Chapter 14
N-Heterocyclic Carbene Complexes in Industrial Processes

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Abstract *N*-Heterocyclic carbene complexes produced on industrial scale are presented in this chapter along with a discussion about their production. Details of processes employing NHC complexes on pilot to industrial scales are discussed. These are frequently oriented towards the synthesis of biologically active molecules, however, examples are given for rubber formation and for 1-octene synthesis, a comonomer for polyethylene synthesis.

14.1 Introduction

The first academic publications introducing the concept of the use of *N*-heterocyclic carbenes as ligands in metal-catalysed applications appeared in the mid 1990s [1]. Since then, an increasing number of scientific groups have explored the scope of potential applications using NHC ligands (see Chapter 1, Fig. 1.1). Similarly to many other catalytic technologies, the time span between the original discovery and the entry of related technology in industrial laboratories is *ca.* 10 years. Currently, there only exists a limited number of publications on NHC complexes

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clearly describing large-scale applications. However, an increasing number of industrial players are filing process patents claiming and protecting the use of such catalysts for their respective applications. This clearly illustrates the great progress achieved by this ligand family that still was, not too long ago, a mere laboratory curiosity. However, NHC-based technologies are still in their early days in terms of industrial uses, and because most companies secure their IP (Intellectual Property) position, process information has not yet been, and might never be publicly disclosed. At this point, gathering information on industrial uses of NHCs proved to be a real challenge. To the best of our knowledge, to date only NHC systems based on ruthenium and palladium [2] have found entries into industrial applications.

In this chapter, we have compiled scientific papers, patent applications and other publicly available information related to large-scale use/commercial applications of ruthenium and palladium NHC complexes. It is not meant to be comprehensive with respect to all applications used to date due to the difficulty met when collecting information. However, this chapter provides a taste of what is currently done on what scale.

14.2 Production of NHC Complexes on Industrial Scale

14.2.1 NHC Complexes Produced on Industrial Scale

As mentioned above, transition metal NHC systems synthesised on industrial scale to date are, to the best of our knowledge, limited to palladium, ruthenium and recently silver [2]. These are listed in Fig. 14.1. For palladium complexes, four types are available: the naphthoquinone-bridged palladium (0) dimers of type **1**, the divinyldisiloxane adducts **2**, the chloride-bridged dimers of type **3**, the monomeric species of type **4** bearing an η^3-alkenic ligand (allyl or cinnamyl) and the 3-chloropyridine-adduct of dimers **3**, the PEPPSI-complexes **5** (PEPPSI: Pyridine-Enhanced Precatalyst Preparation, Stabilization, and Initiation). With respect to ruthenium complexes, there is a wider structural diversity of systems proposed on industrial scale: the benzylidene complexes **6** (Grubbs second generation) and **7**, the butenylidene complex **8**, the indenylidene systems **9** and **10**, the thienylmethylene complexes of type **11**, the ether-boomerang systems **12** (Hoveyda-Grubbs second generation) and the pyridinyl-propylidene complex **13**.

