GREEN CHEMISTRY – THE ATOM ECONOMY

There can be little doubt that a greater understanding of chemistry, particularly over the past century, has dramatically altered the way in which people live. Chemistry has been responsible for revolutionising medicine, transportation, communication, construction *etc.*, leading to evidently better living standards. Somewhat ironically, however, the development of the modern chemicals industry has not been without cost. Waste emanating from chemical manufacturing has, and continues to have, a negative impact on both human health and the environment.

Historically, the response of the chemical industry to environmental legislation has been one of waste treatment after the event rather than prevention at source. However, as *Fig. 1* [1] illustrates, legislative effects are increasingly making waste treatment solutions for the chemical sector, economically unsustainable. In the

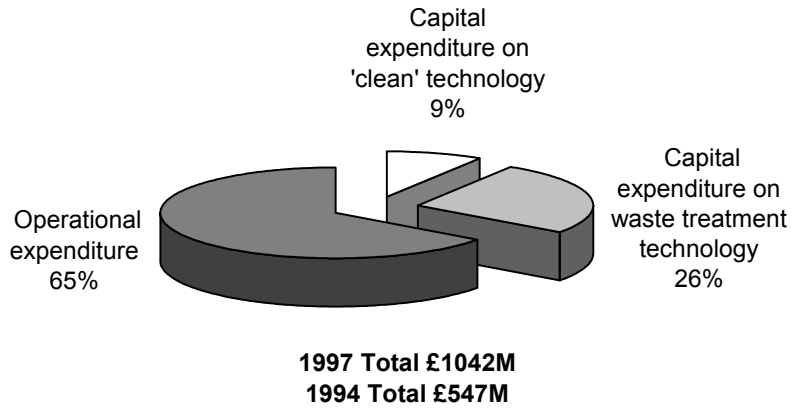


Fig 1 UK chemicals sector expenditure on environmental control (1997) [1]

period 1994 to1997, spending on environmental control almost doubled in the UK [1]. In 1997, over £270 million was spent on waste treatment equipment, while only £100 million went on developing 'clean' technology (*i.e.* processes designed to minimise or prevent waste formation at source) [1]. Increasingly, though, environmental and economic pressures are forcing chemical manufacturers to reassess their operations. The concept of *sustainable products and processes* has been popularised under the Green Chemistry banner and probably represents the fastest growing area of chemistry today. The chemical industry's endorsement of this movement is easy to understand, given the obvious economic benefits. With reference to the UK scene (*Fig. 1*), it is estimated that a three-fold increase in spending on clean technology would lead to a substantial reduction in waste treatment and operating costs [1].

The Green Chemistry Program was established in the US in 1991, following the passage of the *Pollution Prevention Act* the year previous [2]. Broadly defined, Green Chemistry is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances [2]. To help chemists in

their efforts towards practising green chemistry, Anastas and Warner have compiled *The twelve principles of Green Chemistry* [3a].
ITU 4 investigates a particular topic in green chemistry, namely, the concept of atom economy [4,5,6]. This concept asks chemists to consider how many reactant atoms end up in the desired product of a chemical synthesis and, moreover, how many contribute to the formation of waste products. Throughout the unit, however, you will also encounter other aspects of Green Chemistry that are effective in the *sustainable development* of chemical processes.

Scheme 1 outlines the operation of ITU 4. *Section B* examines intrinsic atom economies for different classes of reaction. *Section C* applies the concept of atom economy to drug synthesis. Alternative synthetic approaches are considered in *Section D* and, following on, *Section E* provides you with the opportunity to review the *Principles of Green Chemistry*. For most of this exercise you will be required to work with colleagues in small sub-groups. Each member of the sub-group is expected to make an oral presentation at some stage during the operation of the ITU.

NB You will be expected to do some basic calculations during ITU 4. Please bring a calculator to your designated ITU session. Below is a list of all the atomic masses you will require throughout the unit.

Element	Symbol	Atomic mass (amu)*
Hydrogen	H	1.0
Carbon	C	12.0
Nitrogen	N	14.0
Oxygen	O	16.0
Sodium	Na	23.0
Aluminium	Al	27.0
Sulfur	S	32.1
Chlorine	Cl	35.5
Calcium	Ca	40.1
Bromine	Br	79.9
Iron	Fe	55.8

*All atomic masses are given to one decimal place.

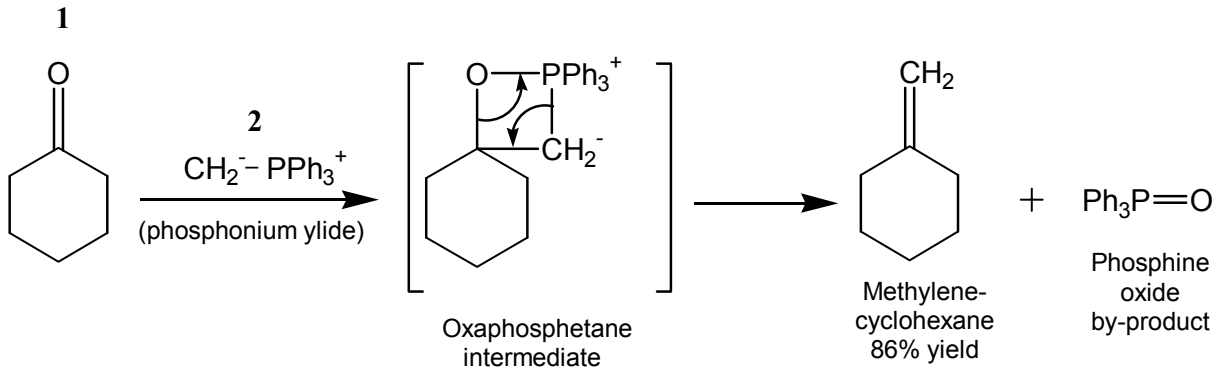
GROUP 1

Often the two major concerns for the process design chemist, when developing a chemical synthesis, are a high yield of the desired product and good selectivity (*e.g.* stereoselectivity). As an unfortunate consequence, numerous synthetic pathways currently utilised by the chemical industry are intrinsically predisposed to the production of waste.

Chemists commonly use the percentage yield calculation (*1*) to ascertain the efficiency of a particular reaction.

$$\% \text{ YIELD} = \text{MOLES OF PRODUCT} / \text{MOLES OF LIMITING REAGENT} \times 100 \qquad (1)$$

USING THIS EVALUATION STRATEGY, A REACTION WITH 100% YIELD IS DEEMED TO BE PERFECTLY EFFICIENT. THE YIELD APPROACH, HOWEVER, DOES NOT PROVIDE THE CHEMIST WITH ANY INFORMATION ABOUT THE EXTENT TO WHICH UNWANTED PRODUCTS ARE FORMED IN A CHOSEN REACTION PATHWAY. IN THE CONTEXT OF PERCENTAGE YIELD, THERE ARE MANY EXAMPLES OF HIGHLY EFFICIENT REACTIONS, WHICH GENERATE WASTE FAR GREATER IN MASS AND VOLUME THAN THE DESIRED PRODUCT. OFTEN APPEARING AS A STEP IN THE SYNTHETIC PATHWAY TO MANY VITAMINS AND PHARMACEUTICALS, THE *WITTIG* REACTION [7A] (*Scheme 2*) IS A PRIME EXAMPLE. THE YIELD OF 86% [7A] SHOWS THIS REACTION TO BE HIGHLY EFFICIENT IN ITS CONVERSION OF THE KETONE TO THE ALKENE FUNCTIONALITY. WHAT THE YIELD CALCULATION FAILS TO TAKE INTO ACCOUNT, HOWEVER, IS THE STOICHIOMETRIC QUANTITIES OF PHOSPHINE OXIDE BY-PRODUCT GENERATED. FURTHERMORE, THE MOLECULAR WEIGHT OF THE PHOSPHINE OXIDE WASTE (278 G/MOL) IS ALMOST THREE TIMES THAT OF THE DESIRED ALKENE PRODUCT (96G/MOL). CONSEQUENTLY THE WASTE IN THIS PARTICULAR REACTION IS OF SIGNIFICANTLY GREATER MASS AND VOLUME THAN THE ACTUAL PRODUCT ITSELF [3B].



Scheme 2. The Wittig reaction [7a].

GREEN CHEMISTRY: THE ATOM ECONOMY CONCEPT

With the inadequacies of the yield calculation clearly established, Barry Trost of Stanford University developed the concept of atom economy [4,5,6], earning him a Presidential Green Chemistry Challenge Award in 1998. This novel approach proposed that as well as the important parameters of selectivity and yield; chemists should also consider how efficiently reactant atoms are utilised in chemical syntheses. In other words, what amounts of reactants end up in the desired product and what amounts are lost as by-products/wastes. *Equation 2* follows on from Trost's work and is used to quantify the level of compliance with the Green Chemistry ideal of atom economy [5].

$$\%\ \textbf{ATOM ECONOMY} = \frac{\text{Formula weight of all atoms utilised}}{\text{Formula weight of all the reactants used}} \times 100 \qquad (2)$$

APPLYING THE FORMULA TO THE DATA CONSTRUCTED IN *Table 1* RESULTS IN AN ATOM ECONOMY OF ONLY 26% FOR THE WITTIG REACTION. THIS FIGURE DROPS TO JUST 22% (0.86 × 0.26 × 100) WHEN TAKING INTO ACCOUNT THE PERCENTAGE YIELD FOR THE REACTION.

Table 1 Wittig reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_6H_{10}O$	98	C_6H_{10}	82	O	16
2 $C_{19}H_{17}P$	276	CH_2	14	$C_{18}H_{15}P$	262
Total $C_{25}H_{27}PO$	374	***Methylene-cyclohexane*** C_7H_{12}	96	***Total*** $C_{18}H_{15}PO$	278

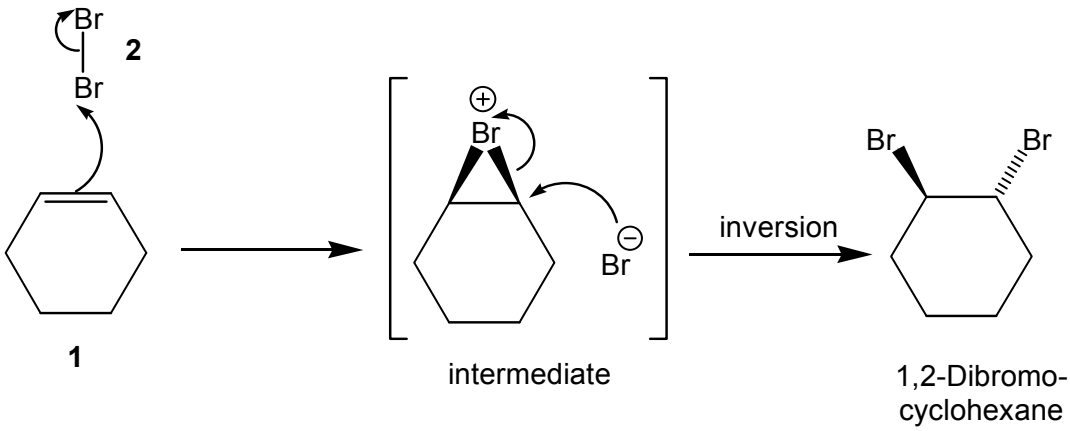
% Atom economy = 96/374 × 100 = 26%

Most chemical transformations can be categorised as rearrangement, addition, substitution or elimination reactions. Rearrangement and addition reactions are generally more environmentally favourable than substitution reactions, whilst elimination reactions are shown to be the least environmentally friendly of the

categories. Therefore in developing a synthesis, the atom economical chemist may choose rearrangement and addition reactions, where possible, over less environmentally friendly substitution and elimination reactions.

GROUP WORK

Consider the following reaction scheme for the bromination of cyclohexene (***1***) [7b]: -



On the acetate provided, complete the following task: -

1. Complete *Table 2* and, hence, deduce the percentage atom economy for the bromination reaction.

GROUP 1 PRESENTATION

Elect a speaker to present the conclusions of your group's problem session to the others. The oral presentation should cover the following points: -

(a) With reference to your reaction scheme, explain the conclusions drawn in Table 2.

(b) State the general classification for your reaction and discuss the implications for atom economy within this class of reaction.

(a)

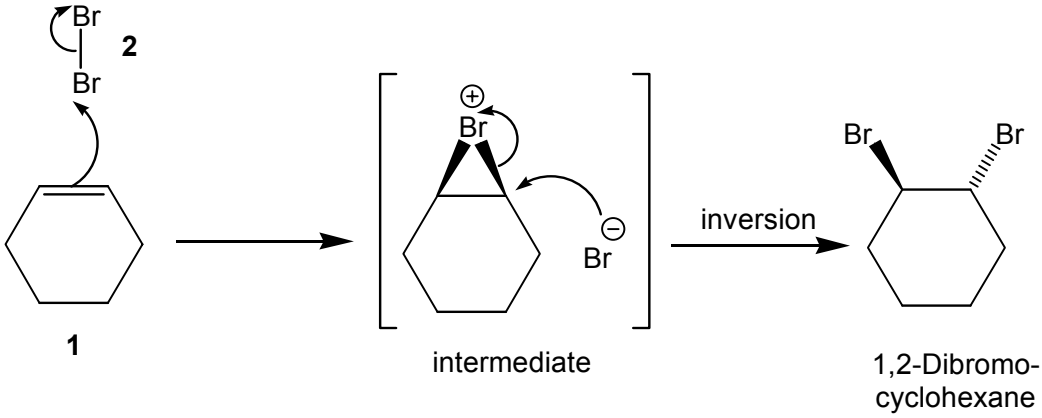


Table 2 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_6H_{10}			82	-	0
2	159.8	Br_2			
Total $C_6H_{10}Br_2$		***1,2-Dibromo-cyclohexane***		***Total***	

% Atom economy =

(b)

Reaction class:

Comments:

GROUP 1 TUTOR ANSWERS

(a)

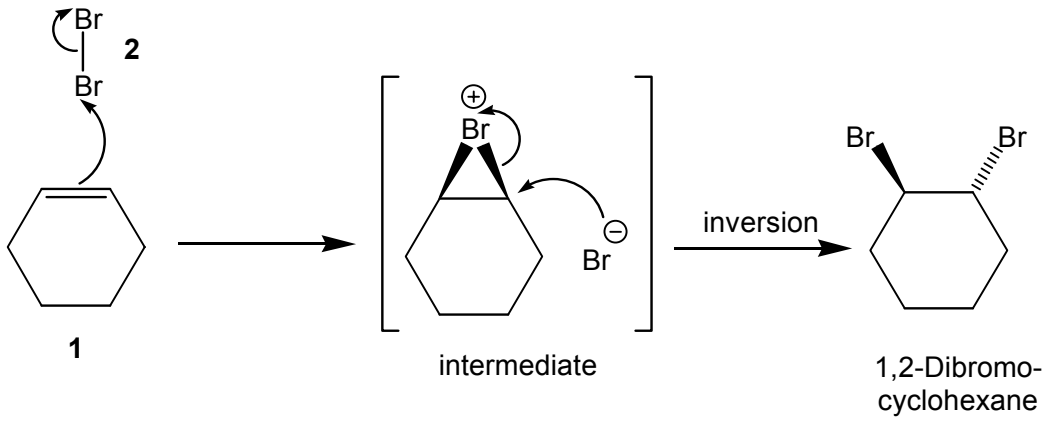


Table 2 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_6H_{10}	82	C_6H_{10}	82	-	0
2 Br_2	159.8	Br_2	159.8	-	0
Total $C_6H_{10}Br_2$	241.8	***1,2 Dibromo-cyclohexane*** $C_6H_{10}Br_2$	241.8	***Total*** -	0

% Atom economy = 241.8 / 241.8 × 100 = 100 %

(b)

Reaction class: Addition Reaction.

Comments: Addition reactions are atom economical as the elements of the reactant are added to a substrate with total inclusion.

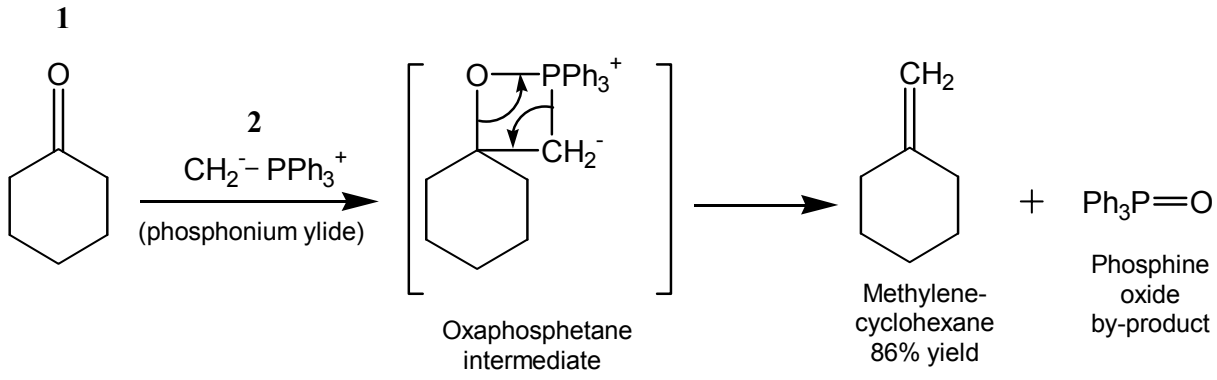
GROUP 2

Often the two major concerns for process design chemists, when developing a chemical synthesis, are a high yield of the desired product and good selectivity (*e.g.* stereoselectivity). As an unfortunate consequence, numerous synthetic pathways currently utilised by the chemical industry are intrinsically predisposed to the production of waste.

Chemists commonly use the percentage yield calculation (eqn 1) to ascertain the efficiency of a particular reaction.

$$\%\ \text{YIELD} = \text{MOLES OF PRODUCT} / \text{MOLES OF LIMITING REAGENT} \times 100 \qquad (1)$$

USING THIS EVALUATION STRATEGY, A REACTION WITH 100% YIELD IS DEEMED TO BE PERFECTLY EFFICIENT. THE YIELD APPROACH, HOWEVER, DOES NOT PROVIDE THE CHEMIST WITH ANY INFORMATION ABOUT THE EXTENT TO WHICH UNWANTED PRODUCTS ARE FORMED IN A CHOSEN REACTION PATHWAY. IN THE CONTEXT OF PERCENTAGE YIELD, THERE ARE MANY EXAMPLES OF HIGHLY EFFICIENT REACTIONS, WHICH GENERATE WASTE FAR GREATER IN MASS AND VOLUME THAN THE DESIRED PRODUCT. OFTEN APPEARING AS A STEP IN THE SYNTHETIC PATHWAY TO MANY VITAMINS AND PHARMACEUTICALS, THE *WITTIG* REACTION [7A] (*Scheme 2*) IS A PRIME EXAMPLE. THE YIELD OF 86% [7A] SHOWS THIS REACTION TO BE HIGHLY EFFICIENT IN ITS CONVERSION OF THE KETONE TO THE ALKENE FUNCTIONALITY. WHAT THE YIELD CALCULATION FAILS TO TAKE INTO ACCOUNT, HOWEVER, IS THE STOICHIOMETRIC QUANTITIES OF PHOSPHINE OXIDE BY-PRODUCT GENERATED. FURTHERMORE, THE MOLECULAR WEIGHT OF THE PHOSPHINE OXIDE WASTE (278 G/MOL) IS ALMOST THREE TIMES THAT OF THE DESIRED ALKENE PRODUCT (96G/MOL). CONSEQUENTLY THE WASTE IN THIS PARTICULAR REACTION IS OF SIGNIFICANTLY GREATER MASS AND VOLUME THAN THE ACTUAL PRODUCT ITSELF [3B].



