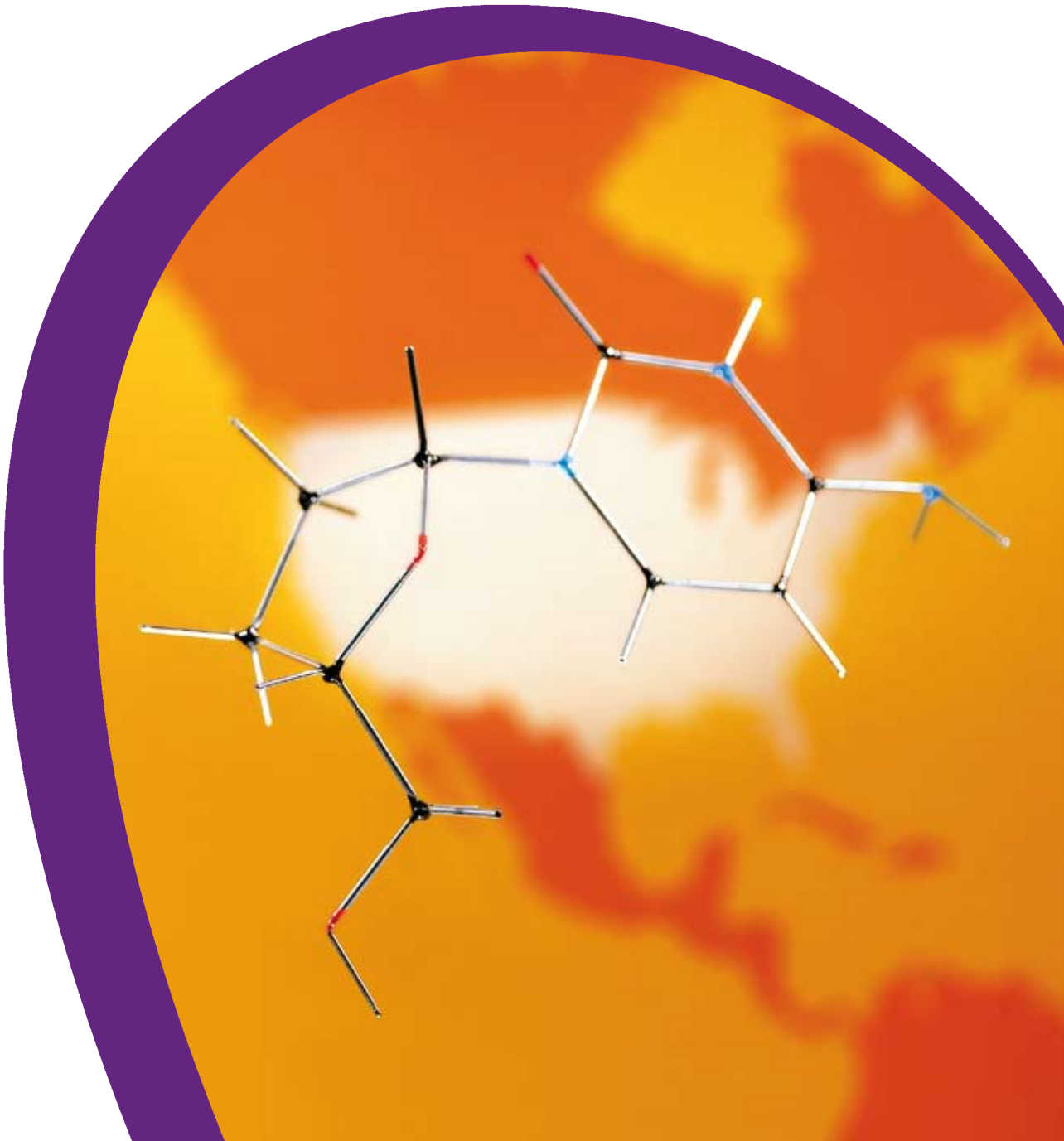
Archimica

Pharma Services & Manufacturing Springfield, MO/USA

Innovative Solutions from R & D to Commercial Production



Solutions Made by Archimica from America's Heartland

4 **cGMP & API Services**
5 Controlled Substances
5 Chemical Research & Development
5 Manufacturing

