Imperial College London	Department of Chemistry Third Year Advanced Practical Organic Chemistry

Experiment 7

Catalytic Asymmetric Dihydroxylation of Alkenes

Imperial College London	Department of Chemistry Third Year Advanced Practical Organic Chemistry

EXPERIMENT 7:

CATALYTIC ASYMMETRIC DIHYDROXYLATION OF ALKENES

Aims of the experiment

To prepare an enantiomerically enriched 1,2-diol using Sharpless' catalytic asymmetric dihydroxylation procedure, and to estimate the enantiomeric purity of the material you obtain.

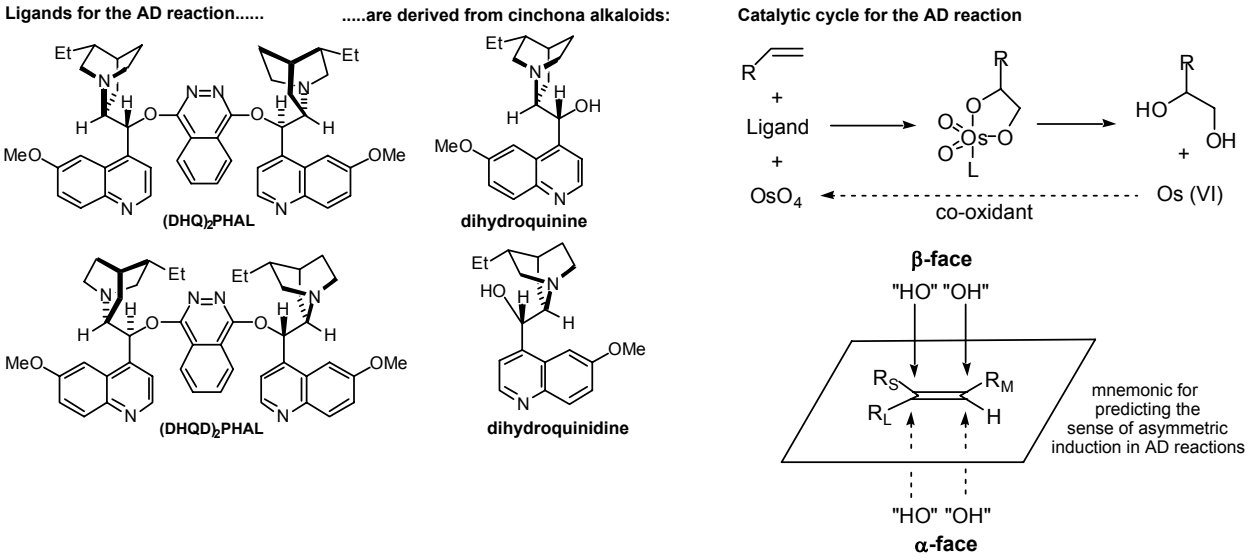
Techniques used/learned:

Asymmetric catalysis; recrystallisation; measurement of optical rotations.

Introduction

The need to prepare compounds such as drug candidates in enantiomerically pure form means that the organic chemist needs at his/her disposal a wide range of small chiral organic molecules from which to construct their target molecules. One source of these chiral starting materials (sometimes called 'chirons') is nature itself. However, such a 'chiral pool' supply is necessarily limited - the pool may not contain a particular type of starting material, or it may only be available as the opposite enantiomer to the one needed.

Thus, chemists have begun to devise methods for the synthesis of ***both*** enantiomers of useful small molecules from achiral starting materials.[1] This can be achieved through temporary attachment of a chiral auxiliary to the achiral material (the synthesis is then diastereoselective, rather than enantioselective); use of chiral reagents; or the use of chiral catalysts. The latter approach,[2] though the less well developed of the three, is potentially the most interesting, since a small amount of chiral catalyst can produce large amounts of enantiomerically enriched product.



One of the pioneers of this field has been Professor K Barry Sharpless of the Scripps Research Institute. The eponymous epoxidation of allylic alcohols[3] was the first practical and reliable catalytic asymmetric reaction, and more recently he has turned his attention to the asymmetric osmium mediated dihydroxylation[4] (see scheme) and aminohydroxylation[5] of alkenes, using modified cinchona alkaloids as chiral ligands for osmium. It came as little surprise when Professor Sharpless was awarded a share of the 2001 Nobel Prize in Chemistry!

