



Specialist for Hazardous Reactions



dottikon

EXCLUSIVE
SYNTHESIS

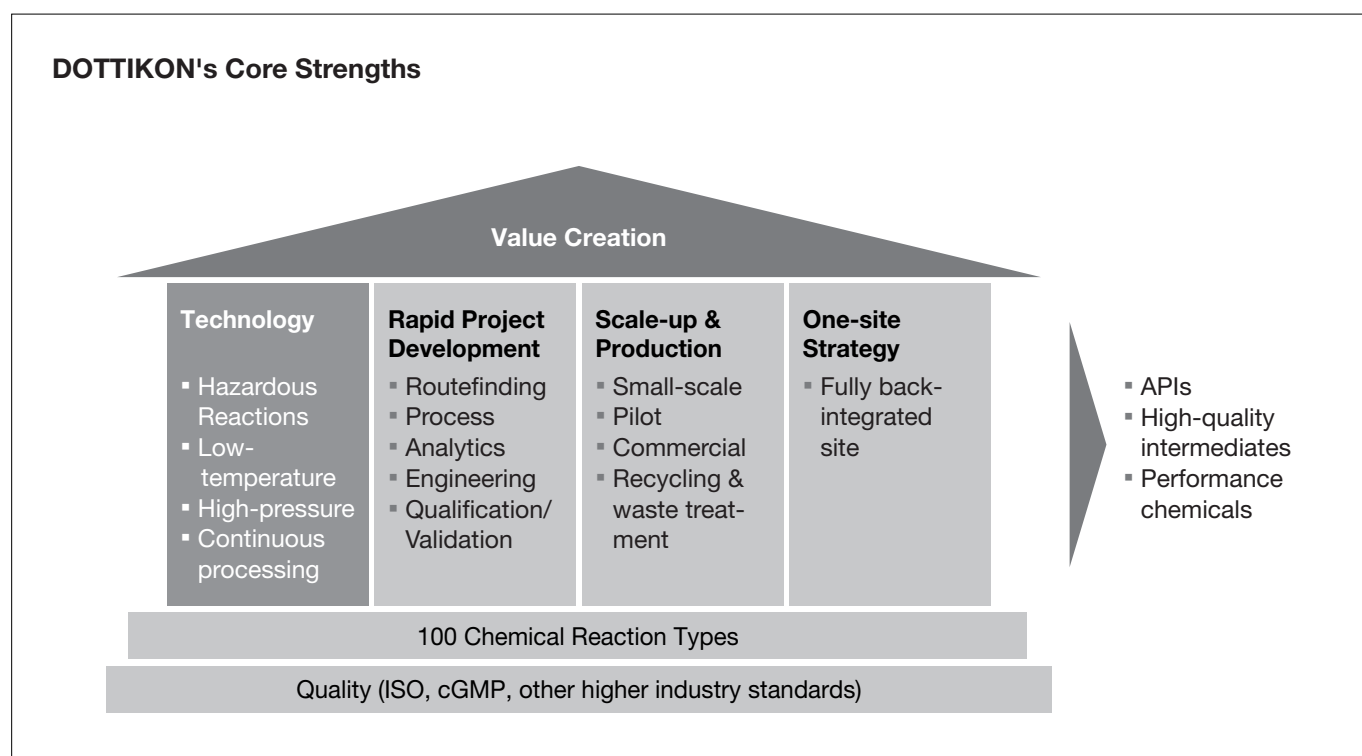
More than Hazardous Reactions.

Introduction

In order to face the challenges of the chemical and pharmaceutical industries today, hazardous reactions in chemical development and in the synthesis of new chemical entities are one approach to innovate more effective performance chemicals and drugs and reduce costs while improving impurity profiles.

This presumes a safety culture of unconditional commitment to constantly identifying risks and the consequent application of economic measures to reduce them. It involves profound education, long-term experience and proprietary know-how in hazardous reactions, chemical processes and equipment supported by dedicated staff with self-discipline, self-responsibility and self-initiative. Having such a safety culture in place allows the use of hazardous reactions to take shortcuts in chemical synthesis, reduce impurity profiles and commercially access new potential bioactive and performance chemicals structures, with a comparable risk profile to conventional chemistry.

DOTTIKON EXCLUSIVE SYNTHESIS (DOTTIKON ES) is a large-scale chemical manufacturer, specializing in hazardous chemical reactions as one of our main pillars within the value creation for our customers.



At the center of our strategy is a customer-driven focus to provide our clients with exclusive custom manufacturing services as well as with fine chemical products and performance chemicals available on catalog. We are flexible and responsive through our rapid problem-solving approach to client needs and we shape our research and development efforts in this manner. Our streamlined decision process and the sophisticated plants and equipment operated by our highly skilled and experienced employees allow us to achieve the ambitious targets of our clients. We seek to further expand on this platform by continuously improving production processes in close interaction with our customers to reach a unique and long-term relationship and to form a strategic development and manufacturing partnership.

