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Traditional Chemistry – an Excellent Basis for Custom-Made Building Blocks

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Abstract. Due to a shift in the competitive environment, the global fine chemicals industry is in the center of a major portfolio change from high-volume raw materials to customer-specific molecules. This article describes how the traditional strength in chemistry and adaptation of business processes throughout the organization allows *Clariant Fine Chemicals* to play a major role as a supplier of advanced building blocks to the life science industry. Key criteria are identification of intermediates according to core technologies, installation of flexible production equipment, production in line with strict quality standards, and efficient exchange of information in strict confidence to establish a basis for mutual success between *Clariant* and its customers.

Introduction

Along with many of the major European chemical companies, the roots of the Fine Chemicals Group of *Clariant* (previously part of *Hoechst* Specialty Chemicals Group) date back to the 19th century. For the first time, synthetic dyestuffs were made available for the rapidly developing textile industry. Intermediates for the dyes and pigments industry represent still a sizeable share of the group's portfolio; in addition, intermediates for agricultural and pharmaceutical applications (initially for further processing inside the group) were introduced with increasing emphasis to build a balanced and robust portfolio. In-line with this strategic reorientation in the product portfolio, the overall business process is being redesigned in an effort to proactively address the challenges of the rapidly changing needs of the market in the life science area. In this assay, we will outline the strength of *Clariant Fine Chemicals* based on the history, the key factors for the successful reorientation of the group towards growing markets and the resulting challenges for future success in this highly competitive environment. Crucial changes relate to the following areas:

1) Technology
2) Production
3) Organization
4) Marketing

Changes in each of these areas will be briefly described and aligned with the characteristics of the market for advanced intermediates.

1. Technology

1.1. *Standard Reactions*

Traditionally, many companies started with the derivatization of basic raw materials like benzene and toluene through a combination of the reaction steps **chlorination**, **nitration**, **reduction**, **aromatic exchange**, **sulfonation**, **alkylation**, **and caustic fusion** to generate as key intermediates substituted anilines and phenols. Downstream chemistry included the formation of sulfonamides, naphthols, arylides and pyrazolones. Although production of many of the respective products was discontinued, the technologies are still resident within the organization as support function in molecules demanding the utilization of many different reaction steps. Of particular emphasis is the chemistry for the synthesis of pyrazolones, since it involves two steps which serve as the foundation for a variety of modern intermediates (*Scheme 1*). Both **phenylhydrazines** and **ketene** derivatives are key building blocks for a multitude of recently developed active ingredients.

1.2. *Advanced Technologies*

In addition to those ubiquitous reactions, amongst other factors the close relation to an agricultural group within the previous organization triggered an expansion of the technology portfolio into additional areas. Derivatives based on the side-chain oxidation of substituted toluenes are of major importance for many end markets. Consequently, different technologies were made available for this transformation: **Side-chain chlorination, air oxidation**, and **nitric-acid oxidation**. Originally developed for commodity-type products like *p*-nitrobenzoic acid or *o*-chlorobenzaldehyde, they now serve as powerful tools for the formation of many substituted aldehydes and benzoic acids; the availability of different reactions to yield the same end products allows the selection of the most cost-efficient, straightforward, and environmentally sound type; each of the reactions works in the presence of different substituents, thereby widening the scope of the portfolio.

In support of these technologies, additional reactions are available to complement the toolbox for the design of **substituted benzoic acids**. Those include more traditional chemistry like acetylation and subsequent haloform reaction as well as introduction of cyano groups by either *Sandmeyer*-type reaction or exchange of chlorine in activated systems. The recently commercialized CO_2-*Grignard* represents yet another technology to unlock additional gateways.

Experience in the handling of **substituted phenols** in combination with the knowledge in the formation of phenylhydrazines served as the basis for a new access to substituted phenols by diazotation of anilines and subsequent degradation of the diazo group to the respective phenol. The reaction adds to the traditional access to phenols by caustic fusion and is of better acceptance regarding the formation of wastes. For the same purpose, the chemistry for the production step of the basic anilines was switched from chemical to catalytic reduction.

Exchange of chlorine atoms in the presence of electron-withdrawing groups according to the reaction in *Scheme 2* was expanded to the formation of **fluoroaromatic compounds** according to the same general reaction scheme. Typical products are 2,4-difluoronitrobenzene and 4-fluoro-nitrobenzene. In a very similar re-

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action, substituted anthranilic acid can be made available (*Scheme 3*).

