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Catalytic Options for Pharmaceuticals from CPhI Some Solutions to Problems

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ABSTRACT

At the Pharmaceutical Industry Ingredients Fair (CPhI), some solutions to the problems that catalysis encounters in its use in the production of drugs, as an alternative to traditional synthesis, were presented. New ligands were developed that increased the activity, chemo and enantioselectivity of homogeneous catalysts, and allowed their heterogeneization, and technologies for their recovery from reaction solutions and new supports to make heterogeneous catalysts more filterable. At the CPhI fair in Madrid, November 2005, the innovation prizes were awarded to three companies that have brought the results of their research to an industrial level: Accentus for a predictive technique and fast screening of crystallization processes (1st prize), Lanxess for the stereospecific fluorination of chiral alcohols (2nd prize) and Novasep for the advancement of chromatographic separation technology that uses supercritical CO_2 as an eluent (III° award).

Keywords: Pharmaceutical Industry Ingredients Fair (CPhI), Chemo, Enantio-Selectivity Homogeneous Catalysts, Crystallization Processes, Chromatographic Separation Technology.

INTRODUCTION

Celebrating the 35 years uniting pharma CPhI [1] will return in Frankfurt in October 2025 – "One-stop-shopping in pharmaceutical outsourcing"– a trade fair on ingredients for the pharmaceutical industry: 2,600 exibiting companies from 166 different countries were present with their products and technologies on the previous years. This year 2025 the performance is scheduled in six countries: Americas (May, Pennsylvania), China (Jun, Shanghai), India (Nov. Delhi), Middle East (Dec. Riyad, Saudi Arabia) and Japan (Apr, Tokyo) as well as again in Europe (May, Warsaw).

The fair was intended for those who sold technology or products or those who wanted to buy them or seek collaboration for the development of products / processes, but it was also a unique opportunity to grasp what the problems of the industry are and what skills are needed in the sector. In addition, it was possible to know which of the new syntheses are only at bench scale or pilot level and which can be immediately used at the

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industrial level [2].

Catalysis for sustainable synthetic strategies will focus only on some aspects of the technologies presented at the Fair, held in Paris (October 2002), those related to catalytic synthesis. Catalysis can successfully compete with traditional synthesis, when it improves the "atom economy", reduces wastewater, can allow to carry out regio- and chemo-selective processes without having to resort to the protection of other functional groups and uses continuous processes to more easily comply with the standards of GMP (Good Manufacturing Practices) and UNI EN ISO, but only if it manages to reduce its costs (by decreasing the amount of catalyst, using less expensive metals and chelators and simpler processes) and solve some of its problems. The problems encountered by homogeneous catalysis, in particular with transition metals, are mainly the contamination of the product with metals and binders, as well as the complexity of the technologies for separating and recovering the catalyst from the reaction mixture [3].

The major problems encountered by heterogeneous catalysis are, however, the following: the slowness of filtration procedures; the problems of diffusion of bulky molecules (typically used in pharmaceuticals) inside the pores; the lower chemo-selectivity compared to homogeneous catalysts due to the non-mild conditions under which many of them operate, with the consequent possibility of attacking other functional groups almost always present in an intermediate for pharmaceuticals; the lower enantioselectivity; the easy deactivation by poisoning, especially by the different functional groups of the reactants, and finally the solubility of its components in the reaction liquid. Various solutions to the problems encountered in the use of homogeneous and heterogeneous catalysis for the production of intermediates and active ingredients for pharmaceuticals were presented at the fair. Some of these solutions (including those of Engelhard) were presented for the first time, while others (such as those of Solvias, Dsm, Omg and Sumitomo), although not entirely new, were commented on and discussed during the conferences on "Custom Manufacturing", held on the same days as the Fair [1].

