

---

# 1 Considerations of Industrial Fine Chemical Synthesis

---

MARK W. HOOPER

*Senior Chemist, Johnson Matthey, Orchard Road, Royston, Herts SG8 5HE, UK*

## CONTENTS

1.1	INTRODUCTION	
	<i>MARK W. HOOPER</i> . . . . .	1
1.2	TYPES OF PROCESSES – FLOW CHARTS . . . . .	2
1.2.1	Classical process . . . . .	2
1.2.2	General catalytic process . . . . .	3
1.3	COSTS ASSOCIATED WITH USE OF CATALYSTS . . . . .	3
1.3.1	Catalyst fabrication costs . . . . .	3
1.3.2	Intellectual property right (IPR) issues . . . . .	6
1.3.3	Separation costs . . . . .	7
1.3.4	Pre-reaction/immobilisation . . . . .	7
1.3.5	Post reaction – separation . . . . .	8
1.3.6	Industrial examples . . . . .	9
	References . . . . .	12

## 1.1 INTRODUCTION

When considering the best synthetic route to a fine chemical, it is very rare for there to be one definite answer. With the ever-expanding range of chemical transformations available, the modern chemist will often be faced with a choice of best options. At any stage there will be decisions made on which chemistry is ‘best’. The decisions will include many factors. Some are general, such as reactivity, yield, selectivity, and are considered equally for academic and industrial use. There are, however, factors that are more relevant to industry than to academic research. These include cost obviously, but also less straight-forward factors such as availability of reagents, regulations on their use, health and safety implications on larger scale,

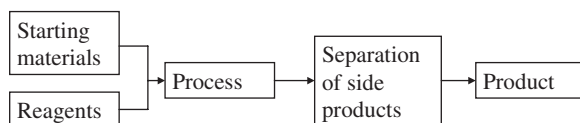
Intellectual Property Rights (IPR) considerations and practical scale-up issues (e.g. column chromatography is difficult on a tonne scale!). The intervention of these ‘secondary’ factors can lead to some superb academic synthetic chemistry being under-used (or impossible) on industrial scale.

This chapter explores some of the issues associated with commercialising catalytic synthesis and provides two examples of where metal catalysed carbon-carbon bond forming reactions are being used in industrial fine chemical synthesis. Other reviews detailing important industrial carbon-carbon bond forming reactions are available.<sup>[1]</sup>

## 1.2 TYPES OF PROCESSES – FLOW CHARTS

The following flow charts highlight differences between running a classical (non-catalytic) chemical process and running a catalytic process. There is also a specific example of a catalytic process where the catalyst contains a precious metal, e.g. palladium or rhodium (Pd or Rh).

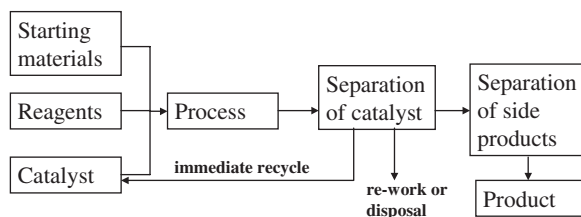
### 1.2.1 CLASSICAL PROCESS



This is a traditional process, using stoichiometric reagents to convert the starting materials to the desired products. Often the processes are well established, e.g. Michael addition, Claisen condensation, and have little or no IPR issues associated with running them. The main costs are the starting materials, the one or more equivalents of reagents, possible multiple-steps needed to achieve the desired transformation and labour costs associated. Also, disposal of a stoichiometric equivalent of side products can involve cost and be detrimental to the environment. Contrary to some opinion, most chemists are strongly in favour of ‘green’ processes and will opt for the ‘cleaner’ option if the costs allow.

Another consideration is the increased cost or low availability of starting materials. Often non-catalytic processes require more expensive starting materials as the chemistry will not ‘go’ with less active, cheaper materials. An example of this is the use of aryl-bromides in place of cheaper aryl-chlorides owing to reactivity constraints. Also, if the desired product is homo-chiral, then the chirality must be introduced through a chiral starting material. The supply of these starting materials are often limited by what is naturally available, i.e. the chiral pool, and this can affect cost and quantity availability.

