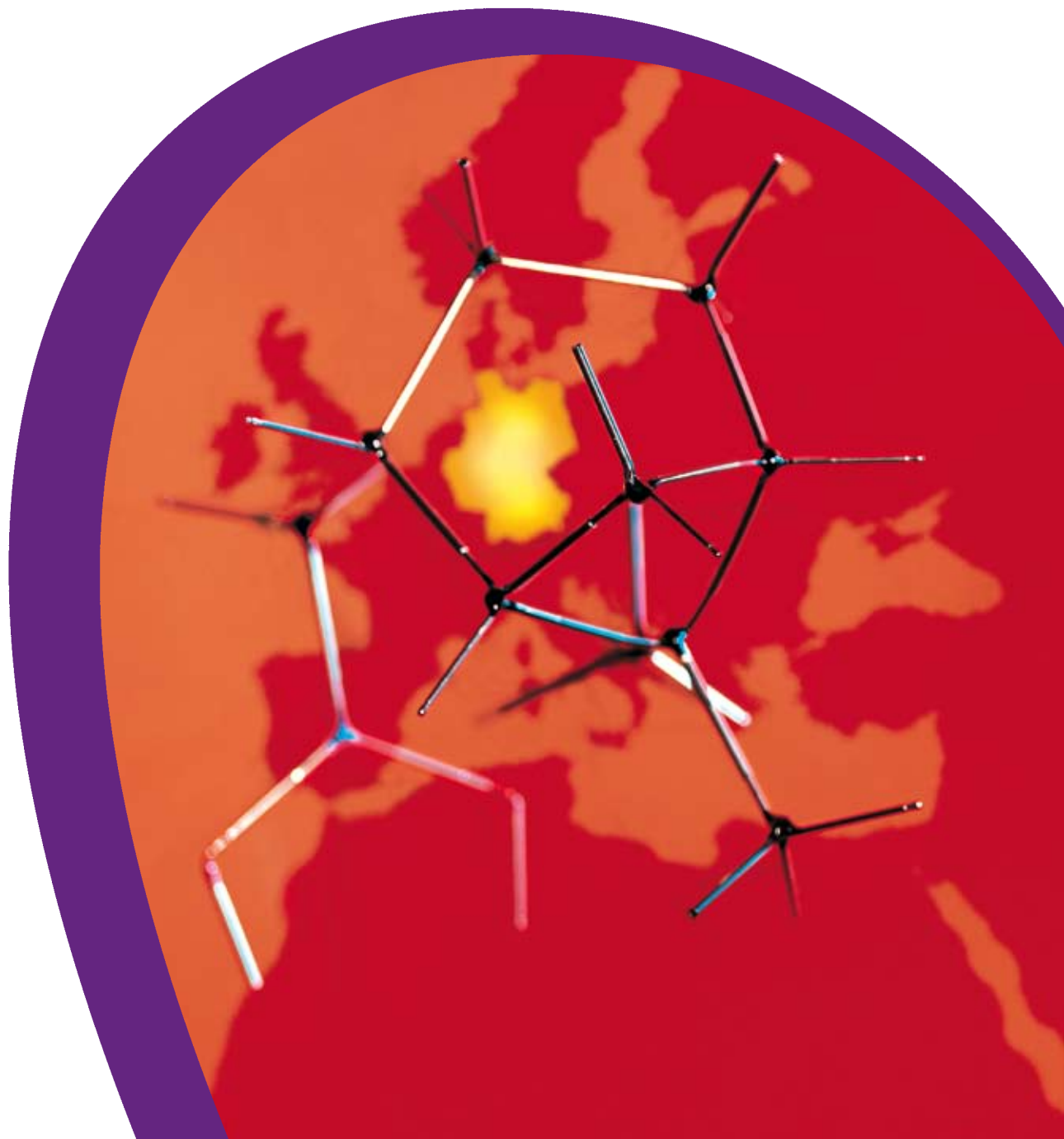


Pharma Services Frankfurt/Germany

Solutions from Drug Discovery to Full Scale Production





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Our Services

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

Experienced in Thinking Ahead

Archimica combines global cGMP manufacturing capability, comprehensive pharmaceutical services, customer-oriented R&D and outstanding technology development assets. With our technology center in Frankfurt/Germany, and operations in Springfield/Missouri, United States, Sandycroft/United Kingdom, Bon-Encontre and Tonneins/France and Origgio/Italy, we are a global outsourcing partner for leading pharmaceutical companies. We offer our customers active pharmaceutical ingredients (APIs), regulated intermediates, and building blocks based on leading technologies.

Our technology center in Frankfurt is specialized in developing processes for the production of intermediates – and actually manufacturing these intermediates – particularly for the pharmaceutical industry. Operating as an independent service unit since 2003 we have established a center of excellence for highly selective synthetic methods like metalorganics, heterocycles and biocatalysis. Motivated project teams, integrative approaches and our position within the Archimica network build a highly efficient and responsive small unit with the reliability of a large multinational company.

Our services cover the entire spectrum of process-related activities – from the development of a synthetic route over the upscaling stage right up to piloting and full-scale manufacturing. Our expertise in the area of custom synthesis is backed up by a wide array of valuable resources:

- decades of experience in chemistry
- highly experienced and qualified staff
- development and upscaling of 200 new chemical steps each year
- versatile multi-purpose plant and ancillary equipment
- comprehensive approvals from the regulatory authorities for complex reactions
- material-sourcing expertise
- environmental and safety management of the highest standards
- Quality Management System according to DIN EN ISO 9001: 2000
- cooperation and transfer of processes to our cGMP sites
- independent QC laboratories operating in accordance with DIN EN ISO 17025

We do our utmost to process your requests quickly and give a delivery time, a price or a process development proposal within a few days.

Know-how Engaged in Your Processes

Production partnership. For many years now, we have been working for and with customers from all parts of the globe developing solutions to a large variety of problems. We stand by our customers with professional and committed support throughout the process and all the individual steps – from the early phases of substance development over the upscaling stage and straight through to full-scale manufacturing. We gain valuable experience during the entire process – the kind of experience that will make us the partner of choice when you commence production on a commercial scale.

For this purpose we make use of a highly diversified technology portfolio including chiral chemistry, organometallics, heterocycles, halogenation and applications of the coupling agent propane phosphonic acid anhydride®T3P.

Success in a team. Our staff includes both highly qualified chemists with many years of experience in process development and young scientists with fresh ideas. Together with committed laboratory technicians, they form teams of experts, according to the demands of every specific task. A campus-like scientific spirit and a flexible, fresh approach to problems lead us to optimal solutions.

In our organization, research is the province of more than 20 chemists. Additional chemists and 30 technical employees ensure that the pilot plant is staffed round the clock.

An intense commitment to quality and communication, as well as a respect for costs and deadlines, are essential components of our philosophy.

Flexible Services for Comprehensive Solutions

Custom Synthesis and Route development. At our laboratories and pilot plant, we manufacture quantities ranging from a few grams to several hundred kilograms. We continually develop new technologies and methods for the benefit of our customers.

Thanks to our position in Archimica's network, this know-how can be transferred to our worldwide production facilities. This enables us to offer our customers integrated services ranging from the manufacture of the first sample quantities in the laboratory over the development of processes right up to regular production.

All of our facilities are in conformance with DIN EN ISO 9001:2000 quality standards. They are equipped to handle nearly any chemical reaction and adhere to high occupational safety and health standards.

Contract syntheses make up a very important part of our custom synthesis service. Using structures specified by our customers we develop feasible routes to gain access to substances and to manufacture them.