ENGELHARD SOLUTIONS

Heterogeneization of a homogeneous hydrogenation precatalyst Engelhard LigandNet, a new heterogeneous pre-catalyst of phosphine ligand-free Rh(COD)2BF4 supported by the use of heteropolyacids. By means of subsequent exchange with phosphines, the equivalent of a homogeneous catalyst is obtained while the latter remains bound to the support. In particular, the LigandNet complex Rh[1,1'-bis(diisopropylphosphine)ferrocene] or Rh(DiPFc) has been proposed, obtained by exchange reaction between Rh(COD)2BF4 and DiPFc. This heterogeneized homogeneous catalyst has high selectivity in the hydrogenation of C=C or C=O in molecules that contain other particularly reactive functional groups, such as bromides or nitrocompounds, or groups, such as sulfides, that normally deactivate the heterogeneous catalysts by conventional. In addition, the use of this type of catalyst does not involve the costly separation operations (crystallization, distillation, precipitation) from the reaction mixture required using homogeneous catalysts. During hydrogenation reactions (e.g. hydrogenation of 4-bromomostyre to 4-bromo-ethylbenzene), no solubilization of the metal was observed and the catalyst after filtration was used again without loss of efficacy (Figure 1).

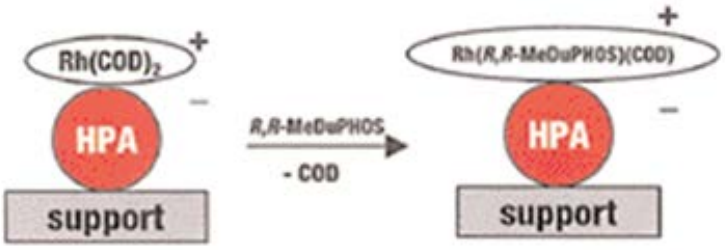


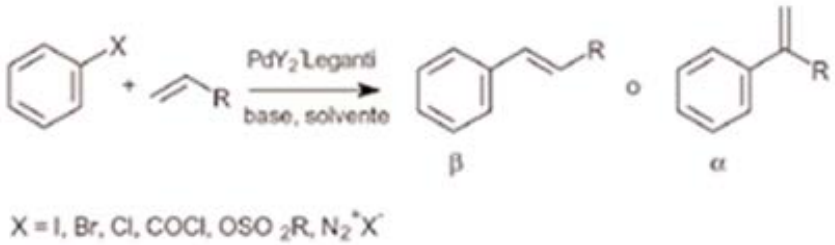
Figure 1

In enantioselective synthesis, homogeneous catalysts are those that exhibit the highest selectivity and turnover. The immobilization of homogeneous asymmetric Rh catalysts is easy with LigandNet Rh(COD)2BF4, exchanging with chiral phosphines. The activity and enantioselectivity of the immobilized catalyst was comparable to that of its homogeneous catalyst. For example, in the hydrogenation of dimethylitaconate, a model substrate, (S)-BINAP, (R,R)-MeDuPHOS, (R,R)-DiPAMP, (S)-DIOP were used as ligands, the excess enantioselectivity (e.g.) has always been 97%. Effective homogeneous catalyst removal systems.

Engelhard also presented a new product, ScavNet. It allows to eliminate traces of platinum group metal complexes (Pd, Pt, Rh, Ru, Ir etc.), with the metal present both as a cationic complex and with zero valence, thus avoiding complicated and expensive recrystallization, precipitation or distillation processes to purify the reaction mixture. At the same time as the metal, binders are also removed. Purification can be carried out with a chromatographic column or directly by introducing ScavNet into the reaction mixture. The metal can then be recovered using the services offered for this purpose by Engelhard. Easily filterable heterogeneous catalysts The slow filtration process of a heterogeneous catalyst not only results in reduced productivity, but can also lead to parasitic reactions. Engelhard has developed a new technology for the production of a new family of catalysts, FastNet. FastNet technology can be applied to a wide range of precious metal-based catalysts and, in most cases, more effective filtration is achieved without any loss of activity and selectivity. The superior performance of this family of catalysts is the consequence of modifications made by Engelhard on the surface of the carbon particles and their shape (e.g. by exercising control over the particle size distribution leading to a higher filtration rate, up to four times higher) [4].