## 1.2.2 GENERAL CATALYTIC PROCESS



A catalytic process should have many advantages to outweigh the basic disadvantage of adding an extra component to the process. A catalytic system is intrinsically 'greener', i.e. environmentally friendly, as it involves a lower energy process with less waste (sub-stoichiometric reagents). A catalyst will often allow a reaction to occur that was previously impossible. In an ideal world, all reactions would be catalytic with no side product and the lowest possible energy utilisation for the process.

In the real, hard world of industry, however, catalysts bring with them various disadvantages that must be considered against the benefits. Firstly, there is the cost of the catalyst. This can be broken down to raw material cost plus the cost of fabricating the catalyst. Both are important. For example, when the raw material is a precious metal (e.g. palladium) which is not recovered, the cost can be significant. However, if a relatively cheap metal is used (e.g. iron) with a multi-step catalyst preparation, then the catalyst can still have significant cost.

The second major issue is the separation after reaction. In the simplest case, the catalyst is truly heterogeneous and can therefore be separated easily by physical means, e.g. filtration. Often, however, the catalyst is homogeneous or partially removed from the heterogeneous support (leaching). In this case a strategy for separation is needed. Various options are discussed later, including immobilising the catalyst and selective or non-selective scavenging. Ideally the catalyst could be re-cycled immediately without any re-work. However, in many (most) cases the active, turnover catalyst is a modified form of the original catalyst introduced, so that immediate re-use is impossible. Another issue is the IPR associated with use of catalysts. Many catalytic systems are relatively new and are covered by patents. This involves both direct costs (licences) and indirect costs (legal fees).

## 1.3 COSTS ASSOCIATED WITH USE OF CATALYSTS

### 1.3.1 CATALYST FABRICATION COSTS

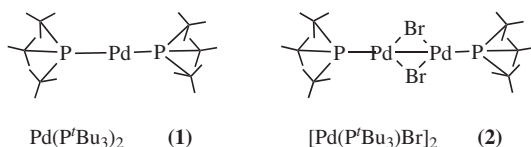
These are costs associated with producing the catalyst or pre-catalyst that is to be added to the process. Various factors contribute to the cost. These include synthesis steps, handling/sensitivity, availability, preparation route and cost of materials. Each is discussed below with an example.

## Synthesis steps

The number of synthetic steps, i.e. separate ‘pot’ reactions needed to prepare a catalyst, is often the major factor in the cost. It is common business practice to allocate overheads such as plant, buildings, marketing support and administration in terms of process hours. Labour costs are also counted in process hours. Therefore, the time taken to prepare a catalyst is crucial to the commercial viability. In general, each extra step will add more time on, so a three-step synthesis costs approximately three times a one-step synthesis. Good development work can reduce this cost, but in turn development is not free! So when considering a new catalyst it is worth bearing in mind how many reaction steps are involved in the preparation of the catalyst.

## Handling/sensitivity

The very nature of a catalyst implies that it is reactive or promotes reactivity. This is advantageous to the chemical process, but can be less helpful in handling, storing and preparing catalysts. A recent example is tri-tert-butylphosphine. This is a remarkably good ligand for palladium-catalysed coupling reactions. In the pure state, however, it is a low-melting, pyrophoric, air-sensitive solid. This makes it difficult, and therefore costly, to handle. There are various alternatives to handling the pure solid include pre-forming into complexes, such as  $\text{Pd}(\text{P}^t\text{Bu}_3)_2$  (**1**) or  $[\text{Pd}(\text{P}^t\text{Bu}_3)\text{Br}]_2$  (**2**), or forming a salt, e.g.  $\text{HP}^t\text{Bu}_3\text{BF}_4$ . These are a lot more stable and can be handled in air.



