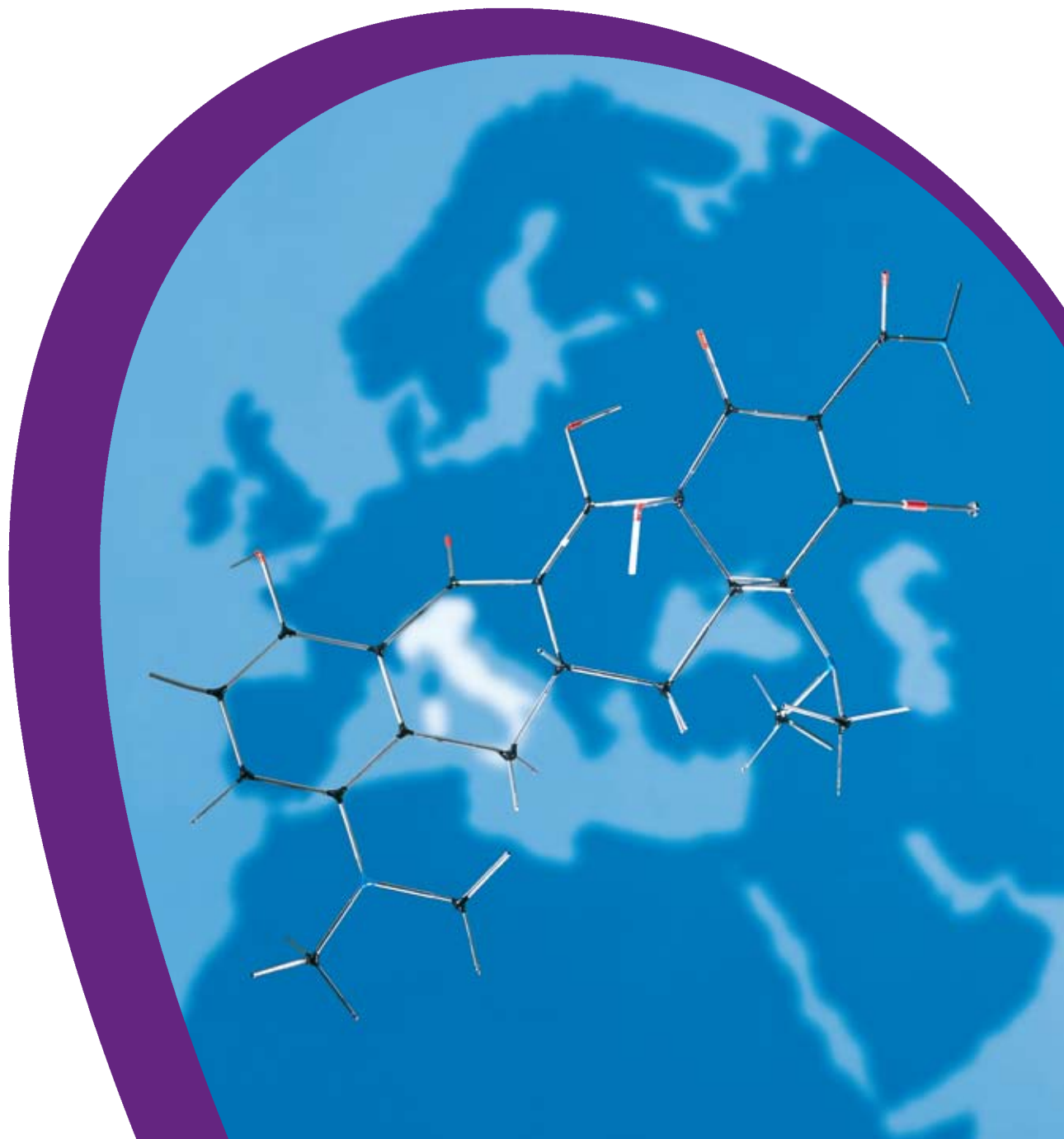


Pharma Services & Manufacturing Origgio/Italy

API Excellence for Drug Development and Commercialization





Pharmaceutical Quality Made by Archimica

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Our Services

Archimica's worldwide cGMP manufacturing and our comprehensive pharmaceutical services focus on API customer needs. Research and development activities are tailored specifically to our customers' projects and to the development of new processes for generic APIs. Our cutting edge technologies and our extensive know-how and expertise make us a favored partner in all stages of the lifecycle of a pharmaceutical product.

Our Italian Site

Archimica is a preferred partner in global-scale production of late-stage intermediates and proprietary innovative active pharmaceutical ingredients (APIs) for major pharmaceutical companies. With customer-oriented services and production sites in Springfield/Missouri, United States, Tonneins and Bon Encontre/France, Origgio/Italy, Sandycroft/United Kingdom, and a new technology development center in Frankfurt/Germany, we are close to our customers around the world. Based on leading technologies, our plants also offer global-scale production of multi-customer active pharmaceutical ingredients (generics) and building blocks using our proprietary and leading technologies. All sites except our German development center operate in compliance with cGMP and hold excellent FDA track records.

Our Italian site excels in multipurpose facilities permitting flexible production of bulk APIs and late-stage intermediates. The site in Origgio comprises cGMP production facilities, pilot plants, R&D, QC, and microbiology laboratories. It fully complies with ICH Q7A regulations, is FDA-inspected and authorized by the Italian Ministry of Health for the production of human and veterinary drugs.

The Origgio site covers a total area of some 163,000 m², with the chemical plant encompassing around 30,000 m².

The facilities at Origgio consist of three manufacturing blocks, one small production scale unit (pilot plant), R&D, QC microbiology laboratories, two warehouses for raw materials and finished goods, and a fully integrated ecological unit with biological wastewater treatment plant, incinerator and solvent recovery unit.

The total capacity of the plant is approximately 550 m³ reaction volume, manufacturing about 500 tons of typical cGMP products per year.

Thanks to our experience at Origgio, hydrogenation – particularly at high pressure – is a core synthetic process chemistry step performed with excellence.

