

Pharma Services & Manufacturing Sandycroft/UK

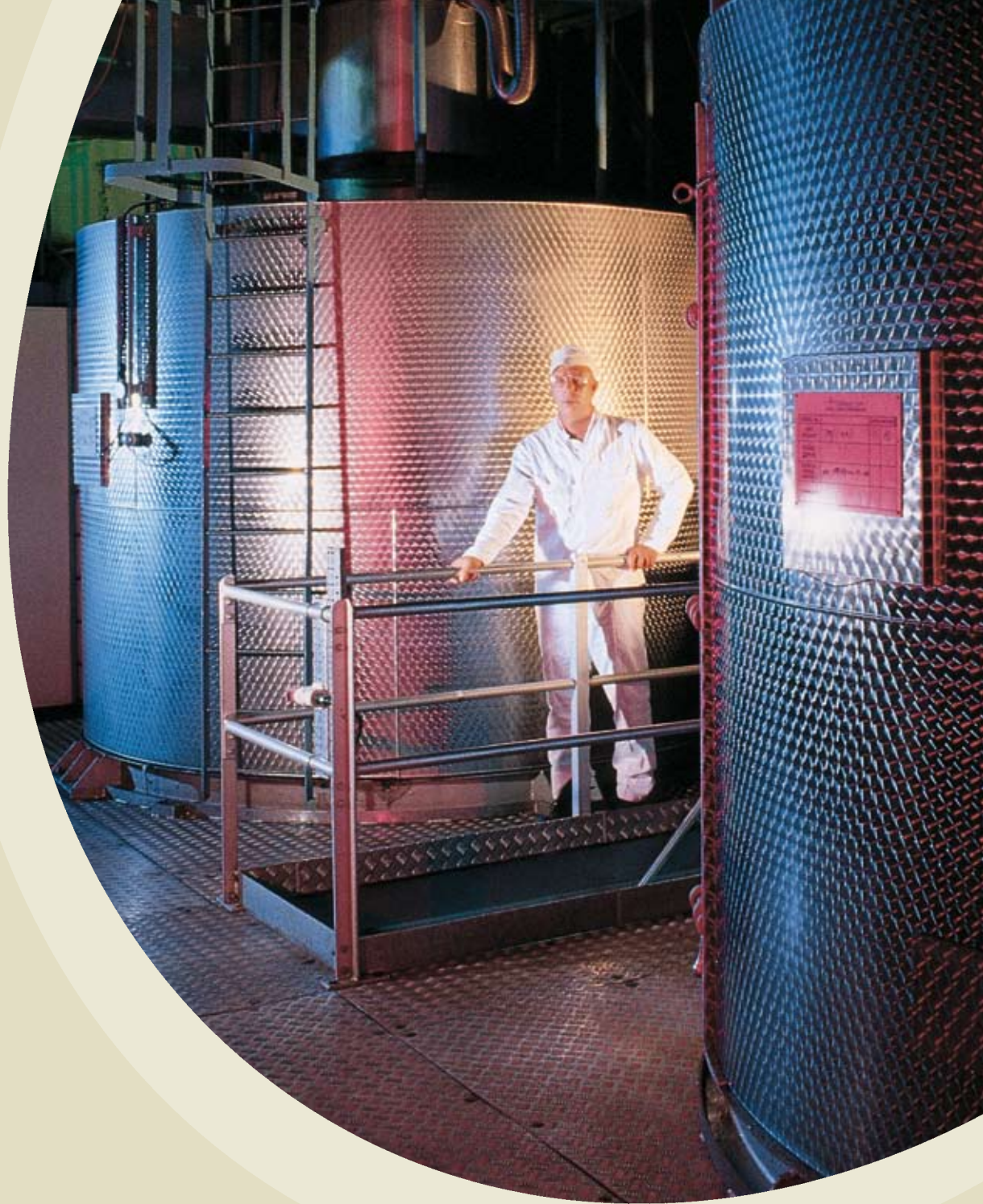
Quality Assured Solutions to Pharmaceutical
Manufacturing Challenges