Process & technology development. The Frankfurt team is responsible for identifying and developing new, interesting fields of technology. Our know-how and the utilization of related technologies is then handed over to our customers.

We aim to develop laboratory processes which have a “scaleable” design from the outset and which meet our customers’ requirements and expectations. Therefore involvement of our customers in the decision-making process and close cooperation including constant and open communication plays a central role.

Scale-up of processes. Very few organizations have as much practical experience in process scale-up from research quantities to development requirements as Archimica. This expertise enables us to ensure constant product quality and minimize variations and impurity profiles.

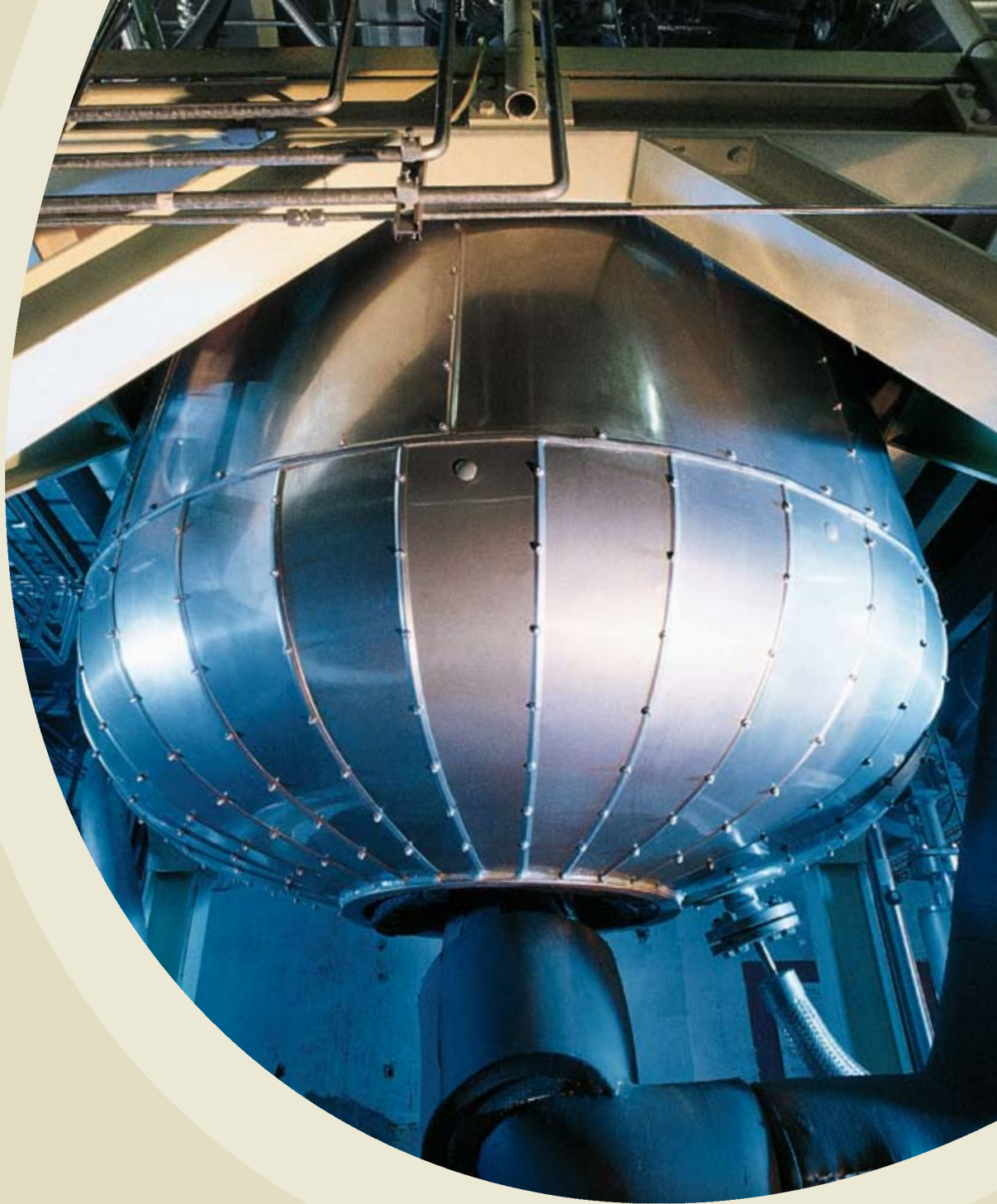
Technology transfer and pilot production. The facilities available at Archimica’s Frankfurt site provide an excellent transition from the laboratory to the semi-bulk kilo lab to reactors in the pilot plant, which mirror full-scale production environments. In addition, the close proximity of all these facilities allows an easy transfer of technology and process know-how.

Our wide variety of technologies enables us to successfully synthesize even highly complex molecules. Some of the more specialized topics are:

- cryogenic reactions (–100°C)
- lithium metal or lithium organyl reactions
- Grignard reactions
- boronic acids
- biphenyls, phenyl pyridines and other biaryls
- metal-catalyzed C,C-, C,N- and C,O-coupling reactions
- ketone arylations
- enzyme-catalyzed reactions
- Friedel-Crafts reactions
- heterocycles (naphthyridines, azaindoles, isoxazoles, oxadiazols, ...)
- dicyclopentadiene cracking
- distillation and fractionation up to a melting point of 120°C

We consistently hold some of the highest standards worldwide for safe process guidance. In addition, a team of experienced analytical chemists is available round the clock for quality control. The main facility is housed in a large building directly connected to the research and development (R&D) and quality control (QC) departments. The plant is fully committed to Archimica’s Environmental, Safety & Health Affairs (ESHA) policy. All effluents, washings and solid waste are disposed of directly on site.

Full-scale manufacturing. Above and beyond the extensive capability of our operations in Frankfurt, we have access to the comprehensive expertise and advanced technical resources of Archimica.



Organometallic Synthesis

Archimica has invested significant efforts in the development of a modern technology portfolio in order to be able to offer our customers state-of-the-art solutions in the areas of C,C-, C,B-, C,O- and C,N-bond forming reactions. In total, more than 100 different products from modern organometallic technologies have been produced by Archimica on an industrial scale for more than a decade.

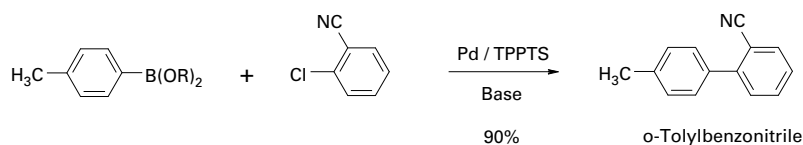
Compounds Available from Archimica's Organometallic Chemistry

- Aromatic boronic acids
- Aliphatic and vinylic boronic acids (including cyclopropyl boronic acid)
- Bi- and multi-functional boronic acids
- Heterocyclic boronic acids
- Pyridyl boronic acids, pyrazolyl boronic acids
- Multi-heteroatom boronic acids
- Aryl alkanes
- Aryl amines, Aryl ethers
- Polycyclic aromatic compounds (carbocyclic and heterocyclic)
- Aliphatic and aromatic aldehydes, acids, esters
- High-purity cis-/trans-cycloalkanes
- Chiral amino alcohols

Biaryl Coupling Reactions: Suzuki Couplings

At Archimica, organometallic chemistry, including organolithium and magnesium compound preparation, is based on our world leading aryl halides 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.