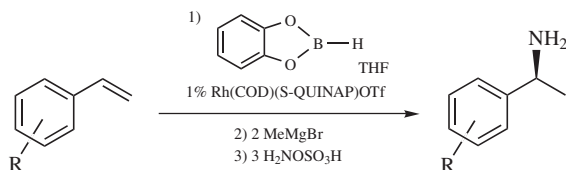
It is important to remember that, in general, organic reactions are run under an inert atmosphere for safety reasons (i.e. don't heat flammable solvents in the presence of air!). It is normally possible to handle liquids and solutions under anaerobic conditions, e.g. nitrogen atmosphere. Most industrial plants, however, are not set up to handle and transfer solids under anaerobic conditions. It is normal practice to ‘load’ the solids under air and then put under nitrogen by vacuum cycling or purging. This means that for most uses, solid catalysts must have stability for up to 30 minutes in air. Catalysts can be stored and supplied under nitrogen, so long term air-stability is less important. Therefore, an industrial definition of critical air-sensitivity of solids is: “can the activity be significantly affected by short-term (up to 30 minutes) exposure to air?”

## Availability

Another issue that affects cost is the availability of certain chemicals on an industrial scale. It is often the case that the cost and availability of a chemical in

a research catalogue do not reflect the situation on a larger scale. This can be illustrated in the following two examples.

Rhodium-catalysed hydroboration is a powerful tool for introducing chirality into a styrene-derivative. (Figure 1.1)<sup>[2]</sup> This was in competition to the established route based on chiral resolution using separation of diastereomers formed from reaction of the racemic amines with homo-chiral acids (natural pool). However, although the process appeared favourable from the chemical synthetic route, the process was practically impossible owing to there being no supplier of catecholborane on large scale at the time.



**Figure 1.1** Rhodium-catalysed hydroboration of a styrene derivative.

A second example is found in ruthenium-catalysed hydrogenation studies. A lot of the academic work is carried out using a catalyst generated *in-situ* from  $\text{Ru}(\text{benzene})\text{Cl}_2$  plus a ligand. This leads to industrial research starting from  $\text{Ru}(\text{benzene})\text{Cl}_2$ . However, most of the major suppliers of transition metal catalysts do not list the benzene complex as a sales product but do list the *p*-cymene complex,  $\text{Ru}(\textit{p}\text{-cymene})\text{Cl}_2$ . This is not due to any major chemical difference in the use or preparation of the two complexes. The complexes are prepared from the corresponding cyclohexadienes, and the *p*-cymene pre-cursor is approximately 10 times cheaper and available on larger scale. So unless there is a specific advantage of the benzene complex, the *p*-cymene complex is used in industrial applications.

### Preparation route

Another factor in the cost is the route of preparation. An example of this can be illustrated using two common palladium pre-cursors,  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$  and  $\text{Pd}(\text{PhCN})_2\text{Cl}_2$ . Again, in academic work it is common to see the benzonitrile complex used, presumably due to its slightly better solubility in a range of organic solvents. However, the acetonitrile complex has better crystallisation characteristics, and is therefore much cheaper to produce. So  $\text{Pd}(\text{MeCN})_2\text{Cl}_2$  is more common in industrial applications.

Other considerations are environmental impact and health and safety. Chlorinated solvents have a bad reputation, with carbon tetrachloride mostly banned owing to its carcinogenic properties, chloroform being phased out and questions over the use of dichloromethane. Therefore, complexes that require the use of chlorinated solvents in their preparation will entail either more care in the synthesis, or more development work towards alternative solvents. Either way more cost is involved.

### Cost of materials

Finally, more complex ligands will generally add extra cost. This can be illustrated in the field of palladium-catalysed coupling chemistry.<sup>[3]</sup> Within the literature two palladium-precursors dominate; Pd(OAc)<sub>2</sub> and Pd(dba)<sub>2</sub> (or Pd<sub>2</sub>(dba)<sub>3</sub>) (dba = dibenzylideneacetone). These are often interchangeable, with no simple pattern to which is more efficient. However, in an industrial setting, the cost of the ligands will affect the overall cost of the catalyst pre-cursor. The acetate ligand is derived from acetic acid, which is substantially cheaper than dba.

### 1.3.2 INTELLECTUAL PROPERTY RIGHT (IPR) ISSUES

When considering the costs of a catalytic process, it is impossible these days to ignore the IPR/legal aspects. With state-of-matter patents and process patents available world-wide, most catalytic routes run the risk of being 'covered' to some extent in a patent. If the process that it is wished to use has been claimed in a patent then there are two basic choices, after determining that it is not possible to avoid the patent by 'designing around'. Firstly some sort of license can be arranged. This commonly involves either paying a straight fee to gain access to use of the technology, payment of an amount linked to the volume/revenue generated from use of the technology, or negotiating some form of cross-licence. These can be considered as direct costs attributable to the process.