DSM SOLUTIONS

"Homeopathic" and binder-free catalysts for CC coupling Substitution reactions on aromatic rings are by far the most important reactions catalyzed by transition metals in the field of fine chemicals, also because they can be conducted under mild conditions and above all they are compatible with different functional groups. In particular, for the Heck reaction, the advantages of using palladium-based catalysts consist in the elimination of strong bases such as n-Bu-Li, a classical reagent for the formation of C-C bonds, in the greater selectivity, in the compatibility with other functional groups and in the possibility of using catalysis at the last stage of a synthesis, avoiding protection/deprotection operations. The cost of palladium, however, penalizes catalytic processes, being used in quantities from 1-5% and in large-scale productions in general. In addition, metal binders are difficult to remove from the reaction mixture (Scheme 1).



Scheme 1

Heck reactions can be conducted at temperatures between 50 and 80 °C with high selectivity to give α products or β aryl substituted. A homogeneous binder-free catalyst was developed for Heck synthesis on aromatic halides from a palladium salt, preferably acetate. In the reaction environment, it is the reactants that cause palladium to enter the catalytic cycle, while in their absence (at the end of the reaction) it precipitates as metallic palladium, making it easy to separate it from the reaction environment. At the same time, the absence of binders avoids any contamination of the reaction mixture.

The entire Pd can be recovered, at the end of the reaction, to be reused (99%) by simply adding I2. Reactions occur at around 50-80 oC with Et_2NH or N-methylpyrrolidinone (NMP) as solvents and 0.5% molar $Pd(OAc)_2$. It has been found that homeopathic amounts of $Pd(OAc)_2$ without ligands (from 0.01 to 0.05% mol) give excellent conversions in the Heck and Suzuki reactions starting from arylbromides. In this

case, there are not only the advantages of using a binder-free catalyst, but also those of a low cost (<5 /kg product).

HECK SYNTHESIS WITHOUT ALKYL HALIDES

Aromatic halides, the starting reagents for the Heck reactions described in the previous paragraph, can be expensive, not readily available and produce significant amounts of saline wastewater.

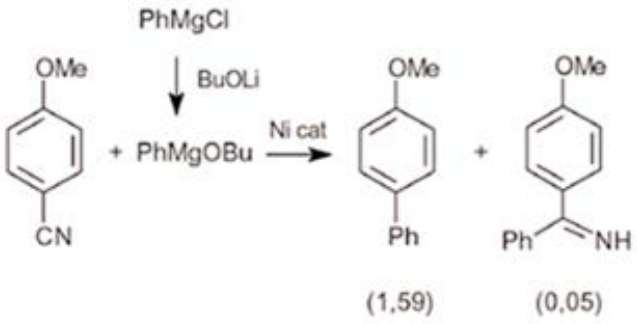
Heck syntheses have been developed using aromatic anhydrides as alternative raw materials that react with olefins containing electronacceptor groups, thus avoiding the production of salts. For example, using benzoic anhydride and n-butyl acrylate, (E)-n-butylcinnamate was obtained with yields of 77% to 100% conversion to NMP and sodium bromide at 160 °C (in 90 minutes). As a co-product, benzoic acid is obtained, which can, however, be recycled. The product of these reactions can subsequently be hydrogenated to arylalkane, thus providing a clean alternative pathway to the Friedel-Crafts reaction. Finally, the complete solution to wastewater problems has recently been found in Heck's synthesis by directly activating the CH bond, using aniline derivatives, with syntheses that can be conducted at room temperature.

For example, in the transformation of the acetoanalide with n-butyl acrylate in (E)-3-(2-(acetylamino)phenyl)butyl propenoic acid butyl stere yields of 70% and selectivity of 100% were obtained, using benzoquinone (BQ) as oxidant and acetic acid as solvent, both at low cost, and p-toluenesulfonic acid (p-TsOH) as a promoter (Scheme 2).

Scheme 2

Catalysts active in the formation of nickel-based C-C bonds, such as $Ni(Acac)_2$, have been developed with triisopropyl phosphite as a binder and with small amounts of zinc as a promoter, which are less expensive than palladium-based ones.