We can offer several highly active systems for the Suzuki coupling of aryl halides. The Pd/TPPTS system couples virtually all aryl bromides and activated aryl chlorides in high yields and very high turnover numbers. It additionally permits working in aqueous systems, enabling easy separation of catalyst and product, and keeps costs under control through easy palladium recycling. We are further using several straightforward methods to reduce the palladium content in products to below 10 ppm.



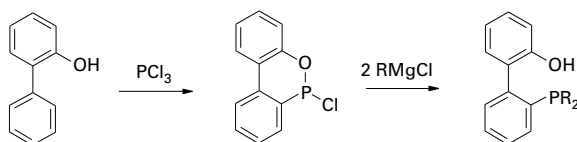
Coupling of Aryl Chlorides

In order to solve the problem of more challenging couplings of non-activated or even deactivated aryl chlorides, we have developed the synthesis of a new ligand class. In contrast to the other systems known today for couplings of aryl chlorides, our methods allow us to synthesize these ligands in large quantities at reasonable prices. | **Fig. 1**

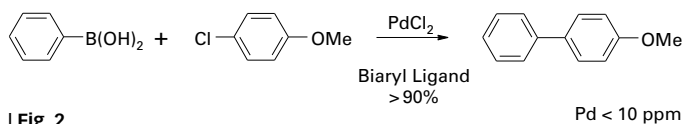
The two-step process depicted below starts from the very inexpensive raw materials 2-hydroxybiphenyl and PCl_3 . The different reactivity of the phosphor-heteroatom bonds allows the

ligands to be tailored to highly complex synthesis problems. One example is the coupling of deactivated 4-chloroanisole. Even here, only traces of Pd/ligand can achieve complete conversion. | **Fig. 2**

The application of this and other catalyst systems allows us to handle almost every coupling combination with high yields and selectivities. In order to be able to offer very quick solutions, we typically test our different catalysts in a parallel screening approach and can rapidly identify the best system for a customer inquiry.



| Fig. 1

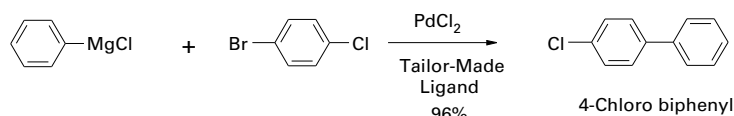


| Fig. 2

Biaryl Coupling Reactions: Grignard Couplings

Aryl bromides. We have already produced several products from Pd- or Ni-catalysed Grignard couplings in ton quantities. One example is the production of 4-chlorobiphenyl as shown below. The purity of the 4-chlorobiphenyl is $> 99.5\%$, the Pd content below 5 ppm. A few grams of Pd catalyst is sufficient to produce 1,000 kg of chlorobiphenyl.

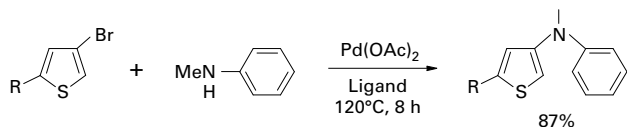
Aryl chlorides. Ligands derived from 2-hydroxybiphenyl also allow Grignard couplings of aryl chlorides. Depending on the substitution patterns, the combination of these ligands with Pd or Ni very frequently can achieve complete conversion to yield the desired products in a very economical process.



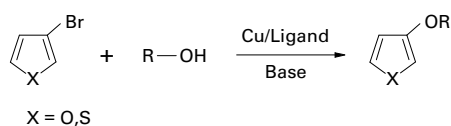
C,N- and C,O-couplings

The application of proprietary sulphonated biphenyl phosphines as highly efficient ligands in Pd catalyzed aminations allows very economic processes for a broad range of substituted amines.

In addition to their high catalytic activity, sulphonated ligands have the advantage of very easy removal of Pd and ligand from the product to levels of < 10 ppm.

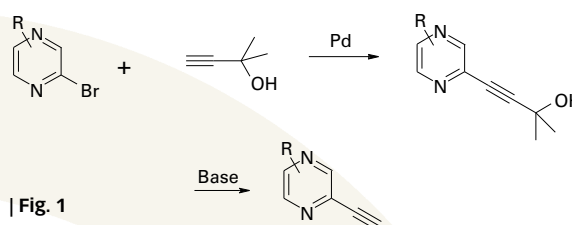


Special ligands for copper-catalysed C,O-couplings are used for the production of high-purity heterocyclic ethers.



Other couplings

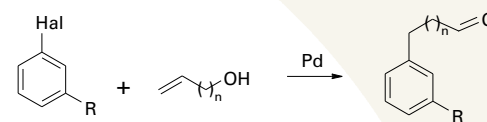
Other couplings applied by Archimica are Heck and Sonogashira reactions. Our method of introducing ethynyl substituents for example consists of substituting the halide with the commercially available dimethyl propargylic alcohol and a subsequent fragmentation as shown below. | Fig. 1



| Fig. 1

Heck reaction. As an example we have broad experience in allylic alcohol Heck reactions, which is a very convenient approach for preparing terminal araliphatic aldehydes. | Fig. 2

These sequences of Heck reactions and Pd-catalysed isomerisations work very nicely with allyl alcohol. The yields are even higher with longer-chain unsaturated alcohols.

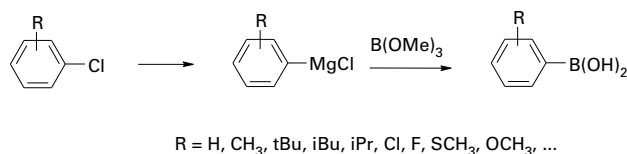


| Fig. 2

Boronic Acids

Aromatic boronic acids from Grignards. In using the reaction of Grignards and trimethyl borate, we have already made about 40 different boronic acids in quantities ranging from 20 kg to several tons. We specialized in generating highly pure boronic acids.

We have also developed a broad range of syntheses for very difficult products or, sometimes, even boronic acids which have not been accessible



| Fig. 1

More complex phenyl boronic acids. A variety of approaches are used for accessing all kinds of substituted phenyl boronic acids. | Fig. 2

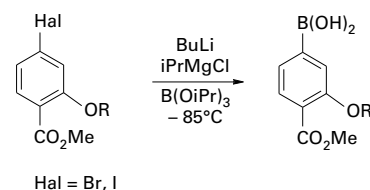
Derivatization of aromatic boronic acids. Several more complex substituted aromatic and heteroaromatic boronic acids are not available using this simple technology. To expand our range of applications, we are constantly adding new technologies to our portfolio to enable us to offer very rapid solutions to new problems. First of all, the surprisingly high stability of C,B-bonds allows us to make a broad range of derivatives starting from readily accessible compounds.