Furthermore, we broadly apply cryogenic processes at Origgio, especially for organometallic reactions and selective reductions. The liquid-nitrogen chilled equipment is available at scales from pilot plant up to large production vessels.

The Origgio site has been regularly inspected by the FDA since 1975, with the last inspection in October 2007. The last Italian Ministry of Health inspection at the Origgio plant was carried out in April 2003.

Technologies

Virtually all technologies used in pharmaceutical synthesis are feasible for us. Most of them have been used regularly on a commercial scale. Our team at Origgio constantly improves and inno-

vates the process chemistry and process technology related to their core competences. In addition, the facilities provide access to an extensive range of further chemical processes.

Core technologies

- Hydrogenation
high and low pressure
 - Cryogenics down to – 80°C
 - Organometallics
Lithium
Magnesium
 - Oxidations
with hydrogen peroxide
in organic solvents
 - Nucleosides
 - Heterocycles
-

Chemical processes (non exhaustive)

- Acylation
 - Alcoholysis
 - Alkoxylation
 - Alkylations
 - Amidations
 - Amide/Peptide bond
formations ([®]T3P)
 - Aminations
 - BF₃ catalysis
 - Biocatalysis
 - Brominations
 - C,N-couplings
 - Carboxylations
 - Chlorinations
 - Condensations
 - Dehalogenations
 - Dealkylations
 - Diazotizations
 - Diels-Alder
 - Esterifications
 - Friedel-Crafts
 - Grignard
 - Kumada couplings
 - Mannich
 - Nitrations
 - Optical resolutions
 - Oxidations
 - Reductions
 - Sandmeyer
 - Saponifications
 - Sulfonations
 - Suzuki couplings
-

Trust

Providing custom cGMP products and services to the pharmaceutical industry is a core competence of our business. For decades we have cooperated successfully with pharmaceutical companies around the world in the commercialization of their new chemical entities. We support our customers with chemistry and products from the early-stage pre-clinical phase to the after-launch and generic phases. Our teams know about the specific requirements of each developmental stage and interact closely with our customers. Because of Archimica's innovative capabilities, we are able to base our services on our own technology, as well as working with specific input such as technology packages provided by our customers.

Due to the confidential nature of many of our products and business relations, we do not publish or use any information on custom developments.

Intellectual Property

Intellectual property represents a major asset for our customers. Our business systems are set up to comply strictly with all requirements of confidentiality within our global organization. As most of our employees worked in the pharmaceutical industry before joining us, professionalism in this vital matter is a fundamental characteristic of our daily work. Our pharmaceutical and customer-oriented culture makes our customers' projects our projects, and ensures that any customer- and project-related information is treated confidentially.

We have developed excellence in drawing up proper agreements concerning confidentiality and intellectual property, properly reflecting any given business situation and case, be it an early project or a full commercial supply contract, while ensuring the necessary speed and compliance at the same time.

Major developments and introductions involving a wide range of highly specialized technologies have increased our level of excellence, particularly in the fields of:

- tetracyclines
- organometallics
- hydrogenations and reductions
- heterocycles
- nucleosides
- chirals
- biocatalysis
- use of chlorinated solvents

Our ability to innovate on demand and the know-how of our staff assures the sustainability of our customers' investments. Our track record on compliance as well as our proven capability in permanently keeping up with the state-of-the-art has led to the introduction of several new chemical entity (NCE) APIs launched by our Italian site in recent years.

Our technology and process excellence have provided many innovative solutions, which we are able to use for our customers' projects. This is the case in every new project. This may even occur before we begin any work, because our patented technologies are extremely useful for solving specific synthesis problems or in cases where our customer may wish to use one of our patented technologies in-house, e.g. for backup supply reasons. Whatever the case may be, we are committed to finding flexible commercial solutions for any use of our intellectual property, regarding a specific case or as background material, for the benefit of our customers. Thus our customers can make the best use of our intellectual property.

In addition, our customers can rest assured that, when investigating generic API activities, we will not infringe upon the intellectual property of the innovating party. In all other cases, permission will be obtained from the customer; by no means will we simply use a customer's own information or processes.

Excellence in Research and Development

The main activities of our R&D laboratories comprise the development of methods to prepare active pharmaceutical ingredients (APIs) both in custom synthesis and for the generic market.

R&D is a multi-disciplinary task and is therefore carried out in teams. Depending on the expertise required, the R&D teams at Archimica's sites cooperate regularly with experts from other Archimica manufacturing sites in Frankfurt/Germany, in Bon-Encontre/France and Springfield/USA. Furthermore, specialized partners or laboratories, part of our businesses' cooperation network, provide the best expertise for our customers' projects.

The R&D team of our Italian site has decades of experience in developing the synthesis of APIs in terms of both generic and custom synthesis for many of the world's leading pharmaceutical companies. Our expertise and equipment assure our customers complete development and efficiency assistance in the manufacturing of their products in any development phase.

The evolution of a manufacturing process for an API has several distinct phases of development. The first step of the experimental work is the selection of a practical route for the preparation of the API. The main targets of this phase are:

- Definition of critical parameters
- Development of in-process controls and their limits
- Definition of specifications for final products and intermediates

Effective process development combines synthetic and analytical methodology, purification technology and practical procedures orchestrated with a view to ensuring safety, product quality, reproducibility, robustness and cost efficiency. The results of this work are:

- A development report containing all basic chemistry data of the process
- Complete knowledge and control of the process
- Efficient guidance for the manufacture of the product, comprising also raw materials testing of possible supply alternatives

For generic market products, the experimental work is initiated via the patent analysis of the product, the processes and the possible intermediates involved in the synthesis. Our long-standing success in the generic APIs business is based on our excellence in process efficiency and development, which is further enhanced by the internationality of our teams and their various industrial backgrounds. We serve our customers by continuously and proactively improving our processes.