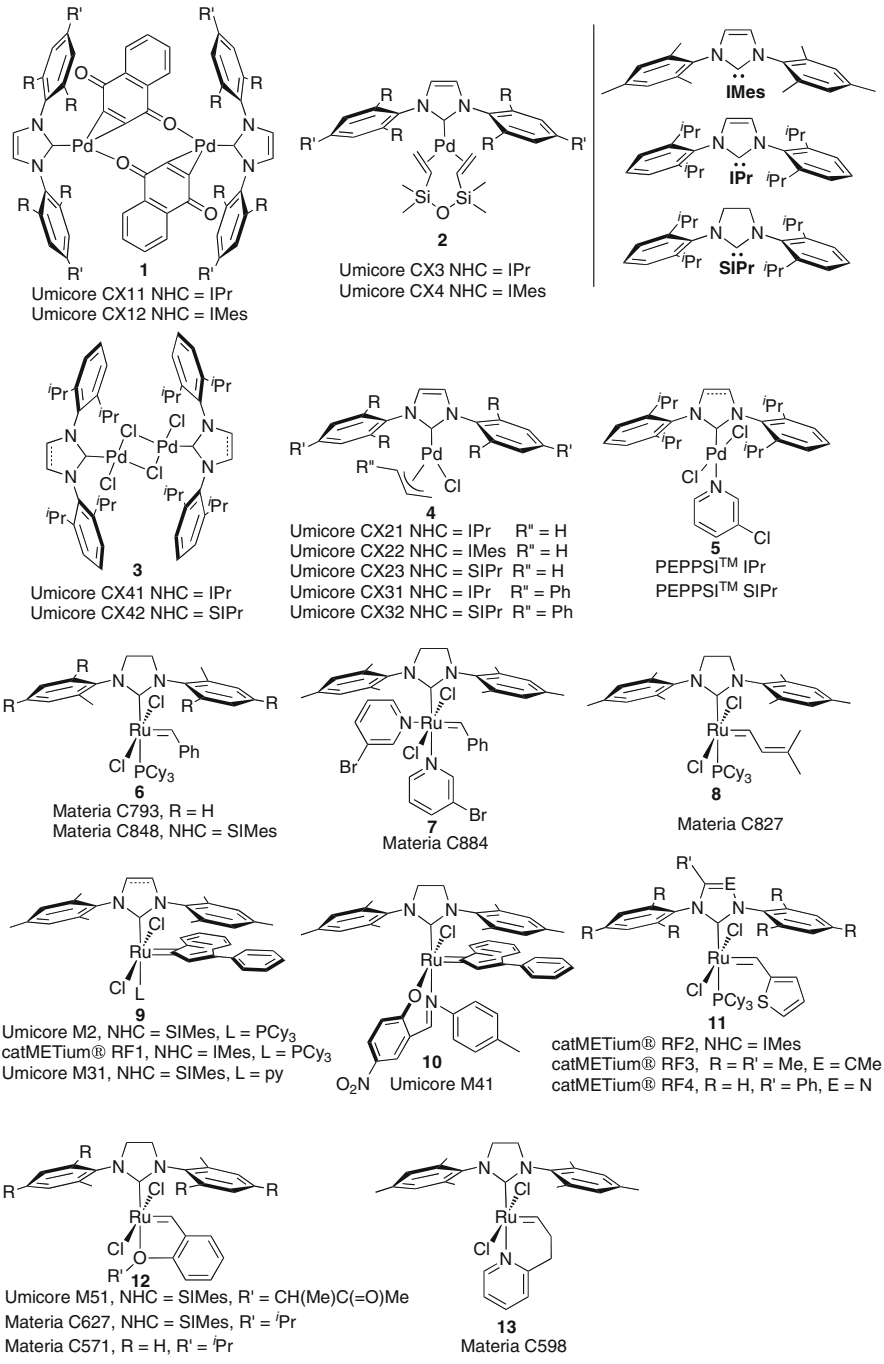

Fig. 14.1 NHC complexes produced on industrial scale

14.2.2 Production of NHC Complexes

Organometallic chemistry requires special techniques not only in chemical laboratories but also at the production scale. The capability of excluding air and moisture throughout a complete process is one main feature for the development of viable and reproducible synthetic protocols leading to the formation of catalytically active species. Whilst in a laboratory, a chemist has much freedom and flexibility in devising strategies for work-up and purification, manufacturing processes at production scale need to exclude any chromatographic purification steps for obvious economic reasons. Another manipulation that is not feasible, for economic reasons, is the evaporation to dryness for product isolation. Accordingly, all Umicore processes [3] are designed to crystallise the product allowing isolation in standard filtration apparatus. Further important aspects of a manufacturing unit for transition metal complexes, particularly when precious metals are involved, are the waste stream/mother liquor treatments. The flow scheme employed by Umicore is designed to directly treat the mother liquid to recycle precious metals in nearly quantitative yields. This ensures cost-efficient procedures for products at any scale. With respect to scale-up strategies, the Umicore approach involves statistical methods permitting the identification of relevant parameters and their optimisation. This allows to determine the possibility of scaling-up laboratory size experiments to 10 L scale using production process technologies. Once validated, the new process is tested on the pilot plant using reactors from 60 to 100 L. Thereafter, the process is transferred to the production unit with reactors >1,000 L (Fig. 14.2).