Secondly, the patent can be challenged. This obviously involves a direct cost of legal fees, which can be very substantial, and indirect costs of time delay and executive time involved. At all stages of the patent process, legal costs are incurred, both in writing and submitting a patent, and in assessing and applying for a licence or for patent revocation. The outflow of cash (ultimately of profit) from the chemical industry to the legal industry is evident at each point. This must be justified by the advantages of the patented system, and adds an extra burden on the choice of route.

Another possible 'indirect' cost of patented technology is the potential loss of control of the process. For example, if a pharmaceutical product of company A has just one synthetic route approved which involves a patented step controlled by company B, then there is potential for company B to exploit the position. This often leads to company A either paying extra legal fees to protect itself, or abandoning the technology. A real example of the control of patented technology is the industrial use of BINAP, which is one of the most versatile and active chiral ligands ever discovered. However, its industrial use has been limited as the patent has been strongly defended. Therefore the potential of the technology has been never fully realised. Often better chemical routes are abandoned due to the costs (direct and indirect) associated with the patents.

Patenting is a strong way of protecting a real or potential source of income. If a process is being run and revenue is being generated, then patenting can defend that income from other entrants. There is a growing tendency of patenting in academic institutions to try and generate future revenues for the researcher/department/institution.

### 1.3.3 SEPARATION COSTS

On using a catalyst in a process, by definition an extra component is being added to the reaction mixture. This means that to get a pure product, the catalyst must be separated at the end of the reaction. There are various strategies for this operation, which can be divided into pre-reaction strategies, such as immobilisation, and post-reaction strategies, including classical routes and selective or non-selective scavenging. Separation can be critical in making a process commercially viable.<sup>[4]</sup> This can be a major difference between academic work and industrial work. For example, many academic reactions end with a purification step *via* flash column chromatography. However, on larger scale chromatography becomes very expensive or impossible, with the volumes of solvents required being costly and certainly not environmentally efficient. Therefore the development of alternative separation techniques can often be the major hurdle in commercialisation of academic technology.

### 1.3.4 PRE-REACTION/IMMOBILISATION

Many catalysts are homogeneous, i.e. they react in the same phase as the substrates. One strategy to aid the separation is to immobilise the homogeneous catalyst onto a support that is heterogeneous to the reaction phase. The catalyst can then be physically separated easily. The important factors for an immobilised catalyst are:

1. The catalytic activity should be as close to the original homogeneous catalyst as possible.
2. The catalyst should not 'leach', i.e. it should stay attached to the support.
3. The support should add as little cost as possible to the catalyst

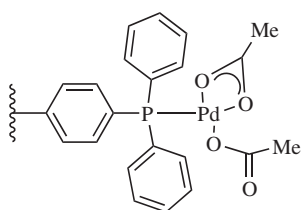
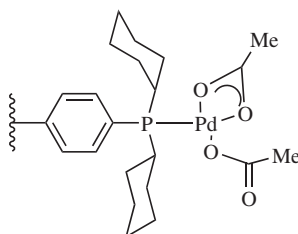
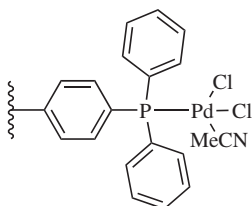
The issue of added cost can be reduced if the immobilisation allows the catalyst to be re-cycled. However, this is often complicated by the application of Good Manufacturing Practice (GMP) discouraging re-use of a catalyst in different batches of product (possible cross-batch contamination). Also, the catalyst is often more sensitive after the reaction, and filtration/storage can lead to catalyst de-activation.

Strategies for immobilisation include supporting the catalysts *via* a ligand, anchoring or absorbing onto a solid surface, and encapsulating the catalyst in a heterogeneous media.<sup>[5]</sup> An example that illustrates some of these concepts is detailed below.