6 **Kilo Laboratory & Piloting**
7 Laboratory Services & Kilo Lab
7 Process Scale-up & Technology Transfer
8 Process Development
9 Pilot Production

10 **Manufacturing**
12 Nitration
13 Bromination
13 Chiral Epoxides
14 Organometallic & Cryogenic Chemistry
14 Ethylhydroxylation
14 Etherification
15 $TiCl_4$ Chemistry
15 Other Reactions

16 **Quality**
17 FDA Inspections and Training
17 Quality Assurance and Customer Support

18 **Environment, Safety & Health**
19 Environment
19 Safety & Health

20 **Equipment**
20 Laboratory, Multi-purpose Pilot Plant and Manufacturing
22 Analytical Laboratory

23 **Contacts**

cGMP & API Services

Innovation requires know-how and passionate enthusiasm, expertise and the spirit of discovery, persistence and flexibility. Based on decades of experience in pharmaceutical synthesis, we are cultivating a tradition of thinking ahead to find optimal solutions for our customers' needs.

Archimica combines global cGMP manufacturing capabilities with comprehensive pharmaceutical services, customer-oriented Research & Development and outstanding technology development assets. With our global network of operations in Springfield/Missouri, United States, Sandycroft/United Kingdom, Bon-Encontre and Tonneins/France, Origgio/Italy, and our Technology Center in Frankfurt/Germany, we are an experienced outsourcing partner for leading pharmaceutical companies. We offer our customers active pharmaceutical ingredients (APIs), regulated intermediates, and building blocks based on a broad portfolio of leading technologies such as organometallic chemistry including lithium technology, cryogenics or chiral chemistry.

Archimica's Springfield site is dedicated to development and manufacture of cGMP building blocks and active ingredients for the pharmaceutical industry. Springfield offers full spectrum services ranging from the manufacture of first quantities in the laboratory for preclinical development, to production of clinical material in the pilot plant and finally, process validation and commercial material at plant scale.

Due to the availability of very large-scale equipment (up to 24 m^3 reactors), we can offer significant economies of scale for large-volume intermediates, building blocks and APIs.

Controlled Substances

The Springfield facility is registered with the U.S. Drug Enforcement Agency for handling controlled substances. The site maintains current DEA registrations for the manufacture, research, analysis and export of Schedule II Controlled Substances. The site is equipped with a DEA inspected storage vault and secure manufacturing and laboratory facilities.

Chemical Research & Development

At our laboratories and pilot plant, we develop processes fit for transfer to commercial manufacture and produce quantities from several grams to several tens of kilograms.

Our processes are performed according to cGMP standards. We continuously develop new technologies and methods and improve our current processes. Our services cover the entire spectrum of process-related activities – from the development of a synthetic route through scale-up to piloting in our multi-purpose unit and to full-scale manufacturing.

We routinely conduct risk evaluation and process safety investigations to assure a newly developed process can be run safely.

Manufacturing

Commercial manufacturing is carried out on a scale from several tons up to multiple hundreds of tons applying a variety of reactions and special operations. Six uniquely designed manufacturing facilities are located on the Springfield site, each operating under cGMP standards.

Kilo Laboratory & Piloting

Springfield operates a full-fledged cGMP kilo lab and attached pilot plant with an experienced team of synthetic organic chemists. Both facilities are run as fast response units for clinical materials supply. We are well recognized for custom synthesis and manufacturing experience in complex multi-step processes. Our project management system controls critical milestones as well as timelines and provides regular feedback to our customers.

Laboratory Services & Kilo Lab

Our laboratories are equipped to handle nearly any chemical reaction that might be requested for synthesis of new substances and route development. Manufacturing quantities range from a few grams to multiple kilograms produced according to cGMP standards.

Process Scale-up & Technology Transfer

Very few organizations have as much practical experience in scaling up a process from research quantities to the commercial level as Archimica's pharma business. Much of our synthesis work focuses on designing processes that can quickly provide material for use in development and, at the same time, are transferable into commercial scale production. Our senior team of chemists is able to draw on our comprehensive synthetic expertise and select the most appropriate project group for each aspect of the development work. These teams manage and monitor a project from developmental trials to the final delivery of the compound, working either in the laboratory or in the pilot plant, ensuring a constant product quality over the whole product lifecycle from the very beginning ('integrated prototyping').

