Archimica

TECHNOLOGY STRENGTHS

Organometallic Chemistry

- More than 60 m³ cryogenic reactor volume / -100°C
- Unique Lithium metal technology (avoiding Butyllithium)
- More than 150 Boronic acids already made – from few kg up to 100+ mtons

Organometallic chemistry is an ideal vehicle to address one of the pharmaceutical industry's greatest challenges — carbon-carbon and carbon-heteroatom bond formation.

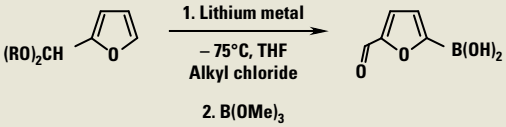
Archimica's organometallic chemistry can be well tailored to reactivity requirements and a wide range of reactions is known for all structural patterns. In addition, these organometallic reactions can be carefully controlled (particularly at low temperatures), and they provide an extraordinarily high degree of selectivity and allow very pure end products.

Many of the compounds achievable through the use of Archimica's organometallic chemistry are simply not available by other routes. In other instances, working with organometallics can reduce the number of synthesis steps required to produce an equivalent molecule. This allows the use of less expensive base materials and permits the synthesis of high value compounds. In each of these instances, the key feature of the organometallic reaction is the high level of value that it adds to the resulting products. At Archimica, we have more than fifteen years of experience in the field of organometallic chemistry, and the global infrastructure to deliver a virtually limitless range of production rapidly, with world-class quality.

A firm foundation

At Archimica, our organolithium and magnesium compound production is based on our world leading halogen organics expertise, our strengths in catalyst development and our ability to perform subsequent syntheses with these compounds. Archimica has expertise in the whole range of halogen aromatics such as chlorine, bromine and iodine compounds in all substitution patterns.

Archimica's lithium technology



General substitution technology for butyllithium

- improved process economy
- high selectivities
- higher yields compared to BuLi (+ 10 %)

Archimica's organometallic technologies

- C,C coupling of aryl bromides/ chlorides/tosylates (Suzuki, Kumada, Heck, Sonogashira)
- C,N and C,O coupling (Pd, Cu)
- Boronic acids from Grignards and organolithium compound (aromatic, heterocyclic, vinyl, aliphatic, multifunctional)
- Cryogenic chemistry (up to 13 m³/-100°C)
- Heterocycle synthesis (naphthyridines, trifluoromethyl pyridines, azaindoles)

Increasingly, we are able to improve economics by substituting other halogens with less expensive chlorides. In addition, we also use bromine compounds (with our expertise in the USA in Springfield, MO) or iodine compounds (with our expertise in Sandycroft, UK), depending on the selectivity or reactivity required for the organometallic step of the reaction.

Archimica's lithium technology

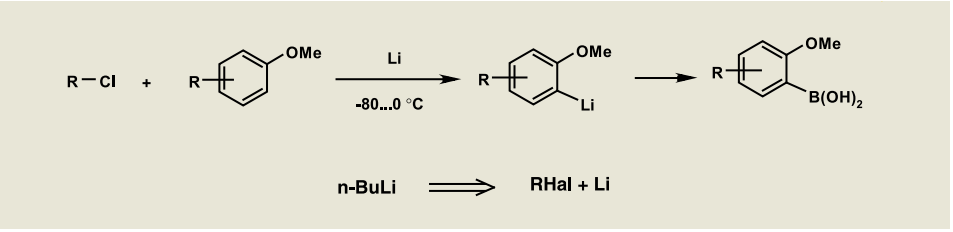
Archimica has developed a new technology for lithiation that allows for the general substitution of commercially available butyl lithium, other alkyl lithiums, or lithium amides – the traditional approaches for lithiation – with lithium metal. These traditional lithiating compounds are characterized by their difficulty in handling and use, by the creation of undesirable side-products in syntheses and often only moderate yields.

Archimica's new lithium technologies consist of two different chemical approaches.

Substitution of aromatic chloro by lithium

These methods have been developed to a level where almost quantitative yield and selectivities in such conversions can be achieved. 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 CN, CO_2H or CO_2R.