DOTTIKON ES is specialized in hazardous reactions. Our history in handling explosives in the past makes us one of the most experienced partners in the industry for conducting exclusive exothermal reactions such as nitrations, oxidations and azide chemistry, to name a few. Further core technologies are catalytic hydrogenations, alkylations and metallation reactions. Our dedicated and multipurpose equipment enables us to manufacture on all scales, from grams to multi-tons, and using batch or continuous processes.

Broad process development experience and technological expertise enables us to offer high-quality chemicals and intermediates, including

- Amines
- Anilines
- Azaindoles
- Benzimidazoles
- Benzoic acid derivatives
- Benzyl compounds
- Boron building blocks
- Chiral compounds
- Cyclohexane derivatives
- Cyclopropyl building blocks
- Indazoles
- Indoles
- N-Heterocycles (various)
- Nitrate esters
- Nitroaromatic compounds
- O-Heterocycles (various)
- Phenols and anisoles
- Pyridine building blocks

Content

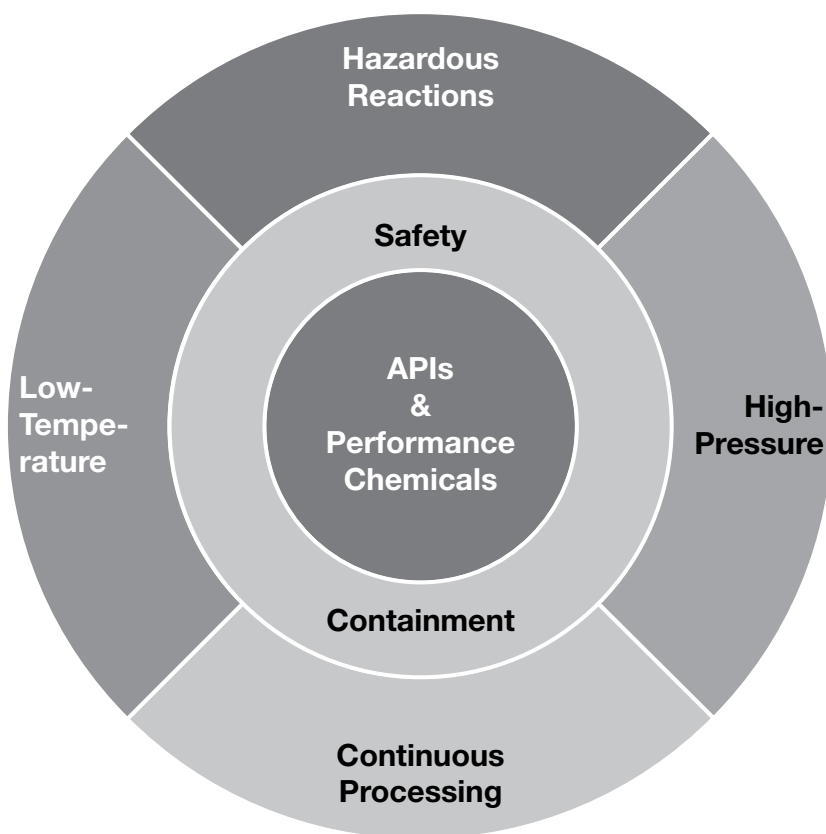
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Technology Platform

DOTTIKON ES achieves technology performance leadership as specialist for hazardous reactions by constantly expanding its technology portfolio. The technology portfolio is built around high-quality performance chemicals, intermediates and exclusive active pharmaceutical ingredients (APIs), and comprises of hazardous reactions, low-temperature and high-pressure reactions as well as continuous processing. In all these technologies we have profound know-how, extensive process development and manufacturing experience in scale-up from grams to multi-tons and in post-launch production transfers. We employ our technologies on dedicated and multipurpose equipment on all scales under ISO as well as cGMP conditions.

DOTTIKON ES seeks and establishes new reaction pathways by initial routefinding, develops chemical processes and manufactures innovative building blocks and products, based on its core technologies or combinations thereof. This enables rapid scale-up and cost-effective access to novel processes with excellent quality and highly competitive yields.

Technology Platform Built around APIs and Performance Chemicals



Hazardous Reactions

DOTTIKON ES is the leading specialist for hazardous reactions, the core technology besides low-temperature and high-pressure chemistry and continuous processing. With over 100 years of experience with hazardous reactions, originating from production of explosives, the historically-grown and established comprehensive safety culture makes DOTTIKON ES the most trusted partner in the field of hazardous reaction chemistry. Typical examples include azide chemistry, oxidations, hydrogenations, alkylations, and handling of unstable or highly active compounds. Our safety lab applies 14 proprietary tests to gather safety data for the development of safe and robust processes, enabling reliable scale-up in dedicated facilities to multi-ton production volumes. The one-site strategy includes waste treatment facilities for safe, cost-effective, reliable and sustainable manufacturing applying hazardous reaction chemistry.