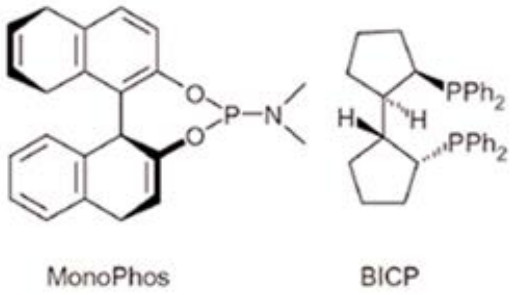
In particular, these catalysts are effective in coupling an benzonitrile with a Grignard aromatic reagent, ArMgX, at low temperature. The reaction proceeds with greater selectivity in the presence of a reagent such as t-BuOLi that transforms ArMgCl into ArMgOBu in situ (Scheme 3).



Scheme 3

NEW CHIRAL LIGANDS FOR ASYMMETRIC HYDROGENATION

To obtain amines with a high enantiomeric excess, DSM has several technologies in its portfolio, such as asymmetrical reduction of imines, resolution by formation of diasteroisomeric salts, enzymatic resolution and the use of chiral auxiliaries. For asymmetric hydrogenation it has almost reached the milestone of 100% yield and 100% enantioselectivity with Rh complexes using MonoPhos and BICP as chiral ligands. Enantiomeric excesses (e.g.) of up to 98% are reported for the synthesis of non-functionalized amines, α or β amino acids and amino alcohols (Scheme 4).

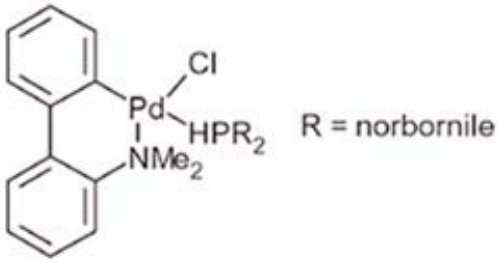


Scheme 4

The reactions are conducted, generally at room temperature, at 5 bar, with a ratio >1,000 moles of product/moles of Rh catalyst (defined as turnover number, TON), even in the presence of air and humidity. The critical factor of these syntheses always remains the cost of Rh. Heck's syntheses were presented by Hans de Vries [5], while the asymmetric syntheses were presented by Rinus Broxtermann of the DSM [6].

SOLVIAS SOLUTIONS

New binders for improved homogeneous catalysts Solvias has developed a new secondary dialkylphosphine ligand for palladium-based catalysts active in the Heck reaction between olefin-deactivated arylchlorides such as styrene, vinyl ether and ethyl acrylates. This can be considered the first example of the application of a secondary phosphine as a ligand for palladium-catalyzed reactions (Scheme 5).



Scheme 5

This catalyst is stable, easily handled, and can be used for other reactions such as arylation of ketones and amination of aryl chlorides. For example, the aforementioned catalyst in the reaction between butyl acrylate and 4-chloroanisole has presented higher yields than those always based on palladium with binders such as $P(t\text{-}Bu)_3$, known by the literature to be the most active. For asymmetric synthesis, Solvias also offers a wide range of ligands, belonging to different families (Josiphos, Walphos, Raphos and Butiphane), even in quantities of a few kilograms [7].

New binders and effective metal recovery technology

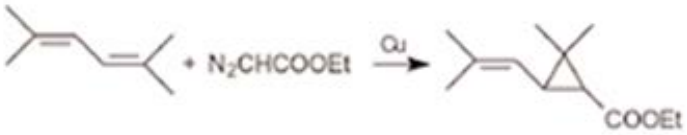
Omg [8,9] has all the catalysts for reactions in which metals from the Pt group are used.

In particular, for Heck syntheses it has new ligands for Pd for amination reactions and CC coupling and also chiral ligands for asymmetric syntheses, such as Dephyphos, Taniaphos and Mandiphos, available on an industrial scale in about six months, while an industrial synthesis, which can produce several kilos, is already available. Rh-based catalysts with these ligands give, for example, in the hydrogenation of the methyl ester of α-acetoamidocinnamic acid e.e. >96. Omg has also developed a technology for the recovery of Rh from spent catalysts called Ecolyst, which has high yields in metal recovery and higher process speed than alternative techniques. The technology is based on a proprietary process of extracting Rh from solutions that contain it, even very diluted, avoiding preventive calcination that always leads to metal loss. The extraction process is accompanied by a second purification stage that leads to the production of an Rh with a purity of 99.9% that can be used again for catalytic cycles.