Integrated Prototyping and Piloting

Our pilot plants play three key roles:

- Providing strategic links between laboratories and industrial production (scale-up)
- Production of compounds with high added value as well as quantities for clinical supply, which are both characterized by small production volumes
- Production of batches for registration purposes

In terms of scaling up new production processes, ever-increasing requirements have to be met, e.g.:

- Safety
- Reproducibility
- Environmental feasibility
- Robustness
- Upscalability

All of these involve one of our key services to our customers: our excellence in integrated prototyping. Any process developed by our Italian and international teams (in laboratory and/or pilot plants) is the result of extensive experience. All features which enable us to achieve the criteria listed above as well as consistent regulatory compliance and continuous further improvement are built in. Thus, a constant quality over the product lifecycle is achieved and tedious re-filing and major process changes are ruled out from the very beginning, paving the way for regular commercial manufacture.

The first scale-up from the lab scale to the pilot plant serves to set the parameters, in terms of safety, quality and process operations, before the move to full-scale manufacturing is made.

We devote special attention to investigating the safety of these processes during the development phase. We have a profound knowledge of the thermal characteristics of a new process, enabling us to carry out the reactions under safe conditions and to control the parameters so as to avoid undesired process behavior.

In addition, we put strong emphasis on minimizing process waste as well as on efficient treatment in cases where waste is inevitable. Wherever possible, we recover solvents within the process and study the most environmentally-friendly process alternatives to comply with our environmental responsibility. Furthermore, we strongly believe in continuous efficiency and process improvement as the best tools for environmental compatibility.

Another role of our pilot plant is to manufacture small volumes of active ingredients with high added value. When new drugs are tested, pharmaceutical companies need to characterize fully all of the effects of the active ingredients. Such studies require the use of active ingredients ranging from a few kilograms (for initial phases of the development process) up to hundreds of kilograms for advanced clinical study phases. Industrial plants usually cannot manufacture such limited quantities.

Naturally, all of our active ingredient development and production activities comply with cGMP regulations. In addition, we optimally integrate the different functions involved in the development of a new product. Both enable us swiftly to fulfill today's market requirements.



Compliance

Our Italian site primarily focuses on meeting strict quality requirements and offering customers top-quality products in all respects. Regular inspections and outstanding quality assurance ensure that these objectives are met.

Quality Assurance

Our principal aim is to optimize the quality of the services we offer our customers. Quality, flexibility, and feasibility are the hallmarks of our success. Archimica's Italian site is constantly subject to inspections by authorities and customers to ensure that they meet health authorities' and customers' quality assurance regulations. The Origgio plant has been successfully inspected by FDA since 1975. Our quality assurance is involved in all issues related to quality systems, approving and reviewing all documents. The responsibilities of quality assurance cannot be divided or delegated. The primary task is to ensure that all procedures at our sites – from the flow of materials through the clinical process and the equipment in use to customer compliance – are in line with the rules and regulations of international Health Authorities, such as FDA, ICH and others.

The Origgio site conforms to cGMP regulations as per the ICH Q7A guideline. We periodically carry out internal audits to ensure compliance to cGMP standards, conduct investigations and follow up on corrective actions to continuously improve our quality systems. We validate produc-

tion process improvements, collect data and prepare critical documentation to be filed in order to obtain authorizations (DMF – Drug Master File).

Our quality assurance department conducts annual reviews of quality parameters related to the manufacture of all cGMP materials. Due to the longstanding excellence of our Italian operations in compliance with WHO (World Health Organization) rules, our Italian quality assurance leads the QA function globally for our business.

Audit history over the last ten years:

Italian Ministry of Health

2003: April 28-30

2006: February 28-March 3

U.S. Food and Drug Administration

1995: November 6-8

1996: February 5-8

1997: January 20-30

2001: January 15-17

2004: December 9-13

2007: October 12-14



Environmental, Safety & Health Affairs (ESHA)

Our Italian site is committed to comply with all applicable environmental, health and safety regulations and to implement the company's strict standards. The ESHA Management System is regulated by corporate guidelines and Standard Operating Procedures issued at the site level. Cooperating with the responsible authorities, the site ESHA experts conduct periodic audits to verify adherence to the company's standards.

Environmental Protection

Internal waste is mainly treated on site through an incinerator plant for hazardous waste, a wastewater treatment plant and a recovery unit for solvents. Prior to every new production, waste that is generated is evaluated. Analyses are performed on samples taken from R&D and the pilot plant in order to establish the best method of treatment.

Air emissions are collected and treated properly by incinerator and other specific air emission treatment systems. Environmental monitoring is performed on air emissions, on waste to be treated and on the wastewater treatment plant. The incinerator is equipped with a continuous air emission monitoring system.

Health & Safety

Archimica's achievements in production safety and environmental protection are internationally best-in-class. Environment protection safety tests and risk assessments are performed on all productions and production plants in order to evaluate and control potential risks, by means of plant modifications, interlock and use of PPE (Personal Protective Equipment). All workers are regularly and periodically trained in basic safety, emergency

procedures and the safety of specific products, including use of personal protective equipment. Emergency first aid and fire fighting personnel are continuously trained and are always present on site. Accidents and near misses are investigated in order to define the causes and implement preventive action. Periodical evacuation tests are performed in order to check emergency procedures.



Active Pharmaceutical Ingredients (APIs)

Our Italian site offers a wide spectrum of APIs tailored to diverse customer requirements and product specifications. We take pride in our extensive expertise in this area.

Added Value for Our Customers

The cost-cutting policy of all governments, as well as the favorable trend in EU legislation towards generic products, represent a challenge to bulk API producers like us in serving our customers. Our Italian site is well positioned in this competitive field due to its long experience in the production of APIs, for custom synthesis as well as for the generics market.

In both cases Archimica's contribution is original and able to improve significantly existing processes, increase yields, and enhance quality. In addition, with its excellent and innovative technologies, Archimica helps companies embark on completely new routes. R&D is well integrated

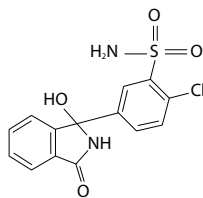
with a quality system based on a modern QC lab, equipped with state-of-the-art instruments (NMR, HPLC, LC and GC mass spectrometry), and on a QA team which ensures compliance with cGMP regulations, from the delivery of the raw material to the final release of the APIs.

