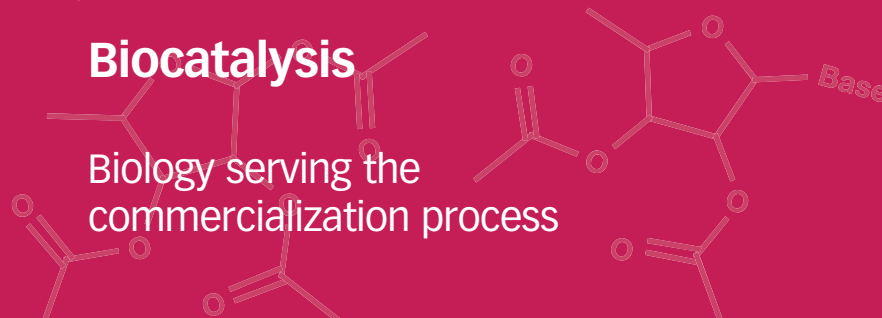


Biocatalysis

Biology serving the commercialization process



Biotransformation, as a synthesis tool, is a key element in Archimica's technology portfolio, and assists in our ability to provide rapid, cost-effective manufacture of high-purity pharmaceutical intermediates at a commercial scale.

Enzyme-catalysed reactions use the selectivity provided by nature to provide efficient reactions under conditions that are ideally suited for the successful commercialization of APIs. Archimica offers a comprehensive biocatalysis capability, including rapid biocatalytic screening and evaluation, process development, enzyme optimization, and both pilot and commercial scale manufacture.

Research and process development

Archimica maintains a strong multidisciplinary approach to biotransformation, employing scientists well versed in both biocatalysis and organic synthesis. This position allows us to select chemical or enzymatic catalysis as is best suited to the needs of the project. Biotransformation finds its primary applications in routes where selective activity is required, including enantioselective, regioselective and chemoselective reactions.

Close interaction with specialist enzyme companies provides us with libraries of enzymes known to be effective in a wide range of conversions and available at large scale. A targeted approach based on our expertise allows us to quickly determine the potential advantages of a particular biocatalytic process and to evaluate its competitiveness against alternative synthetic approaches.

Archimica has an active program to develop new enzymatic routes to solve specific synthesis challenges, and we manage the optimization of enzyme activity to ensure innovative solutions when required by a project.

Pilot and commercial scale manufacture

Starting with commercially available enzymes allows us to begin manufacturing products within exceptionally

short lead times. The Archimica Molecules Synthesis Centre is renowned for rapid, high quality manufacture of complex materials. Often, we can manufacture 50-100 kg quantities in a matter of weeks and we have the technical experience and know-how to efficiently scale-up processes for commercial needs. Added to this capability, Archimica has world-class expertise in multi-step synthesis, which allows us to integrate the biotransformation steps required into both upstream and downstream steps as part of a successful commercial scale-up.

Core capabilities

Archimica has active programs in biocatalysis in a number of areas.

Cyanohydrin technologies

Archimica has developed a range of approaches to chiral cyanohydrin production utilizing enzymatic systems. We have used hydroxynitrile lyase enzymes from both plant and microbiologically engineered sources to produce a broad range of cyanohydrins of both (R) and (S) configuration in high yields and with excellent selectivity. Starting from these highly enantiopure cyanohydrins we have produced a variety of different mandelic acids, amino alcohols and protected cyanohydrins at a scale from a few kilos up to several tons.

Chiral resolution

The use of biotransformations to carry out chiral resolutions is now well established as an efficient and scalable methodology for separation of a single enantiomer from racemic mixtures. Archimica has substantial expertise in resolutions of racemic mixtures of esters, acids, alcohols, amino acids and amines using biocatalysis. Additionally, we have experience with lactone and dioxolactone resolutions, and separation of isomeric mixtures of various compounds using biocatalysis. We typically use hydrolase enzymes in both hydrolytic and synthetic directions to provide the required enantiomer in a way that is optimal for the specific process. Archimica's strength in this area relies on rapid integration of the biotransformation into its broad chemistries, the ability to scale-up and produce multiple kilograms quickly and the ability to transfer such technologies seamlessly into our multi-tonne production facilities.