Solutions Produced by Archimica

4	Manufacturing Services
5	Archimica's UK site
6	Flexible cGMP Manufacturing
7	Utilities
7	Engineering
8	cGMP Quality
9	Quality Systems
9	FDA Inspected
10	Laboratories
10	Laboratory Technologies
10	Other Laboratory Services
11	Commitment to Environment, Safety and Health
12	Active Pharmaceutical Ingredients (APIs)
13	Salicylates
14	Cardiovascular APIs
15	Other Active Ingredients
16	Iodine Chemistry
17	Aliphatic Iodides
19	Aromatic Iodides
20	Bulk Dimethyl Sulfate Handling
21	Dimethyl Sulfate
21	Methyl Ethers
21	Methyl Esters
22	Meeting Chemical Challenges Head On
23	Chlorination
23	Amination
24	Butylation
24	Alkyl Chloroformates
25	Oxidations Using Peroxygens
25	Chiral Epoxides
26	Equipment
26	Plant and Equipment
28	Contact



Manufacturing Services

Established more than 70 years ago in the northeastern corner of Wales, Archimica's production site at Sandycroft has a proven record for bulk active pharmaceutical ingredients (API) manufacture.

Archimica's UK site

Historically used to manufacture salicylates (including ethylene glycol monosalicylate, diethylamine salicylate and ethyl salicylate), the Sandycroft site now produces bulk APIs for use in the following areas:

- cardiovascular agents
- thyroid therapeutics
- antifungals
- analgesics
- antirheumatics
- antivirals

The facility also provides access to an extensive range of chemical processes including:

- alkylation
- allylation
- amination
- butylation
- chlorination
- cryogenic reactions
- esterification
- epoxidation
- methylation
- nitration
- Willgerodt-Kindler

All products manufactured at the site are subject to stringent quality assurance controls based on the principles of good manufacturing practice (GMP). The site is FDA inspected.

Sandycroft is accredited according to the ISO 9001:2000 quality standard. The organization also possesses accreditation to the ISO 14001 environmental standard.

Flexible cGMP Manufacturing

The Sandycroft facilities operate 24 hours a day. This gives us the flexibility we need to keep our processes in line with the ever-changing needs of today's business world. The following three types of manufacturing are carried out at this plant:

- batch
- semi-continuous
- continuous

Some of our facilities are dedicated, producing key products all year round. The others are multi-purpose facilities capable of supporting a variety of unit operations ranging from chemical reactions with separation and filtration to distillation and finally drying. The wide range of equipment on site includes glass-lined and stainless-steel vessels as well as stainless-steel and acid-resistant Halar centrifuges. We have several distillation units, including oil-fired and directly steam-heated equipment (with or without a vacuum).

We are able to produce varying amounts of products, from very small quantities measured in kilograms up to much larger volumes in the neighborhood of several tons. Our unit operations allow us to carry out a broad range of reactions utilizing the wealth of experience we have gained in all these areas over a period of many years.

Utilities

Water. We treat all water used in our manufacturing process in our own reverse osmosis equipment; this is followed by chemical and UV treatment and filtration to control microbiological contamination. We also have a standard demineralization plant and an ‘Aquafin’ unit to produce water meeting pharmacopoeia specifications for purified water.

Steam. Two main boilers produce 5,500 L/h of 10 bar steam from reverse osmosis quality water.