We work under cGMP conditions. A Regulatory Affairs department, as part of our partnership with our customers, assures a prompt release of robust EU and US Drug Master Files for all our APIs as well as Certificate of Suitability to the European Pharmacopoeia. Moreover, in our production of APIs we are conscious of our responsibility for human health.

Regular Portfolio

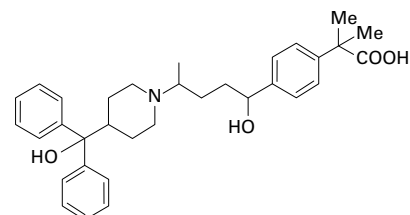
Our regular portfolio of APIs draws on decades of successful multi-customer API business. The products listed below are some major examples and give an overview of the applied chemistry and technologies that we have worked on within nearly all therapeutic classes and at various volume ranges.

Chlortalidone



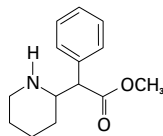
CAS number 77-36-1
 Therapeutic class Diuretic
 Regulatory US/EU DMF & COS

Fexofenadine



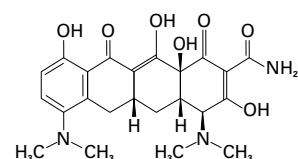
CAS number 83799-24-0
 Therapeutic class Antiallergic

Methylphenidate



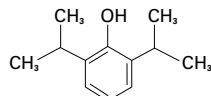
CAS number 113-45-1
 Therapeutic class CNS stimulant
 Regulatory US/EU DMF

Minocycline



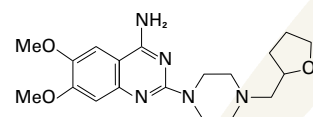
CAS number 113614-98-7
 Therapeutic class Antibiotic
 Regulatory US/EU DMF & COS
 as hydrochloride

Propofol



CAS number 2078-54-8
 Therapeutic class Anaesthetic
 Regulatory US/EU DMF & COS

Terazosin



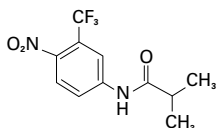
Terazosin
 CAS number 70024-40-7
 Therapeutic class Antihypertensive
 Regulatory EU DMF
 as hydrochloride dihydrate

Terazosin
 CAS number 63074-08-8
 Therapeutic class Antihypertensive
 as hydrochloride anhydrous

New Generics under Development

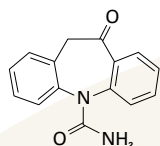
Based on our customers' requests as well as our market expertise, we strive to offer a broad portfolio of interesting products for modern healthcare. Thanks to our excellence in technology and process development, we achieve major advantages in the healthcare products with which we are involved. In our day-to-day business we meet highest quality standards and lead-time targets in close cooperation with our customers. At least four new APIs are introduced into our portfolio each year.

Flutamide



CAS number 11311-84-7
Therapeutic class Antiandrogen
Regulatory US/EU DMF & COS

Oxcarbazepine



CAS number 28721-07-5
Therapeutic class Antiepileptic
Regulatory US/EU DMF



Technologies

We use state-of-the-art technologies to ensure the best possible results and to guarantee original, innovative and best-in-class solutions. To offer our customers new options as well as better routes and products, we continuously improve and develop our core technologies.

Hydrogenation

Hydrogenation is one of the most useful broad-scope reactions available in synthetic organic chemistry. At our Italian site we have the necessary experience and equipment to exploit its full scope and usefulness for our customers. We perform hydrogenations under a wide range of conditions from laboratory to full commercial scale.

Catalytic hydrogenation is one of the most powerful and clean reduction methods. Many functional groups can be reduced under mild conditions with high chemo-, regio- and stereo-selectivity. Several parameters have to be finely adjusted to achieve industrially and pharmaceutically satisfactory results. The main parameters in our optimization program are catalyst, solvent, pressure and temperature.

The choice of catalyst is one of the key steps in optimization. Several factors have to be considered to select the right catalyst: Metal, support and metal concentration need to be combined to obtain the best possible results. Palladium and platinum but also rhodium and ruthenium catalysts are included in various forms in our catalyst library and know-how.

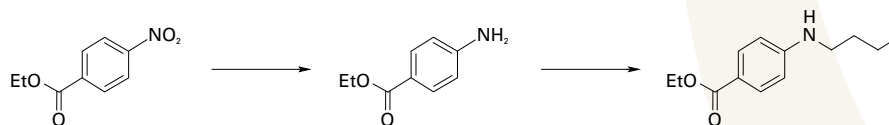
Due to several years of cooperation with the main catalyst suppliers, we have a large number of possible combinations in our portfolio, enabling us to find the best solutions even when it comes to sensitive products or in the presence of other susceptible functional groups. Using the directive properties of the chiral centers of the substrate in combination with our extensive knowledge and catalyst base, highly selective cutting-edge hydrogenations can be achieved creating one or several chiral centers with extremely high enantiomeric or diastereomeric excess in just one reaction step.

The solvent is a parameter that has an influence on various aspects of the hydrogenation reaction and in our experience is an excellent tool to achieve the desired selectivity. The solubility of the hydrogen and the interaction with the catalyst surface can also have a strong impact on the hydrogenation rate. Both factors are taken care of by our know-how in catalysts, equipment and optimization.

Both stainless steel and glass-lined hydrogenators are available at Origgio, to ensure maximum flexibility and efficiency in the choice of the best solvent.

Temperature and pressure are key factors for increasing the hydrogenation rate and reducing catalyst poisoning. In our plant we are able to conduct processes under pressures of up to 80 bar and temperatures up to 120°C.

Nitro Reduction and Reductive Amination. The reduction of a nitro group is one of the most useful methods for synthesizing primary amines, while reductive alkylation is one of the main reactions used for obtaining secondary amines.