Flexibility in the custom synthesis area requires the capability of producing versatile key building blocks. In this respect, *Clariant Fine Chemicals* practices various technologies to produce **C_2 building blocks**. Key intermediates are:

- glyoxal and glyoxylic acid,
- ketene and diketene,
- derivatives of chloroacetic acid.

These synthons are the basis for subsequent **C–C coupling reactions**. Derivatives containing each of the two C-atoms in various oxidation states, mainly derived from the extremely flexible glyoxal system, are commercially available. Further downstream molecules include substituted phenylacetic acids and acetophenons as well as indoles. Additionally, complex aliphatic chains can be formed by consecutive addition of these C_2 elements.

1.3. *Key Technologies*

In cooperation with various customers, this broad basis of technologies was further developed into areas, which are now considered core and supported by a broad research effort and related pilot and production plants. By way of example, each of these technologies, in which *Clariant* holds a leading position worldwide, will be described in some detail.

1.3.1. *Air Oxidation* (*Scheme 4*)

2-Chloro-4-fluorobenzoic acid is a key raw material for several pharmaceutical products. *Via* oxidation with air utilizing a catalyst derived from the traditional Co/Mn system, yields in excess of 90% are achievable. Through efficient recycling, the cost for the catalyst and disposal of waste are minimized; the overall system can be handled economically on commercial scale through the development and installation of tailor-made equipment.

1.3.2. Sandmeyer *Reaction* (*Scheme 5*)

p-Fluorophenol can be found as key building block in various active ingredients in the pharmaceutical and agricultural industry. The most cost-efficient synthesis is based on *p*-fluoroaniline. Installed through a focused research effort, the production of the intermediate can be carried out economically in standard equipment.

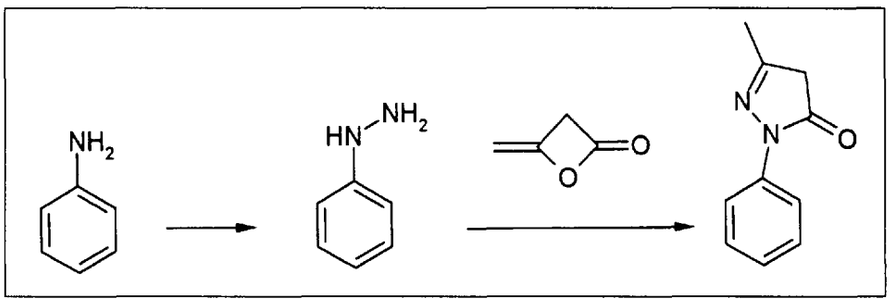
1.3.3. *Introduction of Fluorine by KF Exchange*

As fluorine is able to mimic hydrogen in biologically active systems, it is increasingly used in active ingredients with high activity. Introduction of fluorine is possible by two systematically different approaches: *Schiemann* reaction (diazotation of anilines) or exchange of chlorine by fluorine in activated systems. In the past, the reactions were considered complimentary; KF exchange was impossible in only weakly or non-activated systems leaving *Schiemann* chemistry as the sole possible access.

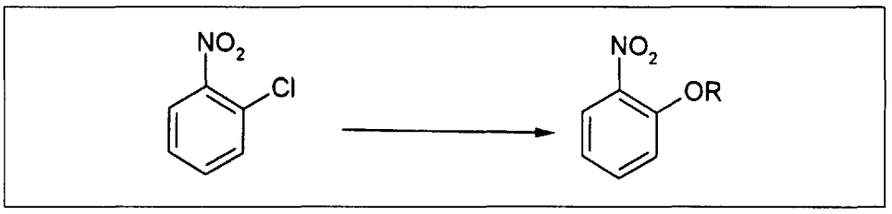
In the meantime, research at *Clariant* developed several sets of catalytic systems, which expand the scope of the reaction into molecules, so far considered inactive towards KF exchange. Typical examples are represented in *Scheme 6*.

Both tranformations are known in the literature, however, require special equipment and aggressive reaction conditions.