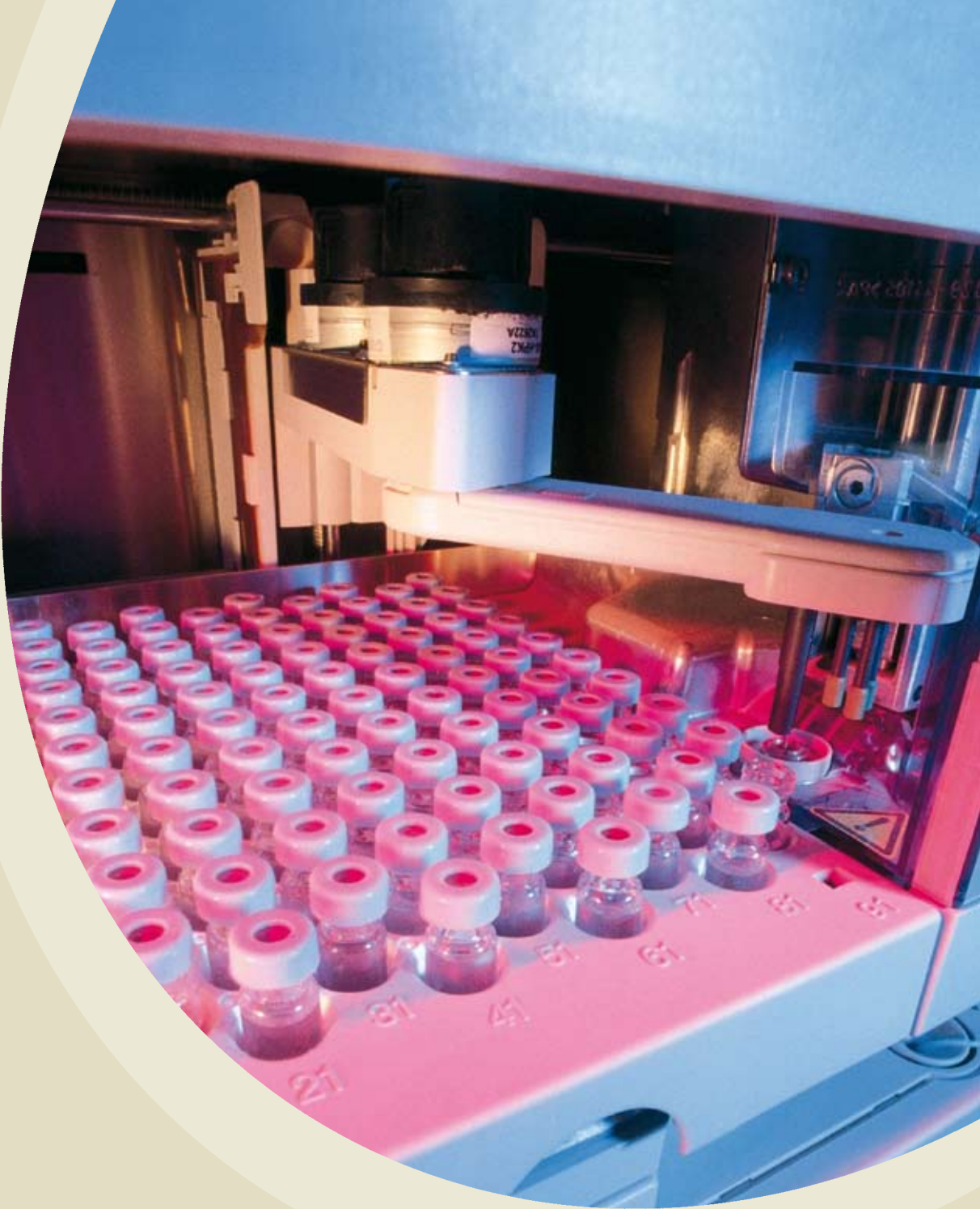
Vacuum. We have a very large selection of vacuum equipment on site to give us the range of vacuums we require (down to 0.5 mbar).

Nitrogen. Produced using a nitrogen generator system, with liquid nitrogen storage for back-up.

Effluent. There is a fully automated biological waste treatment facility on site.

Engineering

Our experienced project engineering team can respond quickly to customers’ needs by either modifying existing plants or installing new equipment to satisfy changed product requirements. All projects are designed and managed “in-house,” using well-established quality and safety-assured contractors for construction and/or installation work. All new equipment is installed to cGMP standards, including qualification and validation where required.



cGMP Quality

On Archimica's Sandycroft site, the quality control and quality assurance functions are carried out by the quality department, which is a separate independent unit that is virtually self-sufficient.

Quality Systems

The site received ISO accreditation as early as 1989; this was the first formal recognition of our quality systems.

Since then this accreditation has been updated to satisfy the requirements of the new procedural based standard ISO 9001:2000. In 2002 the organization was also accredited according to the environmental quality standard ISO 14001. Our continuous conformance to these standards is ensured by regular internal and external audits.

The site operates to current Good Manufacturing Practices – cGMP – standards which are

universally recognized as essential for all pharmaceuticals manufacturers.

All APIs are produced according to the same rigorous quality system, from raw material receipt to finished goods dispatch. All areas work to ICH Q7A, Annex 18, guidelines for API manufacture. A program of continual improvement is the key to our success. We continually upgrade systems and equipment on the site in response to revised standards, new ideas and external recommendations, e.g. from MHRA/FDA or our regular customer audits.

FDA Inspected

Because of our involvement in the manufacture of bulk pharmaceutical actives, we have always assigned a high priority to the entire subject of ‘quality’. From the late 1970s onwards, commercial links with the United States led to inspections by the U.S. Food and Drug Administration (FDA). In addition, the sites undergo numerous customer audits each year.