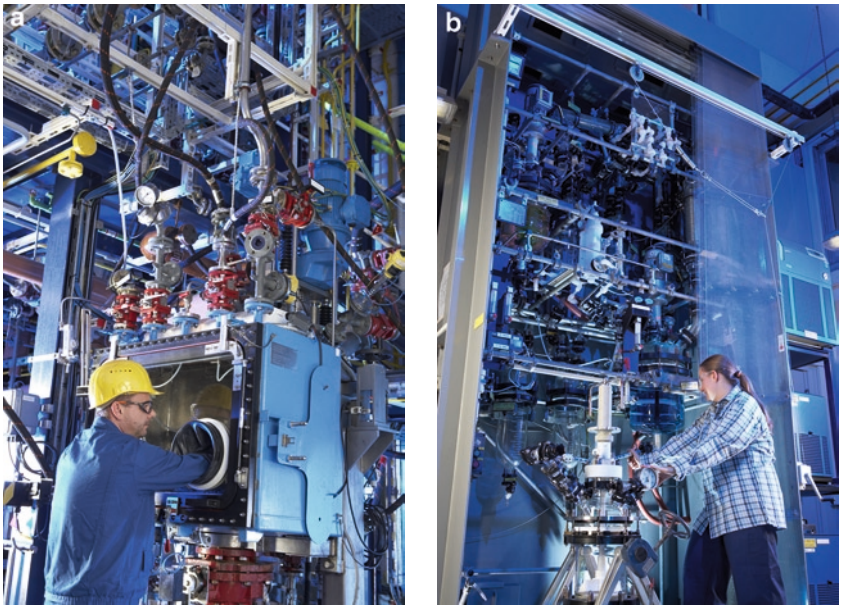

Fig. 14.2 (**a**) Pilot plant (**b**) Kilo-scale laboratory

While implementing production processes into multi kilogram batch sizes for NHC complexes (Fig. 14.1), a complete quality control of the imidazolium or imidazolidinium starting material was required. Therefore, Umicore has implemented large-scale manufacturing of the salts in-house, resulting in stable and reproducible synthetic protocols for the transition metal complexes.

14.3 Industrial Applications of Ru–NHC Catalysts

Ruthenium–NHC complexes exhibit activity in a very wide field of applications. Due to their unique ability to break and reassemble olefin bonds under reaction conditions very favourable to design simple processes, applications in nearly any chemical discipline can be foreseen. This field may span from manufacturing of specialty polymers and rubbers to pharmaceuticals, pharmaceutical intermediates, agrochemicals, fragrances, dyes, specialty chemicals for electronic applications or fine chemicals from natural feedstock and many more. Below are described Ru–NHC catalysed reactions applied from pilot to full commercial scale.

14.3.1 Ring Closing Metathesis (RCM) Reactions Used in the Pharmaceutical Industry

As a key transformation step, RCM is the most prominent and furthest advanced metathesis reaction technology in the pharmaceutical industry. It has been applied by several organisations on large scale to build up large rings that cannot be synthesised easily on an economically viable pathway using standard organic synthetic protocols. RCM permits these assemblies in fewer steps, thereby rendering a long linear synthetic route much less expensive with minimum waste.

14.3.1.1 Kosan's Epothilone Derivative KOS-1584

In 2002, Danishefsky and co-workers reported that 9,10-dehydro-12,13-desoxyepothilones inhibit the growth of tumour cells, and therefore were promising candidates for novel anticancer agents [4]. In a collaboration between Kosan Biosciences Inc. and F. Hoffmann-La Roche [5], the drug candidate KOS-1584 (R-1645) was developed and moved to clinical phase II. The initial Kosan process employed a Grubbs second generation catalyst, whilst Roche improved reaction yield by using an indenylidene-based ruthenium NHC catalyst (Fig. 14.1). The fact that KOS-1584 is undergoing clinical phase II trials means that large

quantities (several kg) of the active substance are produced. The process details have not yet been reported, however, it is likely that KOS-1584 has been synthesised using one of the mentioned catalysts (Fig. 14.3).