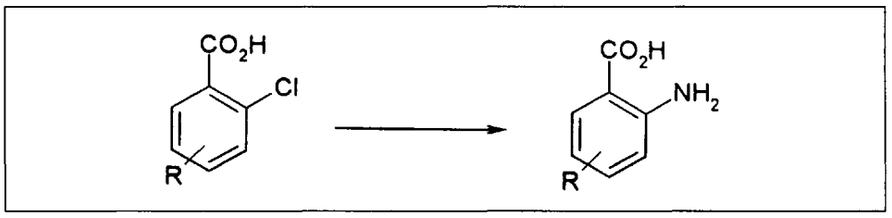
Scheme 1



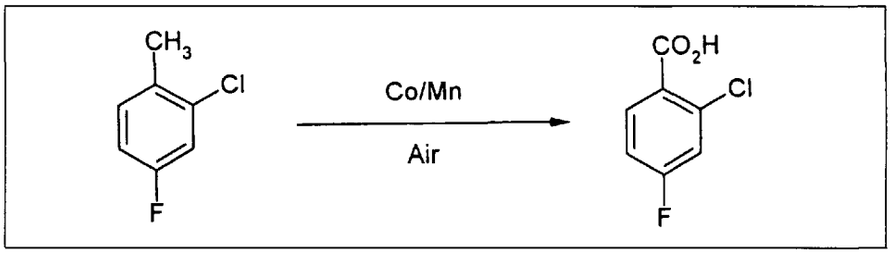
Scheme 2



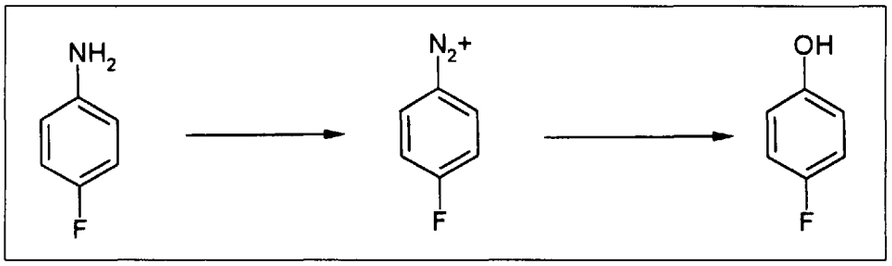
Scheme 3



Scheme 4



Scheme 5



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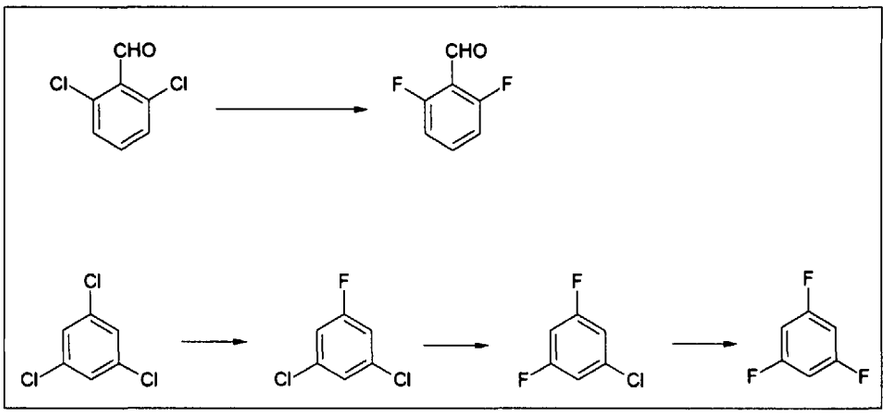
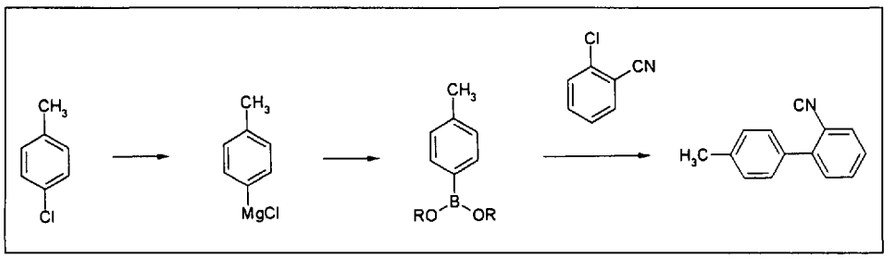
Scheme 6



Scheme 7



Applying our catalyst systems, both reactions can be run economically in high yields in regular equipment.

The selection of both substitution patterns may serve as an example for *Clariant*'s approach utilizing key technologies. Bulk actives with these structures seem to be gaining importance, since the **2,6-difluoro-** and **1,3,5-trifluoro** systems apparently induce biological activity.