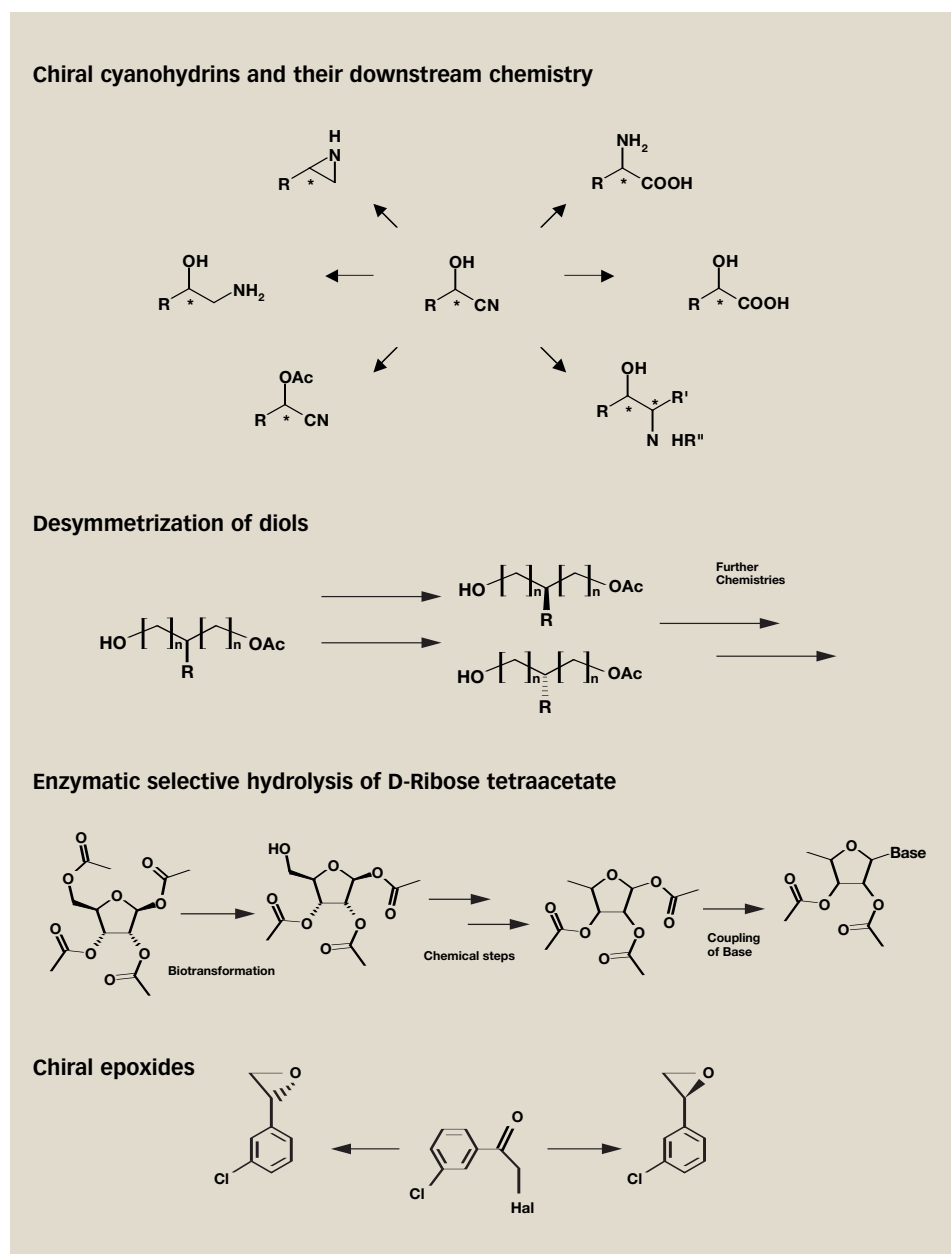
Archimica holds, for example, a key technology patent involving the use of vinyl esters in resolution of chiral alcohols (US 4963492).

Enzymatic production of highly enantiopure epoxides

Starting from halogenated ketones, we have developed a high-yielding enzymatic process for chiral epoxides. In combination with our high-performance distillation equipment, both aliphatic and aromatic epoxides can be produced in highest ee and chemical purities, with very broad functional group tolerance.

Chiral induction

Archimica offers extensive experience in the use of biocatalysis for chiral induction, with particular emphasis on prochiral meso diols, diacids or diesters. These processes offer access to single enantiomers with a theoretical yield of 100% using robust well-developed technologies based around hydrolase enzymes. In many cases enzymatic approaches offer



significant advantages over classical chemistries. We have carried out such biotransformations with both cyclic and acyclic systems, including the formation of single enantiomer 4-hydroxy-cyclopentenyl acetate and desymmetrisation of acyclic diols.

Complex molecular chemistry with multiple reaction sites

At Archimica, our expertise in artificial nucleoside chemistry allows for the

modification of nucleotides or nucleosides as well as artificial or modified sugar moieties. In this area, we have produced excellent results with selective enzymatic deacetylation of sugars in preparation for further chemistries. Classical chemistry routes often require multiple protection/deprotection steps, whereas enzymes can be found which act specifically at a single site and thus reduce costly extra steps while potentially increasing yields.