SUMITOMO SOLUTIONS

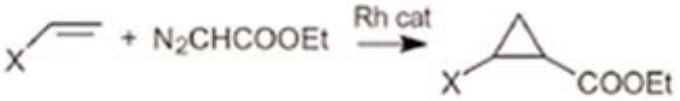
New developments in catalytic cyclopropanation

For years, Sumitomo has been developing various technologies for the synthesis of cyclopropancarboxylic acid derivatives, which are present in many drugs and plant protection products. Some of the industrial cyclopropanation syntheses are, for example, the addition of an ethyldiazoacetate or an α-chlorester to an alkene (Scheme 6).



Scheme 6

For asymmetric cyclopropanation, catalysts were used always having copper as the central atom and chiral ligands based on salicylaldicmine derivatives, obtaining the product with high ee. A new, highly effective cyclopropanation reaction is currently being developed that uses Rh complexes as a catalyst by adding diazoethylacetate to substituted olefins (Scheme 7).



Scheme 7

In particular, with catalysts based on $Rh_2(OCOCPh_3)_4$ and using $EtOCH=CH_2$ as olefin, yields of 90% and a cis/trans ratio of 47/53 of the product were achieved.

Table 1. Yields in cyclopropanation with diazoethylacetate to different olefins

X	*Yields%*	*X*	*Yelds%*	*X*	*Yelds%*
OAc	90	CH_2Cl	88	COOMe	72
CH_2OAc	90	CH_2Br	61	$CH(OEt)_2$	70

To obtain high enantiomeric excesses in products, when enantioselectivity was not sufficient, diastereomeric or enzymatic resolution methods were also used subsequently. Equally important for these products were the methods of racemization and reversal of one or both the chiral centres [10].

The importance of the CPhI ("Convention Pharmaceutical Ingredients") worldwide [1], the last edition of which was held in Madrid, as a technical and commercial meeting point for those working in the chemical-pharmaceutical sector, can be highlighted by recalling that 1,500 companies from all over the world were present and over 20,000 visitors participated. The three innovations that were awarded will be described below, in order to give an idea of what have been considered the driving factors in the preparation of ingredients for pharmaceuticals and fine chemicals. Crystallization and the identification of the suitable crystalline form are certainly among the most important phases in the preparation of a drug, not only to influence its bioavailability and workability properties, but also to prolong patent protection and create protective barriers against competition. There are also more and more drugs and pesticides, including optically active ones, that contain carbon-fluorine bonds; the introduction of fluorine atoms makes it possible to modify their bioavailability and metabolism as a result of changes in lipophilicity and increased oxidation stability. Finally, preparative chromatography is now one of the most widely used techniques in the pharmaceutical industry to purify complex mixtures and to obtain enantiomerically pure molecules. All three innovations aimed to facilitate the transition of the results obtained in the laboratory to the industrial scale and all three were carried out by companies that carry out intense development activities for customers (custom activities). In its core business there is also the use of sound waves to produce crystals, avoiding the introduction of nucleation seeds and allowing to operate at low supersaturation with high reproducibility and good control of the nucleation process [11].

The technique allows a better control of the size of the crystallites, their morphology, the selective production of the desired polymorphs and their purity. The prize was awarded for the development of the CrystalGEM program [12], which is both a predictive and screening technique to quickly produce crystals with optimal properties for the pharmaceutical industry. Crystal growth is most often due to kinetic effects (a supersaturated solution is not, in fact, in equilibrium) and the questions everyone asks is how to predict how many types of polymorphs of a drug are possible and how to control their formation and morphology. The CrystalGEM program is a multi-step methodology. Initially, a prediction of the optimal conditions of temperature, crystallization time and solubility is made, choosing from about 80 solvents and different co-solvents, to obtain certain morphologies and crystal structures. This prediction is made on the basis of the availability of an extensive database, obtained from 12,000 real examples of crystallization and on the basis of the chemical-physical properties and QSAR (quantitative structure activity relationship) parameters of the substances under test. In this first phase, for example, it is possible to select 20 different solvents and three antisolvents, out of an initial proposal of about eighty. In a second phase, a fast screening method based on a few grams of product is suggested, to verify the validity of the conditions proposed by predictive analysis, to subsequently arrive at the production of monocrystals to be analyzed by X-rays and finally to investigate the benefits of sonocrystallization to obtain commercial crystals. It has been estimated that with a traditional screening technique 10,000 mg of compound are needed, 1,200 conditions to be tested, with the result of having 8-10 solvents available to be used in the end, all in 8-10 weeks of work. With CrystalGEM technology, on the other hand, about 100 mg of substance are sufficient and only 46 conditions are proposed to be experimentally tested, to arrive at the final result in 3 weeks of work, thus reducing the cost of screening to 50% compared to traditional techniques and decreasing the risk of scale-up.