To facilitate use of our products by customers across the world, we have prepared Drug Master Files for all our pharmaceutical products. These are prepared on site by the quality management department with the support of staff from other departments.

Laboratories

To carry out its analyses, the quality control laboratory uses a wide range of methods. Some of these methods are specified by customers or are described in pharmacopoeia monographs; others have been developed directly on site. Our analytical techniques make use of state-of-the-art instruments with an impressive computing capability.

One area in the laboratory is dedicated to the microbiological testing of pharmaceutical bulk actives and the site's purified water production facilities. Microbiological testing, which represents the final release stage for many products, is carried out using validated methods equivalent to those described in the United States Pharmacopoeia.

Laboratory Technologies

The equipment/techniques employed include:

- HPLC equipment using both normal and reverse phase separations
- Gas chromatographs, fitted with flame ionization detectors, including head space sampling for volatile organics
- Atomic absorption spectrophotometers for quantification of metal contents
- Autotitrators for acid-base and redox reactions
- Water determinations by KF coulometric and volumetric methods
- Classical wet chemical analyses – titrations, residues, ash, etc.
- Identity tests using infrared spectrometry and refractive index measurement
- Polarimeters for determination of specific optical rotation
- Incubators and autoclaves in the microbiology laboratory

Other Laboratory Services

The laboratory produces all the final product labels for substances manufactured at the site in formats which satisfy all customer and regulatory requirements. Stability testing of APIs is carried out according to ICH guidelines under conditions of controlled temperature and humidity. Liquid and gaseous effluents are also monitored at the site by our chemical analysts.

Commitment to Environment, Safety and Health

At Sandycroft, Archimica operates within the constraints of the following accreditation standard and legislation:

- EPA Regulations (1990)
- BS EN ISO 14001:1996 Environmental Management System
- COMAH (Seveso 11) Regulations

Environmental monitoring of emissions from processes is carried out by both the UK Environment Agency and Archimica personnel. The site has been in compliance and registered under the EPA Integrated Pollution Control (IPC) Regulations for more than 10 years and is now regulated under EPA Integrated Pollution Prevention and Control Regulations (IPPC). During this period it has demonstrated continual compliance with emission limits set by the enforcing authority.

To demonstrate the continued desire to improve environmental performance, the company has registered to BS EN ISO 14001:1996.

Active programs for improving efficiency in energy, services and waste reduction are in place and have resulted in continued environmental improvements.

The on-site effluent treatment plant that has been in operation for a number of years can treat up to 350 m³ of effluent per day. It produces a good-quality final effluent stream that is discharged into the River Dee, which runs along the northeastern site boundary.

The Seveso 11 Regulations are applicable to Sandycroft and the site is currently registered as “upper tier” under these regulations. The relevant safety reports and MAPP have been filed with the enforcing authority; this gives the organization great flexibility in its operations.

During the introduction of new processes, every effort is made to ensure that the best procedures are used in order to minimize environmental impact and maximize safety on the site. This policy ensures the best practice on the site for both Archimica and its customers.



Active Pharmaceutical Ingredients (APIs)

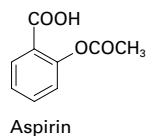
Archimica's UK site offers a range of pure APIs, as well as a number of pre-formulated products designed to ease downstream processing. In addition to our generic products, some of which are described below, we can manufacture APIs for individual customers on an exclusive, confidential basis.

Salicylates

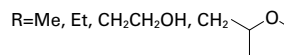
The healing properties of the willow were well known long before the active constituents were identified as derivatives of salicylic acid. We have been making pure forms of a number of these derivatives for many years. The most famous of these is, of course, acetylsalicylic acid, which everyone knows as aspirin.

We also continue to manufacture a wide range of salicylate esters. These materials have anti-rheumatic, analgesic and counter-irritant properties which make them ideal for topical liniments and sprays.

All of these products are available in pure forms meeting the requirements of the U.S., European, British and Japanese Pharmacopoeias, as well as other national standards in effect throughout the world.



Aspirin



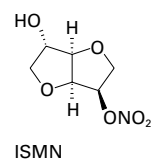
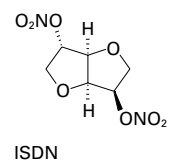
Salicylate esters

Cardiovascular APIs

We have been helping patients with angina pectoris for many years by manufacturing isosorbide dinitrate (ISDN), an effective vasodilator.