Four Categories of Hazardous Reactions

- Nitrations
- Grignard reactions
- Metalations
- Hydrogenations
- Oxidations

Highly exothermic processes

Thermally or mechanically unstable compounds or mixtures

- Nitro compounds
- Azides
- Nitrate esters
- Peroxides
- Diazo compounds

- Hydrides
- Dimethyl sulfate
- Nitric acid
- POCl_3 , PCl_5 , POBr_3 , PBr_3
- SOCl_2 , SO_2Cl_2 , CSCl_2
- $\text{BH}_3 \cdot \text{THF}$

Highly reactive compounds

Highly active compounds

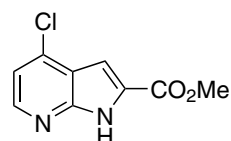
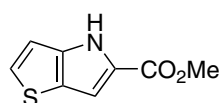
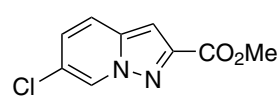
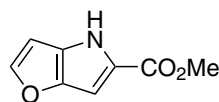
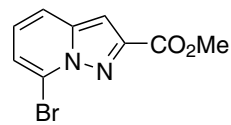
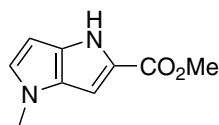
- HAPIs
 - 10 to < 100 $\mu\text{g}/\text{m}^3$
 - 1 to < 10 $\mu\text{g}/\text{m}^3$
- HPAPIs
 - < 1 $\mu\text{g}/\text{m}^3$

Benefits for Customers

New Bioactive Compounds

DOTTIKON ES has profound experience in hazardous reactions to create a benefit for customers on their way to introducing innovative new and more first-in-class drugs. All compounds depicted on the right, for instance, show some interesting characteristics for potential bioactivity. They have good permeability properties to cross cellular bilayers and are able to intercalate by forming H-bridges or π - π -stacking. These new chemical structures linked to other potentially active fragments lead to innovative, specific active compounds, only available on commercial scale via hazardous reactions.

Structures Only Available on Commercial Scale via Hazardous Reactions

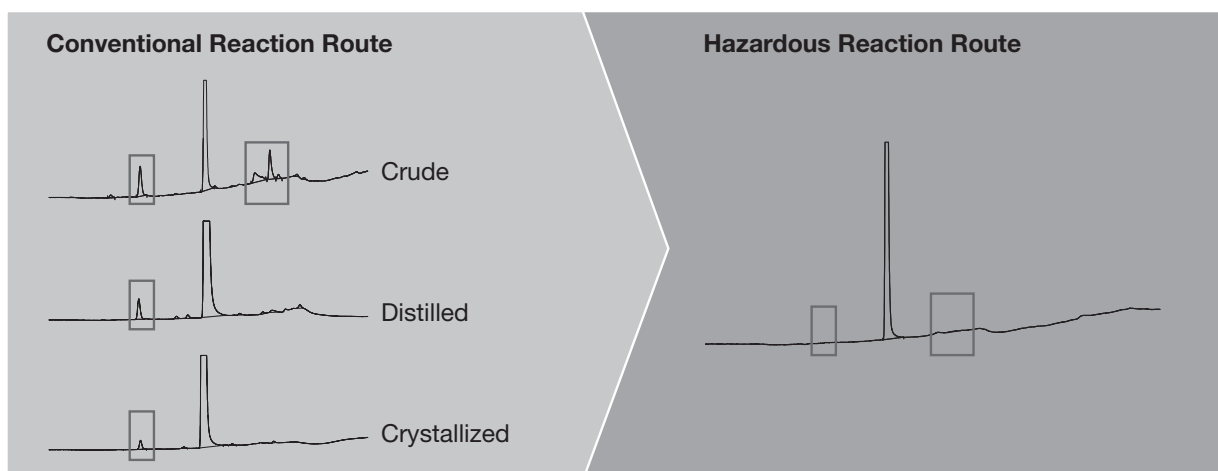


Reducing Costs and Improving Quality

Hazardous reactions not only lead to new chemical structures with interesting properties, but also open ways to improve quality while reducing costs. The HPLC chromatograms below show a chemical compound produced by the conventional route (left side). In this case the crude product received after isolation showed unwanted side products. After distillation and crystallization the side products could be reduced to the specified limit (overall yield of synthesis: approx. 25 percent). In contrast, the hazardous reaction route precipitation of the crude material led directly to a high-purity product (right side) with an overall yield of more than 80 percent. This example gives an idea of what potential can be realized with hazardous reactions to effectively reduce costs and increase quality at the same time.

