http://dx.doi.org/10.1595/147106712X631984 •*Platinum Metals Rev.*, 2012, **56**, (2), 140–142•

FINAL ANALYSIS

Biological or Chemical Catalysis?

A common question asked by process chemists is "Do I use a biocatalyst or one based on a transition metal?". The choice can be an important part of route scouting (1). Unlike many articles that leave the reader waiting to the end, here is the answer: "It depends".

The advantages of using a catalyst rather than a stoichiometric reagent can be summed up by the concepts of 'green' chemistry (2), but the simple way to look at the catalytic approach is that less of a catalyst is used compared to a stoichiometric reagent, so the cost of the material and its removal is reduced.

In the past, processes were designed by chemists who had little familiarity with biotransformations and enzymes. Thus, the use of an enzyme was a means of last resort (3). Now, many companies have process groups which include members who are familiar with enzymes and biotransformations. Indeed, to those who are familiar with biological systems, they seem to be the solution to most problems!

Background Knowledge

One of the criteria for the choice between bio- and chemical catalysis is background knowledge. Our understanding of chemistry is far from complete. However, there is a wealth of information available and the key parameters to control the reaction outcome are known for a wide range of transformations. This knowledge has often been gained by trial and error. As our knowledge has increased, better and more selective catalysts have been developed. Even if we still cannot design the ultimate catalyst from first principles, we can use prior knowledge to obtain a workable catalyst.

For biological systems, trial and error has again been used, but often there are subtle differences between very similar enzymes so that interpretation of the results can be difficult. Examples of this are provided by baker's yeast reductions and pig liver esterase. More recently, our understanding of active sites and how to manipulate them either in a controlled or random way has allowed for the expansion of biomethods to make useful compounds.

Modern screening methods make it almost as easy to determine whether a chemical or a biocatalyst is capable of the desired transformation. However, chemical approaches will often require a more involved analysis, such as high-performance liquid chromatography (HPLC). Although biocatalysts may also need this type of analytical method, much faster methods have been developed and even the survival of the strain can be used.

An Exclusive Approach

Closely related to this consideration is the ability of one system to perform a transformation that is very difficult for the other to accomplish. Examples are the hydrolysis of a *meso*-diester and the coupling of aryl groups. In the first case, chemical catalysts have been developed to hydrolyse just one ester group of a diester to provide a chiral monoester. In contrast, there is a wealth of information on enzymatic examples and for some, as with pig liver esterase, a mnemonic has been developed to predict whether the reaction can be performed with 'wild-type' enzyme and what the stereochemical outcome will be (4).

In the example of aryl couplings, there are many examples and variations of palladium-catalysed Heck and Suzuki reactions (5, 6), to name but two of these types of reaction; these approaches are the methods of choice in most cases. There are very few examples of enzymatic aryl couplings and, thus, this will only be used when alternative chemical methods are not applicable.

Solvent Choice

Another criterion used to decide what type of catalyst is used is that the process must include isolation of the product in acceptable yield and purity. Although significant advances have been made for the use of enzymes in the presence of organic solvents and with substrates that are poorly soluble in aqueous media, problems can still exist. Conversely, if the product is very water soluble, isolation of the desired material can present a significant challenge. Chemical transformations usually have the advantage of a

number of solvent systems being available to perform the transformation and subsequent isolation.

Scaling Up

The scale-up of chemical catalytic reactions is usually an exercise in normal process chemistry. Synthesis of the ligands and transition metal catalyst usually present few problems, as the amounts are much lower than for the reaction itself. However, to improve specificity and efficiency new catalysts have to be prepared and tried. This can be a time-consuming exercise. On the biocatalytic side, modifications to the original enzyme can be made by genetic modifications and rapid screening. This allows selectivity, stability and other issues to be addressed. On the other hand, these studies can be time-consuming and may require more resources than just making a new ligand.