Especially remarkable is the side-chain bromination of tolyl-substituted derivatives. | Fig. 3

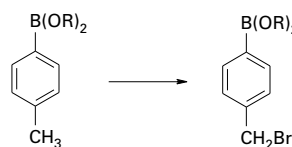
Whereas this reaction hardly works with free boronic acids, simply drying of the compounds to yield the respective anhydride allows for high yields in this bromination. The resulting bromomethyl phenyl boronic acids can be coupled in Suzuki reactions without affecting the bromomethyl side-chain.

at all so far. To start with, the first picture shows the broad range of boronic acids already produced by the “simple” addition of aromatic Grignard compounds to borates. | Fig. 1

Our process know-how allows us to make boronic acid equivalents which are easy to handle on a production scale and which can significantly lower the production costs of a Suzuki process.



| Fig. 2



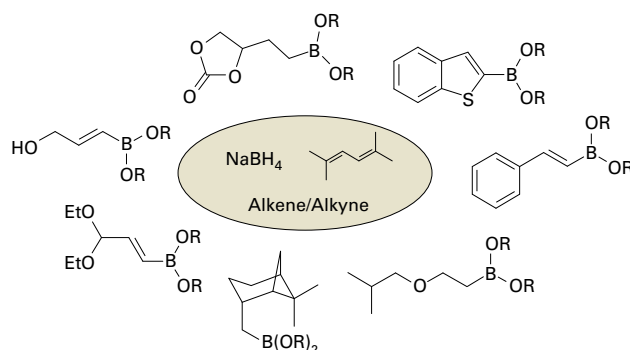
| Fig. 3

Aliphatic and Vinylic Boronic Acids

Grignard approaches for the synthesis of aliphatic and vinylic boronic acids are often described in the literature. The addition of the respective Grignard reagent to a boron equivalent results in the desired boron compound; however, isolated yields are typically below 30%. This is at least partially due to the very high water-solubility of these compounds. To make aliphatic and vinylic boronic acids available on a technical scale, we have developed a process which starts from com-

mercially available raw materials and overall has much higher yields than the approaches described in the literature (the Archimica methodology is proved to have a 55 – 86% yield compared to a yield of below 30% for the literature approaches).

Because of the general features of the hydroboration reactions, this approach additionally has the advantage of showing high selectivities whenever isomeric products can be formed.



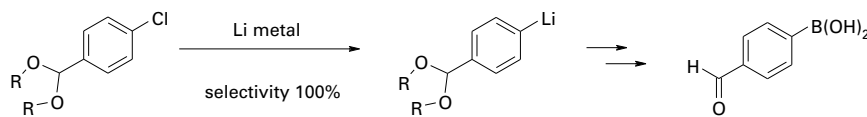
4-Formylphenyl Boronic Acid

4-Formylphenyl boronic acid is available starting from 4-bromobenzaldehyde, via protection of the acetal group, Grignard formation and addition to borate.

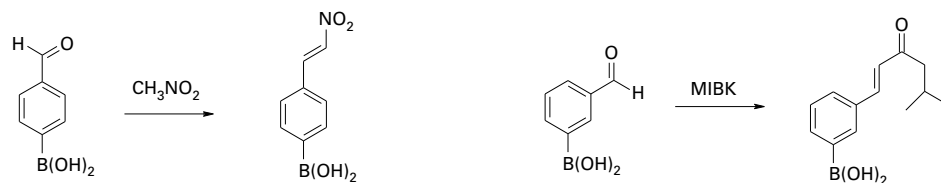
However, the same approach using the less expensive 4-chlorobenzaldehyde is not possible due to the inertness of the respective chloro-acetal in Grignardization approaches. We have developed a proprietary approach for 3- and 4-

formylphenyl boronic acids using metallic lithium as the key reagent. | Fig. 1

When applying our tailored reaction conditions at cryogenic temperatures, the lithiation works with 100% selectivity, and an isolated yield of 90% of the 4-formylphenyl boronic acid can be obtained. Such compounds are very valuable building blocks, as both functionalities can be modified independently. | Fig. 2



| Fig. 1



| Fig. 2

Lithium Technology and BuLi Substitution

We have expanded the technology of substituting chlorine with lithium metal even further. Our butyllithium-substitution technology has led to a breakthrough development. Instead of using the expensive and inconvenient butyllithium, we use a combination of lithium metal and an alkyl chloride for deprotonation reactions. | Fig. 1

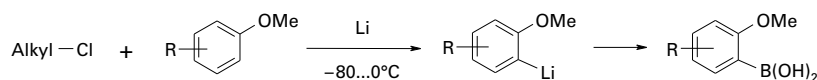
This way, we offer our customers the following advantages:

- No BuLi needed; thus economic benefits
- “Fine-tuning” possible (suitable choice of RCl)
 - Improved yields
 - Higher selectivities leading to higher purities
- Tailor-made solutions: A broad range of low-price alkyl chlorides provides a high degree of flexibility

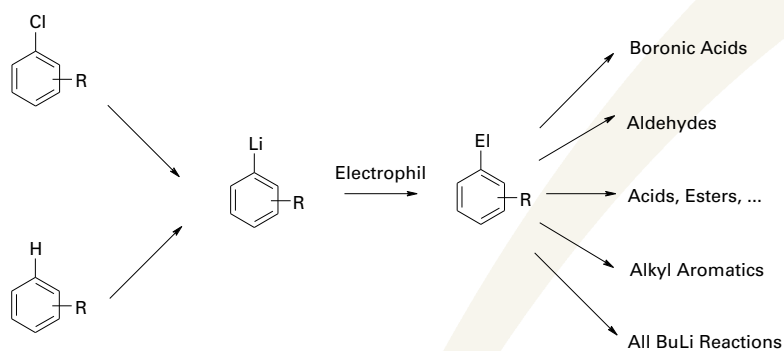
A very critical consideration is process safety. The lithium metal shows remarkable reactivity towards almost all organic compounds. It can produce strongly exothermic reactions, for instance, even with tetrahydrofuran. We have invested significantly in process safety and, as a result, are now able to handle all aspects of reactions pertaining to this metal. Our BuLi-substitution technology has been proven in more than ten examples in the production of boronic acids, aldehydes, acids and many other substances.

We have developed highly economical general processes for both the substitution of $\text{ArCl} \rightarrow \text{ArLi}$ and of $\text{ArH} \rightarrow \text{ArLi}$, and this is the major value-creation part of most organolithium syntheses. | Fig. 2

We offer a very broad range of products based on this technology from highly economic processes and, due to the cryogenic conditions applied, in very high purities. As Archimica also has cryogenic production equipment on a very large scale (total cryogenic cGMP reactor volume $\approx 60 \text{ m}^3$), the scalability of such processes is also guaranteed from early project stages onwards.



| Fig. 1



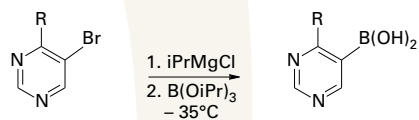
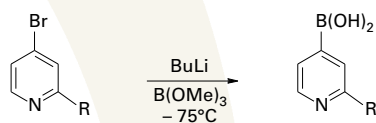
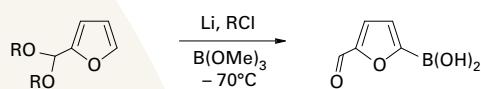
| Fig. 2