The asymmetric dihydroxylation work arose from the observation by Professor Bill Griffith of this department that tertiary amines, and bicyclic tertiary amines in particular, accelerate the rate of osmium tetroxide dihydroxylation of alkenes by co-ordination to the metal.[6] The ligand systems shown above are the result of many years of experimentation by the Sharpless group and others. Note that, since natural alkaloids are only available in one enantiomeric form, the ligands which give rise to opposite enantiomers in the dihydroxylation are derived from two different alkaloids. The ligands are thus not enantiomers of each other, but are termed 'pseudoenantiomeric' by Sharpless.

In this experiment, you will be using the commercial AD-mix - a powder containing an osmium source ($K_2OsO_2(OH)_4$), the chiral ligand ($[DHQ]_2PHAL$ for AD-mix α, $[DHQD]_2PHAL$ for AD-mix β), a co-oxidant for regeneration of osmium (VIII) ($K_3Fe(CN)_6$ and a pH buffer (K_2CO_3) - to perform the dihydroxylation of one of several alkenes.

HAZARD DATA - READ THIS BEFORE GOING ANY FURTHER!

AD-MIX α or β
AD-MIXES contain approx. the following chemicals per 4.2g loading (as used here):
Potassium osmate: 4.4mg
$(DHQ)_2PHAL$ or $(DHQD)_2PHAL$: 23mg
Potassium ferricyanide: 2.94g
Potassium carbonate: 1.24g

POTASSIUM OSMATE:

TOXIC
SEVERE IRRITANT TO EYES AND RESPIRATORY SYSTEM

Violet solid, m.pt. decomposes. Soluble in water, with slow decomposition. OES 0.002 mg/m^3 (Os)

Toxic effects: Toxic by ingestion, or in contact with skin/eyes. Severe irritant to eyes and respiratory system. If ingested can cause abdominal pain and vomiting, and irritation of the respiratory system with coughing. Eye contact results in severe pain, blurred vision and possible blindness.
Hazardous reactions: Incompatible with strong oxidising materials.
Fire hazards: Gives off toxic fumes in fire.
Spillage & disposal: Absorb onto inert material and package in containers for disposal.

POTASSIUM FERRICYANIDE (POTASSIUM HEXACYANOFERRATE(III)):
HARMFUL BY INGESTION

Ruby red crystals or orange powder; m.p. n/a. Very soluble in water. OEL not assigned

Toxic effects: Harmful by ingestion. Irritating to skin eyes.
Hazardous reactions: No known hazards, although solutions should NOT be treated with acid to avoid generation of hydrogen cyanide.
Fire hazards: MAY EVOLVE TOXIC FUMES IN FIRE. Flash point 76°C, ignition temp. not available; extinguish fire with dry powder.
Spillage & disposal: Mop up with plenty of water and run to waste, diluting with copious water. For larger spillages, transfer to container for disposal.

POTASSIUM CARBONATE:
HARMFUL BY INGESTION. IRRITATING TO SKIN/EYES.

White granular powder; m.p. n/a. Very soluble in water. OEL not assigned

Toxic effects: Harmful by ingestion. Irritating to skin eyes, and throat by inhalation of dust.
Hazardous reactions: Can give explosive mixtures with magnesium powder.
Fire hazards: MAY EVOLVE TOXIC FUMES IN FIRE. Flash point 76°C, ignition temp. not available; extinguish fire with dry powder.
Spillage & disposal: Mop up with plenty of water and run to waste, diluting with copious water. For larger spillages, transfer to container for disposal.

$(DHQ)_2PHAL$ and $(DHQD)_2PHAL$
TOXICITY NOT REPORTED - TREAT AS HARMFUL

Reaction liberates:
OSMIUM TETROXIDE:

TOXIC
VERY IRRITANT VAPOUR - CAUSES IRRITATION AND BURNS TO EYES AND SKIN
SEVERE INTERNAL IRRITANT IF INGESTED
EXPOSURE TO VAPOUR CAUSES VISION DEFECTS
OXIDANT

Colourless or yellow solid, very pungent odour; b.p. 130°C, m.p. 40°C. Soluble in water. OES 0.002 mg/m^3 (Os)

Toxic effects: Causes irritation and burns to eyes and skin. Very irritant vapour. If ingested causes severe internal irritation and damage. Continued exposure to vapour

causes disturbances of vision. Continued skin contact causes dermatitis and ulceration.