Scheme 2. The Wittig reaction [7a].

GREEN CHEMISTRY: THE ATOM ECONOMY CONCEPT

With the inadequacies of the yield calculation clearly established, Barry Trost of Stanford University developed the concept of atom economy [4,5,6], earning him a Presidential Green Chemistry Challenge Award in 1998. This novel approach proposed that as well as the important parameters of selectivity and yield; chemists should also consider how efficiently reactant atoms are utilised in chemical syntheses. In other words, what amounts of reactants end up in the desired product and what amounts are lost as by-products/wastes. *Equation 2* follows on from Trost's work and is used to quantify the level of compliance with the Green Chemistry ideal of atom economy [5].

$$\% \text{ ATOM ECONOMY} = \frac{\text{Formula weight of all atoms utilised}}{\text{Formula weight of all the reactants used}} \times 100 \quad (2)$$

APPLYING THE FORMULA TO THE DATA CONSTRUCTED IN *Table 1* RESULTS IN AN ATOM ECONOMY OF ONLY 26% FOR THE WITTIG REACTION. THIS FIGURE DROPS TO JUST 22% ($0.86 \times 0.26 \times 100$) WHEN TAKING INTO ACCOUNT THE PERCENTAGE YIELD FOR THE REACTION.

Table 1 Wittig reaction atom economy

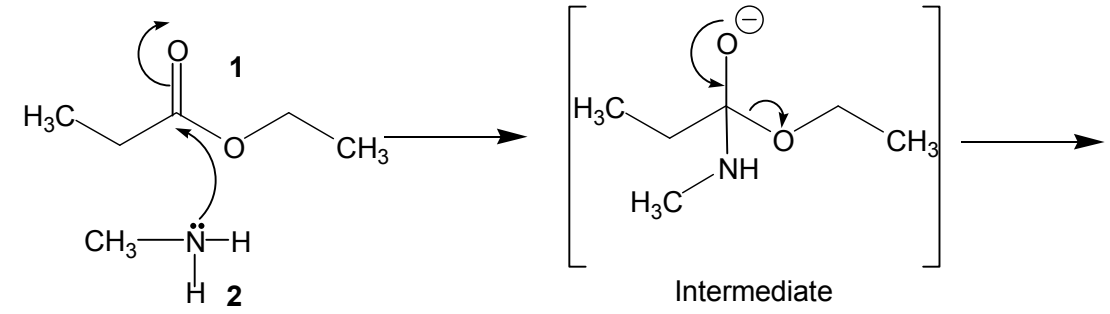
Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_6H_{10}O$	98	C_6H_{10}	82	O	16
2 $C_{19}H_{17}P$	276	CH_2	14	$C_{18}H_{15}P$	262
Total $C_{25}H_{27}PO$	374	***Methylene-cyclohexane*** C_7H_{12}	96	***Total*** $C_{18}H_{15}PO$	278

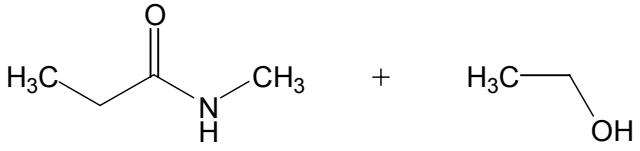
% Atom economy = 96/374 × 100 = 26%

Most chemical transformations can be categorised as rearrangement, addition, substitution or elimination reactions. Rearrangement and addition reactions are generally more environmentally favourable than substitution reactions, while elimination reactions are shown to be the least environmentally friendly of the categories. Therefore in developing a synthesis, the atom economical chemist may choose rearrangement and addition reactions, where possible, over less environmentally friendly substitution and elimination reactions.

GROUP WORK

CONSIDER THE FOLLOWING SCHEME FOR THE AMMONOLYSIS REACTION OF ETHYL PROPIONATE (***1***) WITH METHYLAMINE (***2***) TO YIELD METHYL PROPIONAMIDE AS THE





+

methyl propionamide

ethanol

DESIRED PRODUCT [8A]: -

On the acetate provided, complete the following task: -

1. Complete *Table 3* and, hence, deduce the percentage atom economy for the ammonolysis reaction.

GROUP 2 PRESENTATION

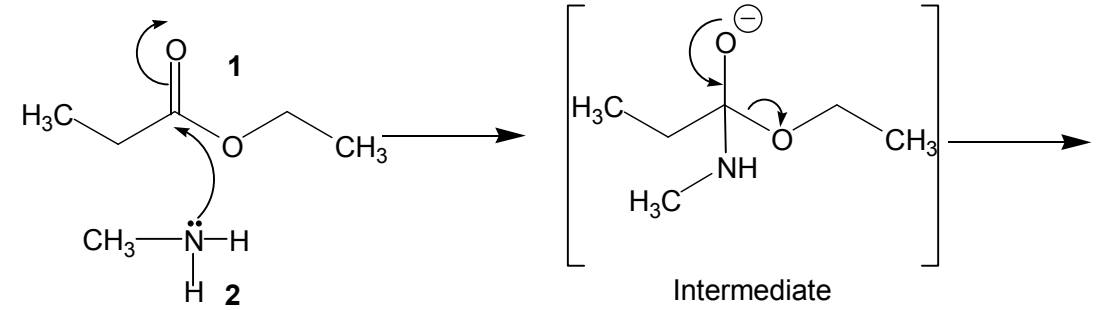
Elect a speaker to present the conclusions of your group's problem session to the others. The oral presentation should cover the following points: -

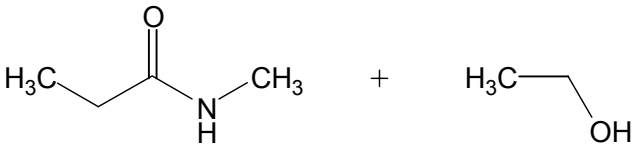
(c) With reference to your reaction scheme, explain the conclusions drawn in *Table 3.*

(d) State the general classification for your reaction and discuss the implications for atom economy within this class of reaction.

GROUP 2 PRESENTATION

(c)





methyl propionamide ethanol

Table 3 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_5H_{10}O_2$			57	C_2H_5O	
2	31	CH_4N			1
Total $C_6H_{15}NO_2$		***Methyl propionamide***		***Total*** C_2H_6O	

% Atom economy =

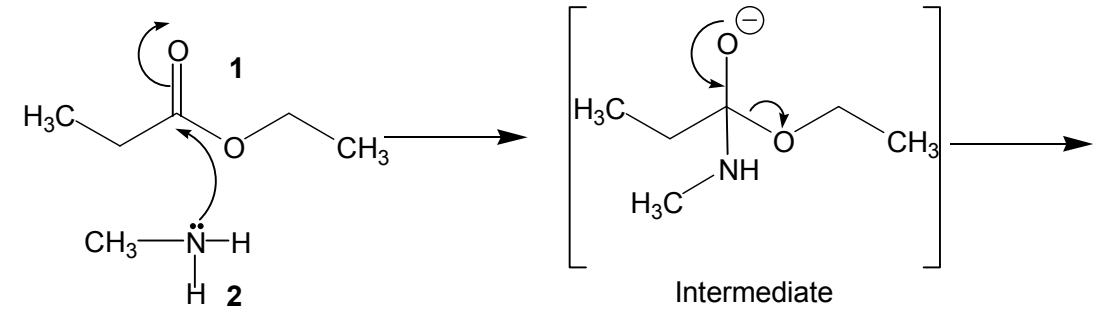
(d)

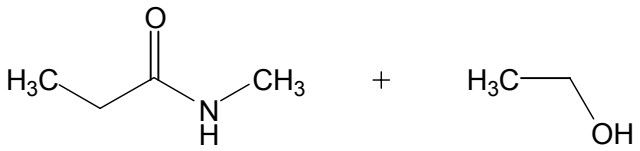
Reaction class:

Comments:

GROUP 2 TUTOR ANSWERS

(c)





methyl propionamide ethanol

Table 3 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_5H_{10}O_2$	102	C_3H_5O	57	C_2H_5O	45
2 CH_5N	31	CH_4N	30	H	1
Total $C_6H_{15}NO_2$	133	***Methyl propionamide*** C_4H_9NO	87	***Total*** C_2H_6O	46

% Atom economy = 87/133 × 100 = 65 %

(b)

Reaction class: Substitution Reaction.

Comments: Substitution reactions involve a substituting group displacing a leaving group, which is not incorporated in the final product. There is, therefore, an intrinsic reduction in the atom economy for this type of transformation. The extent to which the reaction is non-atom economical depends on the nature of the reagents and substrates used.

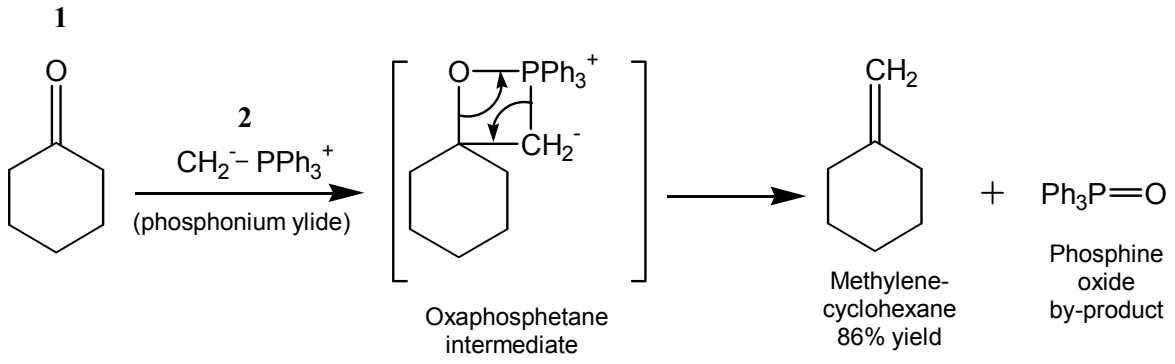
GROUP 3

Often the two major concerns for the process design chemist, when developing a chemical synthesis, are a high yield of the desired product and good selectivity (*e.g.* stereoselectivity). As an unfortunate consequence, numerous synthetic pathways currently utilised by the chemical industry are intrinsically predisposed to the production of waste.

Chemists commonly use the percentage yield calculation (*eqn 1*) to ascertain the efficiency of a particular reaction.

$$\%\ \text{YIELD} = \text{MOLES OF PRODUCT} / \text{MOLES OF LIMITING REAGENT} \times 100 \qquad (1)$$

Using this evaluation strategy, a reaction with 100% yield is deemed to be perfectly efficient. The yield approach, however, does not provide the chemist with any information about the extent to which unwanted products are formed in a chosen reaction pathway. In the context of percentage yield, there are many examples of highly efficient reactions, which generate waste far greater in mass and volume than the desired product. Often appearing as a step in the synthetic pathway to many vitamins and pharmaceuticals, the *Wittig* reaction [7a] (*Scheme 1*) is a prime example. The yield of 86% [7a] shows this reaction to be highly efficient in its conversion of the ketone to the alkene functionality. What the yield calculation fails to take into account, however, is the stoichiometric quantities of phosphine oxide by-product generated. Furthermore, the molecular weight of the phosphine oxide waste (278 g/mol) is almost three times that of the desired alkene product (96g/mol). Consequently the waste in this particular reaction is of significantly greater mass and volume than the actual product itself [3b].



Scheme 2. The Wittig reaction [7a].

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$$\% \text{ ATOM ECONOMY} = \frac{\text{FORMULA WEIGHT OF ALL ATOMS UTILISED}}{\text{FORMULA WEIGHT OF ALL THE REACTANTS USED}} \times 100 \qquad (2)$$

Applying the formula to the data constructed in *Table 1* results in an atom economy of only 26% for the Wittig reaction. This figure drops to just 22% ($0.86 \times 0.26 \times 100$) when taking into account the percentage yield for the reaction.

Table 1 Wittig reaction atom economy

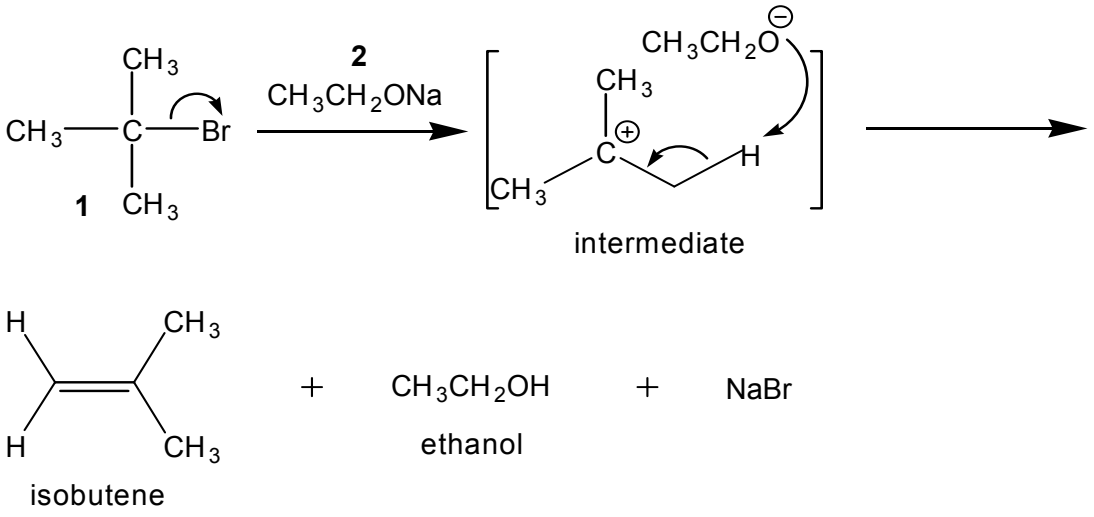
Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_6H_{10}O$	98	C_6H_{10}	82	O	16
2 $C_{19}H_{17}P$	276	CH_2	14	$C_{18}H_{15}P$	262
Total $C_{25}H_{27}PO$	374	***Methylene-cyclohexane*** C_7H_{12}	96	***Phosphine oxide*** $C_{18}H_{15}PO$	278

% Atom economy = 96/374 × 100 = 26%

Most chemical transformations can be categorised as rearrangement, addition, substitution or elimination reactions. Rearrangement and addition reactions are generally more environmentally favourable than substitution reactions, whilst elimination reactions are shown to be the least environmentally friendly of the categories. Therefore in developing a synthesis, the atom economical chemist may choose rearrangement and addition reactions, where possible, over less environmentally friendly substitution and elimination reactions.

GROUP WORK

Consider the following scheme for the dehydrohalogenation reaction of 2-bromo-2-methylpropane (***1***) with sodium ethoxide (***2***) to form isobutene as the desired product [8b]: -



On the acetate provided, complete the following task: -

2. Complete *Table 4* and, hence, deduce the percentage atom economy for the dehydrohalogenation reaction.

GROUP PRESENTATION

Elect a speaker to present the conclusions of your group's problem session to the others. The oral presentation should cover the following points: -

(e) With reference to your reaction scheme, explain the conclusions drawn from *Table 4*.

(f) State the general classification for your reaction and discuss the implications for atom economy within this class of reaction.

GROUP 3 PRESENTATION

(e)

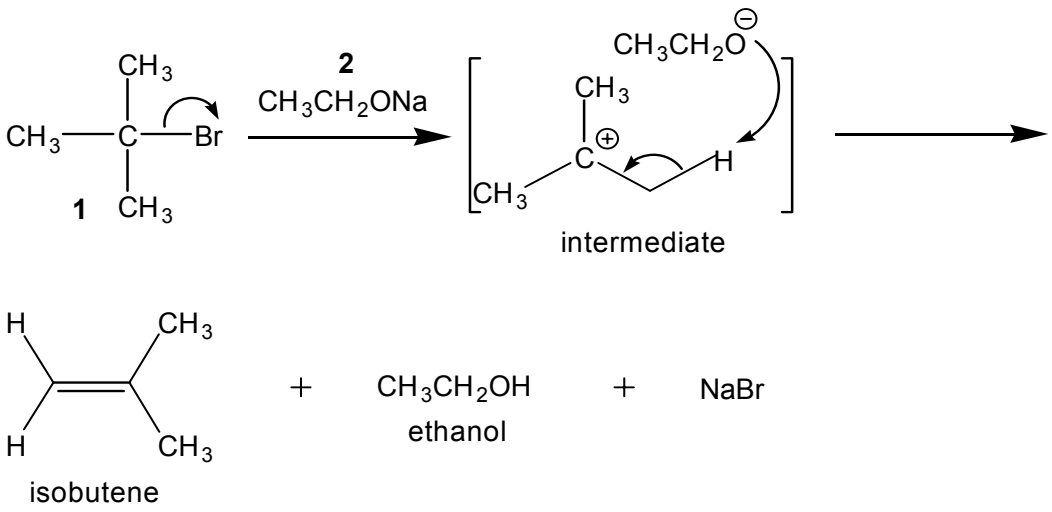


Table 4 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_4H_9Br			56		80.9
2	68	-	0	C_2H_5ONa	
Total $C_6H_{14}OBrNa$		***isobutene***		***Total*** C_2H_6OBrNa	

% Atom economy =

(f)

Reaction class:

Comments:

GROUP 3 TUTOR ANSWERS

(a)

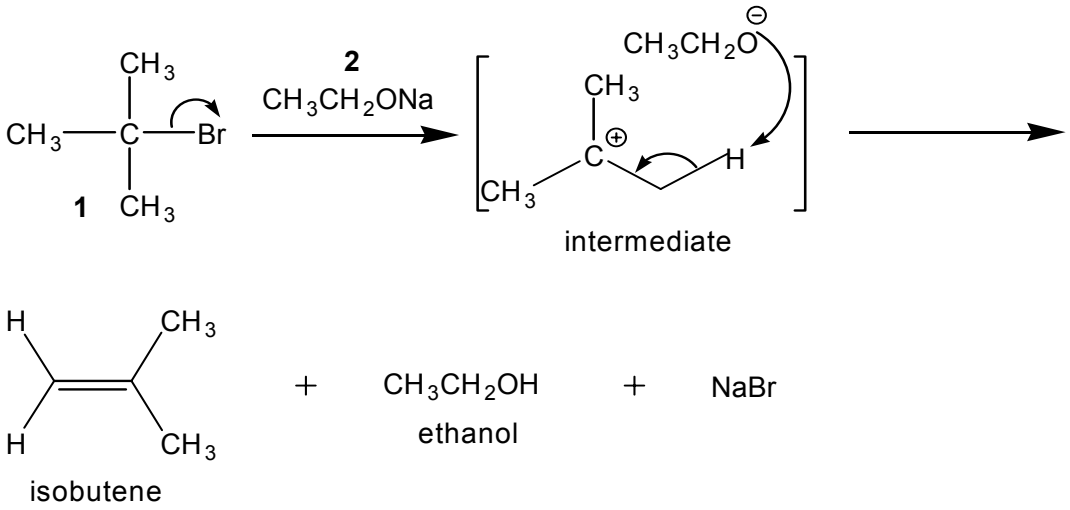


Table 4 Reaction atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_4H_9Br	136.9	C_4H_8	56	HBr	80.9
2 C_2H_5ONa	68	-	0	C_2H_5ONa	68
Total $C_6H_{14}OBrNa$ 204.9		***Isobutene*** C_4H_8 56		***Total*** C_2H_6OBrNa 148.9	

% Atom economy = = 56/204.9 × 100 = 27 %

(g)

Reaction class: Elimination Reaction.