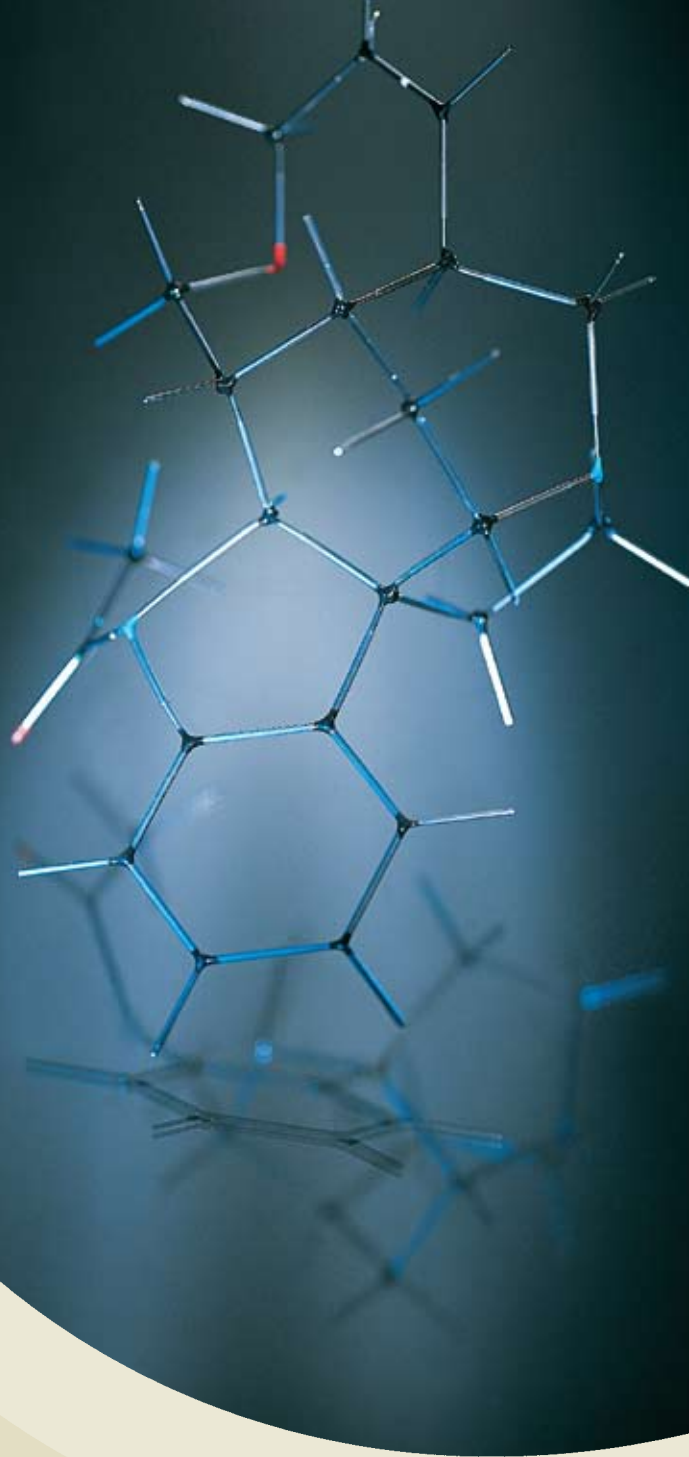


Heterocyclic Boronic Acids

We have already produced several, in part highly complex substituted boronic acids with heterocyclic structures.

Examples for different approaches are shown below. The rapid upscaling of such challenging syntheses is possible via the availability of up to 13 m³ -100°C kettles at our FDA-inspected cGMP sites in Italy and the US.





Chiral Chemistry

Single enantiomer intermediates of high enantiomeric purity are increasingly required by the pharmaceutical industry. Archimica is able to evaluate a range of different approaches – asymmetric catalysis, resolution and chiral pool – to target molecules and to integrate these into its other chemistries to serve customer needs both economically and within defined time lines.

Asymmetric Chiral Technologies

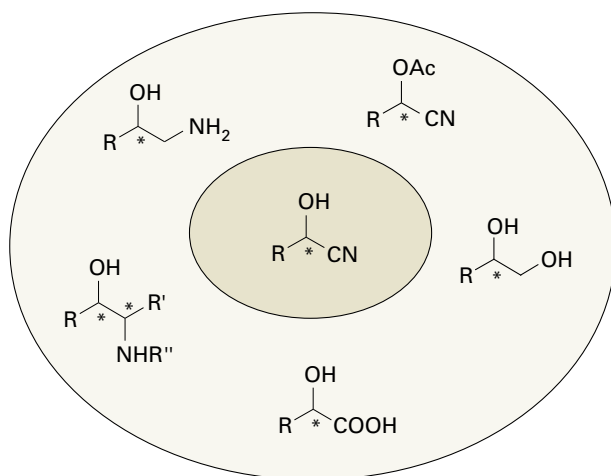
With the increasing availability of high performance asymmetric ligands and technologies for directly accessing single enantiomers, catalysis offers a powerful route for economic production.

Chiral cyanohydrins and mandelic acids. Building on our competences in aldehyde chemistry, Archimica has developed a range of approaches to chiral cyanohydrin production.

We have used both transition metal catalysis and enzymatic technologies to access a range of (R) and (S) single enantiomer cyanohydrins. We can then convert these into a broad range of other single enantiomer compounds by carrying out further chemistries, e.g. hydrolysis to substituted

mandelic acids, which are already produced on a multiton scale. Additionally, using the directive potential of the first chiral carbon atom, we can control the enantiospecific introduction of further chiral carbon atoms, thus enabling highly selective synthesis of multi-center chiral molecules. Hydrogenation, intramolecular acylation and organometallic reactions allow us to deliver amines, extend the carbon chain or provide further substitutions, thereby introducing and controlling chirality beyond the first carbon center.

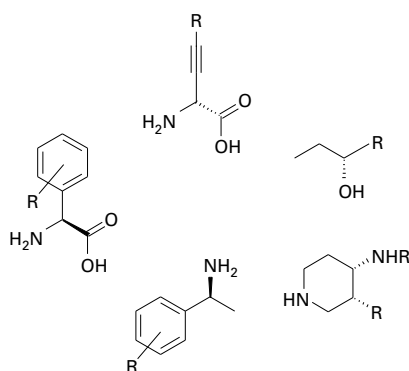
Archimica is able to use its already established technologies to rapidly produce multi-kilogram quantities of cyanohydrins, and to directly use them in further chemistries.



Classical and Biocatalytic Resolution Approaches

Often the most rapid and practical approach to a single enantiomer molecule may involve resolution of racemic materials, especially in combination with facile racemisation of the unwanted enantiomer. Using our own pre-prepared “kits”, we are able to simultaneously screen a large range of commercially available classical resolving agents with different solvent systems, e.g. by using Dutch resolution methods. These provide the basis for further rapid optimization studies. We also hold a large selection of commercially avail-

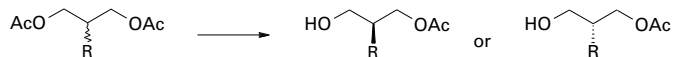
able enzymes on stock, enabling us to rapidly evaluate biocatalytic approaches. This way we are usually able to rapidly find a solution to providing high ee materials. Following preliminary identification of potential approaches our team carries out process optimization, scale-up and provision of materials within tight time constraints. Our experience extends to resolution of alcohols, esters, acids, unnatural amino acids and amines. A few examples are shown below.



Chiral Induction

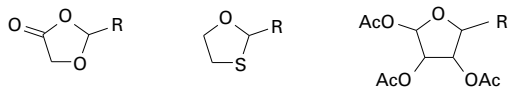
Archimica has extensive experience using biocatalysis for chiral induction, with particular emphasis on prochiral meso diols, diacids or diesters. These processes offer access to single enantiomers with a theoretical yield of 100%, using robust, well-developed technologies based on hydrolase

enzymes. In many cases enzymatic approaches offer significant advantages over classical chemistries. We have carried out such biotransformations with both cyclic and acyclic systems to produce a range of single enantiomeric products.



Unnatural Sugar Analogs

Our biocatalytic expertise makes available a range of different unnatural single enantiomeric sugar analogues. For instance molecules based on the structures shown below have been synthesized

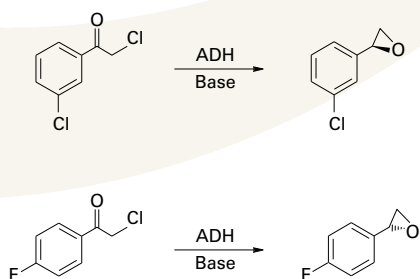


using the selective capabilities of enzymes. Naturally, similar approaches may be envisaged for other related structures.