HPLC Chromatograms of Conventional vs Hazardous Reaction Route

Impurities



Key Skills

Technical Expertise

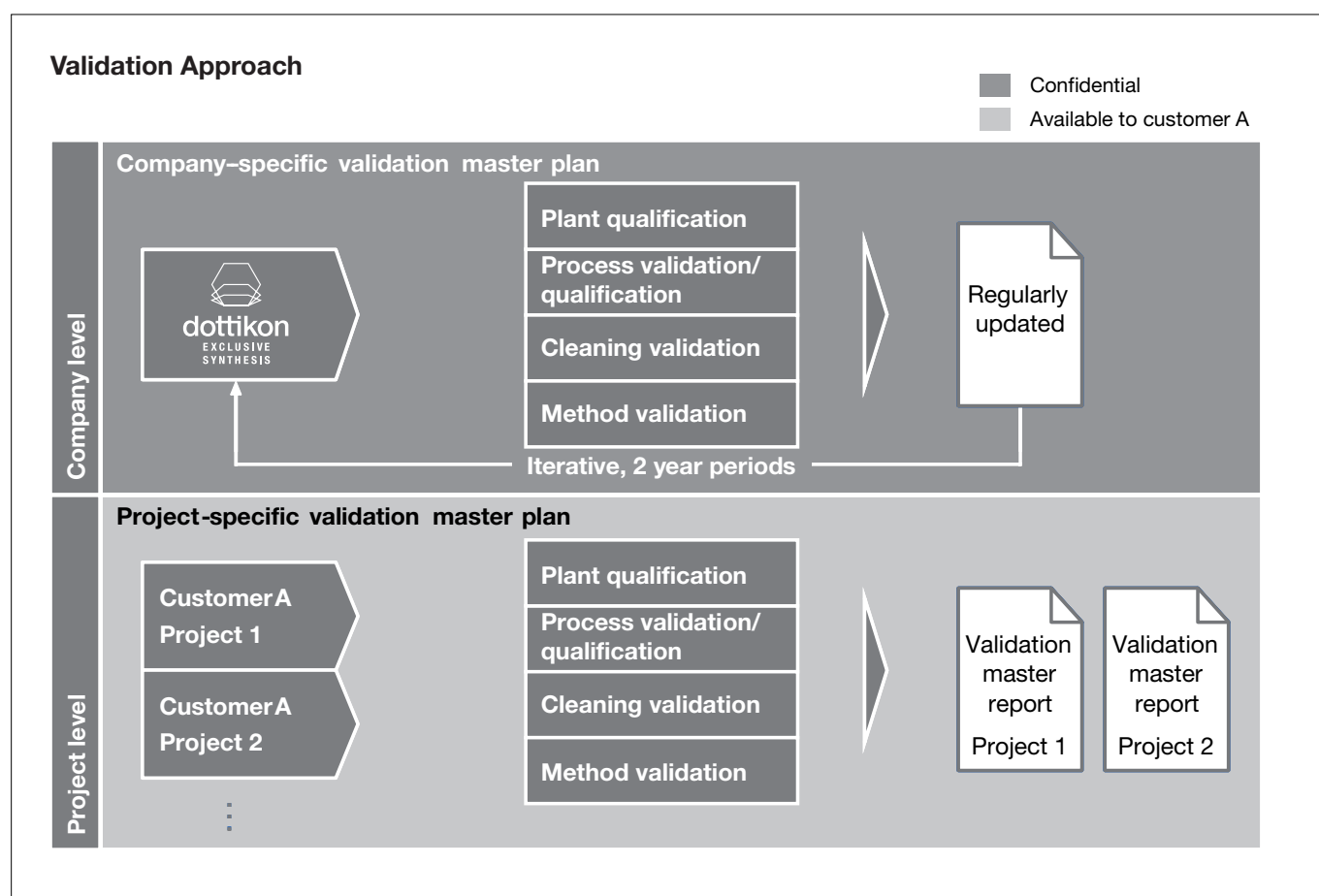
Research & Development supports scale-up of processes in close collaboration with Production. Our staff is highly experienced in handling hazardous raw materials, highly exothermic processes, reactions under high-pressure, highly reactive, highly active, and unstable compounds or mixtures and products with explosive properties.

API Production

Pharmaceutical intermediates and active pharmaceutical ingredients, in compliance with cGMP guidelines, has been manufactured for more than twenty years. The site is approved by the FDA.

Preformulation and Blending

Preformulation of APIs with explosive properties using different excipients. DOTTIKON ES is an established supplier of bulk isosorbide mononitrate, dinitrate, and other nitrate esters.