In its pure form, ISDN is an explosive. It therefore has to be manufactured under tightly controlled conditions in our dedicated nitration facility. It is also necessary to supply this material in safe, diluted forms. We can offer this product in a wide range of formulations to meet customers' individual requirements. The active metabolite of ISDN is isosorbide-5-mononitrate (ISMN).

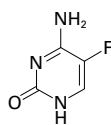
Although it is technically more difficult to manufacture this material, we have succeeded in producing this API in pure form by carefully adjusting the process originally developed for ISDN, and by altering our isolation procedures. Although ISDN continues to be an effective treatment for angina pectoris and other cardiovascular complaints, ISMN has a number of important advantages, including lower dosage requirements and faster action, which make it more suitable for many patients. We have registered Drug Master Files for these substances throughout the world, and have manufactured them under cGMP conditions for more than 25 years.



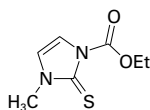
Other Active Ingredients

As well as being an intermediate in the manufacture of antiviral and anticancer drugs, 4-amino-5-fluoropyrimidin-2(1H)-one (flucytosine) is an API in its own right. It is an effective treatment for serious fungal infections of the lungs, urinary tract, central nervous system, blood and heart. It is believed that this drug acts by interfering with the synthesis of nucleic acids in fungal cells, thus preventing their development. Our manufacture of this material is covered by both U.S. and European Drug Master Files.

Carbimazole is used to treat hyperthyroidism. Our manufacture of this material has been the subject of a recent European Drug Master File submission.



Flucytosine



Carbimazole



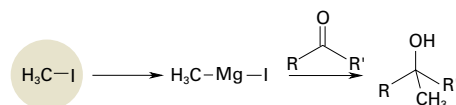
Iodine Chemistry

Iodine chemicals are a specialty of the Sandycroft site. Starting from elemental iodine, we have the capability of producing a range of iodinating agents which we then use to manufacture both aliphatic and aromatic iodine-containing compounds.

Aliphatic Iodides

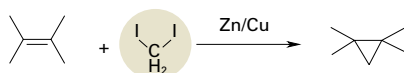
In addition to iodoform, we manufacture a number of aliphatic iodide derivatives using a variety of techniques. We are a major manufacturer of methyl iodide and can supply different grades of this material to satisfy the requirements of a wide range of applications. The product range includes

low-moisture grades suitable for use in Grignard or other organometallic reactions. Because of the volatile nature of methyl iodide, we supply it in specially-designed, secure packaging. A range of pack sizes is available to meet specific customer requirements.

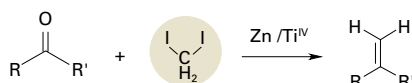


Another important product is diiodomethane. The use of this material in the Simmons-Smith

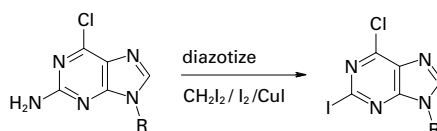
synthesis of cyclopropane derivatives is one well-known application.



Other important uses of diiodomethane can be found in the methylenation of carbonyl compounds...



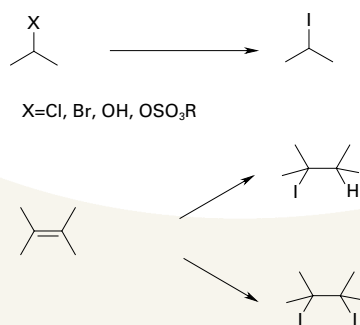
...and as an iodine source in the conversion of aminopurine derivatives to the corresponding iodo derivatives.



Until recently, chloriodomethane was available as a minor by-product of diiodomethane manufacture. We have now developed improved manufacturing methods to increase the availability of this substance, which is used in the preparation of chloromethyl derivatives, including chloromethyl esters.



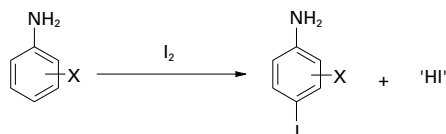
In addition to the materials mentioned above, we can also manufacture longer-chain alkyl iodides starting from a number of convenient raw materials as illustrated below.



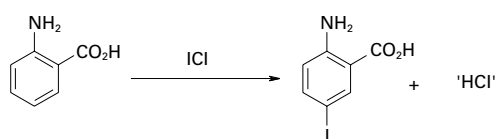
As well as manufacturing iodine chemicals, Archimica has extensive experience of using these materials in the downstream manufacture of more complex products.