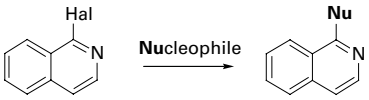
The piloting facilities available in Springfield which simulate full-scale production conditions provide an excellent transition from the laboratory to a production plant.

Process Development

We engage in comprehensive process development according to our customers' requirements taking all aspects of production into consideration – from selection and qualification of raw materials over the actual process design up to treatment of resulting waste streams.

The examples below highlight a few topics we have been currently working on:

Nucleophilic Substitution



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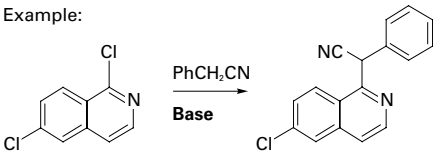
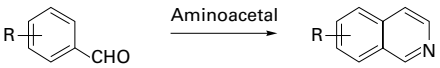
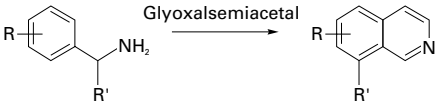
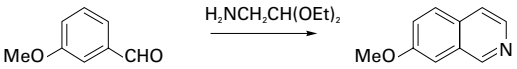


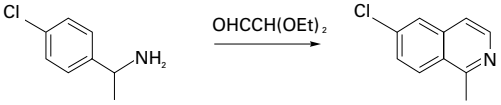
Isoquinoline Synthesis



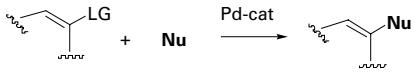


Examples:



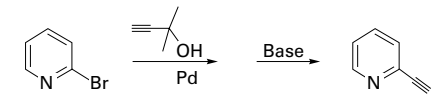


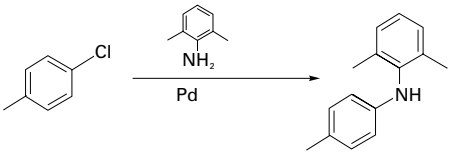
Transition Metal Catalyzed Coupling Reactions
(C-C, C-Heteroatom, C-Met)



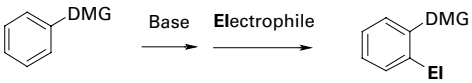
LG = Leaving Group

Examples:





Directed Metalation and Metal-Halogen Exchange



DMG = Directed Metalation Group

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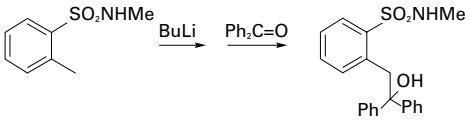
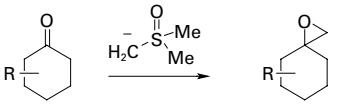


Corey-Chaykovsky Epoxidation



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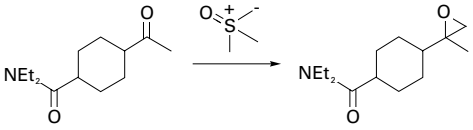
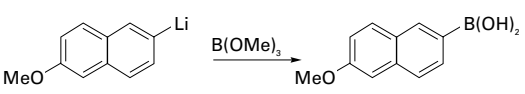


Organometal-electrophilic Quenching Sequencing

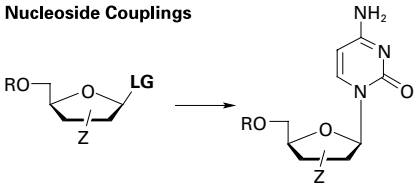
Example:



Pilot Production

Among the various activities at our pilot plant, we produce product quantities ranging from several kilograms to several metric tons according to the requirements of customers. This work usually consists of complex multistage syntheses. Our wide range of technologies, some of which have been developed to a unique level, enable us to successfully synthesize and scale up new compounds. Springfield's kilo lab and pilot plant are part of Archimica's global Molecules Synthesis Center, which specializes in custom developing and small-scale manufacturing of building blocks and active pharmaceutical ingredients.