As one of the main strengths of *Clariant* in production and conversion of fluoroaromatic compounds is the control of corrosion, subsequent transformations on these types of intermediates are generally carried out. These reactions include nitration, denitrating chlorination, oxidation and derivatizations of carbonyl functions. Applied to the examples mentioned above, further modification gives access to 2,6-difluorobenzyl derivatives as well as 2,6-difluorobenzoic-acid derivatives; furthermore, substitution reaction of chlorine or fluorine in reaction 2 leads to 3,5-substituted anilines or phenols.

1.3.4. *C–C Coupling Applying Organometallic Reagents*

Recently, AT-II antagonists as a new class of blood-pressure-lowering agents were introduced into the market. Examples are losartan (*DuPont/Merck*), valsartan (*Novartis*), irbesartan (*Sanofi*), or candesartan (*Takeda*). All drugs have one key building block in common: **2-cyano-4'-methylbiphenyl (OTBN)**. *Clariant* is one of the commercial producers of this intermediate, utilizing the process outlined in *Scheme 7*.

The technology gives access to OTBN through efficient conversion of readily available raw materials. Therefore, its scope is currently expanded into systems including similar biphenyl structures.

The coupling of the two phenyl moieties is just one example for the effort at *Clariant* to develop chemistry based on organometallic catalysis; capabilities for safe handling of *Grignard*-type reactions and butyllithium open many additional opportunities.

2. Production

Typically, the production plants of a fine chemicals manufacturer were built dedicated to one reaction step; as the products were at the beginning of the value-added chain, the equipment had nameplate capacities of several thousand metric tons; main purpose was the cost-efficient introduction of functional groups into benzene and toluene, thus producing mono- and dinitrated or -chlorinated benzenes or toluenes. Since the technology didn't differentiate between isomers, in-depth knowledge was developed and is still available for separation of those isomers by distillation or crystallization. Differentiation in the market worked on the basis of price within the limits of a relatively broad specification.

Since mainly cost position and only to a limited extent technological skills were very low entrance barriers for new competitors, during the late 80s and early 90s companies from low labor-cost areas like India and subsequently China appeared, which gained market share rapidly through aggressive pricing. Very often, waste management was of little importance in sharp contrast to increasing pressure by environmental groups in Europe. Consequently, the economic pressure gave way to the closure of many production units in *Clariant Fine Chemicals* within the last 10 years.

Concurrently, the availability of multipurpose units became of increasing importance. *Clariant* operates three of those units with a reactor volume in excess of 100 m^3 each in the Frankfurt area; all of them possess broad permits allowing a big variety of chemical transformations. Step by step, high-volume products like resorcinol or β-oxynaphthoic acid were replaced by new products developed together with single customers leading to a completely different set of challenges, namely inventory management of intermediates of a multistep synthesis, logistics of intermediates, shorter campaign times due to reduced volumes. Electronic systems were developed, that allowed scheduling and monitoring of capacities within highly intertwined systems. Adaptation of the system guarantees that the traditional production strength of *Clariant Fine Chemicals* remains vivid, although the portfolio changes.

In parallel, quality requirements changed from meeting relatively loose specifications to achieving reproducible product composition. *Clariant Fine Chemicals* received certification according to ISO 9001 in 1997 and is currently working to expand the standard meeting the requirements of ISO 14001. This includes validated cleaning of multipurpose equipment and monitoring batch processes as to their sensitivity toward crucial reaction parameters. The effort takes the concept beyond simple control of product quality to a constant effort to maintain and improve the quality of processes according to **T**otal **Q**uality **M**anagement. It also demands that waste reduction is not an add-on to the development of a process, but an incremental part of product development.

The highest level of quality control is required in the production of pharmaceutical intermediates in-line with cGMP (**c**urrent **G**ood **M**anufacturing **P**ractice) standards. Experience showed that it is very difficult to adjust a typical fine chemicals intermediates plant to the standards man-

dated by the FDA (**F**ood and **D**rug **A**dministration). Although there may be (expensive ways) to adjust current equipment, more importantly cGMP production requires a completely different production approach. In a time-consuming effort, the education of production staff must be improved closely matched by a change toward the necessary quality philosophy.

Consequently, to be considered a viable player in this area, *Clariant Fine Chemicals* acquired a cGMP production plant in combination with the appropriate piloting equipment. The setup allows the parallel production of different intermediates in separated production trains. The plant, located in Fechenheim, produces two bulk actives and was inspected by the FDA. Since expansion of the business in the life science intermediates area is considered strategic to *Clariant*, also investment in expansion of current multipurpose plants is planned.