Comments: In elimination reactions, any reagents used are not incorporated in the final product. Eliminated atoms are lost to the waste stream. Elimination reactions, therefore, are inherently atom uneconomical.

SECTION C

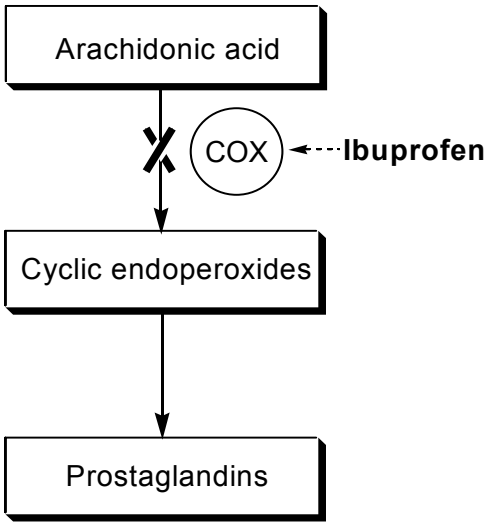
Group 1

The manufacture of pharmaceuticals is consistently shown to be amongst the top performing industrial sectors worldwide. Sales exceeding £207 billion in 2000 illustrates the industry's contribution and importance to the global economy [9]. The continued growth and success of the industry largely depends on the production of lucrative high volume drugs. Analgesics (painkillers) are an important class of drug exemplifying bulk production within the pharmaceutical industry. Ibuprofen is the active ingredient in many analgesics and current production is well in excess of 13,000 tonnes per annum [5]. Brand name products such as Nurofen, Brufen and Ibuleve, to name but a few, incorporate Ibuprofen to provide their analgesic action. In addition, Ibuprofen is a member of the nonsteroidal anti-inflammatory (NSAI) group of drugs, which combat swelling and inflammation.

Pharmacological Aspects of Ibuprofen

MODE OF ACTION

Ibuprofen has been available as a treatment for mild to moderate pain for almost 40 years [5]. The compound exerts its action through reversible competitive inhibition of an enzyme found in the body called *cyclo-oxygenase* (COX), which is active in the arachidonic acid cascade [10]. This C_{20} tetra-unsaturated fatty acid is an important precursor for a range of biologically important molecules. Inhibition of COX by Ibuprofen purposely blocks the synthesis of cyclic endoperoxides and, in sequence, prostaglandin derivatives, as shown in Scheme 3 below [10].



Scheme 3. Inhibition of COX by Ibuprofen [10].

Prostaglandins belong to a diverse biochemical family with a wide range of physiological effects. Ibuprofen, as an analgesic and anti-inflammatory, seeks to prevent prostaglandin formation for two main reasons. Firstly, certain basic pain

mechanisms operational in the body are amplified by some prostaglandins [11]. Secondly, certain prostaglandins are implicated in the inflammatory response to cell trauma (allergic reactions, sprains, *etc.*) [11]. Suppression of prostaglandin synthesis, however, can cause unwanted side effects [11]. The general blockade of the COX enzyme also inhibits the formation of beneficial prostaglandins that help to protect the gut lining. Consequently, complications such as stomach ulceration and bleeding can arise. Importantly, in 1991 researchers showed that the cyclo-oxygenase enzyme was present in two forms, COX-1 and COX-2 [12]. With the subsequent discovery that COX-2 is only present during the inflammatory response, a number of pharmaceutical companies are now working to develop specific COX-2 inhibitors to lower the risk of side effects. In fact, Meloxicam (COX-2 selective) is already being marketed in the UK as a treatment for rheumatoid arthritis [12].

Stereochemical considerations

Stereochemistry is an important field of chemistry dedicated to the structure determination of molecules in three dimensions. Cyclo-oxygenase, as with all other enzymes, has a distinct three-dimensional shape. Ibuprofen's success as a COX inhibitor depends largely on its ability to 'fit' into the enzyme's active site and, subsequently, to form compatible bonding interactions (mainly hydrophobic) [11]. The compound contains a single chiral centre, *i.e.* a carbon bonded to four <u>different</u> substituents. As such, there are two non-superimposable mirror image forms of Ibuprofen, that is, a pair of Ibuprofen <u>enantiomers</u> (*Fig. 2*).

Fig. 2. Enantiomers of Ibuprofen.

During the 1950s, Cahn, Ingold and Prelog devised a set of arbitrary rules to distinguish between enantiomers [13a]. Using these rules, the absolute configuration of the enantiomers of Ibuprofen can be assigned accordingly as (R)-Ibuprofen and (S)-Ibuprofen (shown in *Fig. 2* above). Such notation is vital to modern chemists because although enantiomers are said to be chemically identical, when placed in a chiral environment (*e.g.* living systems) their properties can differ markedly [7c]. The devastating effect of the drug Thalidomide is perhaps the most famous example of differing enantiomeric interactions in the body. Given that there is the scope for enantiomers to display very different properties *in vivo*, it may be surprising to learn that Ibuprofen is widely marketed as a mixture of the (*R*)- and (*S*)- forms, *ie* as the <u>racemate</u> [14]. Although only the (*S*)-enantiomer delivers the desired therapeutic action, the physiological enzyme *mandelate racemase* readily converts inactive (*R*)-

Ibuprofen to the active enantiomorph [14]. Nevertheless, single (*S*)-enantiomer versions of Ibuprofen are currently being developed, with the benefits cited as a reduction in the required dose and a shorter time for therapeutic levels to be reached [15].

The current trend in the pharmaceutical industry is towards the production of single enantiomer compounds. This is highlighted by 13% growth to £85 billion in worldwide sales of single enantiomer drugs for the year 2000 [9]. Furthermore, they accounted for 40% of global drug sales in 2000, up 7% on the previous year [9]. As well as significant advances in technology, regulatory bodies such as the US Food and Drug Administration (FDA) are requiring the development of single enantiomer compounds by pharmaceutical manufacturers [15]. At present the list of the top 100 drugs worldwide contains no fewer than 50 that are single enantiomers [9]. This figure is set to rise significantly in the next few decades.

Group Presentation

Elect a speaker to present the group's summary on the pharmacological and stereochemical aspects of Ibuprofen. Your presentation, using the acetates provided, should cover the following points: -

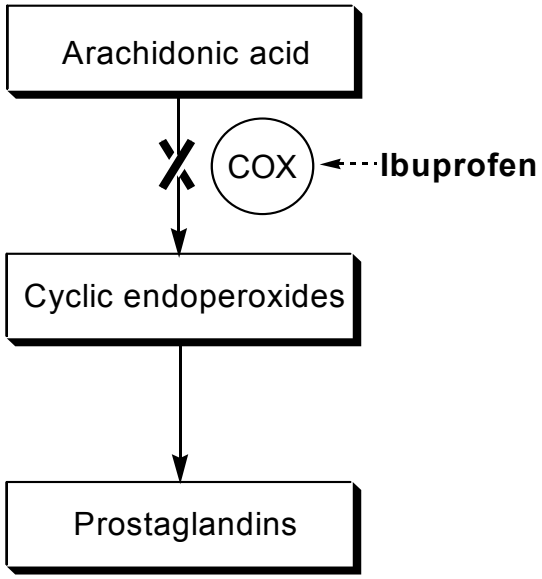
(a) Using *Scheme 3* on the acetate, summarise the inhibitory mode of action of Ibuprofen on the COX enzyme. Also allude to the discovery of COX-2.

(b) Referring to *Fig. 2* on the acetate, explain the stereochemical requirements for Ibuprofen's success as an inhibitor of COX.

(c) Discuss the current trend towards the development of single enantiomer drugs in the pharmaceutical industry.

Group 1 Tutor Answers

(a)



Scheme 3. Inhibition of COX by Ibuprofen.

- Ibuprofen competes with the natural substrate arachidonic acid (C_{20} tetra-unsaturated fatty acid) for the active site of the enzyme cyclo-oxygenase (COX).

- Reversible competitive inhibition of COX by Ibuprofen ultimately blocks the synthesis of certain prostaglandins (*Scheme 3*). This class of biochemical is associated with both the reception of pain and the inflammatory response to cell trauma.

- Ulceration and bleeding of the stomach/gut can occur as a consequence of preventing the formation of protective prostaglandins. However, in 1991 researchers discovered a second distinct form of cyclo-oxygenase (COX-2), which is only present during the inflammatory response. The race is on to develop COX-2 selective inhibitors that will not prevent the synthesis of beneficial prostaglandins.

(b)

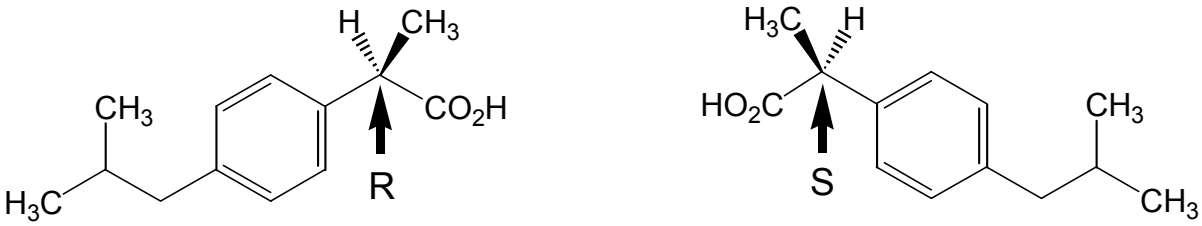


Fig. 2. Enantiomers of ibuprofen.

- COX, as with all other enzymes, has a distinct 3D shape. In its role as an inhibitor of COX, Ibuprofen must 'fit' into the enzyme's active site to form the appropriate bonding interactions (lock and key analogy).

- Ibuprofen has one chiral centre and so exists as a pair of enantiomers (*Fig. 2*). A set of arbitrary rules (Cahn-Ingold-Prelog rules) is used to label the enantiomers as (*R*)- and (*S*)- Ibuprofen (*Fig. 2*).

- The (*S*)- enantiomer delivers the therapeutic action, whereas (*R*)-Ibuprofen is virtually inactive. However, the drug is currently given as an equal mixture of both enantiomers (racemate) as it is enzymatically converted to the active enantiomorph *in vivo*.

- Nevertheless, single enantiomer (*S*)-Ibuprofen is currently in development. Benefits over the racemate are cited as lower dosage requirements and a shorter time period to reach therapeutic levels.

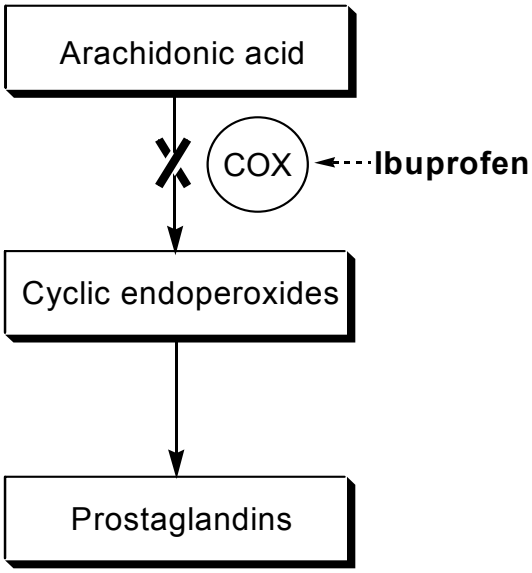
(c)

- The development and production of single enantiomer compounds is a progressive area in the pharmaceutical industry. Global sales of single enantiomer compounds grew 13% to £85 billion during 2000 and, in the same year, accounted for 40% of total drug sales worldwide, up 7% on the previous year.

- At present, the list of the top 100 drugs contains no fewer than 50 single enantiomer compounds. It is likely that this figure will rise in the near future.

Group 1 Presentation

(a)



Scheme 3. Inhibition of COX by Ibuprofen.

(b)

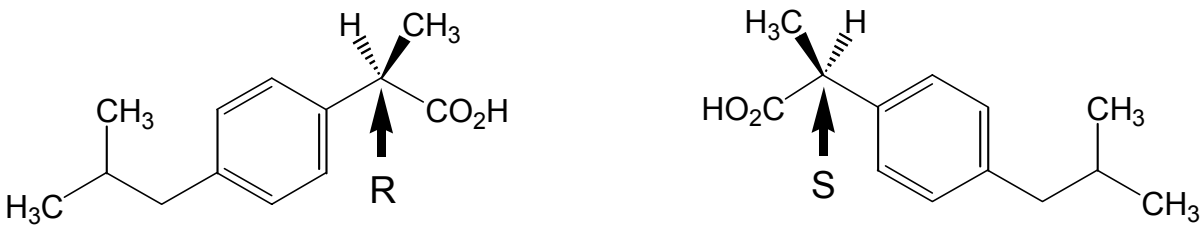


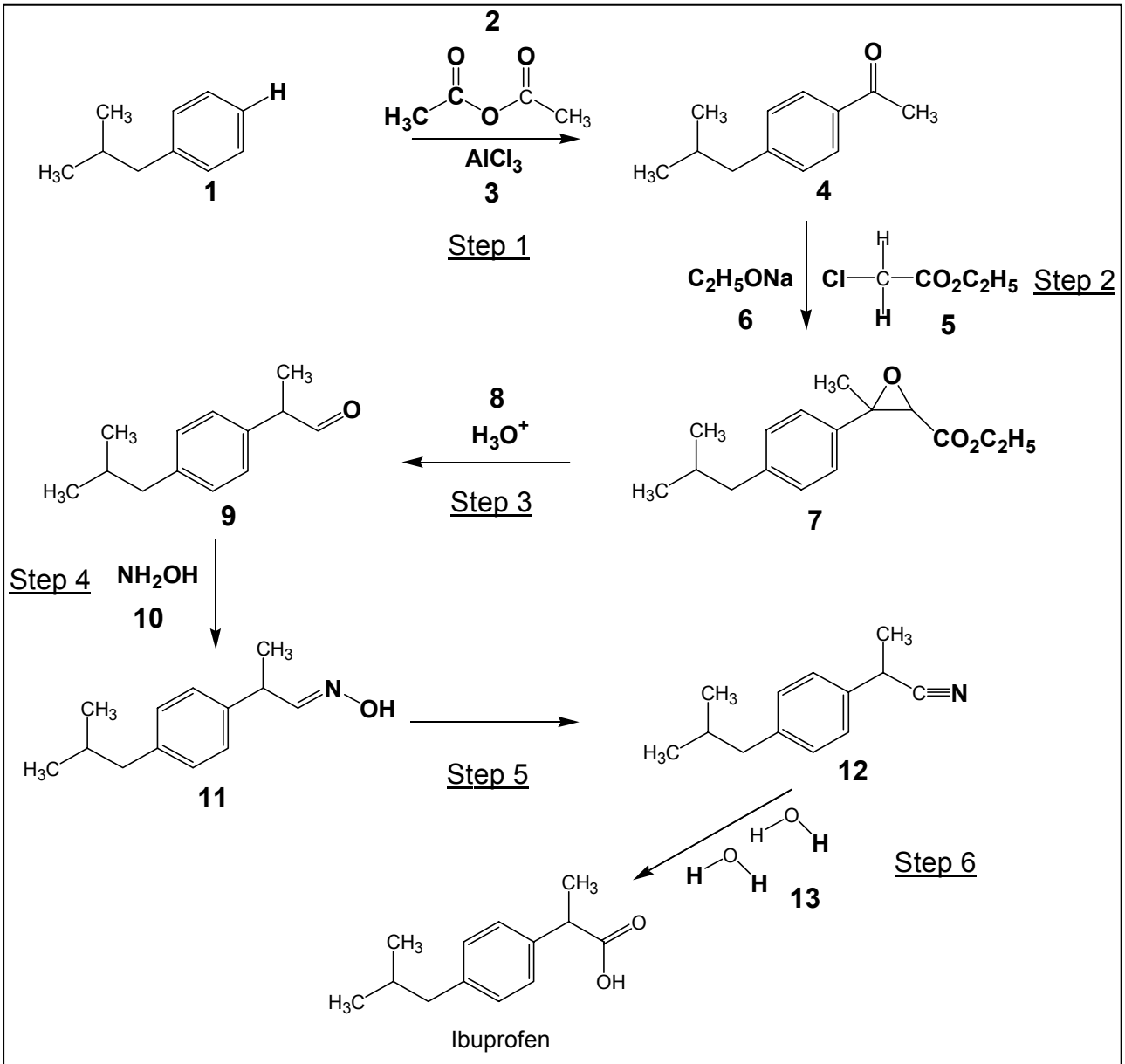
Fig. 2. Enantiomers of ibuprofen.

(c)

Group 2

The manufacture of pharmaceuticals is consistently shown to be amongst the top performing industrial sectors worldwide. Sales exceeding £207 billion in 2000 illustrates the industry's contribution and importance to the global economy [9]. The continued growth and success of the industry largely depends on the production of lucrative high volume drugs. Analgesics (painkillers) are an important class of drug exemplifying bulk production within the pharmaceutical industry. Ibuprofen is the active ingredient in many analgesics and current production is well in excess of 13,000 tonnes per annum [5]. Brand name products such as Nurofen, Brufen and Ibuleve, to name but a few, incorporate Ibuprofen to provide their analgesic action. In addition, ibuprofen is a member of the nonsteroidal anti-inflammatory (NSAI) group of drugs, which combat swelling and inflammation.

The traditional synthesis of Ibuprofen was patented in the 1960's by the Boots Company PLC, Nottingham [5]. Until the early 1990's, industrial synthesis of the drug was almost exclusively by the Boots methodology. The traditional six-step route to Ibuprofen is shown in *Scheme 4* below [5].