Aromatic Iodides

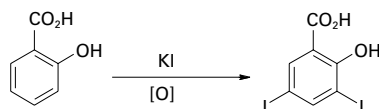
Our Sandycroft site has developed a broad and very variable toolbox to introduce iodine to aromatic rings. Thus, we always are able to select the best method for a new application. Activated aromatic compounds are often readily iodinated by elemental iodine.



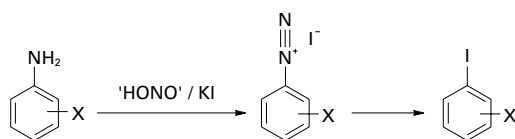
This approach is clearly wasteful of expensive iodine. Oxidizing agents can be used, however, to increase the atom utilization of iodine. One method used at Sandycroft employs chlorine gas to convert iodine to iodine monochloride, which is then used as the iodinating agent.



A number of other in situ methods have been developed which use iodide in the presence of oxidizing agents instead of elemental iodine. These are used, for example, in the manufacture of diiodosalicylic acid.



For inactivated substrates, the Sandmeyer reaction is the method of choice. Both the diazotization step and the decomposition of the intermediate diazonium salt can be carried out under very mild conditions, with no need for Cu catalysts. This means that excellent yields of very pure products can be achieved.





Bulk Dimethyl Sulfate Handling

Many of the traditional products manufactured at Sandycroft were phenolic ethers prepared by alkylation of the parent phenol. As a result, we have many years of experience in handling dimethyl sulfate and other alkyl sulfates with safe, custom-designed bulk handling systems.

Dimethyl Sulfate

Dimethyl sulfate (DMS) is a highly reactive and toxic substance which has to be handled under special precautions. With a well-established safety concept for the use of this material, and Sandycroft's many years of experience in downstream chemistry, we have been able to develop dedicated systems, designed to the highest standards, for safe

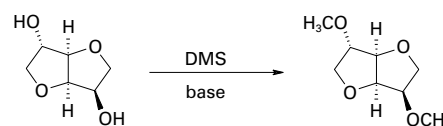
handling of this substance. All of these processes can be carried out under cGMP conditions.

In addition to its use in the manufacture of methyl iodide, DMS can be used to carry out a wide range of O-, N-, and S-methylations. We also have the capability to perform the corresponding ethylation reactions using diethyl sulfate.

Methyl Ethers

The conversion of phenols to the corresponding alkyl ethers using alkyl sulfates is a well-established process at Sandycroft. The dedicated feed systems ensure very accurate metering of the DMS and other reagents into the reaction vessels, thereby minimizing wasteful decomposition of the DMS and maximizing product yields.

Alkylation of aliphatic alcohols is another process carried out at Sandycroft. A good example of this is the formation of dimethylisorbide, a very mild carrier for cosmetic as well as pharmaceutical skin treatments.



Methyl Esters

Although there are many other routes which can be followed to form methyl esters, techniques using DMS are very selective and offer rapid, high conversions under relatively mild conditions. This approach is ideal for the esterification of expensive substrates.





Meeting Chemical Challenges Head On

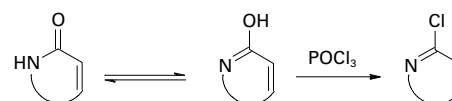
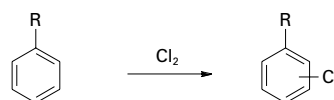
At Sandycroft, we carry out many different reactions, frequently under cGMP conditions. These often involve highly reactive or corrosive reagents which present special challenges.

Chlorination

Our capabilities at Sandycroft allow us to execute chlorinations in various ways. We have a modern facility for the safe handling of chlorine gas and can chlorinate a wide range of aromatic substrates.

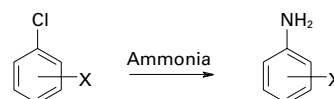
Different catalyst systems can be used to ensure optimum yield and product selectivity.

We also handle phosphoryl and sulfuryl chlorides. Phosphoryl chloride is mainly used in substitution reactions with hydroxyl-substituted hetero-aromatics.