General substitution method for n-Butyllithium (BuLi)



In situ-metalations with lithium metal

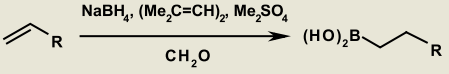
Almost all reactions formerly run using butyl lithium, LDA or other commercially available reagents can be conducted in a very effective manner using this newly developed method. The in situ-generation of an organometallic base by addition of an alkyl chloride to a mixture of substrate and lithium metal, in a suitable solvent, has several unique advantages. Besides economic considerations, the method allows a tailoring of the reaction conditions by using numerous different kinds of alkyl chlorides. In almost all of the applications evaluated so far, a significant increase in yields (sometimes up to 100%) and most often higher product purities have been found.

These lithium technologies have been developed to a very high level of performance. As a general comment, handling of lithium metal in ethereal solvents bears significant risks, as this alkali metal can react vigorously with the solvent. As a result of (a) having the necessary small- and large-scale cryogenic equipment and (b) extensive process development and upscaling work, Archimica is able to work with these technologies even on a production volume of up to 13 m³ at temperatures between < -100 up to 0°C in a safe manner. We do this commercially under cGMP and non-GMP conditions.

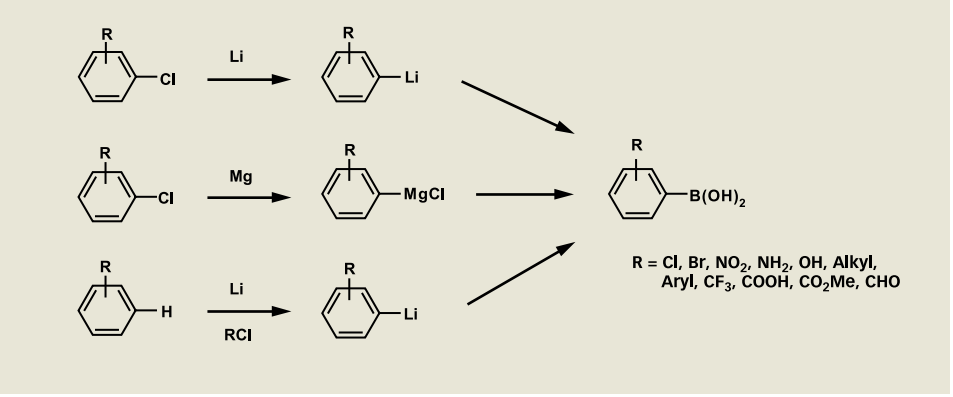
As a short summary of the range of applications, almost all reactions that formerly required butyl lithium or LDA can be improved using this new technology.

Boronic acids

Archimica's technology portfolio includes the ability to deliver virtually any type of boronic acid at volumes from kilograms to commercial scale. This includes boronic acids that are typically very difficult to handle and produce. This capability is made possible by a unique combination of technology platforms in halogen and organometallic chemistry. Special pro-



Boronic acid technologies



cesses in this area also allow for production of high purity boronic acids without borinic acids, isomers and other typical impurities.

An example of Archimica's latest progress in the field of boronic acids is the development of a new method for the synthesis of alkyl and vinyl boronic acids using an in-situ hydroboration. This method solves a problem which so far has limited the availability of alkyl and vinyl boronic acids – the very poor yields in the "classical approach" when reacting a respective Grignard with boron compounds (typical ranges are 10-30%). The new procedure starts with readily available and inexpensive starting materials (sodium borohydride, dimethyl sulfate, tetramethylbutadiene) and in a "one-pot" process results in high yields (up to 86%) of the desired alkyl and vinyl boronic acids. Additionally, the materials produced offer heretofore unknown levels of purity, due to high regioselectivities of the method even in examples where the formation of isomers is possible. The most recent breakthrough in this area is the development of a general coupling technology for such aliphatic and vinyl boronic acids.

An especially challenging area of boronic acids are multifunctionalized heterocyclic boronic acids. A combination of cryogenic methods and special technologies allow the synthesis and isolation of high-purity products in attractive yields and broad functional group tolerance.

C,C couplings

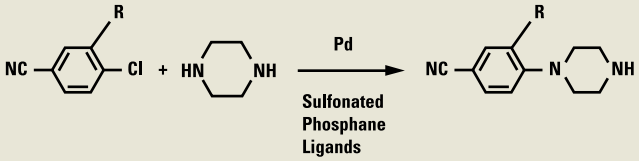
Archimica has also developed unique approaches to biaryl reactions allowing a choice between Suzuki and Grignard coupling reactions. Archimica has optimized Suzuki couplings through a proprietary two-phase process which uses two-phase catalysis – offering easy recycling of palladium and very easy removal of the precious metal to levels < 10 ppm. In this process, Archimica employs tailor-made ligands which are available at the commercial scale. It is the combination of our ligand and reaction expertise that allows synthesis of a broad scope of substitution patterns.