Scheme 4. Boots synthesis of Ibuprofen [5].

THE FIRST STEP IN THE SYNTHESIS IS A FRIEDEL-CRAFTS ACYLATION [13B], WHICH INTRODUCES THE *KETONE* FUNCTIONALITY ONTO THE AROMATIC RING. CONVERSION OF ***1*** INTO ***4*** IS CARRIED OUT USING ACETIC ANHYDRIDE (***2***) AS THE ACYLATING AGENT, IN THE PRESENCE OF STOICHIOMETRIC QUANTITIES OF THE ACYLATION 'CATALYST', ALUMINIUM TRICHLORIDE (***3***). STEP 2 IS A DARZENS CONDENSATION REACTION [16]. TREATMENT OF THE α-CHLOROESTER (***5***) WITH SODIUM ETHOXIDE (***6***) BASE GIVES THE α-CHLOROENOLATE ($ClHC{=}CO_2C_2H_5$), WHICH REACTS WITH ***4*** TO YIELD THE *EPOXIDE* SPECIES (***7***). STEP 3 IS A GLYCIDIC ACID REARRANGEMENT [16], WHERE TREATMENT OF THE EPOXIDE SPECIES WITH AQUEOUS ACID EFFECTS THE REARRANGEMENT OF THE CARBON SKELETON, RESULTING IN THE *ALDEHYDE* FUNCTIONALITY IN ***9***. THE CONVERSION OF THE ALDEHYDE (***9***) INTO THE *OXIME* (***11***) IS CARRIED OUT USING HYDROXYLAMINE (***10***). IN STEP 5, THE OXIME SPECIES READILY LOSES WATER TO YIELD THE CORRESPONDING *NITRILE* (***12***). FINALLY IN STEP 6, THE NITRILE FUNCTIONAL GROUP IS SLOWLY HYDROLYSED (TWO WATER EQUIVALENTS) TO GIVE THE DESIRED PRODUCT, IBUPROFEN.

Group Presentation

Elect a speaker to present the group's summary on the Boots synthesis of Ibuprofen. Your presentation, using the acetates provided, should cover the following points: -

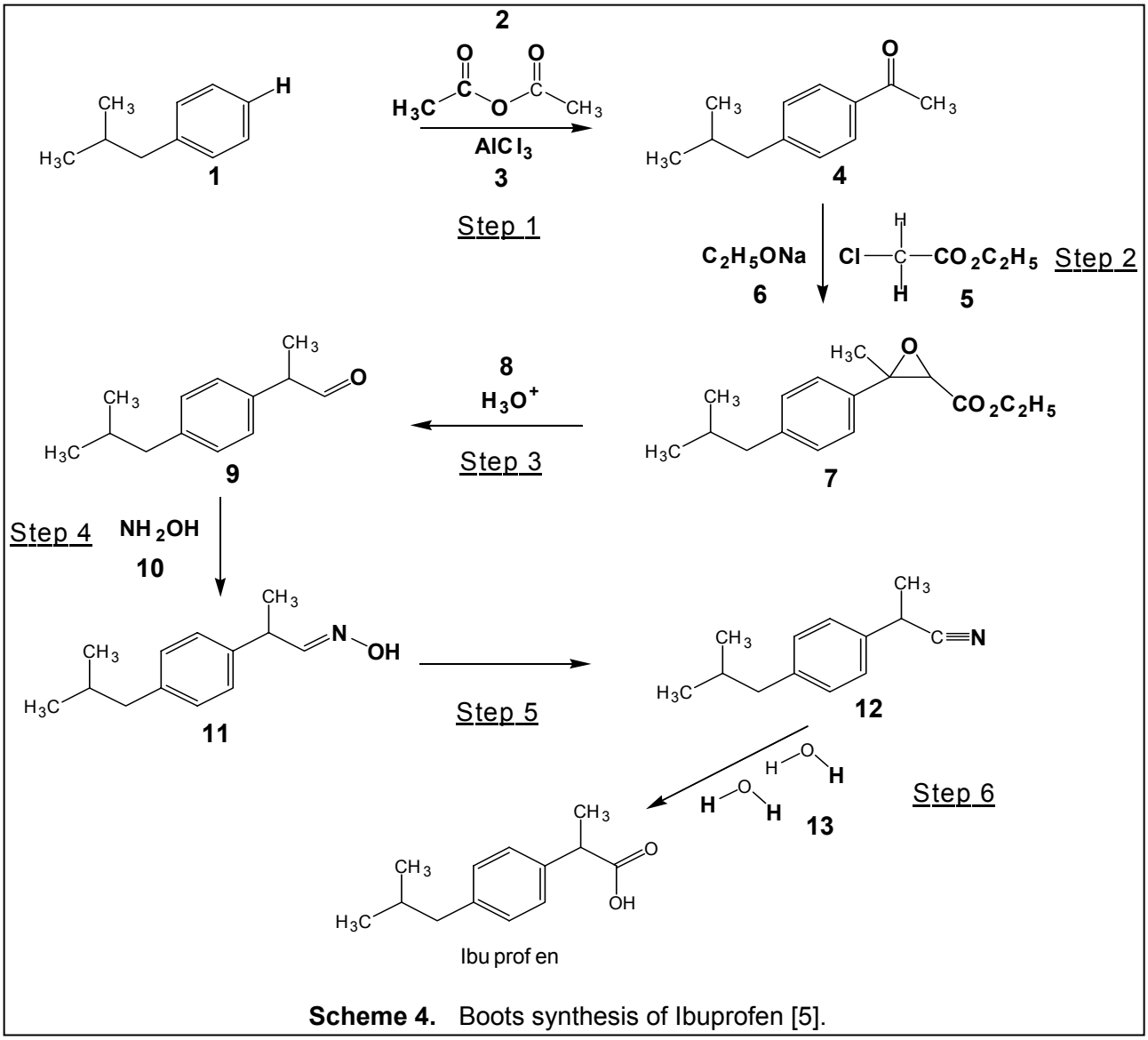
a) Use *Scheme 4* on the acetate to summarise the Boots Ibuprofen synthesis. Outline the various steps in the spaces provided.

b) Complete *Table 5* on the acetate and, hence, calculate the percentage atom economy for the traditional Boots synthesis of Ibuprofen. (Note: atoms shown in **bold** in *Scheme 3* are not incorporated into the desired product, Ibuprofen).

c) With reference to *Table 5* and *Scheme 4*, explain your atom economy results.

GROUP 2 TUTOR ANSWERS

(a)



Scheme 4. Boots synthesis of Ibuprofen [5].

Step 1. Friedel Crafts acylation. Acetic anhydride as the acylating agent, in the presence of stoichiometric quantities of aluminium trichloride.

Step 2. Darzens condensation. The α-chloroester (***5***) is treated with sodium ethoxide (***6***) base to yield the α-chloroenolate ($ClHC{=}CO_2C_2H_5$) which reacts with ***4***, forming the epoxide, ***7***.

Step 3. Glycidic acid rearrangement. Treatment of the epoxide species **(7)** with aqueous acid effects the rearrangement of the carbon skeleton, resulting in the aldehyde (***9***).

Step 4. Oxime formation. The conversion of the aldehyde (***9***) into the oxime (***11***) is carried out using hydroxylamine (***10***).

Step 5. Nitrile formation. The oxime species (***11***) readily loses water to form the corresponding nitrile.

Step 6. Nitrile hydrolysis. The nitrile species is slowly hydrolysed (two water equivalents) to yield the desired product, Ibuprofen.

(b)

TABLE 5 BOOTS IBUPROFEN SYNTHESIS ATOM ECONOMY.

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
2 $C_4H_6O_3$	102	C_2H_3	27	$C_2H_3O_3$	75
3 $AlCl_3$	133.5	-	0	$AlCl_3$	133.5
5 $C_4H_7ClO_2$	122.5	CH	13	$C_3H_6ClO_2$	109.5
6 C_2H_5ONa	68	-	0	C_2H_5ONa	68
8 H_3O	19	-	0	H_3O	19
10 NH_3O	33	-	0	NH_3O	33
13 H_4O_2	36	HO_2	33	H_3	3
Total $C_{20}H_{42}NO_{10}Cl_4NaAl$	648	**Ibuprofen** $C_{13}H_{18}O_2$	206	*Total* $C_7H_{24}NO_8Cl_4NaAl$	442

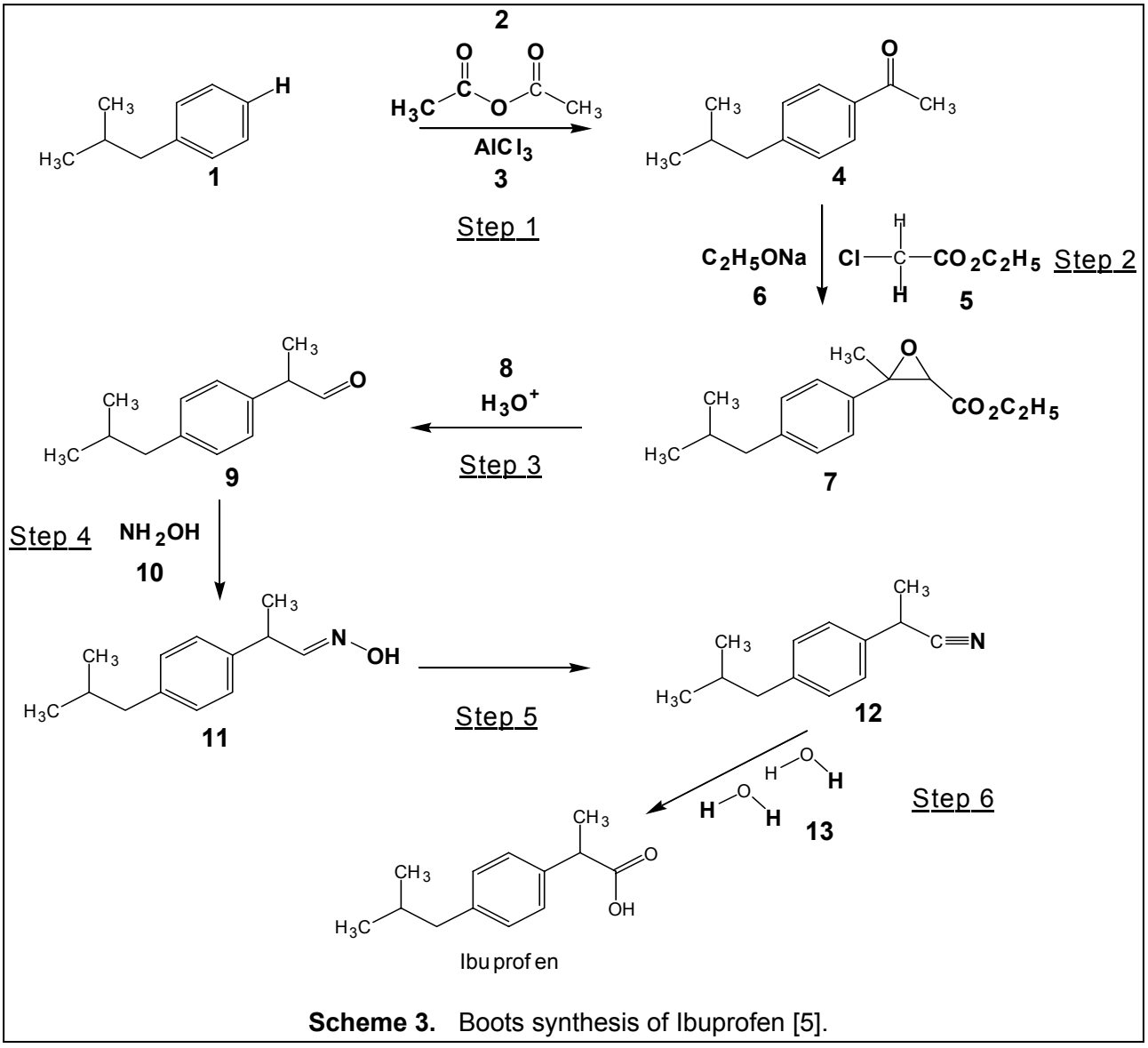
% Atom economy = 206/648 × 100 = 32%

(c)

A quick glance at the table clearly shows an imbalance heavily in favour of the 'not utilised' column. Every reagent used contributes to the waste stream and so the % atom economy of only 32% is to be expected. Steps 1 and 2, in particular, contribute almost 90% of the total mass of atoms not utilised. The number of steps, allied with the use of stoichiometric reagents, makes the Boots synthesis atom uneconomic.

GROUP 2 PRESENTATION

(a)



Scheme 3. Boots synthesis of Ibuprofen [5].

Step 1.

Step 2.

Step 3.

Step 4.

Step 5.

Step 6.

(b)

TABLE 5 BOOTS IBUPROFEN SYNTHESIS ATOM ECONOMY.

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_{10}H_{14}$			133	H	1
2	102	C_2H_3			75
3 $AlCl_3$	133.5	-	0	$AlCl_3$	133.5
5 $C_4H_7ClO_2$	122.5	CH	13		109.5
6	68	-	0	C_2H_5ONa	
8 H_3O	19			H_3O	19
10	33	-	0	NH_3O	
13 H_4O_2		HO_2	33		3
Total $C_{20}H_{42}NO_{10}Cl_4NaAl$		**Ibuprofen**		*Total* $C_7H_{24}NO_8Cl_4$ ***NaAl***	442

% Atom economy =

(c)

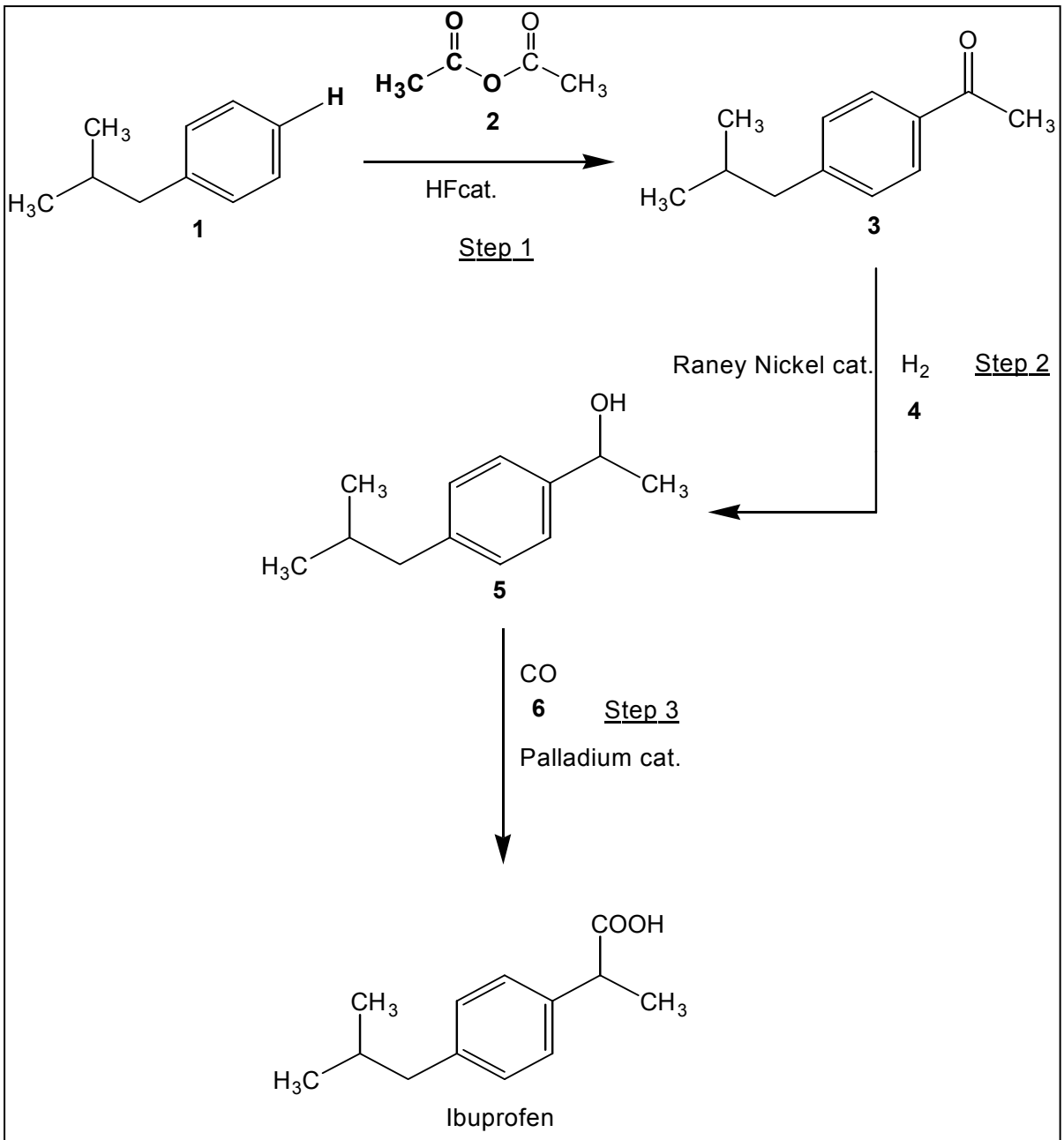
Group 3

The manufacture of pharmaceuticals is consistently shown to be amongst the top performing industrial sectors worldwide. Sales exceeding £207 billion in 2000 illustrates the industry's contribution and importance to the global economy [9]. The continued growth and success of the industry is largely dependent on the production of lucrative high volume drugs. Analgesics (painkillers) are an important class of drug exemplifying bulk production within the pharmaceutical industry. Ibuprofen is the active ingredient in many analgesics and current production is well in excess of 13,000 tonnes per annum [5]. Brand name products such as Nurofen, Brufen and Ibuleve, to name but a few, incorporate Ibuprofen to provide their analgesic action. In addition, Ibuprofen is a member of the non-steroidal anti-inflammatory (NSAI) group of drugs, which combat swelling and inflammation.

The traditional six-step synthesis of Ibuprofen was patented in the 1960's by the Boots Company PLC, Nottingham (your colleagues will describe this process) [5]. Until the early 1990's, industrial synthesis of the compound was almost exclusively by the Boots route. However, the mid-eighties saw the patent expire on Ibuprofen and, furthermore, approval from the Food and Drug Administration (FDA) was given for its over-the-counter use [5]. With the potential economic rewards apparent, a number of companies sought to develop novel methodology for the synthesis of Ibuprofen. The BHC Company, a joint venture between the Boots Company and Hoescht Celanese (now Celanese) had the greatest success. In 1992, the company initiated full-scale production of Ibuprofen at its newly built 4000 tpa processing plant in Texas [17]. The various stages of the BHC process are outlined in *Scheme 5* [5].