Hazardous reactions: Powerful oxidising agent. Catalyses chlorate oxidations. Causes vigorous or violent decomposition of hydrogen peroxide.

Fire hazards: May evolve toxic fumes in fire.

Spillage & disposal: Wear face mask and nitrile gloves. Dissolve any solids in water and add a 25% solution of potassium hydroxide. Add ethanol to precipitate a dark solid, which can be collected and dried on a filter under fume extraction. This can be treated as for potassium osmate above. Alternatively, mix solids with wet sand and absorb liquids on an inert absorbent and package for disposal.

STYRENE:

HARMFUL BY INGESTION AND INHALATION
IRRITATING TO EYES, SKIN AND RESPIRATORY SYSTEM
POTENTIAL CARCINOGEN

Colourless or pale yellow oily liquid with a penetrating odour; b.p. 146°C, m.p. -33°C. Practically insoluble in water. MEL 420 mg/m^3

Toxic effects: Harmful by ingestion and inhalation. Irritating to skin, eyes and respiratory system. Vapour is narcotic in high concentrations. Prolonged exposure may cause systemic effects. Has been found to cause cancer in laboratory animals. Evidence of reproductive effects.

Hazardous reactions: Sources of free radicals can cause runaway polymerisation. Can react vigorously with oxidising materials, ferric chloride, alkali metals and butyllithium.

Fire hazards: Flash point 32°C, ignition temp. 490^{o}C; extinguish fire with foam, dry powder or CO_2.

Spillage & disposal: Wear goggles and nitrile gloves in a well ventilated area. Absorb onto inert material and package in containers for disposal. Wash site of spillage thoroughly with water and detergent.

1-OCTENE:

FLAMMABLE

Colourless; b.p. 122-23°C.

Toxic effects: None indicated.

Hazardous reactions: None indicated but likely to react with oxidising agents.

Fire hazards: Flash point 21°C, ignition temp. not available; extinguish fire with dry powder.

Spillage & disposal: Wear goggles and nitrile gloves in a well ventilated area. Absorb onto inert material and package in containers for disposal.

SODIUM SULFITE:

HARMFUL BY INGESTION AND INHALATION
IRRITATING TO EYES, SKIN AND RESPIRATORY SYSTEM
POTENTIAL CARCINOGEN

Colourless deliquescent crystals or white powder; m.p. n/a. Very soluble in water. MEL not assigned.

Toxic effects: Irritating to skin, eyes and respiratory system. If ingested in quantity can cause gastric irritation, colic, diarrhoea, central nervous system depression and death, due to liberation of sulfur dioxide.

Hazardous reactions: Sources of free radicals can cause runaway polymerisation. Can react vigorously with oxidising materials, ferric chloride, alkali metals and butyllithium.

Fire hazards: May evolve toxic fumes in a fire.

Spillage & disposal: Wear goggles and rubber gloves in a well ventilated area. Mop up with plenty of water and run to waste with copious water. Larger spillages should be placed in containers for disposal.

ETHYL ACETATE:

HIGHLY FLAMMABLE
IRRITATING TO EYES AND RESPIRATORY SYSTEM

Colourless liquid with fragrant odour; b.p. 77°C; slightly soluble in water. Avoid breathing vapour. Avoid eye contact. OEL 1400 mgm^{-3}.

Toxic effects: The vapour may irritate the eyes and respiratory system. The liquid irritates the eyes and mucous surfaces. Prolonged inhalation may cause kidney and liver damage.

Fire hazard: Flash point –4.4°C; ignition temp. 427°C; extinguish fire with CO_2.

Spillage & disposal: Clear area, shut off all sources of ignition. Wear face shield goggles and gloves. Absorb bulk quantities on sand, shovel into buckets. Wash site of spillage with water and detergent. Ethyl acetate should be placed in the non-chlorinated waste container for central disposal.

Experimental Procedure

NOTE: Osmium salts and especially osmium (VIII) tetroxide are extremely harmful by inhalation, ingestion or contact. Osmium (VIII) tetroxide is a volatile compound, and care must be taken not to liberate this outside of the fume hood. NEVER MIX OSMIUM SALTS WITH ACID AS THIS GENERATES OsO_4.