Nucleoside Couplings



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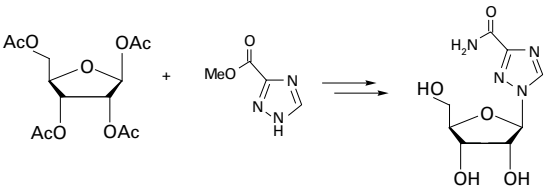
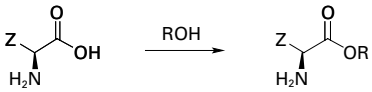


Amino Acid Esterification and Modifications



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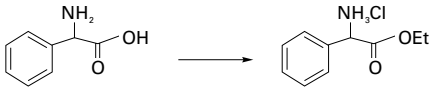
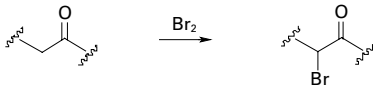
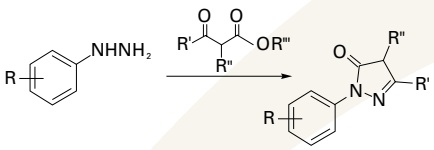


Bromination



Example:

Condensation Reactions



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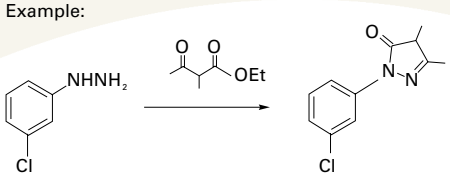
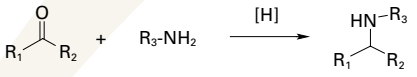


Reductive Amination



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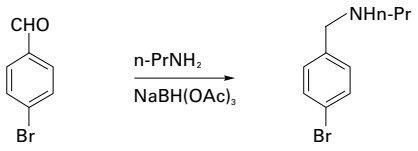


Manufacturing

The Springfield site of Archimica's pharmaceutical services conducts a wide range of reactions and special operations involving the handling of various hazardous substances on a large scale. Manufactured products comprise Active Pharmaceutical Ingredients (Antivirals, Nucleosides, Controlled Substances) and Regulated Intermediates (cGMP/FDA).

Reactions

- **Alkylation**
- Amidation
- Amination
- **Bromination**
- Cyclization
- Diazotation
- Epoxidation
- Esterification
- Friedel-Crafts
- **Metalation**
- **Nitration**
- **Nucleoside chemistry**
- Oxidation
- Reduction
- $TiCl_4$ chemistry

Special Operations

- Anhydrous HCl
- **Butyllithium**
- **Chlorinated solvents** (methylene chloride, chloroform)
- Continuous and semi-continuous process technology
- **Cryogenic conditions** (liquid nitrogen cooling)
- Ethylene oxide
- Fractional distillation
- High temperature
- **HNO_3 handling and chemistry**
- **Lewis acids**
- Low pressure
- Rectification
- **Silanes**
- Sodium cyanide
- Sulfurylchloride
- Thin film evaporator
- $TiCl_4$ handling

Springfield's approximately 100 employees operate this facility with cGMP regulations as standard procedure. Senior management and supervisory groups in manufacturing, QC, QA, engineering, logistics, ESHA and plant management are experienced pharmaceutical personnel. The latest FDA audit occurred in May 2008 with no observations (no 483s). Our customers have also repeatedly audited our US site successfully.

A total cGMP capacity of 360 m^3 stainless steel vessels and 190 m^3 glass-lined vessels is available. Operating temperatures range from –75°C to +220°C; operating pressures from 7 mbar to 5 bar. Crystallization conditions can be varied to deliver optimum crystal structure; milling parameters are established to deliver optimum bulk density. Manufacturing, analytical and maintenance coverage operate around the clock; technical on-shift coverage is available for process start ups.

The site's Maximum Achievable Control Technology (MACT) compliant environmental control system can handle halogenated solvents including methylene chloride and chloroform. The site's Regenerative Thermal Oxidizer (RTO) allows handing of process vents on a large scale.

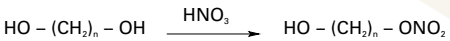
The Springfield site oxidizer is equipped with flue gas scrubbing to remove acids generated by combustion of halogenated solvents. The facility practices cradle to grave management of waste streams. Aqueous streams are treated on site with neutralization, air stripping, steam stripping and equalization. After pretreatment most streams are releasable to the local Publicly Owned Treatment Works (POTW).