Considered key to the overall process, the first step in the new synthesis is a novel Friedel Crafts acylation of isobutylbenzene (***1***). Acetic anhydride is employed as the acylating agent to introduce the ketone functionality onto the aromatic ring. Although the first step in the traditional synthesis of Ibuprofen is an identical acylation, the major distinction between it and the new process is the choice of acylation catalyst. Whereas the traditional synthesis of Ibuprofen utilises aluminium trichloride ($AlCl_3$), the BHC synthesis employs anhydrous hydrogen fluoride (HF). The description of $AlCl_3$ as a catalyst is somewhat misleading given that it is used in stoichiometric amounts and, ultimately, forms large quantities of aluminium chloride hydrate waste [5]. In contrast, HF used in the new process is recovered and reused with $>$ 99.9 % efficiency [17]. Besides its role as a catalytic agent, HF also functions as a solvent for the acylation step in the new synthesis [17]. This negates the need for a co-solvent, making product recovery simpler (vacuum distillation). HF catalyses the conversion of ***1*** into ***3*** with $>$90% yield [17].

The second step in the BHC synthesis is a catalytic hydrogenation reaction. Hydrogen gas and Raney nickel are employed to reduce 4-isobutylacetophenone (***3***) to 1-(4-isobutylphenyl) ethanol (***5***). Raney nickel is a highly active form of the metal produced by the action of sodium hydroxide on a nickel-aluminium alloy ($2Ni\text{-}Al + 2NaOH + 2H_2O \rightarrow 2Ni + 2NaAlO_2 + 3H_2$) [18]. The finely divided nickel formed has a large surface area and is an extremely efficient hydrogenation catalyst, especially at room temperature. Hydrogenation of ***3*** is a heterogeneous process, *i.e.* the catalyst phase (solid) is different to that of the reactants (liquid).



Scheme 5. BHC company synthesis of Ibuprofen [5].

In its liquid state, 4-isobutylacetophenone (***3***) is charged into a reactor in the presence of hydrogen gas and catalytic amounts of solid Raney nickel.

One of the properties of the nickel catalyst is to lower the high-energy requirements associated with the cleavage of molecular hydrogen (H-H $\rightarrow$ 436 kJ/mol), otherwise it is thermally unfavourable to effect a stepwise H addition process [13c]. Selective reduction of the ketone functionality occurs, as hydrogenations of aromatic rings usually require high pressures. The separation of the liquid product (***5***) from the reaction mixture is by simple filtration. At 98 %, the conversion of ***3*** into ***5*** is extremely efficient.

The final step in the BHC synthesis is the carbonylation of 1-(4-isobutylphenyl) ethanol (***5***) to give Ibuprofen. Carbonylation of ***5*** is carried out using carbon monoxide in the presence of the soluble palladium catalyst complex, $PdCl_2(PPh_3)_2$, in an acidic medium [17,19]. This is a homogeneous process where the catalyst phase (liquid) is the same as that of the reactants. Homogeneous catalysts are generally used when selectivity is critical and, importantly, when product-catalyst separation problems can be overcome. In this case, Ibuprofen is removed from the reaction mixture by vacuum distillation [17]. The carbonylation of 1-(4-isobutylphenyl) ethanol (***5***) proceeds with 98% efficiency to Ibuprofen.

By cutting the number of steps to three, all catalytic, the BHC synthesis has dramatically reduced waste quantities associated with Ibuprofen manufacture. Moreover, larger volumes of the drug can be produced in less time and with less capital expenditure [5]. Therefore, as well as being environmentally superior to the traditional synthesis, the BHC route also offers more favourable production economics. The achievements of the BHC Company were recognised with the Kirpatrick Chemical Engineering Award in 1993 [20] and, in 1997, a Presidential Green Chemistry Challenge Award [5].

GROUP PRESENTATION

Elect a speaker to present the group's summary on the BHC synthesis of Ibuprofen. Your presentation, using the acetates provided, should cover the following points: -

d) Using *Scheme 5* on the acetate, summarise the BHC Company synthesis of Ibuprofen.

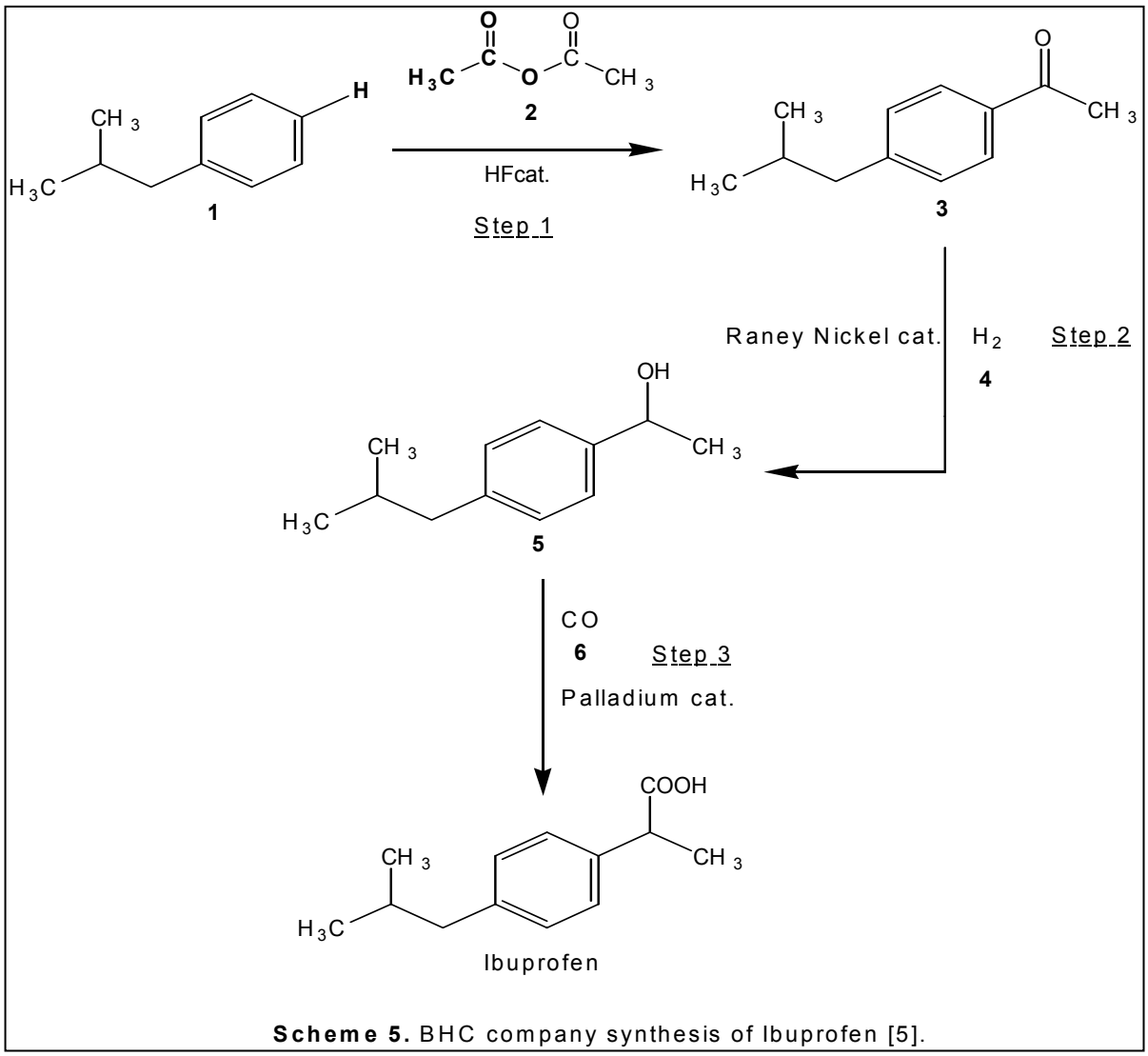
e) Discuss the features and merits of the catalyst employed in each step of the BHC process.

f) Complete *Table 6* on the acetate and, hence, calculate the percentage atom economy for the BHC synthesis. (Note: reagent atoms appearing in **bold** are not utilised in Ibuprofen). Explain your results.

g) Highlight the general environmental and economic benefits of the BHC synthesis when compared with the traditional route.

GROUP 3 TUTOR ANSWERS

(a)



Scheme 5. BHC company synthesis of Ibuprofen [5].

Step 1. *Novel Friedel-Crafts acylation of isobutylbenzene (1). Ketone functionality introduced to give 4-isobutylacetophenone (3). Identical to the first step in the traditional synthesis, but with anhydrous HF as the acylation catalyst. HF also functions as solvent – product separation easier without use of co-solvent.* >90% yield***.***

Step 2. Catalytic hydrogenation of 4-isobutylacetophenone (***3***), forming 1-(4-isobutylphenyl) ethanol (***5***). Hydrogenation takes place in the liquid phase over a solid Raney Nickel catalyst. Ketone functionality in ***3*** reduced to secondary alcohol. Heterogeneous step, therefore easy separation of product-catalyst by simple filtration. *98% efficiency*.

Step 3. Catalytic carbonylation of 1-(4-isobutylphenyl) ethanol (***5***), forming Ibuprofen. Liquid phase carbonylation of ***5*** is achieved with CO in the presence of a soluble palladium catalyst. Ibuprofen is removed from the reaction mixture by vacuum distillation. *98% efficiency.*

(b)

- **Anhydrous HF** catalyst in *Step 1* is virtually all recovered and reused. In the traditional synthesis, however, the acylation 'catalyst' is aluminium trichloride and is lost in the form of large quantities of aluminium trichloride hydrate waste.

- **Raney nickel** catalyst in *Step 2* is virtually all recovered and reused. The catalyst is formed by the action of sodium hydroxide on Ni-Al alloy ($2Ni\text{-}Al + 2NaOH + 2H_2O \rightarrow 2Ni + 2NaAlO_2 + 3H_2$). This highly active form of the metal functions as an extremely efficient hydrogenation catalyst, especially at low temperatures.

- **Palladium** catalyst in *Step 3* virtually all recovered and reused. Exists as a soluble complex $\rightarrow PdCl_2(PPh_3)_2$. This is a homogeneous step, usually applicable where high selectivity is critical and product-catalyst separation problems can be resolved.

(c) Table 6 BHC Company Ibuprofen synthesis atom economy.

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_{10}H_{14}$	134	$C_{10}H_{13}$	133	H	1
2 $C_4H_6O_3$	102	C_2H_3O	43	$C_2H_3O_2$	59
4 H_2	2	H_2	2	-	0
6 CO	28	CO	28	-	0
Total $C_{15}H_{22}O_4$	266	***Ibuprofen*** $C_{13}H_{18}O_2$	206	***Total*** $C_2H_4O_2$	60

% Atom economy = 206/266 × 100 = 77%

(d)

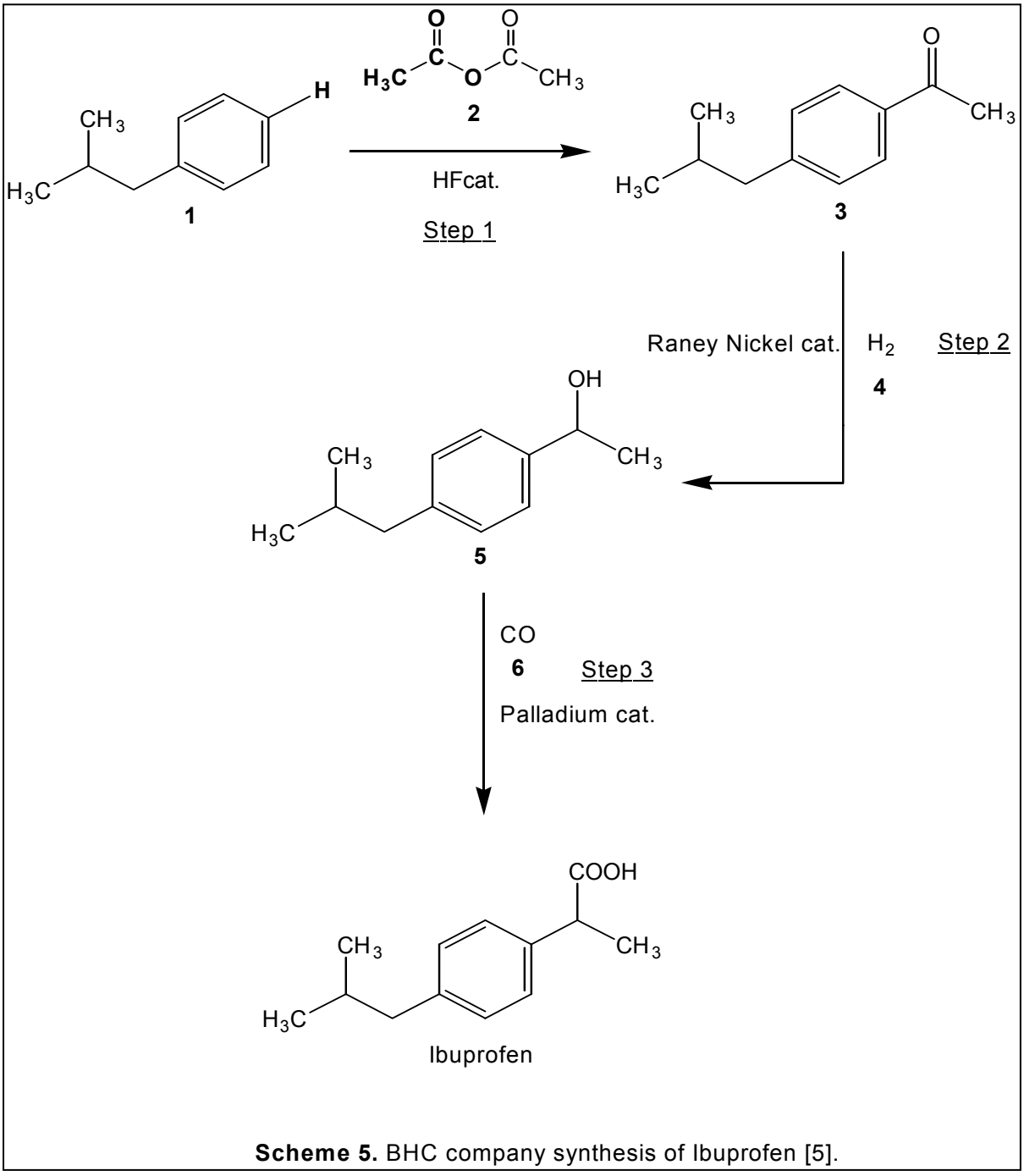
- Three steps, all catalytic, compared with six in traditional synthesis using **stoichiometric** quantities of auxiliary reagents and solvents.

- More efficient both environmentally (*e.g. Step 1*) and economically when compared with traditional synthesis.

- The achievements of the BHC Company were recognised with the Kirpatrick Chemical Engineering Award in 1993 and, in 1997, a Presidential Green Chemistry Challenge Award.

GROUP 3 PRESENTATION

(a)



Scheme 5. BHC company synthesis of Ibuprofen [5].

Step 1.

Step 2.

Step 3.

(b)

(c)

TABLE 6 BHC COMPANY IBUPROFEN SYNTHESIS ATOM ECONOMY.

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1	134		133	H	1
2	102	C_2H_3O			59
4 H_2	2		2		
6	28	CO		-	0
Total $C_{15}H_{22}O_4$		***Ibuprofen***		***Total***	60

% Atom economy =

(d)

SECTION D

GROUP 1

The Ibuprofen case study demonstrates the environmental and economic benefits achievable through alternative synthetic design. Unfortunately, however, a vast number of industrial processes persist that rely on the use of reagents in stoichiometric amounts. It is this deployment of high volume reagents in effecting chemical transformations that, ultimately, has the greatest contribution to the waste stream [21, 22, 23]. The solution to the waste problem in the chemical industry is widely accepted to be the replacement, where possible, of stoichiometric methods with 'greener' catalytic processes [21, 22, 23, 24].

INDUSTRIAL SYNTHESIS OF ETHYLENE OXIDE

Ethylene oxide (*Fig. 3*) is a key feedstock used in the manufacture of a wide range of industrially important compounds [25a]. Its success in this capacity is a direct result of the highly reactive epoxide functionality. Secondary reactions of ethylene oxide occur with a variety of nucleophiles (water, alcohols, ammonia, amines, carboxylic acids *etc*), all involving exothermic opening of the epoxide ring [25a]. At present, of the >15M tonnes [26] of ethylene oxide manufactured worldwide per annum, between 40-60% is reacted with water to yield ethylene glycol (used in antifreeze and also for polyester synthesis) [25a]. Its use in the production of other derivatives such as ethoxylates (surfactants), ethylene glycol ethers (solvents), ethanolamines *etc.* accounts for the remaining demand [25a].

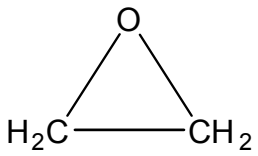
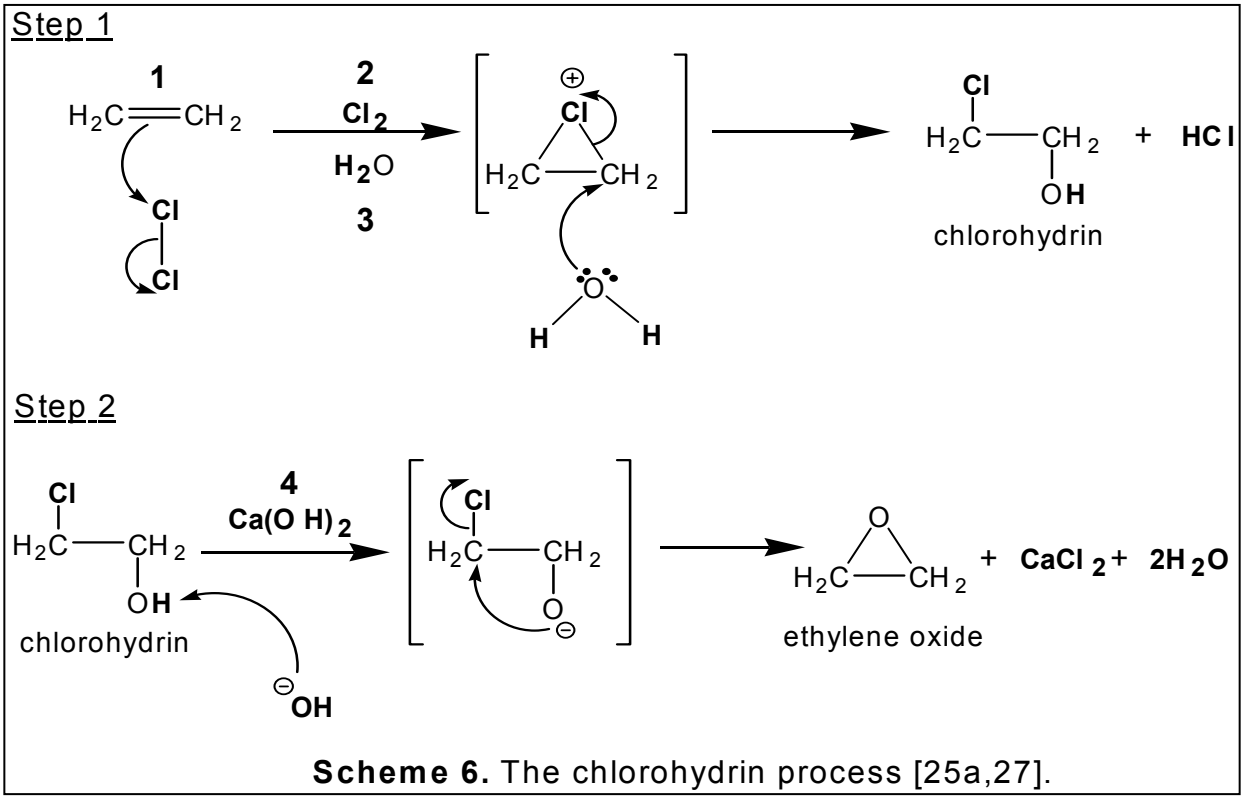


Fig. 3. Ethylene oxide

The classical industrial route to ethylene oxide is the chlorohydrin process [25a]. A two-step process, epoxidation of ethylene (***1***) feedstock is the overall result, as illustrated in Scheme 6 below [25a,27]. Reaction of ethylene with chlorine and water in *Step 1* results in the formation of the chlorohydrin. In *Step 2* the chlorohydrin is treated with base (***4***), which induces ring formation and, ultimately, the production of ethylene oxide.