NEW INDUSTRIAL FLUORINATION TECHNIQUE

Lanxess [13] is a company resulting from the restructuring of Bayer and is active in the production of plastics, rubbers and, in particular, it is specialized in chiral synthesis, cross-coupling reactions and fluorination reactions. Since February 2006 the fine chemicals and pharmaceutical business has passed to the subsidiary Saltigo. Over the years, several fluorination technologies have been developed, the business sector for which the company received the CPhI award, which have allowed it to prepare about 24,000 fluorine organic compounds and to offer samples on the market from laboratory scale to multi tons: 1) the halogen exchange reaction ("Halex with phase transfer catalysts; 2) the use of anhydrous HF or SF_4; 3) the use of fluorinating agents such as Fluorinox [14] and perflurobutansulfonyl fluoride [15].

Lanxess' strategy was to bring to market low-cost, stable, non-toxic and non-hazardous fluorine processes that had high chemo- and stereo-selectivity. The halogen exchange reaction, starting from chlorinated and to a lesser extent brominated compounds, is one of the most widely used techniques for the introduction of fluorine into organic molecules. The new phase transfer catalysts developed and brought to commercial scale, CNC+ and NPC+ (Figure 2, Phase transfer catalysts, CNC+ and NPC+, for fluorination with KF), are easy to produce and therefore have a low cost, have good thermal stability and good catalytic activity in a wide temperature range and are able to operate even with poorly reactive substrates [16].

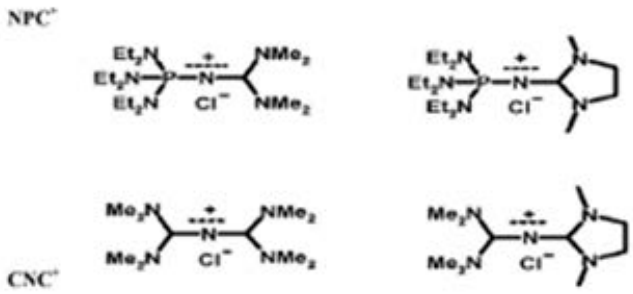


Figure 2. Phase transfer catalysts, CNC^+ and NPC^+, for fluorination with KF.

With them, it is possible to use alkaline fluorides as fluorinating agents, which are poorly soluble in aprotic solvents and in the substrates with which they must react. Fluorinox is a new class of reagents with the general formula shown [for the transformation of alcohols into fluorides and ketones into twin difluorides.

$CHF_2—NR_1R_{2\ (Reagent)} \mid nHF–(R+)_{2\ (promoter)}]$.

These reagents are mild, easy to synthesize and low-cost fluorinants and have the advantage of being able to allow easy separation of the fluorinated compound; in fact, as a transformation product of the Fluorinox reagent, there is the formation of a water-soluble, non-toxic and stable amide. However, the prize was awarded, in particular, for having brought the perfluorobutanesulfonyl fluoride (CF_3-CF_2-CF_2-CF_2SO_2F)/NEt_3 reagent mixture to an industrial scale. 3HF/NEt_3, by means of which it is possible to carry out the highly stereospecific transformation of hydroxy compounds into fluorinated products with an SN2 mechanism.

$$R_1R_2N–OH \xrightarrow{C_4F_9SO_2F} R_1R_2N–F$$

The innovation lies in having been able to industrially develop this method already known and at the time patented by the parent company Bayer [17]. This reaction, which is extremely difficult and can give both racemization and by-products, has so far been carried out with unstable and/or extremely toxic reagents.