The site has cryogenic chillers and evaporators to support process at –40°C, to –100°C. Cryogenic processes can be conducted in both Stainless Steel and Hastelloy reactors with evaporative nitrogen cooling. The site has steam, hot oil and tempered fluids including Syltherm available for heating requirements.

Nitration

Archimica has been performing nitrations for decades. As one of the very few nitrators left in the Western world, Archimica is a tested and reliable partner for nitration projects.

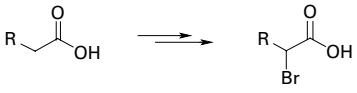
At our Springfield site, nitrations of alcohols are made using semi-continuous processes on commercial scale.



Bromination

Springfield is one of the world's largest sites for manufacture of brominated products used in pharmaceutical synthesis. The site operates a dedicated bromine handling and storage facility and manufactures more than 3,000 tons of brominated products a year. Our back integration in bromination also provides an excellent basis for our organometallic chemistry.

Hell-Volhard-Zelinsky Bromination



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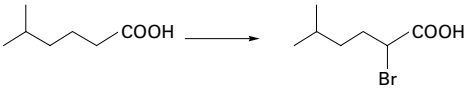
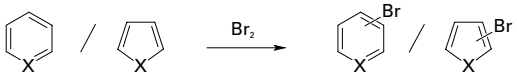
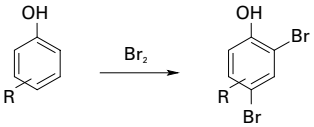


Electrophilic Substitution



X = C or HetAtom

Example:

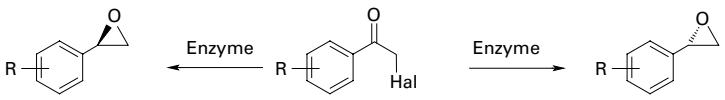


Chiral Epoxides

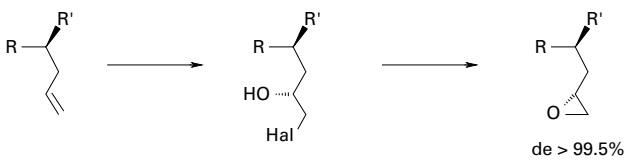
We have developed different high-yielding technologies for the production of epoxides with very high enantio- and diastereoselectivities. Having such a broad selection of complementary technologies enables us to tackle every new project with the best approach from the very beginning.

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 halohydrines first, which can be cyclised with very high diastereoselectivity under very careful process control.



ee > 99.5%

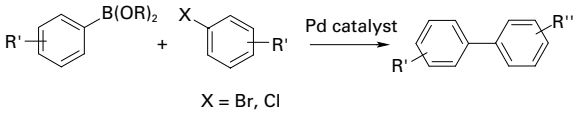


de > 99.5%

Organometallic & Cryogenic Chemistry

Our team of experienced chemists has a solid background in heterocyclic, organometallic and stereoselective chemistry. We exercise modern methods of organic chemistry for Carbon-Carbon and Carbon-Heteroatom bond formation (Suzuki, Heck, Tamao-Kumada, Negishi, Sonogashira and many other coupling reactions). Combined with excellent cryogenic equipment, our knowledge of organometallic chemistry (lithiation, Grignard, boronic acids, silanes) and cross-coupling strategies makes us a partner of choice whenever expertise in low temperature reactions involving labile organometallic intermediates is required. Cryogenic reductions using silanes are conducted on multi-ton scale.

Suzuki cross coupling



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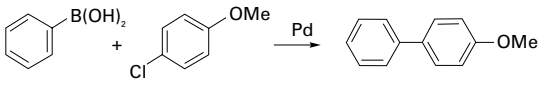
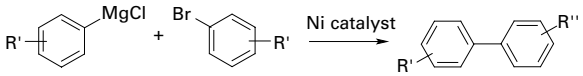


Tamao-Kumada cross coupling



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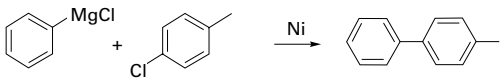
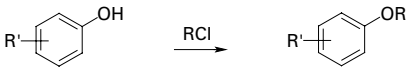


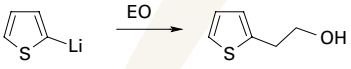
Etherification

Etherification reactions with methylchloride or other agents are carried out at a scale of several hundred metric tons.