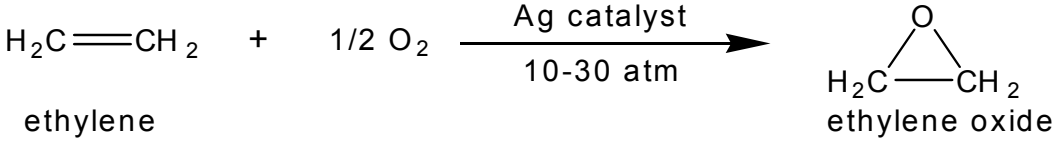


Scheme 6. The chlorohydrin process [25a,27].

Although the above synthesis shows adequate selectivity of 80%, by 1975 it was redundant as an industrial route to ethylene oxide [25a]. In addition to the complete loss of high value chlorine, the production of approx. 350 kg of $CaCl_2$ waste per 100 kg of ethylene oxide meant the process was no longer sustainable [25a].

A CATALYTIC ALTERNATIVE

As early as 1937 Union Carbide had implemented a heterogeneous catalytic process (*Scheme 7*) for the direct oxidation of ethylene [25a]. It is a one-step addition reaction, with all reactants being incorporated into the final product. At present, manufacturers of ethylene oxide almost exclusively utilise fixed bed reactor technology [25a]. Silver is the most active and selective catalyst for the reaction. Selectivity for the catalytic route to ethylene oxide is similar to that of the chlorohydrin process at around 80% [25a]. All ethylene oxide produced worldwide today is exclusively via the catalytic route [25a].



Scheme 7. Catalytic synthesis of ethylene oxide [25a].

Group Presentation

Elect a third speaker to present the group's summary on the industrial production of ethylene oxide. Your presentation, using the acetates provided, should cover the following points: -

a) Using the appropriate acetate (*Fig. 3*), indicate the uses of ethylene oxide and its current global production capacity.

b) Using the appropriate acetate (*Scheme 6*), summarise the chlorohydrin process for the production of ethylene oxide.

c) Using the appropriate acetate (*Scheme 7*), summarise the catalytic oxidation process for the production of ethylene oxide.

d) Complete *Tables 7* and *8* on the acetate and, hence, deduce the percentage atom economies for both routes to ethylene oxide. Compare and contrast your results.

GROUP 1 TUTOR ANSWERS

(a)

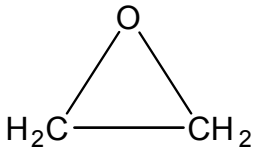
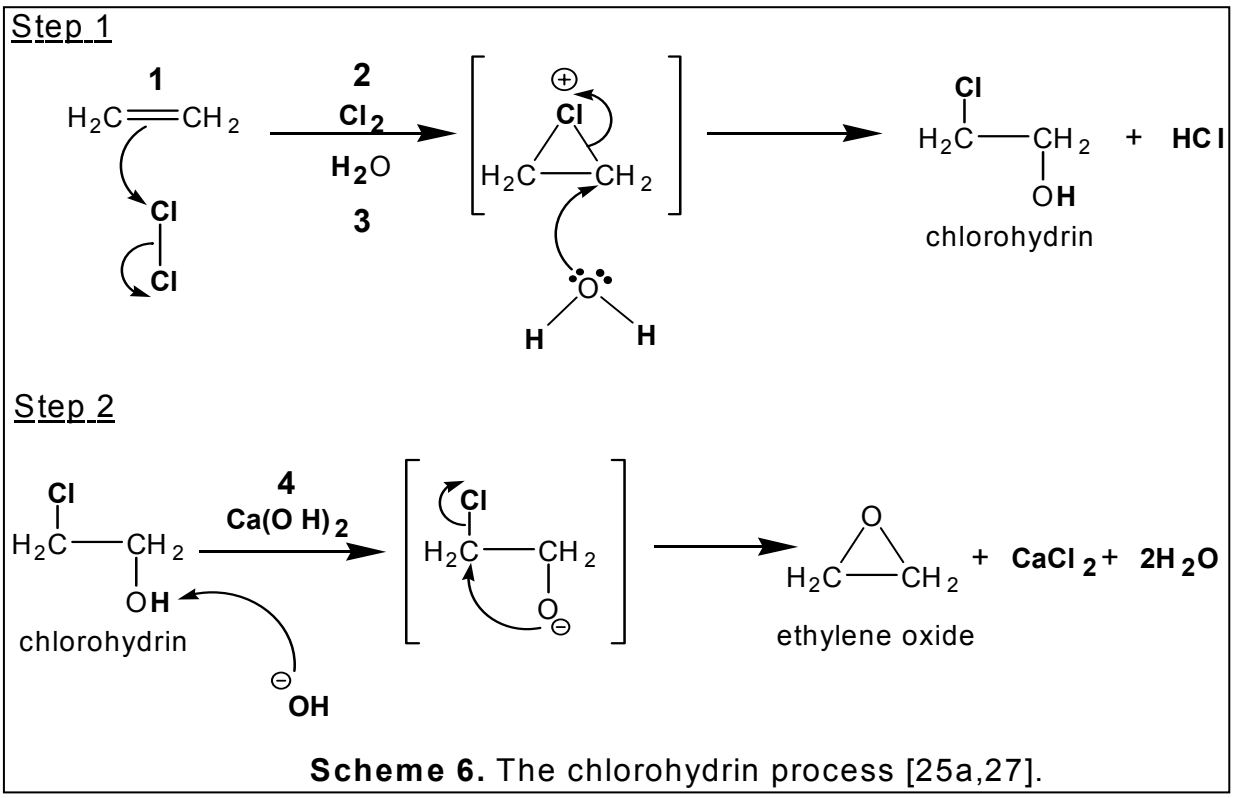


Fig. 3. Ethylene oxide

- Ethylene oxide has a limited number of direct uses, but is a key feedstock for the production of a whole range of important substances.
- Reactions, with many different nucleophilic partners, all involve opening of the highly reactive epoxide ring.
- Current global production capacity is in excess of 15 M tonnes.
- 40-60 % of all ethylene oxide is used to manufacture secondary product, ethylene glycol (antifreeze, polyester synthesis). The rest is used to manufacture other derivatives - ethoxylates (surfactants), ethylene glycol ethers (solvents), ethanolamines *etc.*

TRADITIONAL SYNTHESIS OF ETHYLENE OXIDE

(b)

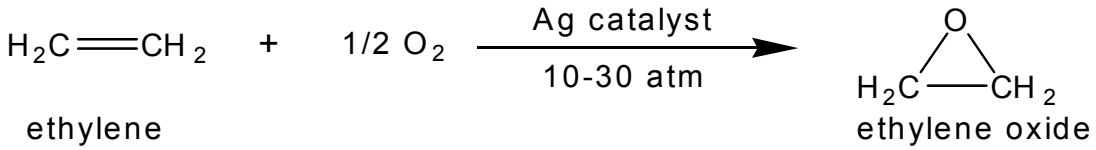


Scheme 6. The chlorohydrin process [25a,27].

- Ethylene feedstock (***1***) is epoxidated in the above overall two-step process (*Scheme 6*), with 80 % selectivity for ethylene oxide.
- *Step 1* employs chlorine and water to transform ethylene into the chlorohydrin.
- Base induced ring formation occurs in *Step 2*, transforming the chlorohydrin into ethylene oxide.
- The chlorohydrin process, however, has been redundant since 1975. Total loss of expensive chlorine and, additionally, the production of approx. 350 kg of $CaCl_2$ waste per 100 kg of ethylene oxide meant the process was no longer sustainable.

CATALYTIC SYNTHESIS OF ETHYLENE OXIDE

(c)



Scheme 7. Catalytic synthesis of ethylene oxide [25a].

- The reaction above (*Scheme 7*) is a heterogeneous one-step addition process.
- Catalytic route to ethylene oxide was implemented as early as 1937 by Union Carbide.
- Virtually all manufacturers utilise fixed bed reactors.
- Silver is the most active and selective catalyst for the reaction.
- Selectivity for ethylene oxide, as with the traditional synthesis, is around 80 %.
- All manufacture of ethylene oxide today is via the catalytic route.

(d)

Table 7 Chlorohydrin process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_2H_4	28	C_2H_4	28	-	0
2 Cl_2	71	-	0	Cl_2	71
3 H_2O	18	O	16	H_2	2
4 $Ca(OH)_2$	74.1	-	0	$Ca(OH)_2$	74.1
Total ***$C_2H_8O_3CaCl_2$***	***191.1***	Ethylene oxide C_2H_4O	44	***Total*** $H_4O_2Ca\ Cl_2$	147.1

% Atom economy = 44/191.1 × 100 = 23%

Table 8 Catalytic oxidation atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_2H_4	28	C_2H_4	28	-	0
2 ½ O_2	16	O	16	-	0
Total ***C_2H_4O***	***44***	Ethylene oxide C_2H_4O	44	Total -	0

% Atom economy = 44/44 × 100 = 100%

- The atom economy for the chlorohydrin process is poor at 23%, whereas the catalytic process shows 100% atom economy as it is an addition reaction.

GROUP 1 PRESENTATION

(a)

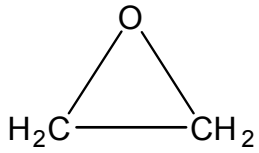
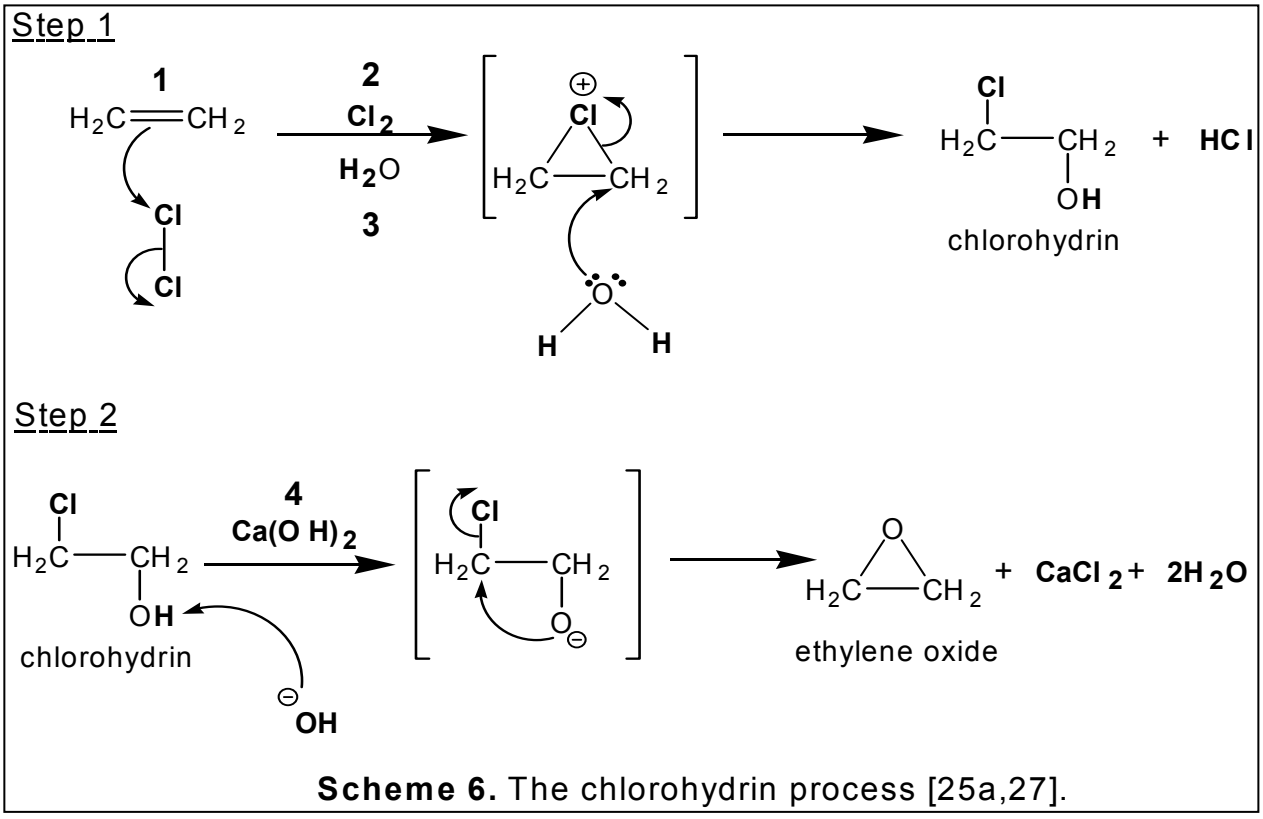


Fig. 3. Ethylene oxide

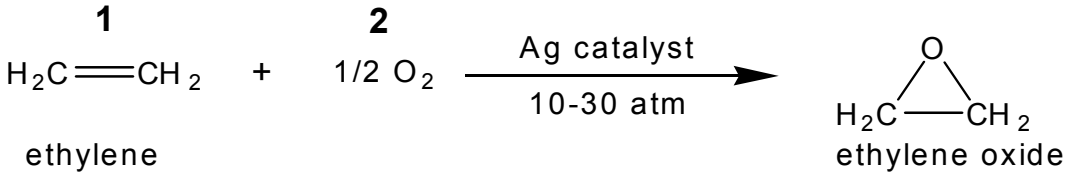
(b)



Scheme 6. The chlorohydrin process [25a,27].

(c)

CATALYTIC SYNTHESIS OF ETHYLENE OXIDE



Scheme 7. Catalytic synthesis of ethylene oxide [25a].

(d)

Table 7 Chlorohydrin process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_2H_4			28	-	0
2 Cl_2	71			Cl_2	71
3	18	O			2
4 $Ca(OH)_2$	74.1	-	0		74.1
Total ***$C_2H_8O_3CaCl_2$***		Ethylene oxide		***Total*** $H_4O_2Ca\ Cl_2$	147.1

% Atom economy =

Table 8 Catalytic oxidation atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1	28	C_2H_4		-	0
2 ½ O_2			16		
Total ***C_2H_4O***		Ethylene oxide		Total	

% Atom economy =

GROUP 2

The Ibuprofen case study demonstrates the environmental and economic benefits achievable through alternative synthetic design. Unfortunately, however, a vast number of industrial processes persist that rely on the use of reagents in stoichiometric amounts. It is this deployment of high volume reagents in effecting chemical transformations that, ultimately, has the greatest contribution to the waste stream [21, 22, 23]. The solution to the waste problem in the chemical industry is widely accepted to be the replacement, where possible, of stoichiometric methods with 'greener' catalytic processes [21, 22, 23, 24].

INDUSTRIAL SYNTHESIS OF ANILINE

Aniline (*Fig. 4*) ranks as one of the most important compounds in aromatic chemistry. Global production capacity for aniline in 2000 was in excess of 3.5M tonnes per annum [28]. By the early 1970's, the manufacture of rubber chemicals was responsible for the majority of global aniline consumption [25b]. Since then, however, demand has grown for isocyanate compounds. MDI (**m**ethane **d**iphenyldi**i**socyanate) is an aniline-based diisocyanate and accounts for over 80% of global aniline demand at present [25b]. The main use of isocyanates is as feedstock chemicals for the production of polyurethanes, which have major applications in industrial sectors such as automotives, construction, refrigeration *etc.* [25b]. Less significant is the use of aniline for the production of commodities such as dyes, pigments, pharmaceuticals, pesticides,*etc.*

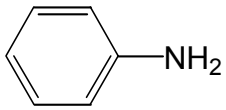
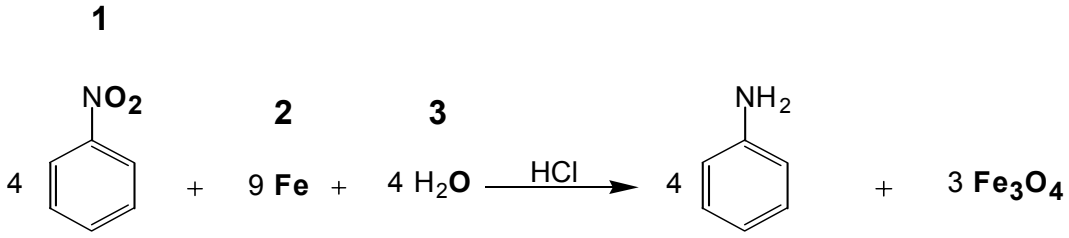


Fig. 4. Aniline

Aromatic amines are most easily synthesised by initial nitration of the aromatic ring, followed by the reduction of the nitro group to the amino group. Consequently, nitrobenzene reduction predominates as the method of choice for the industrial synthesis of aniline [29].

The traditional route to aniline is the Béchamp process (*Scheme 8*) [30]. Nitrobenzene is reduced to the amine with iron filings and water in the presence of small amounts of hydrochloric acid.



Scheme 8. Overall reaction for the Béchamp process [30].