CHROMATOGRAPHIC SEPARATIONS WITH SUPERCRITICAL FLUIDS

Novasep [18] is a company specialized in purification in the pharmaceutical sector, also for third parties, and with expertise in the design of equipment to use chromatography at industrial level.

The prize was awarded for having developed a preparative chromatography using, instead of organic solvents, supercritical CO2, as a separation eluent (SFC) [19]. For the elimination of the large quantities of solvents used in traditional chromatography, the SFC system can certainly be defined as a green technology.

Novasep Supersep (SFC) plants of various sizes are installed in many pharmaceutical companies to supply quantities suitable for pharmaceutical research, preclinical and clinical phases and also for industrial production (i.e. shows a macrolab/pilot scale equipment).

Due to the low viscosity and high diffusivity of supercritical CO_2, the preparative chromatography developed by Novasep ensures faster separation than traditional HPLC chromatography. The CO_2 operates in supercritical conditions during the chromatographic phase (Figure 3), while, at the exit of the column, the mobile phase is decompressed and the product in the form of droplets or crystals is separated with a cyclone (patented by the owner company) from the gaseous CO_2 which is 99% recoverable.

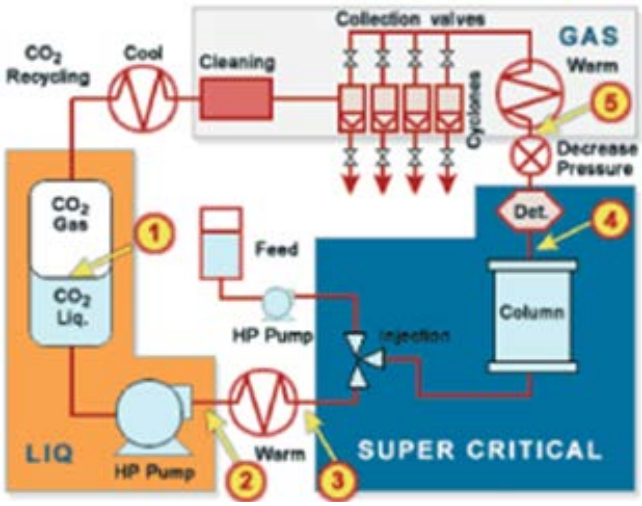


Figure 3. Scheme of a preparative SFC system.

Subsequently, the gaseous CO_2 (together with any co-solvent), after purification, is recycled, thus reducing separation costs. Supersep units can range in size from 5-50 g per day for laboratory implants, 0.1-1 kg per day for pilot implants, and 1-10 kg per day for commercial implants.

This technique can work at high pressure up to 250 bar and with temperatures that can reach 60 °C; the polarity of the effluent can be modified by mixing the CO2 with a co-solvent, usually EtOH, to improve the solubility of the products to be purified. SFC has the advantage of being able to obtain a high productivity, 3-5 times higher, compared to traditional HPLC preparation, also as a result of the possibility of modulating the force of the diluent by means of a pressure gradient along the column. The SFC technique, compared to other chromatographic techniques, is optimal in the separation of molecules of medium to low range, as shown in Figure 4.