Carry out ALL of the procedures up to and including the short silica pad filtration in the fixed fume hood provided for the experiment only. Gloves (nitrile) as well as lab coat and safety glasses are to be worn at all times. Notify a demonstrator of any spillages. Place the aqueous osmium waste from this reaction in the labelled bottle.

AD-mixes also contain $K_3Fe(CN)_6$ which liberates cyanide anion in solution. Do not ingest AD-mix, and NEVER add acid to the salts, your reaction mixture or glassware (this would liberate lethal HCN).

In a 100ml round-bottomed flask equipped with a reflux condenser and magnetic stirring bar was place *tert*-butyl alcohol (15 ml), water (15 ml) and AD-mix-α or β as assigned to you (4.2g; weighed out in a fume cupboard). Stir the mixture at room temperature until two clear phases are produced; the lower (aqueous) phase should be bright yellow. Vigorous stirring is required to dissolve all the AD-mix. Cool the mixture was to 0^oC (some of the dissolved salts may precipitate). Add 3 mmol of the alkene you have been allocated and continue to stir the mixture vigorously at 0^oC (temperature is important!), following the progress of the reaction by TLC.

Upon completion of the reaction, or 1 hour before the end of the lab session (whichever is sooner), add solid sodium sulfite (4.5g) whilst stirring at 0^oC and then allow the mixture to warm to room temperature and stir for a further 45 mins. Add 30 ml ethyl acetate to the mixture and separate the two layers. Further extract the aqueous layer with ethyl acetate (3 x 15ml). **The aqueous layer should be placed in the bottle marked "Aqueous Osmium Waste" in the fume hood where you have done the reaction.** Dry the combined organic extracts ($MgSO_4$) and then remove the solvent **on the rotary evaporator in a fume hood - not to be done on the bench!** The product diol can be separated from the ligand by running the crude product through a short pad of silica gel using EtOAc as the solvent. Evaporate the ethyl acetate to obtain your 1,2-diol, and dry over silica gel in a dessicator.

Record the ^1H nmr and IR spectra, m.pt. and optical rotation of your product. Details of the latter procedure can be found in Harwood and Moody. Use a concentration of 1.0g/100 mL of EtOH. You will need 10 mL of this solution to fill the cell. Note that this sample can be recovered after recording the optical rotation. Use the sign of rotation to obtain the absolute configuration of the product (by comparison with literature optical rotation values) and the type of AD-mix you used (α or β) to correlate the sense of induction you obtained with that which would be predicted using the Sharpless mnemonic.

From the optical rotation, estimate the enantiomeric excess of your material, assuming a linear fit of *ee* to rotation (not always a valid assumption - why not? Discuss in your report!)

Find a suitable solvent for recrystallisation of your diol, and perform the recrystallisation, drying your crystals in air as before. Now re-measure you optical rotation at the exact

same concentration as you used before. Calculate the enantiomeric excess of your recrystallised material. Is there a difference?

Write up

The write up should conform to *Organic and Biomolecular Chemistry* style (Title, Abstract, Introduction, Results and Discussion, Experimental, References). Your introduction must include discussion of the following points:

1. one recent (2003 or later) synthetic applications of the asymmetric dihydroxylation reaction in organic synthesis from the primary literature;
2. one example from the recent (2003 or later) primary literature of another type of catalytic asymmetric reaction.

References and Notes

1. "Asymmetric Synthetic Methodology", D. J. Ager and M. B. East, CRC, New York, 1996. Note that David Ager is an Imperial College graduate!
2. "Catalytic Asymmetric Synthesis", ed. I. Ojima, VCH, Weinheim, 1993
3. For an excellent account of the discovery of the Sharpless AE reaction, see: C. H. Behrens, K. B. Sharpless, *Aldrichimica Acta*, **1983**, *16*, 67; see also: R. A. Johnson, K. B. Sharpless, in "Comprehensive Organic Synthesis", eds. B. M. Trost, I. Fleming, Pergamon, New York, 1991, vol 7, p389
4. H. C. Kolb, M. S. van Nieuwenhze, K. B. Sharpless, *Chem. Rev*., **1994**, *94*, 2483. Hartmuth Kolb obtained his Ph.D. from Imperial College in 1992!
5. G. G. Li, H. T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.,* **1996**, *35*, 451
6. M. J. Cleare, P. C. Hughes, W. P. Griffith, M. J. Wright, *J. Chem. Soc., Dalton Trans.*, **1977**, 941