The overall reaction illustrated in *Scheme 8* aims to represent the series of complex stepwise reactions described by equations (a) – (c) below [30]: -

(a) $2\ C_6H_5NO_2 + FeCl_2 + 6\ Fe + 10\ H_2O \longrightarrow 2\ C_6H_5N_3Cl + 7\ Fe(OH)_2$

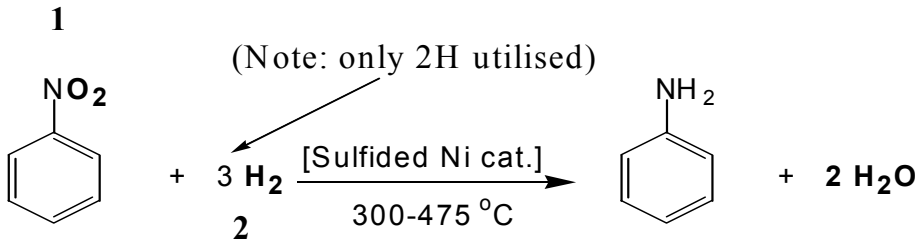
(b) $C_6H_5NO_2 + 6\ Fe(OH)_2 + 4\ H_2O \longrightarrow C_6H_5NH_2 + 6\ Fe(OH)_3$

(c) $Fe(OH)_2 + 2\ Fe(OH)_3 \longrightarrow Fe_3O_4 + 4\ H_2O$

The trigger for the Béchamp reduction is the continuous formation of $FeCl_2$, resulting from the reaction between the iron filings and HCl. It is, therefore, the iron that provides the reducing action in the process. The reduction mechanism, although not extensively studied, is presumed to proceed through a series of free radical species (*ie.* a molecule or atom with one or more unpaired electrons) [31]. A significant volume of iron (II, III) oxide (Fe_3O_4) sludge is also formed in the reaction as a by-product. In the past the Béchamp reduction proved economical as valuable iron oxide pigments could be extracted from the resultant sludge [25b]. However, the demand for aniline has greatly exceeded the market for iron pigments. As a consequence, *direct catalytic hydrogenation* techniques now account for the overwhelming majority of aniline capacity worldwide [25b].

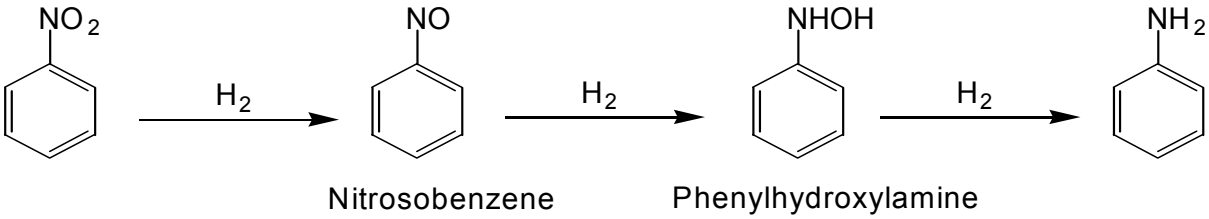
A CATALYTIC ALTERNATIVE

Catalytic hydrogenation processes for the production of aniline also employ nitrobenzene as the feedstock. As Scheme 9 below indicates, water is the only by-product arising from the synthesis. The reaction is a heterogeneous process, occurring in the gas phase, over a sulfided nickel catalyst [25b]. Selectivity for aniline is >99 % [25b].



Scheme 9. Catalytic hydrogenation of nitrobenzene [25b].

As with the Béchamp reduction, the catalytic hydrogenation of nitrobenzene proceeds through a series of intermediates. Although not accounting for dimeric intermediates (*e.g.* azobenzene), Scheme 10 below outlines the catalytic hydrogenation pathway from nitro benzene to aniline [32].



Scheme 10. Nitrobenzene hydrogenation pathway [32].

Group Presentation

Elect a third speaker to present the group's summary on the industrial production of aniline. Your presentation, using the acetates provided, should cover the following points: -

e) Using the appropriate acetate (*Fig. 4*), indicate the uses of aniline and its current global production capacity.

f) Using the appropriate acetate (*Scheme 8*), summarise the Béchamp process for the industrial synthesis of aniline.

g) Using the appropriate acetate (*Scheme 9 and 10*), summarise the catalytic hydrogenation process for the industrial synthesis of aniline.

h) Complete *Tables 9 and 10* on the acetate and, hence, deduce the percentage atom economies for both routes to aniline. Compare and contrast your results.

GROUP 2 TUTOR ANSWERS

(a)

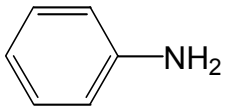
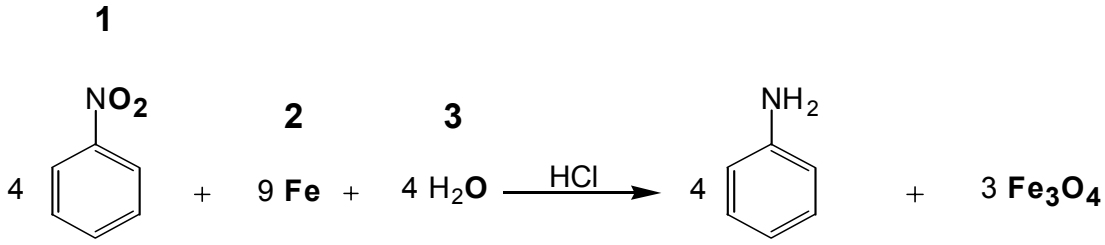


Fig. 4. Aniline

- Aniline is one of the most important compounds in aromatic chemistry. At present, global production capacity stands at over 3.5M tonnes per annum.
- Until the mid-seventies, its main use was in the manufacture of rubber chemicals. Since then, however, its demand has correlated with the growing demand for isocyanate compounds.
- The manufacture of MDI (**m**ethan**e** **d**iphenyldi**i**socyanate), using aniline as the feedstock, accounts for over 80% of global aniline consumption. MDI is used in the synthesis of polyurethanes, utilised in automotives, refrigeration, construction, *etc.* Remaining aniline demand is for the production of commodities such as dyes, pigments, pharmaceuticals, pesticides, *etc.*

TRADITIONAL SYNTHESIS OF ANILINE

(b)



Scheme 8. Overall reaction for the Béchamp process [30].

(a) $2\ C_6H_5NO_2 + FeCl_2 + 6\ Fe + 10\ H_2O \longrightarrow 2\ C_6H_5N_3Cl + 7\ Fe(OH)_2$

(b) $C_6H_5NO_2 + 6\ Fe(OH)_2 + 4\ H_2O \longrightarrow C_6H_5NH_2 + 6\ Fe(OH)_3$

(c) $Fe(OH)_2 + 2\ Fe(OH)_3 \longrightarrow Fe_3O_4 + 4\ H_2O$

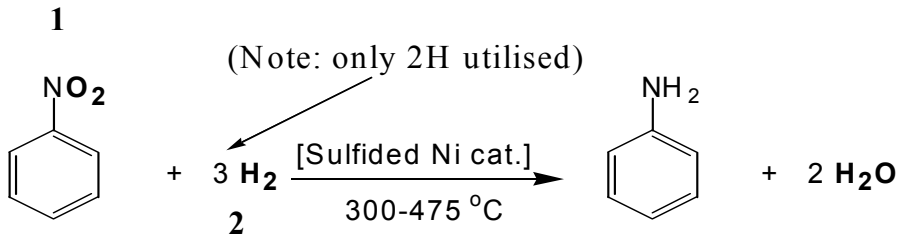
- The trigger for the Béchamp reduction is the $FeCl_2$ formed in the reaction between small amounts of HCl and iron filings. Shown in Scheme 8, the overall reaction is possibly better described as the series of stepwise reactions, (a) – (c) above.

- It is widely believed that the reaction proceeds via a series of free radical intermediates.

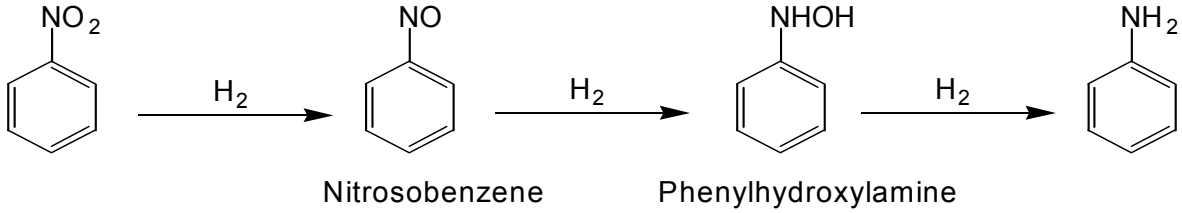
- The process generates significant volumes of iron oxide sludge. Historically, the economic viability of the process has depended largely on the extraction and sale of iron oxide pigments from the resultant sludge. Aniline demand, however, has greatly exceeded that of iron oxide pigments. Consequently, the Béchamp reduction has been virtually phased out.

CATALYTIC SYNTHESIS OF ANILINE

(c)



Scheme 9. Catalytic hydrogenation of nitrobenzene [25b].



Scheme 10. Nitrobenzene hydrogenation pathway [32].

- The gas phase hydrogenation of nitrobenzene, over a sulfided nickel catalyst (*Scheme 9*), is a heterogeneous process.

- Water is the only by-product.

- Selectivity for aniline is >99 %.

- The reaction proceeds through a series of intermediates as illustrated in *Scheme 10*.

(d)

Table 9 Béchamp process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_{24}H_{20}N_4O_8$	492	$C_{24}H_{20}N_4$	364	O_8	128
2 Fe_9	502.2	-	0	Fe_9	502.2
3 H_8O_4	72	H_8	8	O_4	64
Total $C_{24}H_{28}N_4O_{12}$ Fe_9 1066.2		***Aniline*** $C_{24}H_{28}N_4$ 372		***Total*** Fe_9O_{12} 694.2	

% Atom economy = 372/1066.2 × 100 = 35 %

Table 10 Catalytic hydrogenation atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
$C_6H_5NO_2$	123	C_6H_5N	91	O_2	32
H_6	6	H_2	2	H_4	4
Total $C_6H_{11}NO_2$ 129		***Aniline*** C_6H_7N 93		***Total*** H_4O_2 36	

% Atom economy = 93/129 × 100 = 72 %

- There is a significant improvement in atom economy with the catalytic hydrogenation. Atom economy increases to 100% if water is considered to be an innocuous by-product.

GROUP 2 PRESENTATION

(a)

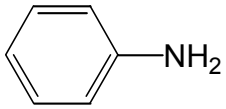
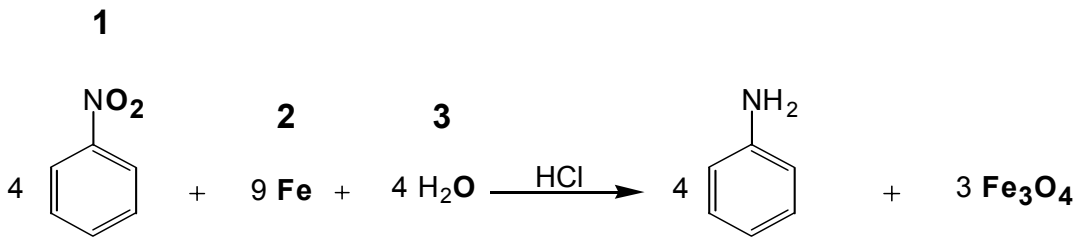


Fig. 4. Aniline

TRADITIONAL SYNTHESIS OF ANILINE

(b)



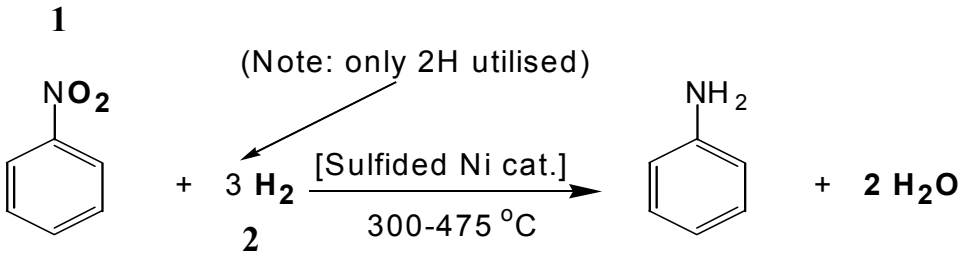
Scheme 8. Overall reaction for the Béchamp process [30].

(a) $2\ C_6H_5NO_2 + FeCl_2 + 6\ Fe + 10\ H_2O \longrightarrow 2\ C_6H_5N_3Cl + 7\ Fe(OH)_2$

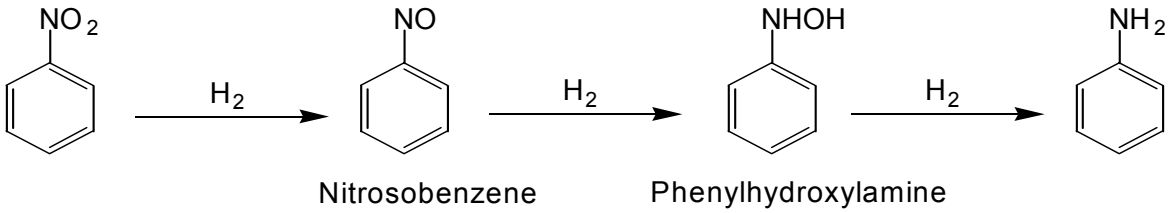
(b) $C_6H_5NO_2 + 6\ Fe(OH)_2 + 4\ H_2O \longrightarrow C_6H_5NH_2 + 6\ Fe(OH)_3$

(c) $Fe(OH)_2 + 2\ Fe(OH)_3 \longrightarrow Fe_3O_4 + 4\ H_2O$

(c)



Scheme 9. Catalytic hydrogenation of nitrobenzene [25b].



Scheme 10. Nitrobenzene hydrogenation pathway [32].

(d)

Table 9 Béchamp process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_{24}H_{20}N_4O_8$	492	$C_{24}H_{20}N_4$	364	O_8	
2	502.2			Fe_9	502.2
3 H_8O_4		H_8	8		64
Total $C_{24}H_{28}N_4O_{12}$ Fe_9		***Aniline***		***Total*** Fe_9O_{12}	694.2

% Atom economy =

<u>Table 10</u> Catalytic hydrogenation atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 $C_6H_5NO_2$	123		91	O_2	
2	6	H_2	2		4
Total $C_6H_{11}NO_2$		***Aniline***		***Total*** H_4O_2	36

% Atom economy =

GROUP 3

The Ibuprofen case study demonstrates the environmental and economic benefits achievable through alternative synthetic design. Unfortunately, however, a vast number of industrial processes persist that rely on the use of reagents in stoichiometric amounts. It is this deployment of high volume reagents in effecting chemical transformations that, ultimately, has the greatest contribution to the waste stream [21, 22, 23]. The solution to the waste problem in the chemical industry is widely accepted to be the replacement, where possible, of stoichiometric methods with 'greener' catalytic processes [21, 22, 23, 24].

INDUSTRIAL SYNTHESIS OF NITROBENZENE

The global manufacturing capacity for nitrobenzene (*Fig. 5*) currently stands at over 3.6M tonnes per annum [28, 33]. The production of aniline, a secondary product of nitrobenzene, accounts for approximately 95% of all nitrobenzene consumption [25b, 29, 33]. Consequently, the production capacity and demand for nitrobenzene closely correlates with that of aniline. The remaining demand for nitrobenzene is as an intermediate in the synthesis of dyes, pharmaceuticals, pesticides, or directly as a solvent or mild oxidising agent [25b].

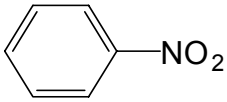
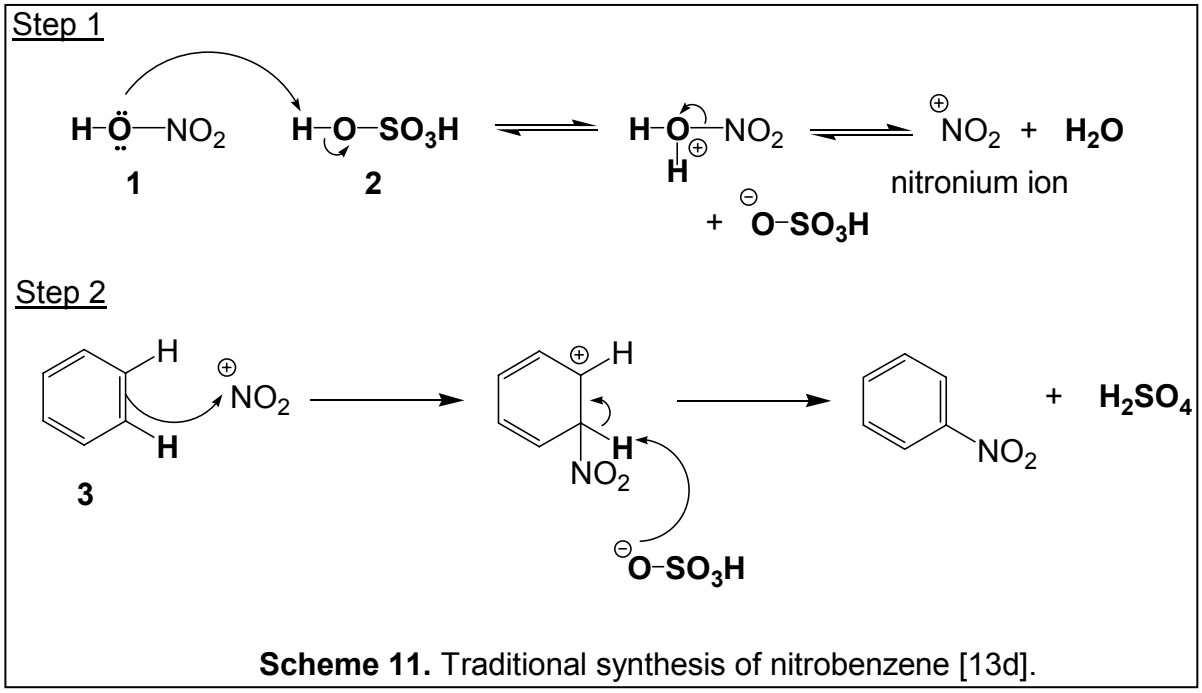


Fig. 5. Nitrobenzene

Surprisingly, the industrial synthesis of nitrobenzene (*Scheme 11*) has remained virtually unchanged since its inception in 1834 [25b,29,13d]. The traditional route involves the direct nitration of benzene (***3***) using a mixture of conc. nitric acid (***1***) and conc. sulfuric acid (***2***). The acid mixture is often referred to as nitrating acid because the reaction between them affords the nitronium ion as the nitrating species (*Step 1*). Selectivity for nitrobenzene is very high at >98%, with only a very minor amount of *m*-dinitrobenzene formed as a by-product [25b].



Scheme 11. Traditional synthesis of nitrobenzene [13d].

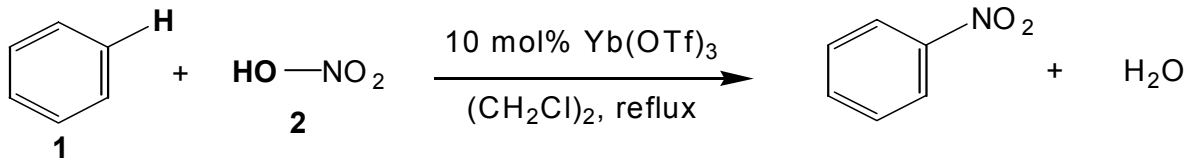
The major waste product from the reaction is a significant volume of spent sulfuric acid, which has to be collected and re-concentrated for use again in the process [29]. Another burden for nitrobenzene manufacturers is associated with wastewater treatment. The crude nitrobenzene product has to undergo a series of washing steps to remove any residual acid or organic impurities. Necessary treatment of the contaminated water resulting from the washing steps represents a significant added expense [29].