#### **FibreCat<sup>®</sup>**

FibreCat<sup>®</sup> is a new generation of catalysts, which combine the selectivity of homogeneous catalysts with the ease of handling and separation of heterogeneous catalysts.<sup>[6]</sup> The catalysts are anchored to a series of functionalised fibres; the composition of the fibres can be modified to ensure compatibility with a wide range of solvent and reaction systems. FibreCat<sup>®</sup> catalysts demonstrate activities that are comparable to their homogeneous analogues.

FibreCat<sup>®</sup> catalysts consist of a polymer fibre that is inert and insoluble in all solvents to which functional groups, ligands and the precious metal can be added. The fibres are functionalised *via* graft co-polymerisation, which results in a high density of active functional sites being generated on the polymer. Further modification of the functional groups on the fibre is then possible to meet any linking requirements. It is also possible to have the reagents directly associated with the catalyst so that they do not need to be added to the process. The functionalised polymer can then be used as a support for particulate metal catalysts or for metal complexes that are active homogeneous catalysts. The range of products is suitable for many catalytic reactions, for example the FibreCat<sup>®</sup> 1000 series for carbon-carbon coupling reactions. These include: FibreCat<sup>®</sup> 1001, FibreCat<sup>®</sup> 1007 and FibreCat<sup>®</sup> 1026.

FibreCat<sup>®</sup> 1001PPh<sub>2</sub>-fibre/Pd(OAc)<sub>2</sub>FibreCat<sup>®</sup> 1007PCy<sub>2</sub>-fibre/Pd(OAc)<sub>2</sub>FibreCat<sup>®</sup> 1026PPh<sub>2</sub>-fibre/PdCl<sub>2</sub>/MeCN

### 1.3.5 POST REACTION – SEPARATION

There are many ‘classical’ separation techniques used in chemical processes. These are equally applicable to separating out catalysts.

Common techniques include:

- crystallisation of product or catalyst,
- distillation of the product,



- phase-separation using an added non-miscible component, e.g. solvent extraction,
- chemical treatment to destroy or precipitate the catalyst or product.

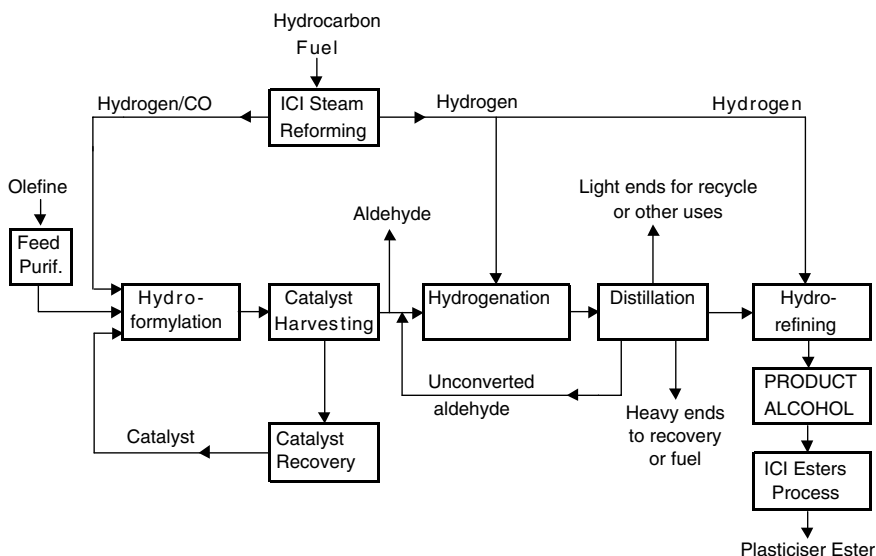
It is also common to use scavengers to remove catalysts from the product. These can be non-selective, i.e. absorbing both catalyst and product, or selective, i.e. targeting just the desired component/catalyst. Examples of non-selective scavengers include activated charcoal/carbon, silica, alumina and Keiselgel. Generally, column chromatography is not favoured in industrial applications.