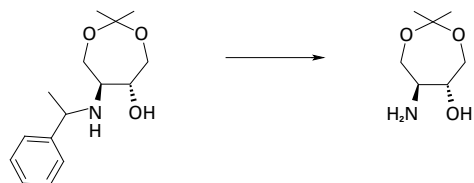
Both reactions can be performed by hydrogenation, so it is possible to perform the transformation of a nitro group to a secondary amine via a two-step, one-pot approach.

Nitrile Reduction. Nitrile groups can be reduced to primary amines but particular conditions have to be applied to avoid dimerization to secondary amines.

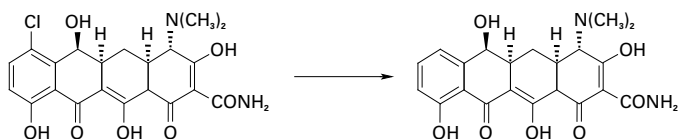


Debenzylation. The benzyl group is widely used for protection for both hydroxyl and amino functions.

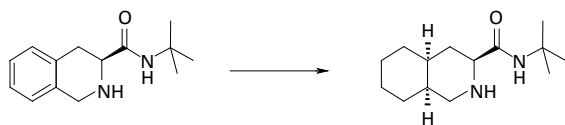
The nitrogen and oxygen benzyl bonds undergo hydrogenolysis allowing for a very mild and selective cleavage of the protective group.



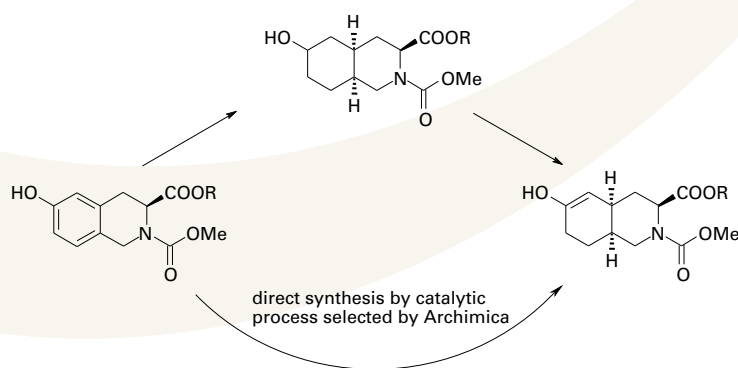
Aromatic Dehalogenation. Many halogen-carbon bonds are cleaved easily by means of catalytic hydrogenation. The hydrogenolysis can be done very selectively in the presence of other easily-reducible groups, even with sensitive precursors.



Aromatic Hydrogenation. Aromatic rings can be reduced without difficulty. Major solutions by our experts in this reaction concern maintenance of other functions and control of the regioselectivity.



In our experience, in some cases it is possible to stop the hydrogenation at a partially reduced product through the selection of catalyst.



Complex Hydrides. We are able to use complex hydrides that allow very selective functionalizations. In specific cases our expertise enables us to

substitute some of these for very mild and easy-to-handle catalytic hydrogenations, for example as an alternative to Li-Selectride or DIBAL-H.

Organometallic Chemistry

Organometallic chemistry is one of the most interesting and most rapidly growing areas of organic chemistry. Organolithium and organomagnesium compounds are among the most-used classes of organometallic products.

We have developed excellence in metallation as well as in coupling reactions.

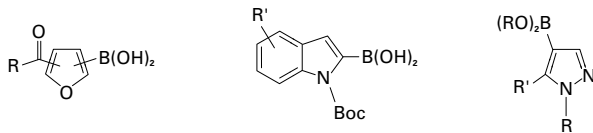
Our methodology for creating compounds in an efficient, cost-effective manner and our organometallic expertise ensure the availability of

compounds which are simply not accessible by other routes. In other instances, by working with organometallics we can reduce the number of synthesis steps required to produce the desired product. This in turn allows for more economical intermediate and API production. In addition, we can realize highest levels of product purity due to the often extremely high selectivities of our organometallic reactions.

Boronic Acids

Based on our strength in halogen aromatics (fluorine, chlorine, bromine, iodine) and metallation, we have developed more than 60 different boronic acids on a commercial scale. These in-

clude a large number of complex substitution patterns. The derived solutions enable us to apply these innovations to new customer projects.



Aliphatic Boronic Acids. Archimica has recently published a new technology for making aliphatic and vinyl boronic acids. A traditional synthesis approach to creating these compounds – reacting Grignards with a boron compound – will usually result in low-purity products at low yields (often only 20%) because of the high water-solubility of the reaction products. With Archimica's new method, the aliphatic or vinyl boronic acids are

isolated as derivatives such as pinacol esters, for example, with the additional advantage that they can be isolated as crystalline materials in very high purities and selectivities which reach > 99%. With this route, Archimica is approaching yields of 86%. The structural scope of this new synthetic method is large, for example aryl, alkyl, trimethylsilyl, dialkylacetal and protected primary hydroxy groups are well tolerated.

Coupling

Suzuki Coupling. Archimica, the first chemical company to develop an industrial-scale Suzuki process, offers a broad portfolio of customized solutions for catalytic C,C-coupling processes from grams to large commercial scales.

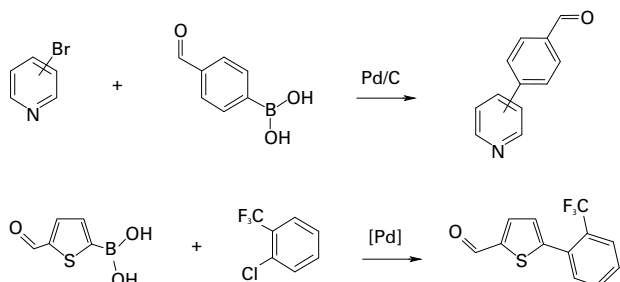
The Suzuki coupling reaction – the transition-metal catalyzed C,C-bond formation between a boronic acid and an organohalide or sulfonate – is a valuable tool for the organic chemist. It is, although still constantly being improved, widely used for construction of biaryl and heterobiaryl structures.