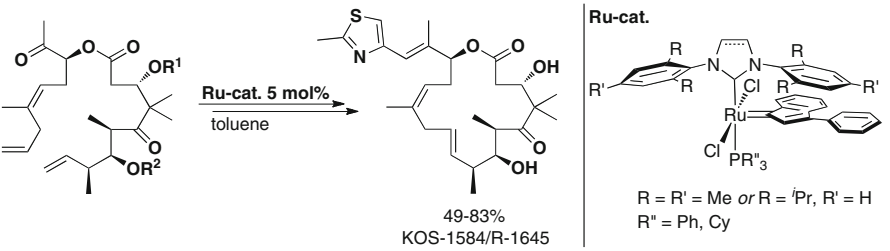

Fig. 14.3 Synthesis of KOS-1584/R1645by RCM

14.3.1.2 Glaxo Smith Kline SB-462795

The Glaxo Smith Kline (GSK) chemical process development group conducted a large-scale RCM reaction leading to the formation of a seven-membered ring. This moiety is a fragment of the molecular architecture of cathepsin K inhibitor SB-462795 [6], a drug candidate for the treatment of osteoporosis. This impressive piece of synthetic and process development work demonstrated the significant influence of the nature of the substrate on yields and on potential side-reactions while conducting RCM reactions. In summary, two synthetic strategies were explored, both involving as key-step a RCM of a chiral diallylic substrate. Both appeared suitable for further scale-up, one was selected and scaled to an 80 kg batch size with a relatively low catalyst loading resulting in nearly quantitative yields of the desired product. In this process, the complex employed is a boomerang-type catalyst (Fig. 14.4).

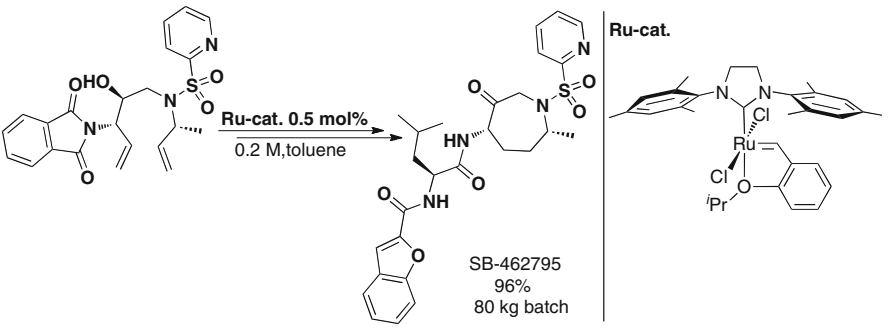

Fig. 14.4 Synthesis of Glaxo Smith Kline SB-462795

However, SB-462795 is no longer in the Glaxo Smith Kline development pipeline – most likely the reason why the GSK researchers were allowed to publish details of this process campaign.

14.3.1.3 Synthesis of HCV Protease Inhibitors

Independently, the Pharmaceutical companies Boehringer Ingelheim (BILN-2091) [7], F. Hoffmann-La Roche (ITMN-191) [8] and Tibotec Pharmaceuticals Ltd., a Johnson & Johnson company (TMC-435) [9] are or have been developing drug candidates for the treatment of Hepatitis C. While Boehringer Ingelheim was the first to successfully scale-up a RCM step to produce >100 kg substrate (using a first generation Hoveyda type catalyst *i.e.* not containing a NHC ligand) both Johnson & Johnson and F. Hoffmann-La Roche have been able to advance their drug development programmes to clinical phase I. We will remind the readers who are not familiar with the pharmaceutical jargon that clinical phase I would require multiple kilogram of active drug substance. There was therefore a need, in these campaigns, to scale-up the RCM step. Unfortunately, as is too often the case in pharmaceutical drug development, the Boehringer Ingelheim drug candidate failed in early clinical testing and resulted in a complete stop of the development of this molecule. Researchers of all three pharmaceutical companies have published, either in scientific publications or in patents, the details of the process chemistry. This chemistry represents a veritable Herculean endeavour, the chemistry evolving from these targeted molecules is simply first rate and teaches much about conformation directing RCM reaction. We strongly encourage the Reader to browse this literature to fully appreciate the intricacies associated with what looks on paper like a simple RCM transformation [10]. In brief, the main achievements for all drug candidates deal with solving the serious initial problem of having to conduct the RCM reaction at high dilutions. Considering the space/volumes requirements in an industrial setting, such high dilutions are costly and impractical, but mostly economically costly. If the reaction was conducted in high concentrations, undesired oligomers/polymers formed which reduced the valuable starting material into waste side-products. High dilution was therefore initially required. The process researchers, after much effort, succeeded in conducting RCM reactions (forming macrocycles possessing ring size of >12) to acceptable concentration levels of up to 0.5 M. This represents a significant advance as the initial Boehringer Ingelheim campaigns required dilutions of 0.01 M. These made use of a first generation metathesis catalyst (non-NHC bearing). All along the aim was and is to conduct the RCM reactions at highest possible concentration to project manageable throughput and reactor capacity use and efficiency. These groups have been able to reduce catalyst loadings significantly to levels of below 0.5 mol% ruthenium loading, another significant achievement, made possible by second generation ruthenium catalysts (NHC-bearing). The Roche and Johnson & Johnson drug candidates have entered clinical phase IIb in 2009 (Fig. 14.5).