There has recently been extensive development of selective scavenging systems. These include ion-exchange resins (beads), functionalised polymers<sup>[7]</sup> and functionalised silica. The scavengers can target the whole active catalyst, or just the metal or ligand components if desired. It is possible in some cases to remove the catalyst from the scavenger and recycle it directly.

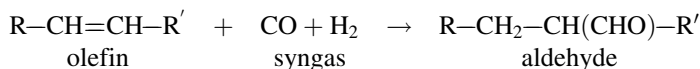
### 1.3.6 INDUSTRIAL EXAMPLES

Two examples are highlighted below where precious metal catalysts are used to produce fine chemicals on an industrial scale via carbon-carbon bond forming reactions. The first (a) is rhodium-catalysed hydroformylation in the ‘oxo-process’, which is a well established industrial process. The second (b) highlights a new process developed by Lucite involving a palladium-catalysed methoxy-carbonylation. Many of the points mentioned above in this article are illustrated in the examples, with efficient recycle of catalyst (precious metal) and the extra cost of ligands being justified by the costs savings of the novel chemistry.

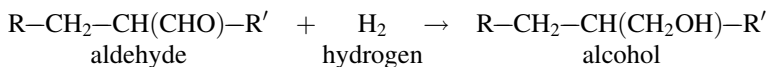
#### (a) Rh Oxo process (developed by ICI)



The Rh Oxo process comprises two main steps, hydroformylation followed by hydrogenation. The hydroformylation is carried out in the liquid/gas phase with a homogeneous rhodium catalyst. This is the carbon-carbon bond forming step.



This is followed by a hydrogenation reaction, which is carried out in the vapour or liquid phase over heterogeneous catalyst



### *Characteristics of unligated rhodium (I)*

In general, a rhodium catalyst is used as it efficiently converts olefin to alcohol:

e.g. Heptenes  $\rightarrow$  iso-Octanol, Octenes  $\rightarrow$  iso-Nonanol, Nonenes  $\rightarrow$  iso-Decanol

Unligated rhodium has the ability to hydroformylate a wide range of different olefins, both branched internal forms as well as linear. Virtually no water is used or created in the process (unlike a cobalt-catalysed system which needs water for catalyst recovery). Other key advantages of a rhodium (I) system are:

- Rhodium has very little hydrogenation capability, which minimises by-product formation. (Cobalt is an alternative hydrogenation catalyst, which leads to significant alcohol formation and causes the formation of acids and esters including formates).
- Rhodium produces only a low yield of heavy by-products (unlike cobalt).
- Rhodium is an isomerisation catalyst. This feature can be used or not by the correct choice of temperature.
- Rhodium is a highly efficient hydroformylation catalyst. It is only used in very low concentration typically 4 ppm (cf. 400 ppm cobalt catalyst).
- Approximately 1% of the olefin is hydrogenated to paraffin during hydroformylation.
- When hydroformylating a Linear Alpha Olefin (LAO), rhodium inserts the aldehyde group 52% onto carbon one (70% for cobalt) and 48% onto carbon two (30% for cobalt).
- Rhodium will hydroformylate LAOs to an aldehyde of sufficient purity to use directly to make derivatives, e.g. hydroformylation of a LAO C<sub>12</sub>-C<sub>14</sub> will produce:

Aldehyde	94% w/w (44.6% cobalt)
Light Ends	1.4% (3.7% cobalt)
Heavy Ends	3.9% (37% cobalt)
Formate	not detected (4.3% cobalt)
Alcohol	not detected (10.4% cobalt)

- The catalytic entity is a rhodium carbonyl species. To be present, this requires high partial pressures of carbon monoxide and hydrogen. Hence, hydroformylation with unliganded rhodium requires the use of high pressure (in excess of 200 bar).

As it is of significant value, the rhodium is recovered and recycled very efficiently and it has little environmental impact.