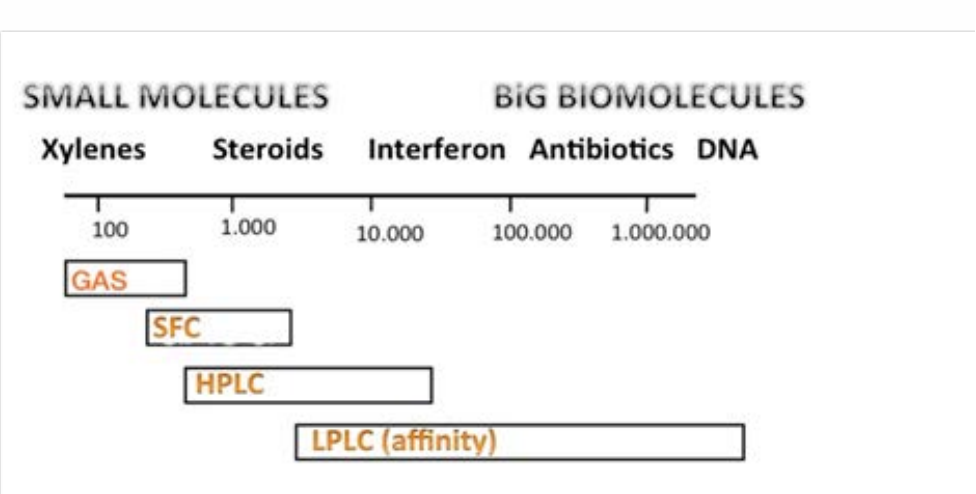


Figure 4. Optimal chromatographic techniques as a function of molecular size.

CONCLUSIONS

For hydrogenation, hydrosilylation, hydroformylation, carbonylation, CC coupling, cyclopropanation reactions, homogeneous catalysis remains the most important solution, as an alternative to classical organic synthesis.

Heterogeneous catalysis, on the other hand, has expanded its field of application in catalyzed acid and base synthesis, in oxidation, hydrogenolysis and dehydrogenation reactions. Since the last CPhI, Paris 2002, it has been possible to see that homogeneous catalysis is quickly solving its problems in applications to fine chemicals and pharmaceuticals.

New active catalysts have been developed in homeopathic quantities, without binders or with less expensive central metals and, moreover, with the discovery of new ligands, 100% yields, chemo, stereo, diastereo and enantioselective yields are being achieved for many catalytic synthesis.

The difficulties of separating the catalyst from the reaction environment are being solved, both by developing new systems that allow the catalytic complex to be anchored to a solid, and through the development of effective technologies for the purification and recovery of metals and binders from the reaction liquid and through the development of easily filterable supports.

There are now several companies that offer their service for catalyst screening, pilot plant trials, scale up, industrialization and "trouble shooting" of the plant. So all pharmaceutical and custom manufacturing companies can easily think and immediately switch to the catalytic option when choosing sustainable synthetic strategies.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. http://www.cphi.com/
2. Trifirò F. (2006). Innovazioni nello scale –up farmaceutico. La Chimica e l'Industria. 88(4):16-19.
3. Trifirò F. (2002). Opzioni catalitiche per la farmaceutica.

La Chimica e l'Industria. 84(10):1-4.

4. Fair engelhard solutions. For information, Engelhard phone: 02/281975.1; (email: milan.catalysts@engelhard.com).
5. https://cdnsciencepub.com/doi/abs/10.1139/v01-033
6. www.google.com/search?q=Rinus+Broxterman-n+of+the+DSM&rlz=1C5CHFA_enIT689IT689&o-q=Rinus+Broxtermann+of+the+DSM&aqs=-chrome..69i57j69i60.2895j0j4&sourceid=-chrome&ie=UTF-8. (P.O. Box 18, 6160 MD Geleen, Netherlands).
7. https://www.cphi-online.com/catalysis-technology-prod538137.html (Klybeckstrasse 191 CH 40002 Basel)
8. https://www.cphi.com/en/digital-products/digital-products/digital-marketing.html (for information Omg Rodenbacker Chausse 4 D.63457 Hanau-Wolfang, Germany).
9. https://pubs.acs.org/doi/10.1021/acs.chemrev.7b00776
10. CPhI sumitomo solution. The conference was presented by Jim Birnie, Custom Synthesis Business, Sumitomo, Brussels (Belgium).
11. Ruecroft R, et al. (2005). Organic Process Reseach & Development. 9:923-932.
12. https://onyxipca.com/solid-state/crystallization-development/?utm_source=google&utm_medium=cpc&utm_campaign=solidstate_crydevadgroup&gad_source=1&gbraid=0AAAAAB30U4S-ezMquDhurKmsuPOtW8z6x
13. http://www.lanxess.com/
14. http://www.anopol.com/products/
15. US20090105502A1.
16. Pleshke A, et al. (2004). Journal of Fluorine Chemistry. 6:1031.
17. Vorbrueggen H. Bennua-Skalmowski, US Pat. 5760255 (Bayer).
18. http://www.novasep.com/
19. Majewski W, et al. (2005). Journal of Liquid Chromatography & related Technologies. 28(7-8):1233.