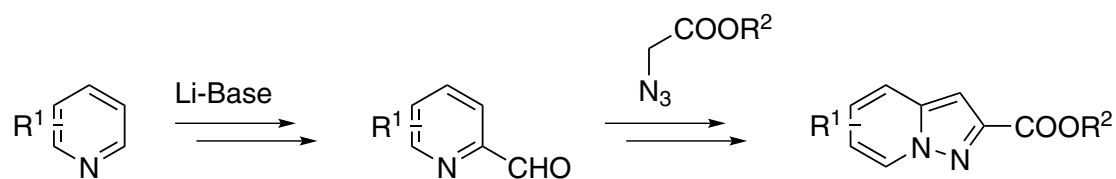


Specialist for Hazardous Chemistry

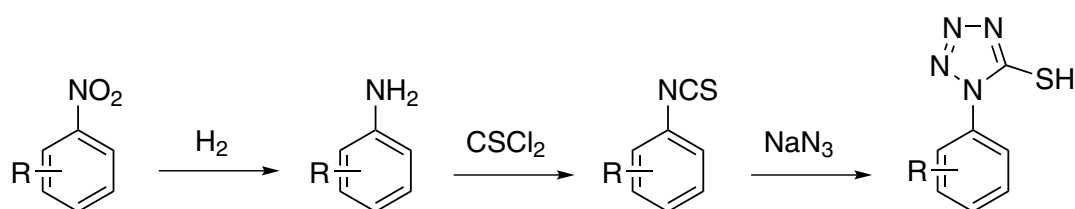
Hazardous Reactions	Reagents
Azide chemistry	NaN_3 , organic azides such as DPPA
Bromination	Br_2 , POBr_3 , PBr_3 , NBS
Chlorination	Cl_2 , SOCl_2 , SO_2Cl_2 , POCl_3 , PCl_3 , PCl_5 , NCS, oxalyl chloride, C_2Cl_6
Cyanation, Strecker reaction	NaCN , HCN (in-situ)
Diazotation, Cyclopropanation	Nitrous acid (HONO), Bestmann-Ohira reagent
High-pressure chemistry	H_2 , CO, CO_2 , NO, NH_3 , NHR_2 , high-temperature reactions
Hydrazine chemistry	NH_2NH_2 , alkylhydrazines
Hydride reduction and handling	LiAlH_4 , AlH_2R_2 , BH_3 , $\text{Na}^+[\text{H}_3\text{BCN}]^-$, NaH, NaBH_4
Iodation	I_2 , NaI
Methylation	Me_2SO_4 , MeI and other alkylhalides
Nitration	conc. HNO_3 , $\text{HNO}_3/\text{H}_2\text{SO}_4$, glacial HNO_3/AcOH
Nitroaldol reaction	MeNO_2 , EtNO_2
Organometallic chemistry	Grignard, BuLi, HexLi, LDA, LiHMDS
Oxidation	HNO_3 , KMnO_4 , <i>m</i> CPBA, DDQ, H_2O_2 , $(t\text{-BuO})_2$, peracids
Thiophosgenation	CSCl_2
Miscellaneous	EDA (Ethyl diazoacetate), Epichlorohydrine, P_2O_5 , HOBT hydroxybenzotriazole), DIAD (diisopropylazodicarboxylate)

DOTTIKON Hazardous Reactions Platform – Examples

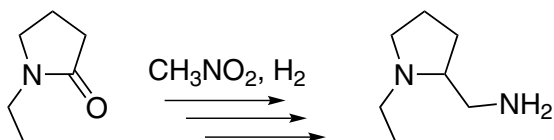
Lithiation/Azide Chemistry



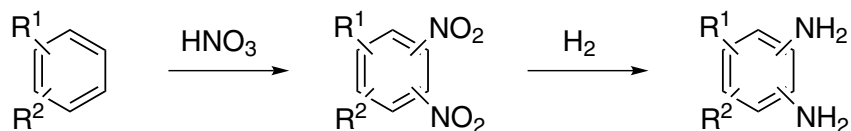
Reactions with Thiophosgene



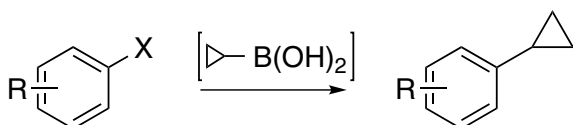
Reactions with Nitromethane



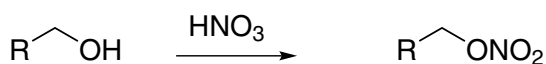
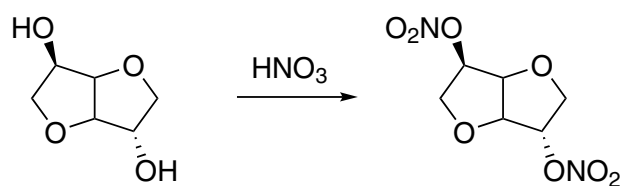
Nitration/High-pressure Chemistry