### *Characteristics of 'liganded' rhodium (I)*

By attaching a ligand containing a Group V element to rhodium, the stability of the Rh:CO linkage can be changed. Phosphorus was the element of choice. By attaching three phenyl groups to the phosphorus (triphenyl phosphine, TPP), the selectivity to linear aldehydes is enhanced. CO and hydrogen will attach to rhodium liganded with TPP and the complex is stable at low pressures unlike unliganded rhodium. If the pressure is increased, the CO displaces the TPP. This problem was solved by operating with a large excess of TPP to maintain the stability of the rhodium:TPP

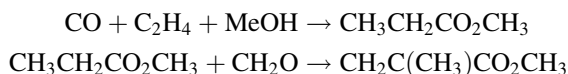
The presence of the large TPP group attached to the rhodium makes the rhodium less active catalytically. Hence, a higher concentration of rhodium is required and the process is used for hydroformylating the most active olefins. The large size of the rhodium:TPP species brings with it steric effects: for an alpha olefin, insertion of the aldehyde group is almost entirely on carbon atom one (> 90%); for branched, internal olefins, little or no insertion takes place. The liganded rhodium catalyst is retained within the plant, but at long intervals it is taken out for rhodium recovery and replacement with a new charge of catalyst.

### **(b) Methylmethacrylate process (Lucite's new homogeneous palladium-catalysed process)**

Methylmethacrylate (MMA) is the building block for a wide range of products. It polymerises easily to form transparent resins and polymers, e.g. kitchen and bathroom surfaces, co-polymerises with other monomers, and is used in paints and coatings.

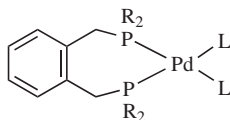
#### *Lucite's 'alpha process'*

This is a new technology developed by Lucite (formerly Ineos, formerly ICI).<sup>[8]</sup> It involves a two-step process: a liquid phase methoxy-carbonylation followed by a gas phase condensation.



The first step involves a homogeneous palladium-catalyst based on a chelating bis-phosphine (3). Some general features of the process are:

- 1 kg of catalyst will produce 200 tonnes of methyl propionate.
- Catalyst allows mild conditions: 10 bar, 100 °C.
- Virtually no by-products. Pilot plant in operation at Lucite, Teeside.
- 100,000 tonne/year plant planned for 2006.
- 20% cost advantage over conventional cyanohydrin technology.



R = <sup>i</sup>Pr, Cy, <sup>t</sup>Bu, Ph

Lucite's methylpropionate catalyst (3)

Key issues associated with the process are the efficient use of catalyst, high turn-over numbers, high selectivity of catalyst to prevent by-product formation, effective separation of metal from product in high yield and quick recovery of metal, refining and recycle as fresh catalyst.

## REFERENCES

1. *Asymmetric Catalysis on Industrial Scale* (ed. H.U. Blaser and E. Schmidt) Wiley-VCH, Weinheim, **2004**; *Metal-Catalyzed Cross Coupling Reactions* (eds. F. Diederich and P. J. Stang) Wiley-VCH, Weinham, **1998**; *Transition Metals for Organic Synthesis* (eds. M. Beller and C. Bolm) Wiley-VCH, Weinheim, **1998**.
2. C. M. Crudden and D. Edwards, *Eur. J. Org. Chem.*, **2003**, 4695–4712; J. M. Brown et al. *Chem. Commun.* **1997**, 173–4.
3. For advances in fine chemical synthesis using homogeneous palladium catalysts see: A. Zapf and M. Beller, *Topics in Catalysis*, **2002**, *19*, 101.
4. For example the recycle of palladium catalysts is very important in commercially-viable Heck-type reactions see: J. G. de Vries, *Can. J. Chem.*, **2001**, *79*, 1086–92.
5. For a recent review on asymmetric C-C and C-heteroatom bond-forming reactions using polymer-bound catalysts see: S. Bräse, F. Lauterwasser and R. E. Ziegert, *Adv. Synth. Catal.*, **2003**, *345*, 869–929.
6. S. Collard in *Catalysis of Organic Reactions* (ed. D. G. Morrell) Marcel Dekker, New York, **2002**, 49–60.
7. For example Smopex<sup>®</sup>, S. Buckley, *Speciality Chemicals*, October **2002**, 12–13.
8. (a) *European Chemical News*, 23–29 September **2002**, 29. (b) Clegg, W.; Eastham, G. R.; Elsegood, M. R. J.; Tooze, R. P.; Wang, X. L.; Whiston, K. *Chem. Commun.*, **1999**, 1877.