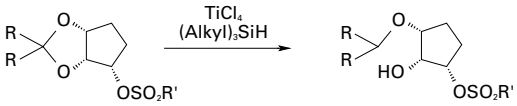
Ethylhydroxylation

Ethylene oxide (EO) can be used on commercial scale for ethylhydroxylations.



$TiCl_4$ Chemistry

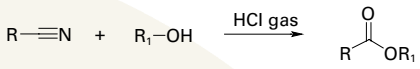
$TiCl_4$ is a very versatile reagent in organic synthesis, which has been used in countless applications, for instance Mukaiyama reactions. One disadvantage are the difficulties in handling this compound on a large scale. Our Springfield site is able to handle this reagent in different reactions up to a multiton scale, which opens the realm of formerly academic synthetic methodologies to industrial full-scale manufacturing.



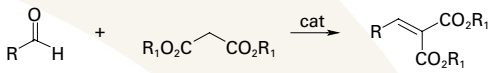
Other Reactions

Many other reactions are/or can be conducted at significant commercial scale. A few examples are listed below.

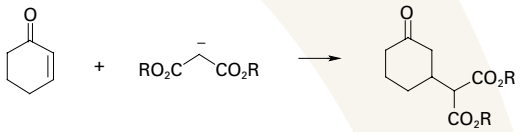
Pinner Synthesis

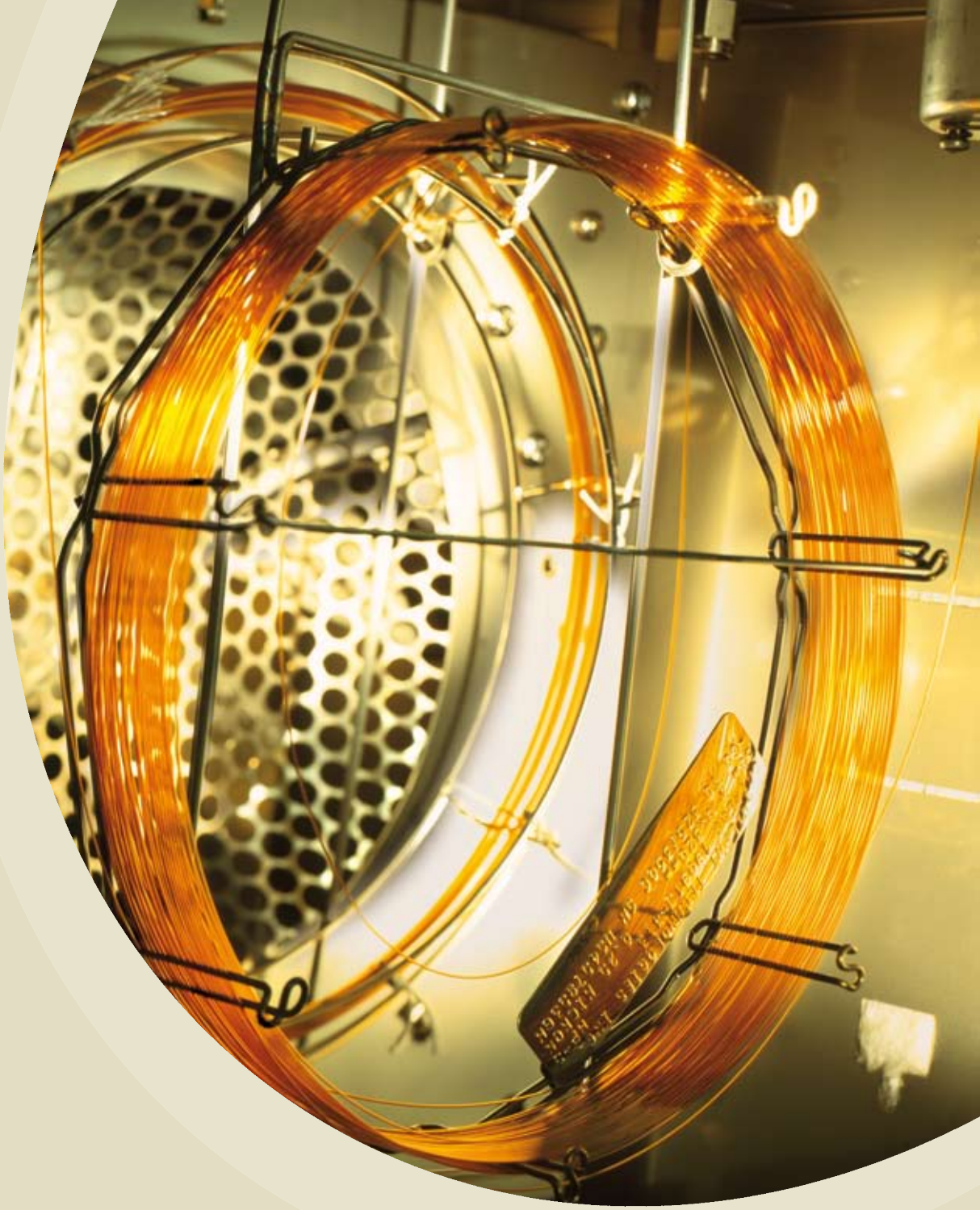


Knoevenagel Condensation



Michael Addition





Quality

Archimica is committed to completely fulfilling all customer requirements for products and services. Regulatory and customer compliance requirements have the highest priority to ensure that integrity and quality at all stages in the manufacturing process will result in products meeting specifications and relevant cGMP regulations.

The Quality Assurance Group leads the team to excellence by establishing common quality assurance standards in Archimica's global business, and by incorporating quality management systems into all development and manufacturing operations at the site. Quality management systems incorporate internal Standard Operating Procedures (SOP's) and national/international standards and regulations (e.g. FDA cGMP, ICH Q7A).

FDA Inspections and Training

The Springfield facility is regularly inspected by the FDA for cGMP compliance and has the distinguished record of 15 years without any observations (no 483s) being issued.

We value customer and regulatory quality/cGMP audits to ensure that the elements of our quality systems are continuously improved and meet industry best practices. To assist the FDA, we developed FDA Inspector training material for regional new inspector training programs.

Quality Assurance and Customer Support