Amination

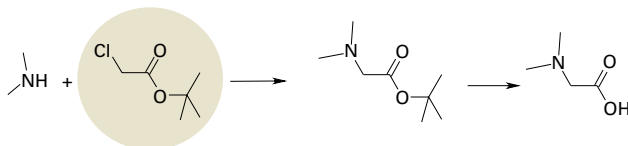
Aminations using anhydrous ammonia are another specialty of the Sandycroft site. Gaseous ammonia is fed from bulk containers into dedicated reactors which can operate at pressures of up to 5 bar.



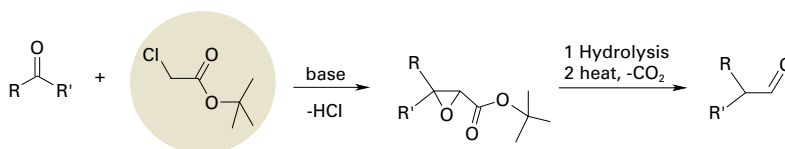
Butylation

Another liquefied gas used regularly at Sandycroft is isobutylene. This can be used to produce tert-butyl derivatives of aromatics and tert-butyl ethers. However, it is mainly used in the production of tert-butyl esters. One of these products, tert-butyl chloroacetate, finds extensive use in

the formation of N-acetic acid derivatives, since the tert-butyl ester intermediates are more readily hydrolyzed than the corresponding ethyl esters prepared from ethyl chloroacetate or the more expensive bromo analogues.

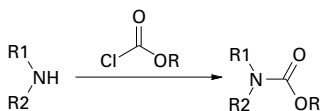


Another useful reaction making use of tert-butyl chloroacetate is the glycidic ester (Darzens) condensation which, in this case, enables aldehydes or ketones to be converted into aldehydes containing one extra carbon atom.

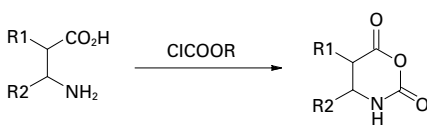


Alkyl Chloroformates

Alkyl chloroformates are very reactive, lachrymatory materials. They are handled safely at Sandycroft using systems identical to those for handling dialkyl sulfates. The main use of alkyl chloroformates is in carbamate formation, as shown below.



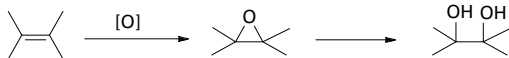
When two nucleophilic groups are available, ring compounds are possible, e.g. oxazinane-diones, which are key intermediates in the manufacture of a wide range of APIs.



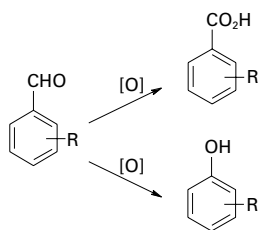
Oxidations Using Peroxygens

One of the most recent additions to our technology range is oxidation using environmentally friendly peroxygen reagents. Handling these substances requires scrupulous precautions to prevent wasteful and potentially hazardous decomposi-

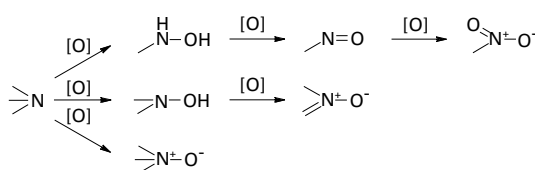
tion of these reagents. With the systems we have in place, a wide range of oxidation reactions is now feasible including oxidation of olefins, | Fig. 1 aldehydes | Fig. 2 and nitrogen- and sulfur-containing compounds. | Figures 3 + 4



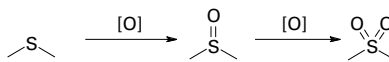
| Fig. 1



| Fig. 2



| Fig. 3



| Fig. 4

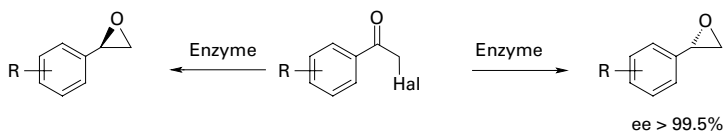
Chiral Epoxides

We have developed different high-yielding technologies for the production of epoxides with very high enantio- and diastereoselectivities. Having such a broad selection of complementary technologies enables us to tackle every new project with the best approach from the very beginning.