To meet the needs of a large-scale Suzuki process, we have developed a catalyst system which can easily be recycled and provides the product in high yields with high selectivity at low overall palladium usage. Furthermore, the reaction conditions allow extremely simple separation of the product from the reaction mixture and from palladium, easily achieving residual Pd levels of < 10 ppm.

One of our patented process technologies uses the commercially available water-soluble ligand tris-(3-sulfonatophenyl)-phosphine (TPPTS) to allow for easy reuse of the aqueous phase carrying the catalyst while the product is isolated from the organic phase. Several hundred tons of various Suzuki products have been produced by us using this process.

Coupling of Heteroaromatic Substrates. Heteroarylphenyl and biheteroaryl derivatives are becoming more and more important as pharmaceutical building blocks, especially those involving

pyridine- and furane-derived structures. Both heteroarylboronic acids and heteroaryl halides can be used to assemble these structures.

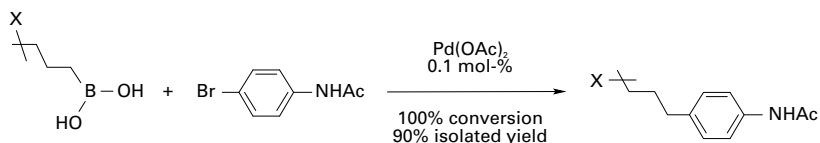


Alternatively to the Suzuki-type couplings, we have developed low-catalyst loading solutions for Grignard, Heck and Sonogashira couplings by using tailored ligands. The option to chose be-

tween these technology variations enables us always to find a solution for our customers and then to industrially optimize it.

Coupling of Aliphatic Boronic Acids. In one of the latest innovations in the field of coupling, Archimica has developed new methods with very

broad scope for coupling aliphatic and vinylic boronic acid with aryl halides, achieving high yields.



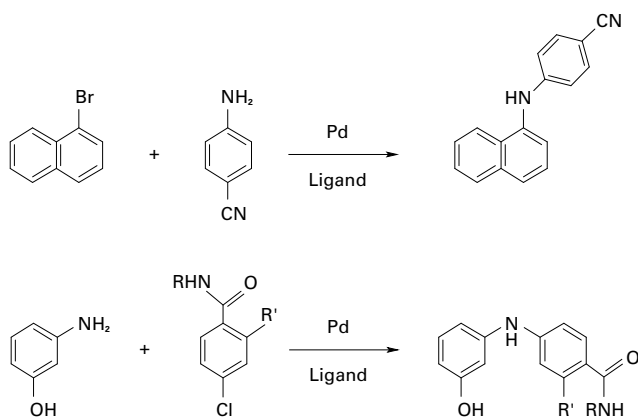
While a few couplings of this type have previously been described in literature, each had suffered from limitations that made them impractical for commercial scale synthesis (e.g. 35 mol-% of palladium). Archimica's new methodology requires only traces of palladium along with innovative ligands derived from oxaphosphorinchloride. The reaction takes place in a single step, offering the pharmaceutical industry an economical new way for making highly complex substituted alkyl- and

vinylarenes that were formerly either very difficult to access or were not available at all. Based on recent experience, this new technology seems to be a general and long-sought-after solution for couplings of aliphatic boronic acids. This new technology allows totally different synthetic approaches for both new and old molecules, allowing for shorter and more efficient solutions than the complicated synthetic workarounds that were earlier practiced.

C,N-coupling – A New General Method

C,N-couplings can be used in producing a broad range of substituted amines. Several catalytic systems have been developed, often characterized by high loadings of expensive catalysts, which is not ideal for commercial scale manufacture. Expensive tertiary alcoholate bases, inflexibility of solvents utilized and, most importantly, the difficul-

ties of removing catalyst and metal traces from the final product – since these final products are often very efficient in binding catalysts such as palladium – have now been solved by what can be considered an important breakthrough in the field of C,N-coupling technology.



Archimica has developed sulfonated hydroxy-biphenyl phosphane ligands that yield highly polar ligand/catalyst systems while using non-expensive bases. These systems show very high

catalytic activities at very low concentration. They allow work with a broad range of solvents, and thanks to their specific properties allow the easy removal of the catalyst/ligand system.

Lithium Technology

Organometallic species are usually formed by Grignard reaction or halogen-metal exchange using an aryl halide as the starting material. However, many aryl chlorides fail to undergo the Grignard reaction, and in general chlorides are not suitable for halogen-metal exchange, hence classically expensive bromides have been used. To overcome this deficiency Archimica has developed its lithium technology – the chloroarene precursor is lithiated using solid lithium metal, and the resulting organolithium species can then be reacted in any desired way.

Moreover, our lithium technology allows the fine tuning of the lithiation activity to the substrate which gives us high yield and quality as well as access to industrial volumes of materials that have not been accessible before.

Our new technology for lithiation allows for the general substitution of commercially available butyl lithium, any other alkyl lithium or lithium amide with lithium metal. These traditional lithiating compounds are characterized by difficulty in handling and use, by the creation of undesirable by-products in synthesis and – despite the application of these expensive reagents – the often moderate yields they deliver.

Archimica's new lithium technologies comprise two different chemical approaches:

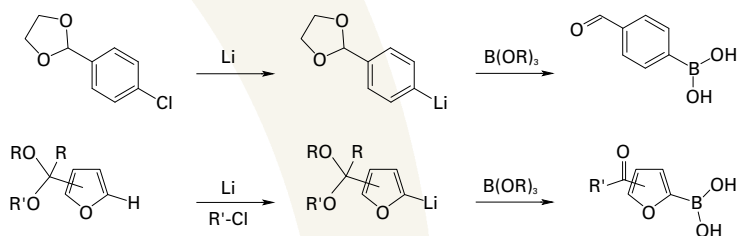
Conversion of aryl chlorides to aryl lithiums.

These methods have been developed to achieve an almost 100% yield and selectivity in such conversions. As these reactions are often performed under cryogenic conditions, this technology tolerates a wide range of functional groups, in some instances even labile groups like nitriles or esters.

In-situ technologies for butyl lithium reactions.