Other Applications of Enzymes

By using a combination of ADH reduction of halogen ketones and tailored high-performance distillation equipment, we have developed very economical access to highly pure chiral epoxides.

This method works for many aliphatic, aromatic and heterocyclic systems with broad functional group tolerance.

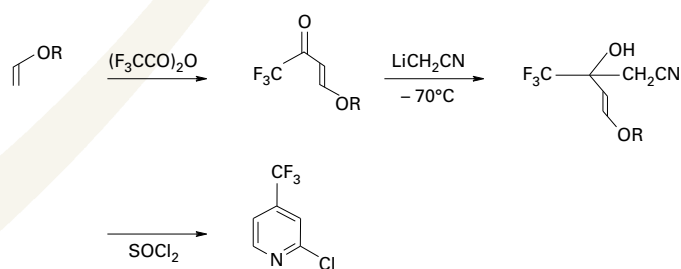




Heterocyclic Chemistry

Our experience in manufacturing heterocyclic compounds includes the development and production of more than 350 different heterocycles containing between one and ten ring heteroatoms. In addition to numerous pyridines, pyrimidines, quinolines and other 'standard heterocycles', less common compound classes, e.g. different positional isomers of azaindoles and naphthyridines, are at the core of our heterocyclic technologies.

Based on decades of experience in the synthesis of heterocyclic products, we have developed numerous proprietary technologies for the synthesis of a broad variety of such products. To show only one example, we recently have developed a new and high-yielding process for trifluoromethyl-substituted pyridines.



Other heterocycles under development and production include pyridines, furanes, thiophenes, isoxazoles, oxadiazoles, pyrazoles, naphthyridines, azaindoles and many more.

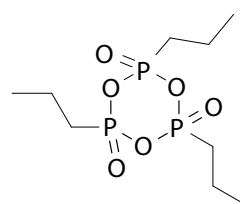


®T3P – Propane Phosphonic Acid Anhydride

®T3P is a superior coupling and water removal agent with low toxicity and low allergenic potential. Thus, compared to many other coupling reagents, overall process costs are reduced and processes may be developed to commercial scale with reduced health and environmental risks. The benefits of this reagent are demonstrated by the annual production quantity of hundreds of tonnes.

Together with other phosphor organic compounds, [®]T3P has been produced in our Frankfurt plant for many years. To facilitate handling [®]T3P is normally supplied as a 50% (w/w) solution in DMF, ethyl acetate, butyl acetate or methylene chloride. Alternatively, we can provide any other formulation specific to our customers' needs. The use of [®]T3P in coupling reactions is simple, yet effective. [®]T3P produces a product with high yields and minimum epimerization. Additionally, in some cases the use of protecting groups is no longer required. As a result of the ionic nature of the reaction by-products of [®]T3P, high purity separation can be achieved by simple phase extraction. This removes the need for expensive chromatography purification currently used in many processes. It is definitely worth testing!

Recent performance comparisons between [®]T3P and other leading coupling agents in peptide bond formation show [®]T3P to be the optimum with regard to end-product purity, epimerization, yield, toxicity and overall product costs.



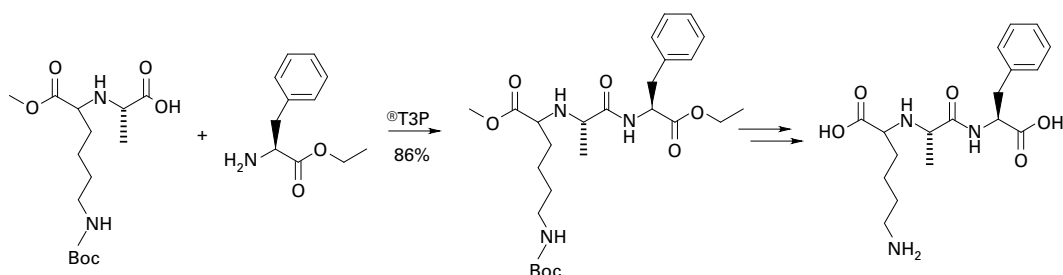
[®]T3P can also be used widely in organic synthesis as a coupling and water removing reagent, and stands at the cutting edge of high-purity and cost-effective manufacture of amides, esters and other interesting applications in the pharmaceutical and fine chemical industries. [®]T3P can offer a promising alternative approach, especially in those cases in which classical coupling methodologies fail due to substrate sensitivity.

There is also the possibility to perform many other reactions when effective removal of water is needed, e.g. in the formation of heterocyclic compounds, in acylation reactions or in the formation of nitriles or isonitriles.

Ideal Amide Coupling Agent

As the usage of high-value building blocks, including chiral amides and amino acids, continues to increase in the pharmaceutical industry, companies must focus on optimizing the process costs of coupling reactions through high yields

and low epimerization – particularly in late stage syntheses. ®T3P is the ideal coupling agent for these applications, delivering outstanding performance at moderate costs with low toxicity and easy work up.



Thus, ®T3P has low toxicity and produces an easily purified product with high yield and low epimerization.

- Carbodiimides such as DCC are toxic compounds, which give moderate yields and frequently lead to high levels of epimerization. Additionally, purification after using DCC is cost-intensive.
- Although reagent costs of TBTU/HBTU are comparable to ®T3P, these reagents have two

key disadvantages. Both have sensitizing properties and the purification of the resulting products is cost-intensive.

- BOP generates high yields and low epimerization, but BOP and its resulting by-products are highly toxic, which requires additional handling costs and safety measures.
- HOBT is an efficient suppressor of epimerization, but it recently has been re-classified as an explosive, posing severe hazards.

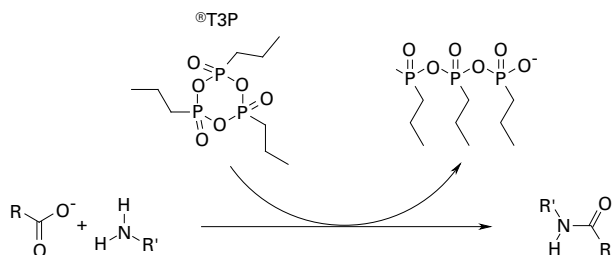
	Purification	Yield	Epimerization	Toxicity	Price/gram
®T3P	• easy	• high	• low	• low	• medium
EDC (WSC)	• easy	• medium	• medium	• high	• medium
TBTU/HBTU	• difficult	• high	• low	• medium	• medium
PyCloP	• difficult	• high	• low	• medium	• very high
BOP	• difficult	• high	• low	• very high	• high
DCC/HOBT	• very difficult	• medium	• medium	• high	• low
DCC	• very difficult	• low	• high	• high	• low

®T3P converts the oxygen of a carboxylic acid into an ionic leaving group. The hydrolyzed ®T3P is easily extracted from the product by phase separation instead of cost-intensive chromatography. | Fig. 1

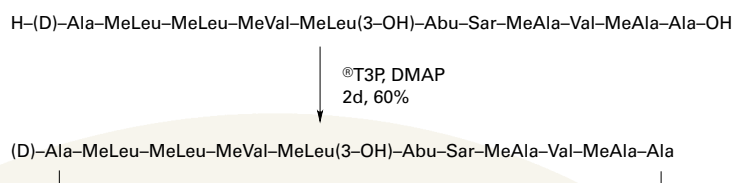
Even in the synthesis of oligopeptides, mostly no epimerization occurs, and there is no need for protection of free OH groups. | Fig. 3