Cost and Speed

The criteria of cost and speed also contribute to the choice of catalyst system. In the early stages of development of a drug candidate, speed is of the essence but cost is still important. Precedence and the availability of the catalyst will be key factors. For larger scale work, the pendulum may swing from a chemical method to a biocatalytic one. For commercial production, biological routes are often cost effective.

However, it must be remembered that the catalytic step is usually part of a synthetic sequence. The substrate for the catalytic step has to be prepared and the product converted to the final target molecule.

As an example, consider the synthesis of (*S*)-2,3-dihydro-1*H*-indole-2-carboxylic acid. It was necessary to replace an inefficient route that used a late stage resolution. Many alternatives were considered but the most efficient used a copper-catalysed cyclisation to form the product. To prepare the substrate for this reaction, three enzymatic approaches were identified (**Figure 1**). When the alternative methods were compared in terms of costs and efficiencies (including the number of steps), the ammonia lyase approach was the route of choice as the starting material is readily available (7, 8). Although there are a number of approaches to *ortho*-halocinnamic acid (8), the Heck reaction provides an efficient synthesis. Without the use of this palladium-catalysed reaction, the remainder of the sequence would not be efficient. Thus, the overall sequence shows that biocatalysts and chemical catalysts are required to effect an efficient, sustainable process.

Conclusion

In summary the choice between a chemical and a biological catalyst depends on many factors. The background literature plays an important role, as

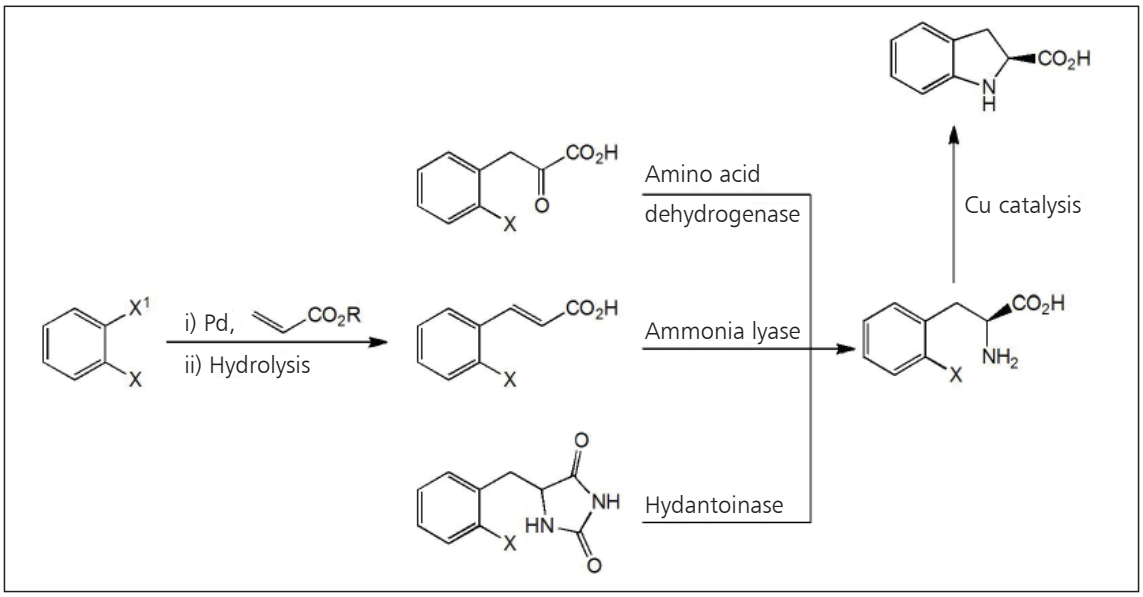

Fig. 1. Some routes to (S)-2,3-dihydro-1H-indole-2-carboxylic acid

does cost and speed to implement the process. There are some transformations where both types of catalysts excel. Chemical catalysts can work well with a specific and well documented range of substrates, and in particular palladium finds wide use in essential reactions such as Heck coupling. Enzymatic approaches can have a broader application but may be less well understood. In the end, both transition metal catalysts and biocatalysts may be required to produce an efficient process.

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