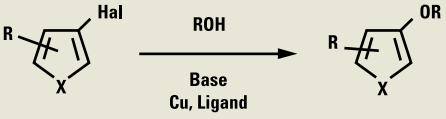
Archimica's Suzuki and Grignard coupling technologies also use palladium and proprietary ligands. The quantities of palladium required for these processes are small enough to not require recycling – a feature that lowers processing costs while at the same time often allowing to use aryl chlorides as starting materials.

For the production of arylpyridines, other arylheterocycles, and heteroaryl boronic acids, Archimica has developed different technologies, all characterized by high selectivities, good yields and very pure products.

C,N and C,O couplings

Archimica has developed special type of sulfonated phosphane ligands which give high yields in C,N coupling reactions and, by their highly polar nature, allow the easy removal of Pd and ligands from the products, allowing economic access to high-purity complex amines.

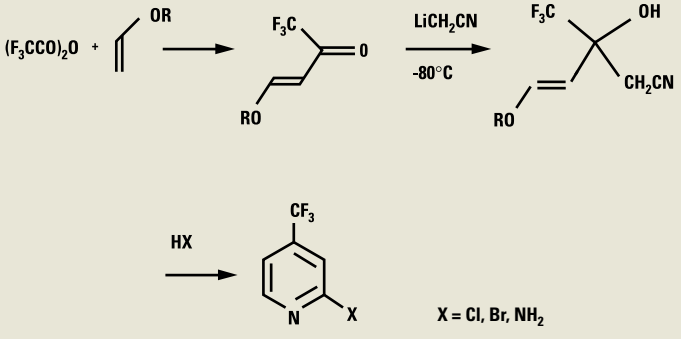




Organometallic synthesis of heterocyles

Organometallic technologies are used for the synthesis of multifunctional heterocycles which are difficult to access by "classical" chemistries.

These methods complete Archimica's broad portfolio of production methods for all kinds of heterocycles, allowing even access to very complex substitution patterns (e.g. different positional isomers of Azaindoles and Naphthyridines).



Tailor-made technologies for high-purity products

- Methods for reduction of palladium
- Methods for high isomeric purities
- Special isolation technologies for labile boronic acids

Catalyst systems

Archimica has an extensive proprietary, patented process and catalyst position that allows us to select an optimum solution for couplings including biphenyls, heterobiaryls, aliphatic couplings, oligophenyls, as well as reactions such as Heck reactions and C,N and C,O bond formation. Many times the syntheses of the catalyst ligands require organometallic expertise.

At Archimica, we understand the catalyst properties needed for your process, and have the ability to deliver an effective solution through our broad experience. The improvement of catalyst systems is an area of continuing R&D at Archimica. As the synthetic targets in pharmaceutical fine chemicals synthesis are getting more and more complex, we are often combining our capabilities in organometallics, cryogenic and enzymatic chemistry for identifying the best solutions.

World-class organometallics infrastructure

Today, Archimica manufactures organometallics at four facilities in Europe and the United States. This is a full spectrum manufacturing capability, with developmental quantities at the gram level available, with pilot scale production in the 10-500 kilogram range in our organometallic technology development center in Germany. Processes can be transferred to our cGMP centers in Italy and the United States for commercial production up to the several hundred tonne range. Each of these facilities features cryogenic production down to -100°C.

Archimica's organometallic technology is backed by state-of-the-art expertise in solvent recycling that is compliant with pharmaceutical standards and improves purity and economics. Archimica also practices catalyst recycling and metals removal down to and beyond levels required by the pharmaceutical industry.

Compounds available from Archimica's organometallic chemistry

- Aromatic boronic acids (incl. high purity, complex substituted products)
- Aliphatic and vinylic boronic acids
- Bi- and multi-functional boronic acids
- Heterocyclic boronic acids (incl. pyridyl, isoxazolyl, pyrazolyl, indolyl boronics, multi-heteroatom boronic acids)
- Arylamines, arylethers
- Polycyclic aromatic compounds (carbocyclic and heterocyclic), e.g. naphthyridines, azaindoles
- Aliphatic and aromatic aldehydes, acids, esters
- Amino alcohols, complex amines, non-natural amino acids