Both batch and continuous process technology can be used for the production of nitrobenzene [29]. Batch operations generally charge all reactants into a single reaction chamber, and after the reaction is complete, the desired product is extracted. In contrast continuous production methods deliver a continuous feed of reactants, usually through a cascade of small reaction vessels, yielding a continuous flow of product. Virtually all nitrobenzene manufacturers now employ continuous processes as the method offers greatly enhanced production economics [29]. Batch nitration of benzene typically takes 2-4 hours compared to 10-30 minutes for continuous nitration [29]. A 150 litre continuous nitrator offers the same production capacity as that for a 6,500 litre batch nitrator [29]. Labour costs are also significantly reduced with continuous nitration [29]. The use of batch technology in industry is usually restricted to the manufacture of low volume, high value, products (*e.g.* pharmaceuticals).

A CATALYTIC ALTERNATIVE?

Recent research conducted at Imperial College, London, has demonstrated that aromatic nitration, on a laboratory scale, can be effected using lanthanide (III) triflate catalysts [34]. Triflates are compounds containing the trifluoromethanesulfonate ($-OSO_2CF_3$) group, abbreviated to OTf. Lanthanide triflates are Lewis acids (they have unfilled valence orbitals and so can accept a pair of electrons). Unlike common

Lewis acids (*e.g.* $AlCl_3$, BF_3), however, which decompose in aqueous media, lanthanide triflates are water stable and remain Lewis acidic in aqueous solution [34,35]. Utilising a ytterbium triflate ($Yb(OTf)_3$) catalyst, the researchers have shown that nitrobenzene (> 95 % conversion) can be prepared according to *Scheme 12* below [34].



Scheme 12. Catalytic nitration of benzene [34].

Experimental results are consistent with the formation of the nitronium ion in the reaction mixture and, subsequently, nitration of the aromatic ring [34].

Two main reasons are cited as to why the catalytic nitration (*Scheme 12*) represents a more efficient and environmentally friendly process than the classical route. First, the only by-product formed is water. Secondly, the catalyst is easily recovered and can be reused for further nitrations without any downturn in performance [34].

Chris Braddock of the Department of Chemistry at Imperial College, London, was the recipient of the Jerwood Salters' Environment Award, 2000, for his work in developing the catalytic route [34]. However, it remains to be seen whether the technique can be practised successfully on an industrial scale.

Group Presentation

Elect a third speaker to present the group's summary on the production of nitrobenzene. Your presentation, using the acetates provided, should cover the following points: -

i) Using the appropriate acetate (*Fig. 5*), indicate the uses of nitrobenzene and its current global production capacity.

j) Using the appropriate acetate (*Scheme 11*), summarise the traditional route for the industrial synthesis of nitrobenzene.

k) Using the appropriate acetate (*Scheme 12*), summarise the catalytic route for the <u>laboratory scale</u> synthesis of nitrobenzene.

l) Complete *Tables 11 and 12* on the acetate and, hence, deduce the percentage atom economies for both routes to nitrobenzene. Compare and contrast your results.

GROUP 3 TUTOR ANSWERS

(a)

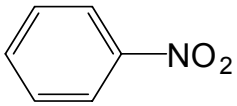
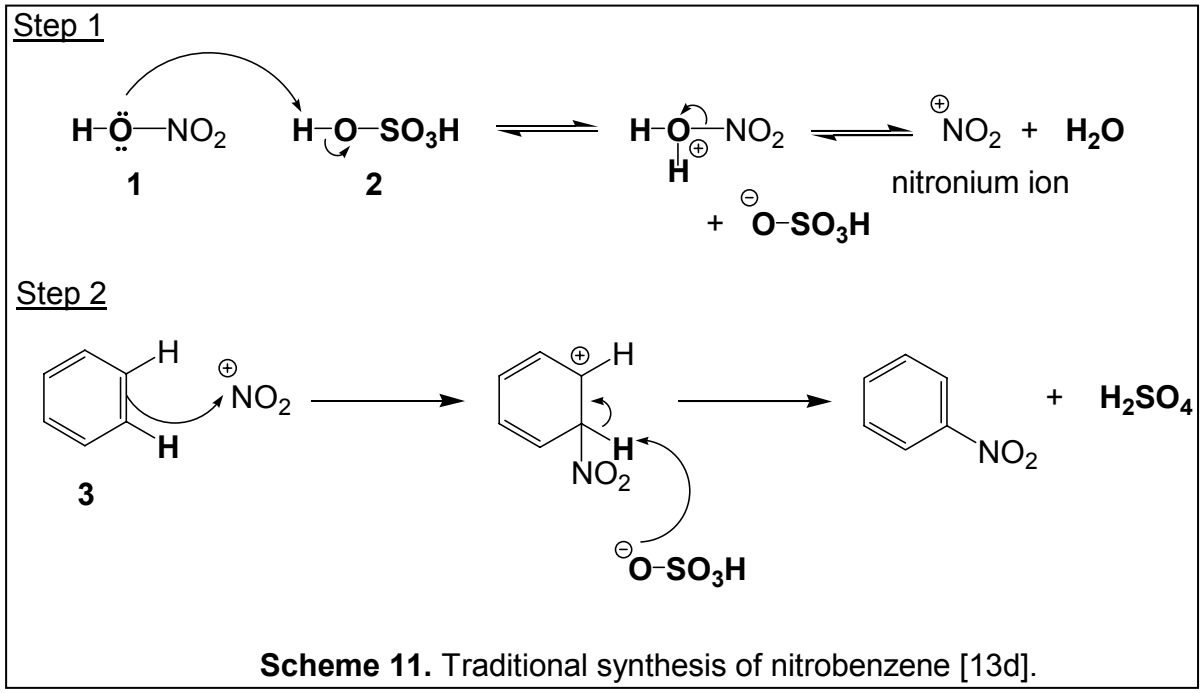


Fig. 5. Nitrobenzene

- The global manufacturing capacity for nitrobenzene currently stands at over 3.6M tonnes per annum.
- The production of aniline, a secondary product of nitrobenzene, accounts for approx. 95% of all nitrobenzene consumption. Consequently, the capacity and demand for nitrobenzene closely correlates with that of aniline.
- The remaining demand is as an intermediate in the synthesis of dyes, pharmaceuticals, pesticides, or directly as a solvent or mild oxidising agent.

(b) TRADITIONAL SYNTHESIS OF NITROBENZENE



Scheme 11. Traditional synthesis of nitrobenzene [13d].

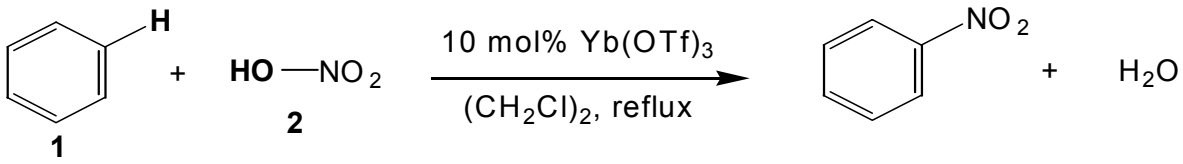
- The industrial synthesis of nitrobenzene has remained essentially unchanged since its inception in 1834. A mixture of conc. nitric and conc. sulfuric acid (nitrating acid) generates the nitronium ion as the nitrating species (*Step 1*). Direct nitration of benzene occurs with >98% selectivity (*Step 2*).

- A significant quantity of waste sulfuric acid is formed, which has to be collected and re-concentrated for use again in the process.

- The crude nitrobenzene product is also washed to remove any residual acid or organic impurities. Necessary treatment of contaminated water resulting from the washing steps represents a significant added expense for manufacturers.

- Both batch and continuous methodology can be used to manufacture nitrobenzene. However, most manufacturers utilise continuous technology, owing to better production economics.

(c) CATALYTIC SYNTHESIS OF NITROBENZENE



Scheme 12. Catalytic nitration of benzene [34].

- Nitrobenzene can be prepared on a laboratory scale using a ytterbium (lanthanide metal) triflate catalyst (*Scheme 12*).

- The catalyst is a Lewis acid, which unlike most common Lewis acids (*e.g.* $AlCl_3$, BF_3) is water stable and active in aqueous solution. It is easily recovered and can be reused for further nitrations without any downturn in performance.

- Conversion to nitrobenzene is >95% in *Scheme 12*.

- Experimental results were consistent with the formation of the nitronium ion in the reaction mixture and, subsequently, nitration of the aromatic ring.

- The only by-product formed is water.

- The route was recognised by the Jerwood Salters' Environment Award, 2000.

(d)

Table 11 Traditional process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 HNO_3	63	NO_2	46	OH	17
2 H_2SO_4	98.1	-	0	H_2SO_4	98.1
3 C_6H_6	78	C_6H_5	77	*H*	1
Total $C_6H_9NO_7S$ 239.1		***Nitrobenzene*** $C_6H_5\ NO_2$ 123		***Total*** H_4SO_5 116.1	

% Atom economy = 123/239.1 × 100 = 51 %

Table 12 Catalytic process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1 C_6H_6	78	C_6H_5	77	H	1
2 HNO_3	63	NO_2	46	OH	17
Total $C_6H_7\ NO_3$ 141		***Nitrobenzene*** $C_6H_5\ NO_2$ 123		***Total*** H_2O 18	

% Atom economy = 123/141 × 100 = 87 %

- Significant improvement in the atom economy for catalytic route - only by-product is water.

GROUP 3 PRESENTATION

(a)

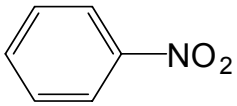
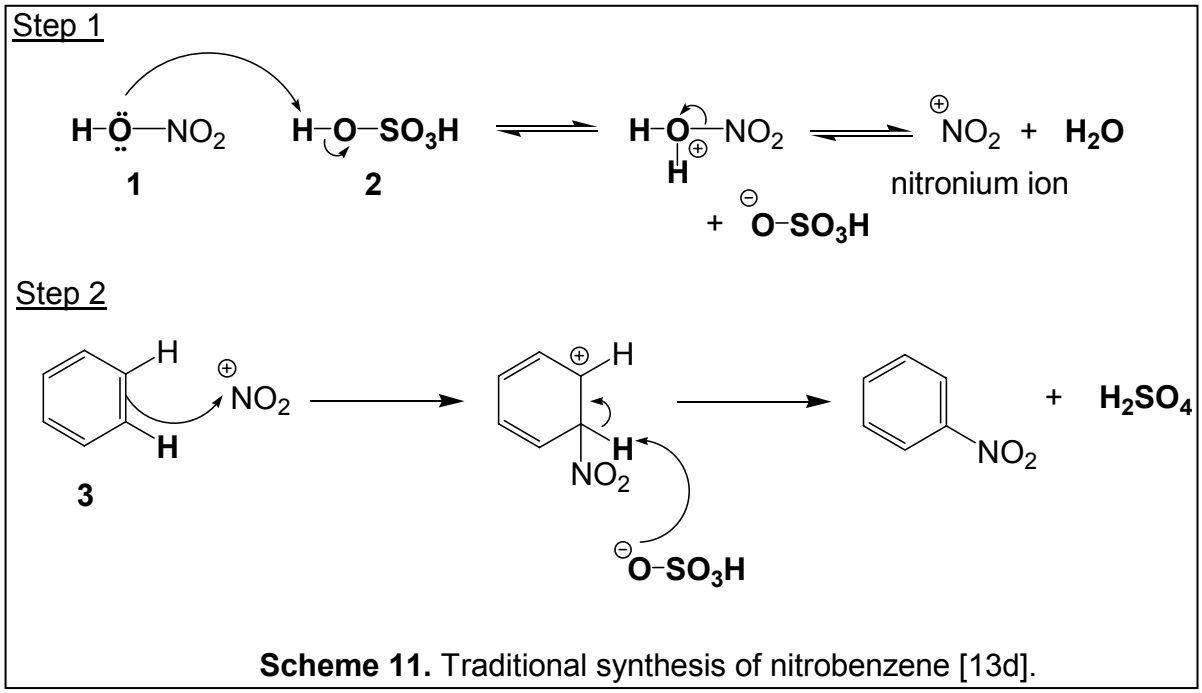


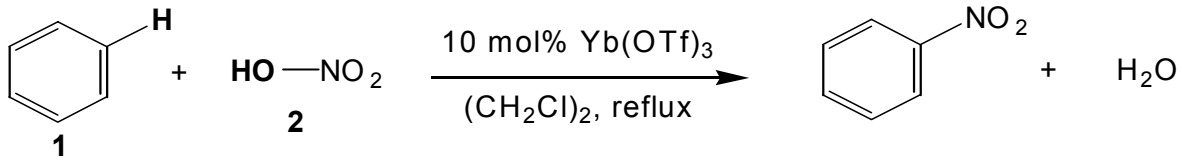
Fig. 5. Nitrobenzene

(b)



Scheme 11. Traditional synthesis of nitrobenzene [13d].

(c)



Scheme 12. Catalytic nitration of benzene [34].

(d)

Table 11 Traditional process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1	63	NO_2	46	OH	
2 H_2SO_4	98.1				98.1
3 C_6H_6			77	*H*	1
Total $C_6H_9NO_7S$		***Nitrobenzene***		***Total*** H_4SO_5	

% Atom economy =

Table 12 Catalytic process atom economy

Reactants		Utilised		Not utilised	
Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)	Formula	Formula weight (g/mol)
1	78	C_6H_5	77		
2 HNO_3		NO_2		OH	17
Total $C_6H_7\ NO_3$		***Nitrobenzene***		***Total***	18

% Atom economy =

SECTION E

Tutorial Group A

As explained earlier during the unit introduction, Anastas and Warner have established *The twelve principles of Green Chemistry*. List five Green Chemistry principles your group feels are inherent in ITU 4. Restrict your answers to a few sentences.

1.

2.

3.

4.

5.

Tutorial Group B

As explained earlier during the unit introduction, Anastas and Warner have established *The twelve principles of Green Chemistry*. List five Green Chemistry principles your group feels are inherent in ITU 4. Restrict your answers to a few sentences.

6.

7.

8.

9.

10.

Tutorial Group C

As explained earlier during the unit introduction, Anastas and Warner have established *The twelve principles of Green Chemistry*. List five Green Chemistry principles your group feels are inherent in ITU 4. Restrict your answers to a few sentences.

11.

12.

13.

14.

15.

Tutorial Group D

As explained earlier during the unit introduction, Anastas and Warner have established The Twelve Principles of Green Chemistry. List five green chemistry principles your group feels are inherent in ITU 4. Restrict your answers to a few sentences.

16.

17.

18.

19.

20.

Tutorial Group E

As explained earlier during the unit introduction, Anastas and Warner have established *The twelve principles of Green Chemistry*. List five Green Chemistry principles your group feels are inherent in ITU 4. Restrict your answers to a few sentences.

21.

22.

23.

24.

25.

PLENARY SESSION

Check-list of ITU 4 Green Chemistry Principles

1. Historically, the efficiency of a reaction has been measured by percentage yield. ITU 4 introduces what will undoubtedly become a new standard measure of reaction efficiency for practising chemists, *ie* atom economy.

✓ ***Anastas & Warner: Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.***

2. ITU 4 has demonstrated the need for a paradigm shift in the chemical industry's attitude towards waste. Environmental and economic drivers necessitate the discontinuation of end-of-pipe waste solutions. Prevention at source is undoubtedly the best remedy.

✓ ***Anastas & Warner: It is better to prevent waste than to treat or clean up waste after it is formed.***

3. Auxiliary substances such as solvents have widespread use in the manipulation of chemicals. Many have been identified as carcinogens (methylene chloride, chloroform, *etc*.), while others have had detrimental effects on our environment (*e.g.* CFCs). The BHC synthesis discussed in ITU 4 highlights a synthetic route where the reagents constitute the reaction medium, for a truly solventless process.

✓ ***Anastas & Warner: The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.***

4. ITU 4 has shown the advantages of alternative catalytic systems in reducing the waste burden associated with chemical manufacture. In contrast, stoichiometric systems tend to produce quantities of waste similar to, or in many instances, in excess of that of the desired product.

✓ ***Anastas & Warner: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.***

5. To protect human health and the environment, there is a need to minimise or eliminate the risk of exposure to synthetic chemical toxins. ITU 4 embraces the ideology of Green Chemistry, which is to exploit chemistry in a way that is both beneficial to humankind and the environment.

✓ ***Anastas & Warner: Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.***

Coursework

Table 14 below presents the *E* factors for four major sections of the chemical industry. The *E* factor, defined as the mass ratio of waste to product, varies widely across the sectors. Somewhat surprisingly, the data shows that it is the pharmaceutical industry that generates the greatest mass (kg) of waste per kg of product. By comparison, oil refining and the production of bulk chemicals are relatively 'clean' processes, owing to the widespread use of catalysis [36].

Table 14 *E* factors in the chemical industry [22]

Industry sector	Product tonnage	*E* ($kg_{waste}/kg_{product}$)
Oil refining	$10^6 - 10^8$	<0.1
Bulk chemicals	$10^4 - 10^6$	<1-5
Fine chemicals	$10^2 - 10^4$	5 - >50
Pharmaceuticals	$10 - 10^3$	25 - >100

Write a brief essay (one page of text, *ca* 500 words), using relevant examples, to justify advances in pharmaceutical processing, which could potentially effect a significant decrease in the *E* factor for this sector. Your essay should focus on the following four areas of development: -

(i) Solvents
(ii) Catalysis
(iii) Synthetic methodologies
(iv) Bio-based/renewable feedstocks

You are encouraged to read the following article [37], which is available on short loan from the Chemistry Branch Library (CBL).

Paul T. Anastas and Mary Kirchhoff, Origins, Current Status and Future Challenges of Green Chemistry, *Accounts of Chemical Research*, 2002, **35**, 9, p 686-694.

Your essay needs to be well structured, neat and easy to read. Typed reports are not obligatory. Diagrams, chemical equations and tabulated data are encouraged. Marks will be deducted for poor grammar and spelling.

Essays need to be handed in to your ITU tutor two weeks from the operation of the unit. Late coursework will incur a penalty and coursework received over one week late will not be marked. Results will be posted on the chemistry department notice board. Scripts will also be returned.

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Acknowledgements.

The authors acknowledge financial support from the University of Glasgow Learning and Teaching Development Fund. The issues highlighted are not original and due reference has been made to the primary literature when ever possible. The general concept of this ITU was inspired from reading reference [5] and from meeting with chemical educators at the IUPAC Workshop on Green Chemistry Education (Venice, 2001). The Royal Society of Chemistry is thanked for providing financial assistance that permitted attendance at that Workshop.

Department of Chemistry, University of Glasgow, January 2004.