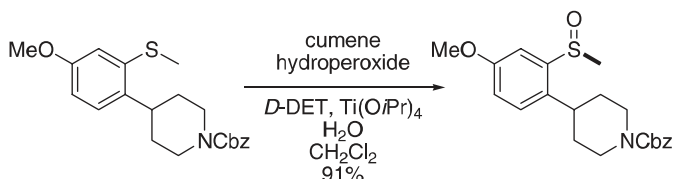


To a vigorously stirred solution of the sulfide (7.47 g, 33.3 mmol) in THF (22 mL), MeOH (22 mL), and H_2O (22 mL) at 0°C was added Oxone (57.3 g, 93.2 mmol) portionwise. After 5 min at 0°C , the white suspension was warmed to room temperature and stirred for 30 min. The reaction was poured into H_2O (500 mL) and extracted with CH_2Cl_2 (3×150 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated to give the sulfone (8.54 g, > 99% yield) as a white solid.

Reference: Voight, E. A.; Roethle, P. A.; Burke, S. D. *J. Org. Chem.* **2004**, *69*, 4534–4537.

3.5.4 Kagan Asymmetric Sulfur Oxidation

Considerable advances have been made recently towards the enantioselective oxidation of sulfides to sulfoxides. The reactions can be technically challenging but high enantioselectivities can be achieved.



(–)-Diethyl *D*-tartrate (12.04 g, 58.4 mmol) was dissolved in CH_2Cl_2 (109 mL) and the water content of the resulting clear solution determined by Karl Fischer titration. This solution was transferred to a thoroughly dried reaction vessel containing the sulfide (10.85 g, 29.2 mmol) under an inert atmosphere and stirred to give a pale yellow solution. Titanium isopropoxide (8.96 mL, 29.2 mmol) was added, followed by distilled water (0.50 mL, 27.8 mmol, 0.95 equivalents, to bring the total amount of water to 1.00 equivalents). The reaction mixture was cooled to -15°C and cumeme

hydroperoxide (5.56 mL of an 80% w/w solution, 30.7 mmol) added dropwise over 60 min, maintaining the temperature at $-15\text{ }^{\circ}\text{C}$. After 5–16 h the reaction was complete, and a solution of 3 M HCl (60 mL, 200 mmol, 6.84 equivalents) was added, allowing the mixture to warm to $20\text{ }^{\circ}\text{C}$. (*Note: This addition is strongly exothermic!*) This was stirred at $20\text{ }^{\circ}\text{C}$ for 1 h after which the pale yellow lower CH_2Cl_2 phase was separated from the bright orange upper aqueous phase and returned to the reaction vessel. A solution of 4 M NaOH (66 mL, 264 mmol, 9.04 equivalents) was added to the organic phase and the mixture heated to $40\text{ }^{\circ}\text{C}$ for 1 h before cooling back to $20\text{ }^{\circ}\text{C}$. (*Note: This addition can be exothermic at first if there is residual HCl left in the organic phase.*) The phases were separated, and the lower CH_2Cl_2 phase was washed twice with water (66 mL each, 6.1 volumes) before concentration under reduced pressure to give the crude sulfoxide compound as a pale yellow oil (10.34 g, 91.4% yield, 93.6% ee).

Reference: Bowden, S. A.; Burke, J. N.; Gray, F.; McKown, S.; Moseley, J. D.; Moss, W. O.; Murray, P. M.; Welham, M. J.; Young, M. J. *Org. Proc. Res. Dev.* **2004**, *8*, 33–44.