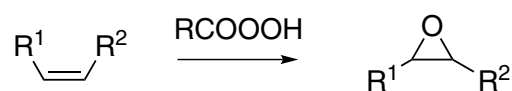
Reactions with Cyclopropylboronic acid



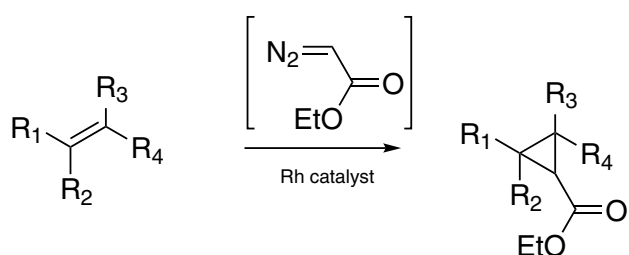
Nitrate Ester Formation



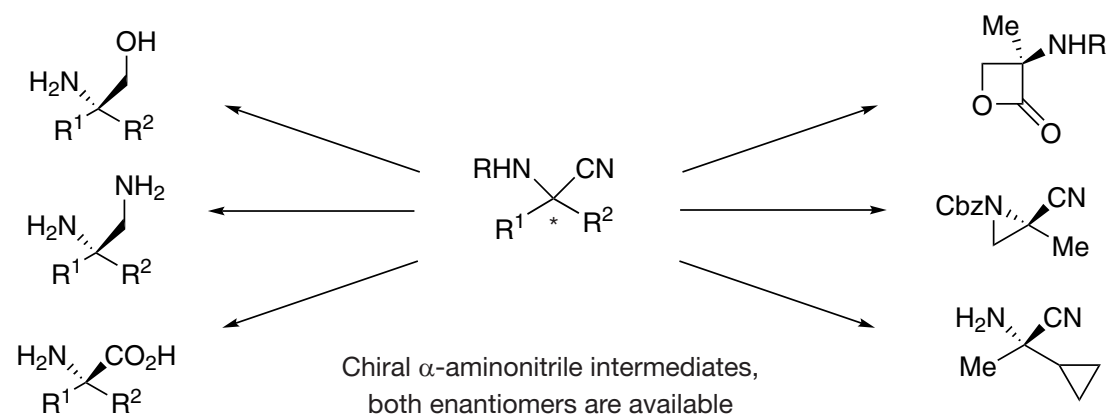
Oxidation/Epoxidation



Cyclopropanation with Ethyldiazoacetate



Cyanation Chiral Quaternary Building Blocks



Capabilities

DOTTIKON ES covers the entire production volume range from grams to multi-tons. Our high-standard facilities are well equipped

- Research & Development
 - 3 Routefinding labs
 - 15 Process development labs
 - 3 Technology labs (hazardous reactions, high-pressure [100 bar], low-temperature [−80°C])
 - 3 Analytical development labs
 - Safety lab
 - Over 3'000 Projects
 - Over 20 development projects simultaneously
- Small- and pilot-scale
 - 5 cGMP pilot and small-scale plants (hazardous reactions, high-pressure [60 bar], low-temperature [−80°C], continuous processing)
 - Over 130 different chemical reactions
 - Over 80 reaction steps per year
- Multipurpose and specialized plants for multi-tons
 - 9 cGMP production plants, up to 12.5 m³ reactors (hazardous reactions, high-pressure [50 bar], low-temperature [−100°C], continuous processing)
 - Over 100 different chemical reactions
- Recycling and waste treatment
 - Thermal recovery
 - High-temperature incineration
 - Waste water treatment and purification

Safety Lab

- Thermal stability tests
 - Differential scanning calorimetry (DSC)
 - Radex
 - Sedex
 - Dewar
- Reaction calorimetry
 - Calo 2310 pro (SYSTAG)
 - RC1e RTCal
- Special test equipment
 - 14 Established methods

Equipment

- Small-scale/pilot plant
 - Total volume: 15 m³
 - Reactor range: 15 l to 1'000 l
 - Material: stainless steel, glass-lined, Hastelloy C22
 - Separation: pressure filters and centrifuges
- Production
 - Total volume: 300 m³
 - Reactor range: 4 m³ to 12.5 m³
 - Material: stainless steel, glass-lined, Hastelloy C22
 - Separation: pressure filters and centrifuges
- Dedicated equipment for
 - Explosives
 - High-pressure
 - Low-temperature
 - Continuous processing
- Drying capabilities
 - Vacuum tray dryer (520 l, Hastelloy C22)
 - Spherical dryer (0.1 m³, Hastelloy C22)
 - Paddle dryers (1 m³ to 6 m³, stainless steel / Hastelloy C22)
 - Spherical dryers (1.5 m³ to 3 m³, Hastelloy C22)
- Distillation capacity
 - Rectification
 - Thin film evaporator
 - High-vacuum distillation, 3 mbar