3. Organization

The only constant in the custom-manufacturing arena is the change. New actives need to be developed as quick as possible to leverage ideas to the maximum extent. By the same token, the entire life cycle of products is shortened, thereby reducing the time to recover up-front investments into research and equipment. Intermediates' suppliers need to respond to these challenges by installing a flexible organization to keep pace with the quantity requirements and parallel development of the most efficient process and production equipment.

Clariant Fine Chemicals realized quickly that the traditional functional approach needed to be adapted to meet those diverse challenges. Development of new intermediates is now handled by cross-functional teams, which permanently include representatives from research, analytical department, production, and marketing. As the emphasis shifts during the development, additional experts are added on demand: representatives from the patent department, regulatory affairs, safety department, engineering, registration and purchasing department. This is the only approach possible to assure quick and efficient development and scale-up of new processes.

As a new molecule progresses through the development process, the overall coordination of a project shifts, thus assuring the particular importance of every given development phase. Usually, the baton is passed from research *via* piloting to production.

Prior to the development of an intermediate, the selection of the most appropriate molecule is one of the key success factors. Within *Clariant*, we take the time to carefully select the most appropriate new molecules. This is done in a joint effort on the basis of criteria (in-line with profitability considerations) like fit with core technologies, patent position, and production equipment as more internally focused criteria, but equally as important an estimation of the customer position in the respective market segment and intent to cooperate with *Clariant*. Once a molecules passes this sometimes cumbersome and time-consuming process, we are committed to meeting the overall success criteria like providing timely quantities from a laboratory, pilot and production scale, and developing the product in-line with customer expectations. We will establish *Clariant* as the driving force behind timely development of an intermediate by providing a complete service. This approach is riskier on *Clariant*'s end, however, opens the opportunity for higher reward at the other end.

4. Marketing

In the custom-manufacturing area, marketing can be considered the expansion of the above described team effort including customer representatives from various functions. However, this most efficient 'organization' requires careful preparation and a change of philosophy on both sides.

First and foremost, it is based on the selection of customer's prepared to join this cooperative approach, as the development of new chemical entities became so complex that equal attention to every customer is virtually impossible. This requires the establishment of a common base prior to identification of distinct product opportunities. *Clariant Fine Chemicals* is represented with people with a broad experience base in the major regions US, Japan, and Europe, which are capable of in-depth discussion about our technology base. An efficient exchange of information inside the group allows to fully meet the global interactions our customers increasingly demand.

To identify distinct projects within a well-structured relationship, we consider confidentiality and trust as key elements. Flow of information in both directions occurs very often within the limits of written agreements. More importantly, *Clariant* practices the highest level of confidentiality as a daily routine. The transfer of ownership of *Fine Chemicals* from *Hoechst* to *Clariant* helped conveying this message to the market, since we left back the captive pharmaceutical and agricultural businesses.

Additionally, the emphasis shifted from a traditional, internally focused technological orientation towards a balanced approach including all functions. It allows the appreciation of the flow of information in two directions: Exchange of detailed information about our own processes on one hand and acceptance of technological information from the customer side on the other hand. Utilization of this concept requires involvement in the exchange of information on various levels within an established framework.

Summary

In conclusion, a successful supplier of custom-made intermediates needs to change the organization towards the needs of the customers. Those are defined by the accelerating speed of the development of molecules of increasing complexity due to novel combinatorial research approaches. Many customers in the life science area try to escape the pressure on sourcing by concentration on a reduced number of key suppliers.

Within this environment, suppliers need to proactively define and detail their area of expertise towards the market. This requires a precise understanding of the driving forces in the respective application areas of their intermediates. Even more complex molecules mandate a change in decision criteria away from volume of sales product to value generation in the synthetic chain as the product of price and quantity. Accordingly, the production equipment needs to get adjusted.

Last, but not least, a supplier needs to be prepared to step on new ground, as *Clariant* did by establishing research and production equipment for intermediates requiring organometallic catalysis. Additionally, this is currently demonstrated by the trend of many fine chemical producers to become actively involved in production of chiral intermediates through either chemical or biological synthesis. Yet the next challenge will be, how to serve the needs of virtual companies entering the pharmaceutical area with a high innovative potential and very little production and marketing background.

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