This makes scale-up relatively straight-forward. Another example is the high-performance application of ®T3P in the conversion of acids to aldehydes via Weinreb amides. | Fig. 2

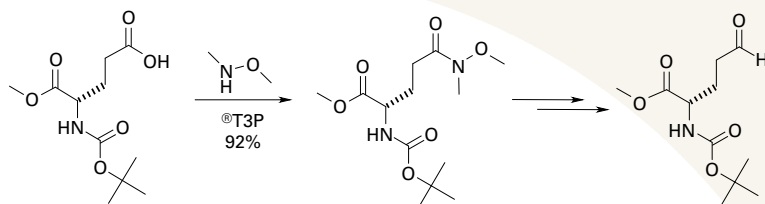
Due to its superior performance characteristics, ®T3P is the first choice in the synthesis of high-value products – particularly in late-stage syntheses.



| Fig. 1



| Fig. 2



| Fig. 3

Standard Lab Procedure for Amide/Peptide Bond Formation using ®T3P

- 1 mol acid, 1 mol amine, 2 – 4 mol base (preferably: n-methylmorpholine or diisopropylethylamine), 1.15 mol ®T3P in a solvent.
- Stir at 0°C for 20 minutes and overnight at room temperature.
- Separate phases, wash and evaporate solvent.

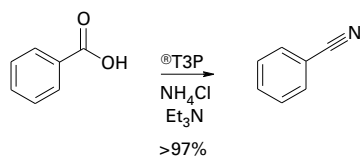
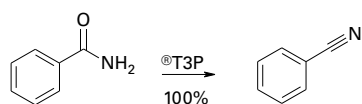
Detailed procedures for various substructures are available on request.

Not Just Amide Coupling

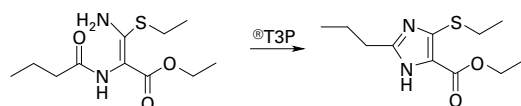
In view of its ability to remove water from systems under mild reaction conditions, ®T3P can be used in many other reactions, especially, for instance, where there is need for an effective removal of water, and when the products or substrates may

be sensitive to more extreme conditions or to epimerization. In the following a few of the types of successfully tested reactions are shown; many others may also be considered.

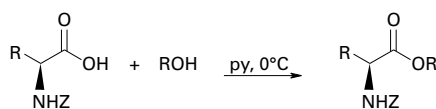
Nitrile Production



Condensation

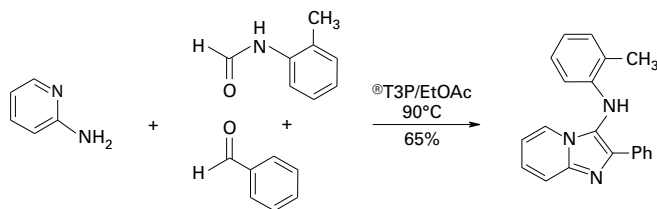


Esterification

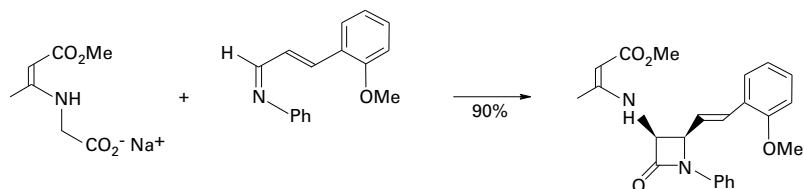


Z-Tyr(tBu)-O-cyclohexyl, 91%
 Z-Tyr(tBu)-O-n-butyl, 78%
 Z-Tyr(tBu)-O-n-hexyl, 85%
 Z-Tyr(tBu)-O-isopropyl, 83%
 Z-Tyr(tBu)-O-tBu, 76%

Isonitrile generation and conversion



β-Lactame formation



Archimica's Free Application Program

Our 20 years of industrial experience with ®T3P provides the basis for our synthesis experts to integrate the coupling and extraction steps required in your upstream and downstream process stages. This is part of our Free Application Program for your commercial scale-up.

Archimica provides this free program under a Confidential Disclosure Agreement. This way, the knowledge we gain in cooperation with you remains under your control. The purpose of this program is to allow you to acquire expertise with

®T3P while our experienced staff quickly evaluate and examine your defined process targets with respect to yield, selectivity, and quality. This enables us to determine how ®T3P can benefit your process.

If required, our experience with different processes allows us to tackle the issue of properly disposing of the low toxic and water-soluble decomposition products of ®T3P while dealing with any aspects of treatment your process may encounter.

Technical Package

We have prepared a detailed technical package including a broad variety of different reactions, including amide/peptide bond formations and several new applications. As a service to our customers, we are offering this on request.

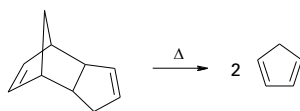


Distillation

Our multi-purpose pilot plant is exceptionally well equipped with distillation columns, rectification apparatuses and thin layer evaporators made of high-grade steel and hastelloy. By using columns with very high numbers of theoretical plates, almost all thermal separation problems can be solved. Line heating allows the separation of substances with melting-points up to 120°C.

The thermal splitting of dicyclopentadiene is a case in point. | **Fig. 1**

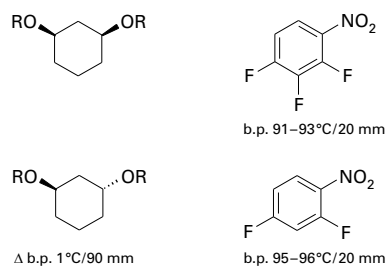
With the utmost attention to safety, our procedures supply cyclopentadiene monomers in very high purity. Subsequent to cracking, dimerization or oligomerization represents potential safety and quality problems. We are able to carry out short-term storage in low-temperature equipment, or ideally use material directly in the next reaction step.



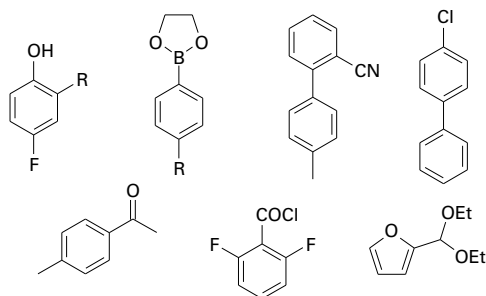
| **Fig. 1**

Using columns with the appropriate number of theoretical plates and a carefully selected reflux ratio, we have the experience and capabilities to separate materials with very small boiling-point differences. We can obtain separation of such materials in high yields and with purities > 99%. | **Fig. 2**

The distillation of corrosive media and materials, as well as thermally sensitive products, are operations we frequently handle successfully, particularly with our thin-film evaporation equipment. | **Fig. 3**



| **Fig. 2**



| **Fig. 3**



Quality Control

High standards in product and service quality call for precise quality control. Independent QC laboratories constitute a service unit available around the clock. They work in conformance with DIN ISO EN 17025 and have the status of accredited independent testing laboratories.

The analytical services of these QC laboratories include analysis of customer samples, drawing-up of analysis certificates, and development of validated analytical methods. These facilities, with their teams of experienced analytical chemists, are essential for our synthetic activities and crucial to the success of this aspect of our operations. The resources of these independent analytical laboratories include:

- GC, GC-IR, GC-MS, headspace-GC, chiral columns
- LC, LC-MS, chiral columns
- preparative HPLC
- NMR (^1H , ^{13}C , ^{31}P , ...)
- FT-IR, NIR, UV/VIS
- ion chromatography
- metal trace analytics (AAS, ICP-MS, ICP-OES, Hg analyzer)
- classical titration methods, e.g. determination of water content with the Karl-Fischer method, acid value, etc.
- physical parameters (density, melting point, color index, etc.)
- RC1, DSC
- stability tests

Equipment

Located at the Höchst Industrial Park in Frankfurt/Germany, our expertise in the area of custom synthesis is backed up by state-of-the-art technical equipment. Moreover, the outstanding infrastructure at the Höchst Industrial Park enables us to address a very broad range of chemical questions.