Safety

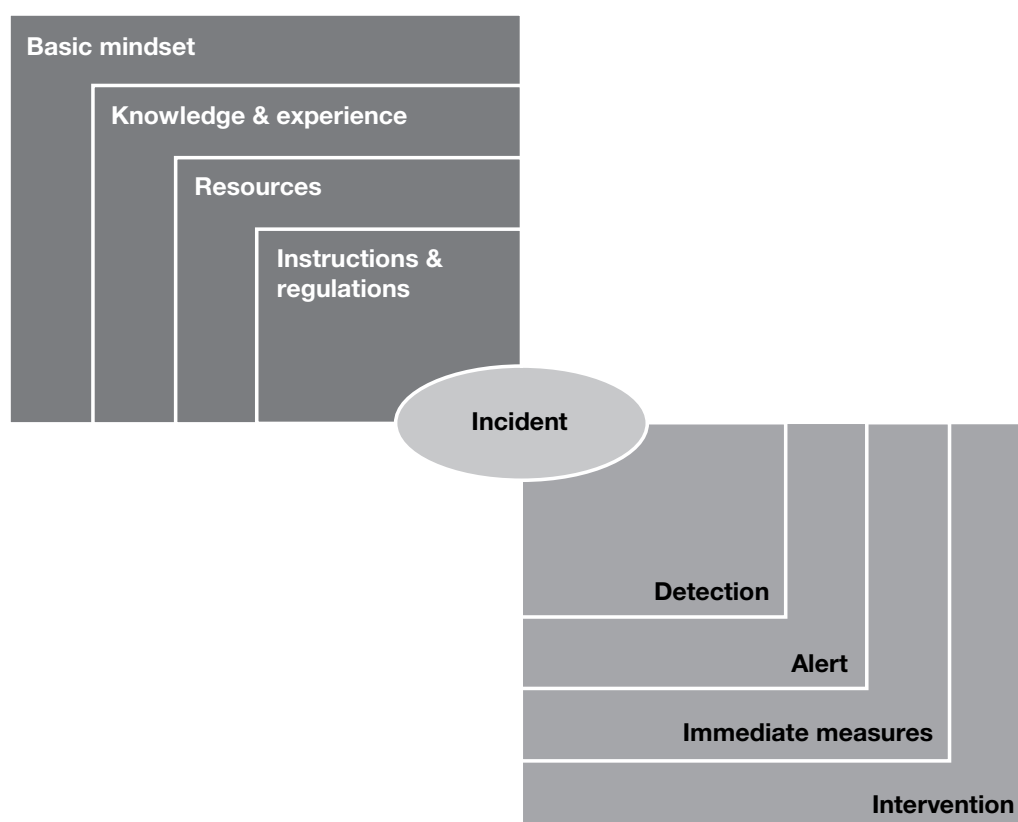
In the past, the use of hazardous reactions was avoided whenever possible in chemical manufacturing processes due to lack of know-how, equipment and technologies and the related resulting safety issues.

A study by the US Chemical Safety and Hazard Investigation Board showed that only 25 percent of all chemical incidents occur in the reactor area. 75 Percent of the incidents happen in adjacent areas such as extraction or centrifugation, transportation in pipes or containers, storage in tanks and drums, recycling, and disposal. The study showed that the risks involving hazardous reactions are far more complex and not just limited to the chemical process in the reactor. Performing hazardous reactions presumes a safety culture of unconditional commitment to constantly screening for and identifying risks and the consequent application of economic measures to reduce them. It involves profound education, long-term experience and proprietary know-how in hazardous reactions, chemical processes and equipment operated by dedicated staff with self-discipline, self-responsibility and self-initiative.

DOTTIKON ES Safety Concept

The DOTTIKON ES Safety Concept differentiates between the preventive and the responsive levels. Whereas many organizations often focus on having a written proof in place to allocate responsibility in case of an incident, the DOTTIKON ES Safety Concept focuses on prevention first.

Safety Concept – Preventive and Responsible Levels



DOTTIKON ES is built around this safety culture. The selection and performance measurement demands from all employees the right mindset of self-responsibility, the willingness to take responsibility for what they do or don't do; self-initiative, the competence to act on their own initiative and their own responsibility to address challenges and solve problems; as well as self-discipline, doing the before said exactly within the framework of given regulations and instructions. Reliability is a prerequisite. Experience and specific technological know-how in handling hazardous reactions are shared and trained among the staff. Dedication to performance leadership and the aspiration for continuous improvements are required. Appropriate resources are provided when needed and human resources qualified and selected without compromise. Instructions and regulations define processes precisely whenever appropriate, so that they can be followed step by step. This preventive level deserves the highest attention by all employees.