Almost all reactions formerly run using butyl lithium or other commercially available alkyl lithium or lithium amide can be conducted in a very effective manner using this newly developed method. The in-situ generation of an organometallic base by the addition of an alkyl chloride to a mixture of substrate and lithium metal in a suitable solvent has several unique advantages. Besides economic considerations, e.g. the expense of butyl lithium, this method allows a tailoring of the reaction conditions by using different kinds of alkyl chlorides.

Archimica's lithium technology is more than just a replacement for problematic materials. The lithium compounds accessible by these unique technologies are very reactive and highly selective. It offers substantial benefits in applicability, yields and the quality of end products – and allows great improvements in financial terms.



Chiral Solutions for the Pharmaceutical Industry

Archimica has an extensive global network of cGMP manufacturing sites available to serve all customer requirements. This is combined with an excellence in process development and a broad portfolio of innovative technologies. Exploiting this powerful combination, Archimica is able to deliver start-to-finish solutions for novel chiral, enantioselective and peptide syntheses, and to develop highly innovative separations.

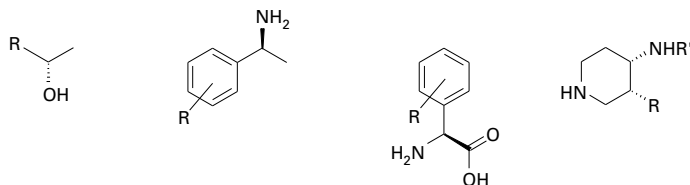
Our focus on in-house development of new enantioselective biocatalytic syntheses and on close cooperation with leading technology partners enables us to offer a broad selection of chiral products and related technologies.

Primary areas of focus include:

- Metalorganics in selective syntheses
- Stereoselective hydrogenations
- Enzymatic chemistry using oxynitrilases, lipases, esterases, alcohol dehydrogenases, transaminases and other enzymes
- Chiral epoxides from halogenated ketones
- Chiral cyanohydrins and mandelic acids
- Biocatalytic resolution of esters, acids, epoxides, hydroxy and amino compounds
- Non-natural α - or β -amino acids (enzymatic or chiral pool syntheses)
- Resolutions of racemates
- α -Hydroxyaldehydes by separation
- α -Substituted carboxylic acids

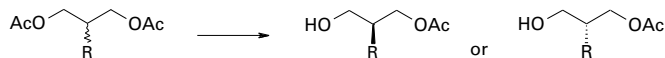
Classical and Biocatalytic Resolution. Using ‘resolution libraries’ (chemical and enzymatic) and parallel screening, we make new chiral compounds quickly accessible as building blocks to be

manufactured and used in cGMP products and APIs with high enantiomeric purity. Examples include alcohols, esters, acids, unnatural amino acids and amines.



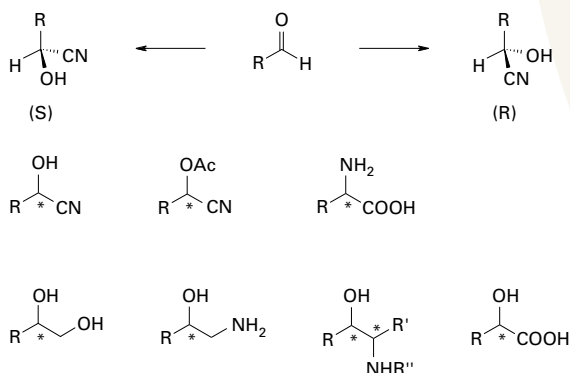
Chiral Induction. By using hydrolase enzymes for chiral induction, we produce single enantiomers, starting from prochiral mesodiols, diacids or diesters with a theoretical yield of 100%. In many

cases such enzymatic approaches offer significant advantages over classical chemistries with both cyclic and acyclic systems.



Chiral Cyanohydrins. Archimica has developed a range of approaches to chiral cyanohydrin and mandelic acid production, using both transition metal catalysis and enzymatic technologies to access both (R) and (S) products. Additionally,

using the directive potential of the first chiral carbon atom, we synthesize chiral molecules with several stereocenters. Using these technologies, we have already synthesized products at a > 10 to/year scale.



Asymmetric Reductions/Hydrogenations. At Archimica we have decades of experience in classical reductions/hydrogenations using a variety of different reductants and catalysts and have large-scale equipment available. We are able to develop

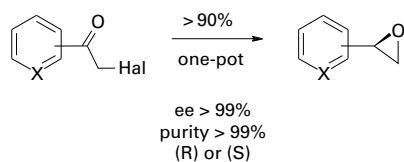
any specific molecule quickly and to scale up rapidly from pilot plant to large-scale production.

One example to mention are Arylhydrazones. These challenging substrates are hydrogenated with enantiomeric excesses of > 99%.

Chiral Oxiranes. In a further effort to expand the potential and the range of chiral chemistry, Archimica has recently developed a cutting edge technology for the synthesis of enantiomerically pure oxiranes, which is highly efficient, and offers high yields and economically sound production. Chiral oxiranes have the potential to serve as highly valuable building blocks in diverse products such as chiral amino alcohols.

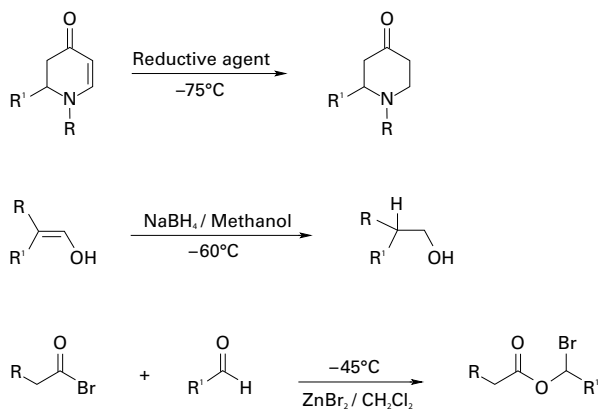
The new technology features an enzymatic reduction starting from substituted acetophenones.