The quality systems employed at the facility comply with all national and international standards for quality management systems as defined by cGMP and ICH Q7A guidelines.

As a manufacturer and developer of life science products we are fully committed to current Good Manufacturing Practices (cGMPs). Our staff have the skills necessary to support customer regulatory submission requirements (e.g. DMF, NDA, and CMC).

Environment, Safety & Health

It is Archimica policy to comply with all applicable laws and to be responsible stewards of the environment. Effective management systems, technological leadership and continuous improvement are cornerstones of this policy and the environmental management at the Springfield site.

Environment

Applicable permits. Archimica project management checklists assure all permits required by federal, state and local authorities are in place for new projects as applicable.

Air emissions control. The primary control device used to remove organic pollutants contained in equipment vents is the site regenerative thermal oxidizer (RTO). This unit is also capable of treating halogenated solvents and organic gases.

Waste material generated at the site is disposed or treated at approved and audited vendors.

Wastewater is treated either chemically or physically to meet applicable discharge limits and discharged to the City of Springfield's Publicly Owned Treatment Works (POTW) for further treatment.

Safety & Health

Safety program. Safety is an integral part of all activities at the Archimica plant. Job safety analysis, incident investigations and self-audits combine to continuously assure and improve the safety of operations at the site. A high emphasis is placed on active employee involvement in these programs.

Process safety management. Archimica employ a proven program for managing process safety which is based on OSHA requirements and internal management systems and standards.

Industrial hygiene. The site preferentially uses engineering controls to minimize worker exposure to chemical and physical hazards at the site. Personal protective equipment is used as an additional measure of protection. The site's certified industrial hygienist quantitatively verifies that exposures are below applicable governmental and industry standards.