Employees are trained to detect incidents, alert, and take the right immediate measures. Intervention forces are on site, well equipped, trained and informed daily on the type of chemistry that is performed. Setting up and living such a safety culture is not a one-time effort but a continuous process. In line with the safety culture in place, chemical process risks must be carefully evaluated at each step of the development and implementation. Appropriate independent methods have to be used to determine safety-critical parameters. The process risk analysis has to start on lab-scale and is typically updated for each scale with a new assessment, i.e. small-scale, pilot plant, and large-scale production. It is an integral part of operation. Risks are analyzed and characterized by magnitude and probability of an incident. The risk analysis comprises the systematic search for hazards and their evaluation, including the definition of measures according to the risks, to minimize them to a manageable level.

Measures are taken on technical (e.g. safety valve), organizational (e.g. check visa), and personal levels (protection suits, e.g., permanently equipped with sensors). Knowledge and experience are constantly updated and enlarged with mandatory training. However, theory alone is not enough. A prerequisite for workers is the right basic mindset, to learn and improve, and to apply what they have learned.

Containment

Health Protection

- Technical measures
 - Closed charging/discharging systems
 - Closed sampling
 - Air locks
- Organizational measures
 - HAZOP compatible procedures
 - Education/training
 - Monitoring
- Personal protection equipment
 - Protection suits
 - Working clothes with glasses and gloves
 - Full protection clothes
 - Decontamination
 - Breathing protection
 - Dust protection mask
 - Protection mask with filter P3
 - Forced air ventilation
- Health check
 - Company medical officer

Environmental Protection

- High-temperature incinerator for toxic waste
- Activated carbon filter for waste water pretreatment
- Biological waste water treatment plant

Notes

Notes

Contact

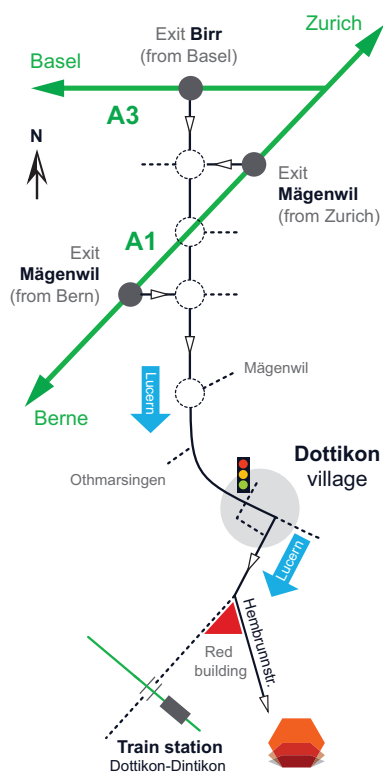
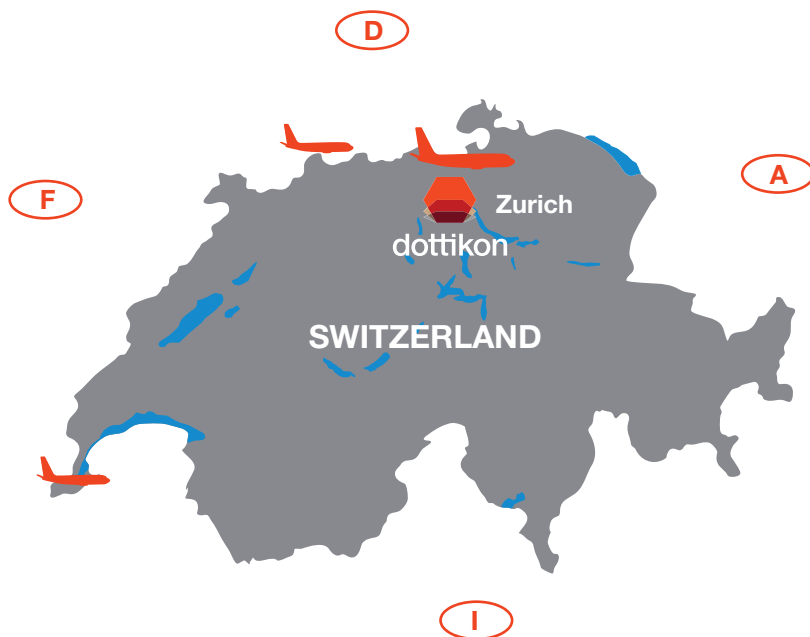


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SYNTHESIS

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