The process can make both enantiomers of oxiranes available. It is essentially a 'one pot' procedure that provides very mild conditions, so that functional groups which might typically be considered 'difficult' can be handled. The process combines high yields – up to 100% – with product purities that are above 99% ee. Archimica can isolate these highly reactive intermediates with high-performance (up to 100 plates) distillation equipment, crystallization and low-pressure capabilities, to achieve even higher product purities. Both aliphatic and aromatic epoxides have been produced using this new technology.



Cryogenic Reactions

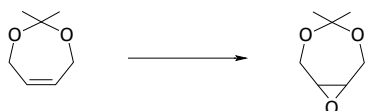
Our cryogenic reaction capability provides suitable conditions for performing reactions involving highly reactive species, achieving a controlled and more selective conversion through the use of low temperatures. Cryogenic reactors are also central to multi-ton production involving organometallic reactions.



Use of Hydrogen Peroxide

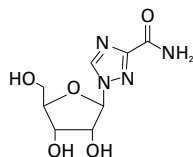
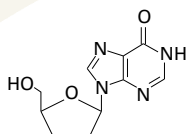
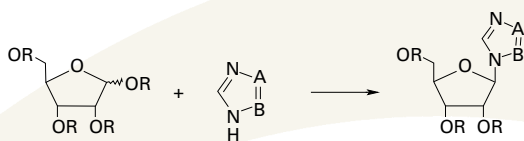
Hydrogen peroxide by itself is a relatively poor oxidizing agent in organic chemistry. Based on our experience, we are able to use it in combination with 'activating' agents to obtain easily several very useful reagents such as peroxy acids and dioxiranes, which yield very selective functionalizations.

For several years we have been industrially optimizing the chiral opening of oxiranes e.g. using Sharpless technology or similar. Many examples in various stages of development and volume have been performed for our customers.



Nucleoside Chemistry

Many applications are currently under evaluation in regular application for use in fighting viral diseases (hepatitis, HIV), cardiovascular or Parkinson's disease. We offer our customers many years of experience in a variety of areas, ranging from the creation of building blocks based on cutting-edge technologies (pseudosugars and bases) to innovative and highly selective couplings and modifications of both sugar moiety and base. Our coupling technology allows for couplings with high syn/anti-ratios and enantiomeric excesses, whereas classical technology delivers extremely low yields, selectivities and industrial feasibility. In addition, the enzymatic approach to production or modification of nucleosides is being pursued by our R&D.



Equipment

With a wide variety of multipurpose equipment combined with dedicated lines for key technologies, Archimica's sites have the flexibility to react promptly to market requirements and achieve custom molecules involving almost any kind of chemistry.

Manufacturing Equipment at the Origgio Site

Total area: 163,000 m² (chemical plant about 30,000 m²)

3 manufacturing units with a total capacity of 550 m³

Average vessel size: 6,000 L

Glass lined, stainless steel and hastelloy reactors,
dedicated and classified finishing areas,
up-to-date isolation area for APIs

<i>Reactor</i>	<i>Capacity</i>	<i>Total Number</i>
Glass Lined	from 800 L to 13,500 L	37
Cryogenic	from 3,000 L to 8,000 L	10
Stainless Steel	from 400 L to 12,500 L	37

<i>Hydrogenation Vessels</i>	<i>Capacity</i>	<i>Max Pressure</i>	<i>Total Number</i>
Glass Lined	from 400 L to 16,500 L	up to 65 bar	4
Stainless Steel	1,500 L	up to 85 bar	1

<i>Centrifuges</i>	<i>Diameter</i>	<i>Total Number</i>
Anti-acid	1,500 mm	3
Hastelloy	1,250 mm to 1,500 mm	3

<i>Dryers</i>	<i>Capacity</i>	<i>Max Pressure</i>	<i>Total Number</i>
Filter Dryer	from 2,000 L to 3,000 L	up to 4 bar under vacuum	3

Pilot Plant at the Origgio Site

Reactors/Hydrogenators

<i>Material</i>	<i>Capacity</i>	<i>Total Number</i>
Glass Lined	from 50 L to 1,500 L	5
Glass Vessels	from 75 L to 150 L	2
Filter Dryer	from 200 L to 500 L	2
Hastelloy	300 L	1
Stainless Steel	from 1 L to 1,550 L	7

- Approved also for the production of commercial APIs.
- The small scale production is equipped with a filter dryer and tray dryer with a capacity of 1 m³.
- Its laboratory equipment includes: HPLCs, analytical scales and Karl-Fischer.

Laboratory Equipment

R&D. New process methods for screening and development, method transfer and optimization hoods, semi-pilot, mechanical pumps for high vacuum, low/high pressure preparative chromatograph, HPLCs, GLCs, standard glassware, glassware for hydrogenation reaction up to 6 bar, ultra thermostat, PCs for database access (Chemical Abstracts, STN), LC-MS and GC-MS, NMR.

A kilolab is used for making first kg quantities as well as for studying upscaling effects.

QC. UV spectrophotometer, FTIR spectrophotometer, HPLCs, GLCs, complete equipment for TLC, pH meters, automatic melting point unit, DSC, differential scanning calorimeter, atomic absorption spectrometer, refractometer, polarimeter, thermostat-controlled vacuum ovens, Karl Fischer unit for water determination, automatic potentiometric titration unit, climatic cabinets and laser particle analyzer for regular analysis and analytical development.

Microbiology. Microbiology lab equipped with laminar flow hood, TOC analyzer, Milliflex system, colony counter, thermostats, ovens, freezer, autoclave, microscope, balance, incubators and mixer.

Others

Warehouses. Controlled temperature (< 25°C) and humidity (< 60%) API warehouses, room temperature for intermediate and raw material warehouse, cold/warm rooms for temperature sensitive materials, toxic solid warehouse, packing room material warehouse, flammables warehouse and quarantine warehouse for goods received.

Ecological Unit. Biological waste-water treatment plant, incinerator.

Solvent Recovery Unit. Two continuous distillation columns (2,000 kg/h each), two stripping columns (2,000 kg/h each), one column for washing water-soluble solvents (3,000 kg/h).

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