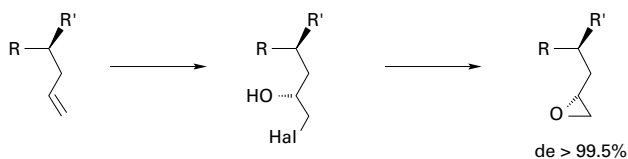
As only one example from our technology portfolio, we have developed and scaled an enzymatic process for chiral epoxides starting from halogenated ketones. Both aliphatic and aromatic

epoxides can be produced in very high ee yield and chemical purity, with very broad functional group tolerance.

Other methods involves diastereoselective cyclisation reactions starting from vic-Diols, 2-Haloalcohols and Olefines. In the latter case, we are converting these into halohydrins first, which can be cyclised with very high diastereoselectivity under very careful process control.



ee > 99.5%



de > 99.5%

Equipment

Archimica's manufacturing facilities are organized into self-contained departments, most of which are in separate buildings. This gives us the flexibility to carry out a wide variety of chemical operations without risk of cross contamination between products.

Plant and Equipment

<i>Plant</i>	<i>Material of Construction</i>	<i>Volume</i>	<i>Description</i>
Department 3	Glass-lined steel	2,270 L	5 reactors
	Glass-lined steel	4,545 L	2 reactors
	Stainless steel	2,270 L	1 reactor
	Stainless steel	4,545 L	1 reactor
	Stainless steel	3 m ²	1 vacuum filter dryer
	Stainless steel	–	1 vertical vacuum paddle dryer
	Titanium	2,270 L	1 reactor/mixing vessel
Department 4	Stainless steel	–	1 horizontal vacuum rotary dryer
	Stainless steel	–	1 horizontal double ribbon blender
Department 5	Glass-lined steel	1,360 L	1 reactor
	Stainless steel	1,360 L	1 reactor/mixing vessel
	Stainless steel	4,545 L	1 reactor
	Stainless steel	–	1 horizontal basket centrifuge
	Stainless steel	–	2 horizontal vacuum tray dryers
	Stainless steel	–	1 horizontal rotary blender
Department 9	Glass-lined steel	1,360 L	2 reactors
	Stainless steel	450 L	1 reactor
	Stainless steel	680 L	1 reactor
	Stainless steel	910 L	1 reactor
	Stainless steel	–	1 vertical vacuum paddle dryer
	Stainless steel	–	1 horizontal basket centrifuge
	Stainless steel	–	1 horizontal double ribbon blender

<i>Plant</i>	<i>Material of Construction</i>	<i>Volume</i>	<i>Description</i>
Department 12	Glass-lined steel	910 L	1 reactor
	Glass-lined steel	2,270 L	1 reactor
	Glass-lined steel	4,545 L	1 reactor
	Glass-lined steel	–	1 vertical vacuum double cone dryer
	Halar-lined steel	–	1 horizontal basket centrifuge
Department 15	Glass-lined steel	225 L	1 reactor
	Glass-lined steel	450 L	1 reactor
	Glass-lined steel	2,270 L	1 reactor
	Glass-lined steel	4,545 L	3 reactors
	Stainless steel	1,360 L	1 reactor
	Stainless steel	4,545 L	1 reactor, refrigeration capability to – 50°C
	Stainless steel	4,545 L	1 reactor/mixing vessel
	Stainless steel	–	1 horizontal vacuum paddle dryer
	Stainless steel & glass	–	1 distillation plant (still, column & receivers)
Department 16	Glass-lined steel	1,360 L	1 reactor
	Glass-lined steel	2,270 L	2 reactors
	Stainless steel	2,270 L	2 reactors
Department 17	Glass-lined steel	450 L	2 reactors
	Glass-lined steel	680 L	1 reactor
	Glass-lined steel	2,270 L	3 reactors
	Glass-lined steel	4,545 L	1 reactor
	Stainless steel	1,360 L	1 reactor
	Stainless steel	2,270 L	2 reactors
	Stainless steel	4,545 L	1 reactor
	Stainless steel	–	1 horizontal basket centrifuge
	Stainless steel	–	2 horizontal vacuum tray dryers
	Stainless steel	–	3 vertical double cone blenders
	Stainless steel	–	3 horizontal rotary sifters



Archimica
Prince William Avenue
Sandycroft
Deeside
Flintshire
CH5 2PX
UK

Phone: +44 (0)1244 520777
Fax: +44 (0)1244 537216

E-mail: sales.uk@archimica.com
Internet: archimica.com