Equipment

Laboratory, Multi-purpose Pilot Plant and Manufacturing

	Vessels	*Isolation*	*Purification*	*Finishing*	*Conditions*
Laboratory/ Kilo lab	3 Glass reactors (10, 32 and 104 L) Various flasks (12-20 L)	1 Buchi rotavap (20 L) 1 Halar sock filter 1 AURORA filter dryer	1 Biotage purification system 1 Thin film evaporator	1 SS tray dryer 1 AURORA filter dryer	–40°C to 130°C (reactors)
Pilot plant/ Multi-purpose unit (S-12)	7 GL (120-1,200 L) 2 SS (120-1,200 L) 1 SS sparkler press (40 L) 1 GL (1,200 L)	1 SS centrifuge (50 cm) 1 Halar nutsche (200 L) 1 Hastelloy filter dryer (1 m^2)	1 SS continuous extractor 1 GL fractionation unit (10 plates)	1 SS double cone dryer (200 L) 1 Universal mill 1 Hastelloy filter dryer (1 m^2)	–25°C to 260°C Vacuum (0.5 mbar) Steam (8 bar)
Manufacturing					
S-3	Drying facility			1 SS Double cone rotary dryer (1.5 m^3)	5°C to 100°C 10 mbar vacuum
S-4	13 GL (2,000-6,000 L) 1 SS (4,000 L) 1 SS bulk storage (109 m^3)	Inert powder charging	2 GL column (15 plates)		5°C to 140°C 1 mbar vacuum
S-14	4 GL (25 m^3) 1 Ha (8 m^3) 4 SS (56 m^3) 2 CS storage tank (396 m^3) 1 SS (10 m^3)	1 SS centrifuge (600 cm) Inert powder charging	1 SS column (12 plates)	1 SS conical screw dryer (2,500 L) 1 SS hammer mill	–75°C to 140°C cylinder handling of butyllithium and $TiCl_4$

	Vessels	*Isolation*	*Purification*	*Finishing*	*Conditions*
Manufacturing					
S-19	6 GL (52 m^3) 14 GL (58 m^3) 20 SS (185 m^3) 16 SS (64 m^3) 5 SS (12 m^3) Bromine facility (38 m^3) MeCl facility (45 m^3) Anhydrous HCl facility Bulk storage SS (257 m^3) CS (143 m^3)	1 Rosenmund filter (10 m^2) 1 Hastelloy centrifuge (600 mm)	4 SS columns (17 plates each)	1 drum flaker	–40°C to 220°C
S-25	34 SS/CS (400 L-60 m^3)		1 SS column (25 plates) 1 Hastelloy thin-film evaporator (1 m^2)		–20°C to 220°C Bulk handling of butyllithium and ethylene oxide
S-28	2 Ha (16 m^3) 1 GL (8 m^3) 1 SS (8 m^3)	1 Hastelloy centrifuge (1,000 mm)	1 SS column (36 plates)	1 Ha helical conical dryer (2,500 L) 1 Ha mechanical mill	–25°C to 140°C Vacuum (1 mbar)

Analytical Laboratory

The analytical and quality control laboratory supports product manufacturing, equipment cleaning verification, environmental control, and process development. Archimica also provides a wide range of analytical services for our external customers, including various types of analyses, analytical methods development, validations, API stability studies, etc.

Capabilities and equipment summary

Chromatography

- LC/MS (ESI, APCI probes)
- GC-MS
- HPLC (low and high-pressure mixing, UV, RI and fluorescent detection)
- TLC
- GC (FID and TCD detection)
- Headspace gas chromatography
- All chromatography equipment networked in one computerized data collection system

Potentiometry titration systems

- Mettler Toledo Karl Fisher titrators (volumetric and coulometric)
- Automatic titrators

Other Equipment

- Spectrophotometer (200-800 nm)
- FT-IR (reflection and transmission)
- NMR (^{1}H, ^{13}C), DEPT, COSY, HETCOR at ambient temperature
- Refractive Index
- Polarimetry (at 6 wavelengths)
- Viscosimetry
- Conductivity
- Gravimetric analysis (USP methods for heavy metal analysis, loss on drying, non-volatile residue, sulfated ash, residue on ignition and others)
- Volumetric analysis (titrations, all types)
- Automated melting point apparatus
- Particle size

Contacts

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December 2009