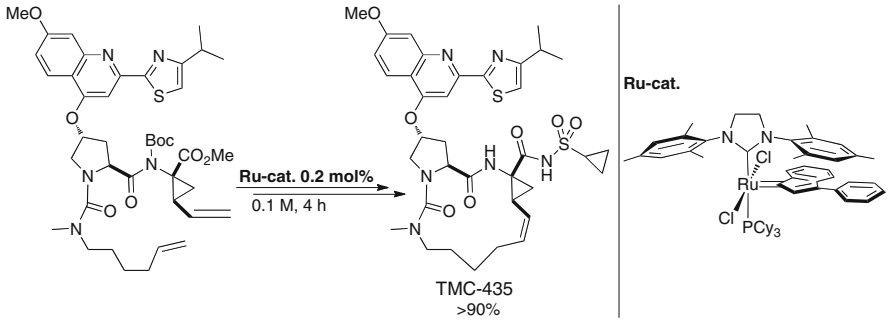

Fig. 14.5 Synthesis of Johnson & Johnson TMC-435

14.3.2 Cross Metathesis of Nitrile Rubber with 1-Hexene

In a series of patents, Lanxess has described its process for manufacturing Hydrogenated Nitrile Butadiene Rubbers (HNBR) with improved properties [11]. By a metathetical degradation of the nitrile rubber in a cross metathesis step with 1-hexene, the resulting HNBR exhibits a lower molecular weight distribution hence also a lower viscosity. This new "Therbane AT" (AT = Advanced Technology) exhibits improved processability in subsequent moulding practices. With different Therbane AT grades, large volume mould with more sophisticated structures can be filled in less time. The patents describe the use of NHC–Ru catalysts.

14.4 Industrial Applications of Pd–NHC Catalysts

Palladium-based homogeneous catalysts are used frequently on large scale in various industries. For instance, the Suzuki-Miyaura, Mizoroki-Heck and Sonogashira coupling reactions are used to synthesise pharmaceutically active ingredients and fine chemicals (see Chapter 6). In the bulk and commodity chemicals sector, there exist two major palladium-based processes, namely the synthesis of methyl methacrylate in the recently introduced Alpha Technology process of Lucite [12], and a process carried out by Dow Chemical for the synthesis of 1-octene. Both processes have an output of > 100,000 metric tons of product annually, both however are performed using a palladium catalyst bearing phosphines as ligands, the *Old Guard*. However, the telomerisation of butadiene involved in the 1-octene process was demonstrated by Oxeno on pilot-scale with Pd–NHC system [13]. On the pilot-scale, more than 25 metric tons of product have successfully been produced with an extremely low catalyst loading, using [Pd(IMes)(dvds)] as catalyst (Fig. 14.6). In spite of these very promising results, the IP (Intellectual Property) owner has not yet decided to implement the technology into a running large-scale process.

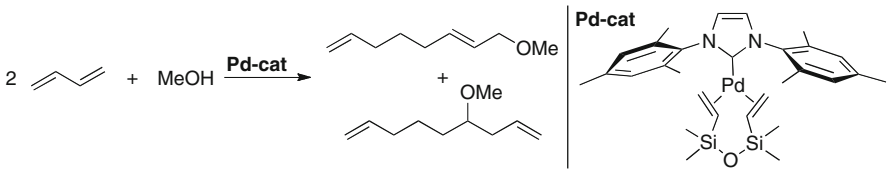

Fig. 14.6 Oxeno telomerisation of butadiene

14.5 Conclusions

The uses of NHC-metal complexes in industrial applications might appear at a very early stage by the relatively few examples provided in this chapter. However, it is clear that much information has not been publicly disclosed for obvious industrial interest reasons. The few examples provided show how efficient the catalysts can be, and how low a catalyst loading can be achieved in large-scale production. Many more larger-scale applications are being carried out using metathesis reactions in their many incarnations, of that we are certain. This initial industrial perspective is hopefully intriguing enough to warrant a further description of the area in a few years. The NHCs have so far caused quite a stir in industry and we can safely say that more will come of these robust ligands.

In view of a future edition, the authors welcome any information that could assist to update the field of use of NHC complexes on industrial scale.

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