Multi-purpose Pilot Plant

Reaction Vessels

<i>Designation</i>	<i>Material</i>	<i>Volume</i>	<i>Description/ancillary equipment</i>
C146	Glass-lined steel	270 L	Mounted condensers with receivers. Permanently connected scrubber. Connected to R179.
R179	Glass-lined steel	270 L	Quench vessel. Connected to B136 and C146.
R136	Glass-lined steel	270 L	Quench vessel. Connected to R179 and C146.
R545	Glass-lined steel	300 L	Reflux condenser. 2 dosing vessels. Connected to R546.
R546	Glass-lined steel	300 L	Reflux condenser. 1 dosing vessel. Solids dosing. Connected to R545.
R388	Glass-lined steel	335 L	Column with 2.4 m Montz A3 packing and condenser made of 2.4617, several glass receivers for distillate and starting material.
R334	1.4571	1,000 L	Mounted condenser without receivers. Solids dosing. Can be connected to R389.
R389	1.4571	1,000 L	Mounted condenser without receiver. Hydrogenation up to 6 bar. Can be connected to R334.
R385	1.4571	870 L	Grignard apparatus with monitored reflux, receivers and interlocked solids charging system.
R1250	1.4571	1,500 L	Low-temperature reactor operating down to –100°C with direct nitrogen cooling. 2 x 500 L dosing vessels. Interlocked solids charging system.
R072	Glass-lined steel	2,300 L	Mounted condenser with phase separator and low-boiler removal. 4 m glass-lined steel column (Mellapack M 750). Quench vessel for R1250.
R157	Glass-lined steel	2,500 L	Mounted condenser with receivers, connected to R1250. Quench vessel for R1250.
R902	Glass-lined steel	100 L	Mounted column with 40 plates. Dephlegmator. Glass pipe with splash protection. 35 L glass-lined steel receivers. Trace heating/cooling from +100°C to –20°C. Cracking apparatus for cyclopentadiene dimer.
R488	Glass-lined steel	1,800 L	Mounted condenser with receivers. Quench vessel for R1275.
R1275	Glass-lined steel	1,000 L	Connected to R488.

Compact Unit. The compact unit consists of the following interchangeable plant components:

<i>Designation</i>	<i>Material</i>	<i>Volume</i>	<i>Description/ancillary equipment</i>
R180	Glass-lined steel	370 L	Glass reflux condenser. Volatiles receiver. Connected to agitated pressure vacuum filter with bottom discharge system F178.
R398	1.4571	230 L	Glass reflux condenser. Connected to agitated pressure vacuum filter with bottom discharge system F178.
R807	Glass-lined steel	130 L	Glass reflux condenser. Connected to agitated pressure vacuum filter with bottom discharge system F178.
F178	2.4617	170 L	Agitated pressure vacuum filter. 0.2 m ² filter area and condenser, can be heated and cooled. Automatic discharge.
R806	Glass-lined steel	300 L	Glass reflux condenser. Glass receivers. Filtrate receiver for agitated pressure vacuum filter F178. Connected to R180.

Distillation Columns

<i>Designation</i>	<i>Material</i>	<i>Vol. of still</i>	<i>Packing</i>	<i>th. plates</i>	
K174	1.4571	500 L	9 m Sulzer CY	100	Pressure column up to 50 bar.
K333	1.4571	500 L	11 m Sulzer CY	100	Lines and receivers can be heated to 90°C.
K444	1.4571/ 1.4401	1,500 L	6 m Montz-Kloss	30	Lines and receivers can be heated to 120°C for EP products.
K740	St./Em./ Glass	40 L	1 m variable	40	20 L dosing vessels. Two 10 L distillate receivers.
K520	1.4571	2.5 m ³	11 m Montz A2	25	Lines and receivers (some heatable), phase separator (glass).
K650	Glass, Pack. 2.4610	50 L	1.5 m Sulzer CY	12	Two 20 L distillate receivers.
K505	1.4571/ 1.4435	1,000 L	9.4 m Mellapack	20	Several receivers from 20 to 200 L, phase separator.

The columns can be connected to the existing vacuum pumps (oil pumps, steam-jet apparatus, water ring pumps) via the vacuum distribution main. A vacuum down to approx. 2 mbar can be achieved.

Multi-purpose Pilot Plant

Thin-layer Evaporators

<i>Designation</i>	<i>Material</i>	<i>Area</i>	
Luwa-DSV W441	1.4571, glass receiver	0.2 m ²	Optionally, a 10-plate column can be connected. Working area starting at 50–100 L.
W381	2.4617, glass receiver	0.2 m ²	Combined with 200 L glass-lined steel container for the separation of low boiler components followed by product distillation. Lines heatable up to 100°C.

Ancillaries

<i>Designation</i>	<i>Material</i>	<i>Volume</i>	
F114	2.4605	350 L	Pressure vacuum filter. 0.5 m ² filter surface. Can be heated/cooled.
F1256	1.4541	170 L	Pressure vacuum filter. 0.3 m ² filter surface.
F258	1.4571	120 L	Pressure vacuum filter. 0.2 m ² filter surface. Can be heated/cooled.
F1262	1.4571	430 L	Pressure vacuum filter. 0.7 m ² filter surface. Can be heated/cooled.
Skimmer centrifuge	1.4571		for 150 kg, solid matter
T284	1.4571	200 L	Vacuum dryer (separated area).

Several open vacuum filters made of plastic.
Two vacuum tray dryers (approx. 40 kg fill weight)
Drying and homogenizing unit (200 L, 1.4571).
Two 20 L autoclaves (1.4571) up to 9 bar.
Locked dosing chamber for dosing liquid CMR substances.
Vacuum pumps.

Energy, Gas

Oxygen from bulk supply.
Hydrogen from bulk supply.
7 m³ liquid nitrogen tank for low-temperature plant (–100°C).
Refrigeration unit for down to –30°C coolant supply.

Environmental Protection Equipment

Waste gas flare stack.
Waste gas purification and activated carbon bed absorber.
Jet scrubber with mounted column (mobile).
Two washing columns for methylene chloride absorption.

Laboratories

Synthesis Laboratories

36 hoods, including 8 walk-in hoods, conforming with general standards and equipped with inert gas connections.

Distillation columns with a wide variety of lengths and diameters, can be equipped with a wide range of packaging (ranging from simple Raschig rings to Sulzer packaging).

Thin-layer evaporators.

200 ml autoclave for testing pressure reactions (hydrogenations, etc.).

A wide variety of autoclaves of varying capacity and materials of construction for reactions performed at pressures up to 80 bar.

20 L rotary evaporators.

Cryostats for reactions down to -100°C .

Parallel reactors with easy handling.

Special equipment for enzymatic chemistry.

Dedicated HCN laboratory.

Kilo Laboratories

63 L glass lined reactor ($-100 \dots +170^{\circ}\text{C}$).

100 L glass reactor.

Two 20 L Büchi rotary evaporators.

Pressure filters (1.4571, glass lined).

Thin-layer evaporator (glass).

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