Microwave-Enhanced Palladium-Catalysed Reactions

Microencapsulated palladium has been shown to be compatible with microwave heating, offering benefits such as increased yields, higher purities and simple work-up procedures, and permitting access to many previously unattainable molecular assemblies.

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Dr Ian R Baxendale holds the Royal Society Wolfson Fellowship and is a Fellow of Sidney Sussex College, University of Cambridge. As the Director of New Technologies, he heads a new laboratory under the control of Professor Steven V Ley, aimed at process intensification and cleaner solutions to synthetic chemistry problems.

Dr Mike Pitts is Project Leader for microwave technology at Reaxa Ltd (Manchester, UK). Reaxa is a technology company addressing the chemical synthesis priorities of the life sciences and chemical industries – safety, cost-effectiveness and sustainability. The company grew from a partnership between industry and academia that set out in the mid-1990s to develop cleaner homogeneous catalysis; the programme was shared between Cambridge University, AstraZeneca, Syngenta and Avecia Pharmaceuticals. Following initial product launch at CPhI 2003, Reaxa was spun out of Avecia in mid-2005, and is now a combined venture between its management team, Cambridge University, Avecia and private investors. Dr Pitts's first degree was in Chemistry at Loughborough University, after which he completed a PhD with Professor Chris Moody at the University of Exeter, and a postdoctoral stay at the University of Vienna with Professor Johann Mulzer.

Given regulatory imperatives, the increasing complexity of new drugs and the rising cost of production, technological advances are becoming increasingly essential in pharmaceutical process operations. These include technologies to reduce impurities, increase production speed via automated processes and which use cleaner processes for a lower environmental burden.

Precious metal catalysis has evolved as a mainstay in pharmaceutical production over the past decade. In particular, homogeneous palladium-catalysed processes now represent a significant proportion of the 'high-value' reactions regularly utilised by the fine chemical and pharmaceutical manufacturing industries.

Processes for carbon-carbon and carbon-heteroatom bond formation have become established pivotal transformations in the synthetic chemist's tool-kit. Such methods are mechanistically well understood, tolerant of a wide range of functional groups and can be used to construct a variety of complex molecules.

However, there is a concerted need for practical and economical translation of these techniques into large-scale, environmentally sustainable manufacturing processes. Efficient recovery and re-use of catalyst, safe handling and precious metal contamination of products are all key concerns when employing such processes. In fact, economic work-up of platinum metal group (PMG) catalysed reactions is often overlooked until surprisingly late in a development process.

Aside from stringent heavy metal limits set for APIs (active pharmaceutical ingredients) by regulatory bodies such as the FDA, metal contamination of intermediates in a process can also be a serious issue for the manufacturer due to interference with downstream chemistry. Furthermore, waste stream contamination increases disposal costs and aqueous pollution can seriously affect water treatment plants.

In addition, the prevention of deposited palladium zero (so called palladium mirror formation) in the reactor vessel is a significant issue resulting in a potentially costly reactor clean-down and recommission.

The industry has pioneered numerous approaches to facilitate the removal of catalyst contaminants, although many offer only limited levels of success (1). The relatively simple and effective research approach of using specific metal scavenger resins has – in general – not been widely adopted by the process scale manufacturing groups. A number of reasons are cited for this such as the relatively high price and lack of availability at scale, coupled with regulatory concerns and poor integration into existing chemical plant processes. These issues have been addressed with the introduction of QuadraPure™ resins, facilitating highly efficient scavenging of low level metal contaminants in a GMP manufacturing process.

Although such resins represent a significant technological and economic development, a more sustainable solution would be to avoid generating the metal contamination problem in the first place. The traditional way to achieve this has been to maximise the efficiency of the homogeneous catalyst. However, over recent years, the introduction of immobilised homogeneous catalysts such as the Pd EnCat™ range has provided the chemist with an attractive alternative strategy.

MICROWAVE-ENHANCED CHEMISTRY

Microwave assisted chemistry is an increasingly important tool in the medicinal chemist's quest to speed up drug discovery (2). With the development of commercial focussed microwave reactors, reactions can be carried out safely and reproducibly at a useful laboratory scale. These systems have been quickly integrated into library synthesis, and increasingly lead candidates have been prepared *via* a route that involves at least one microwave assisted step.

Transition metal catalysed reactions particularly lend themselves to microwave heating, since the transition states and reaction intermediates involved readily absorb microwave energy due to their highly polar nature. Such species tend to have longer life-times than the frequency of energy input, and thus gain energy more quickly than it can be dissipated – creating a non-equilibrium state and a resulting increase in reaction rate. These reactions tend to proceed in minutes as opposed to hours under conventional conditions, with significantly reduced (thermal) side reactions.

Microwave heating has successfully been used to make palladium-catalysed reactions more economic and increasingly environmentally friendly. For Suzuki couplings, it has been shown that 'ligand-free' reactions are possible in simple cases and that water can be used as a solvent. As lower and lower levels of palladium were employed (3), it was successfully shown by Leadbeater (4) that levels of palladium below those specified for APIs were capable of mediating certain Heck and Suzuki couplings of aryl bromides in aqueous media (Figure 1).

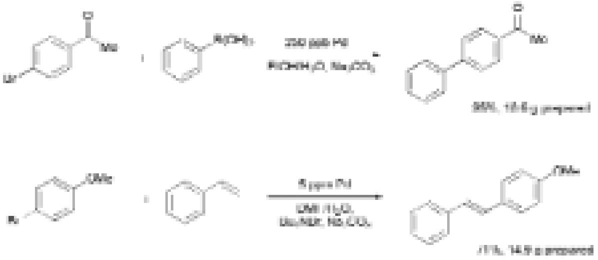

Figure 1

Clearly such conditions would be highly desirable for GMP manufacturing, but they suffer from certain substrate limitations. Poor conversions were obtained when using aryl chlorides or deactivated aryl bromide, restricting the applicability of the methodology. Leadbeater was forced to move to palladium on carbon (also using water as a solvent) to efficiently couple these cheaper and more readily available aryl chlorides (5). To further increase the efficiency and selectivity of this reaction, the technique of simultaneous cooling was employed (6). The method involves passing

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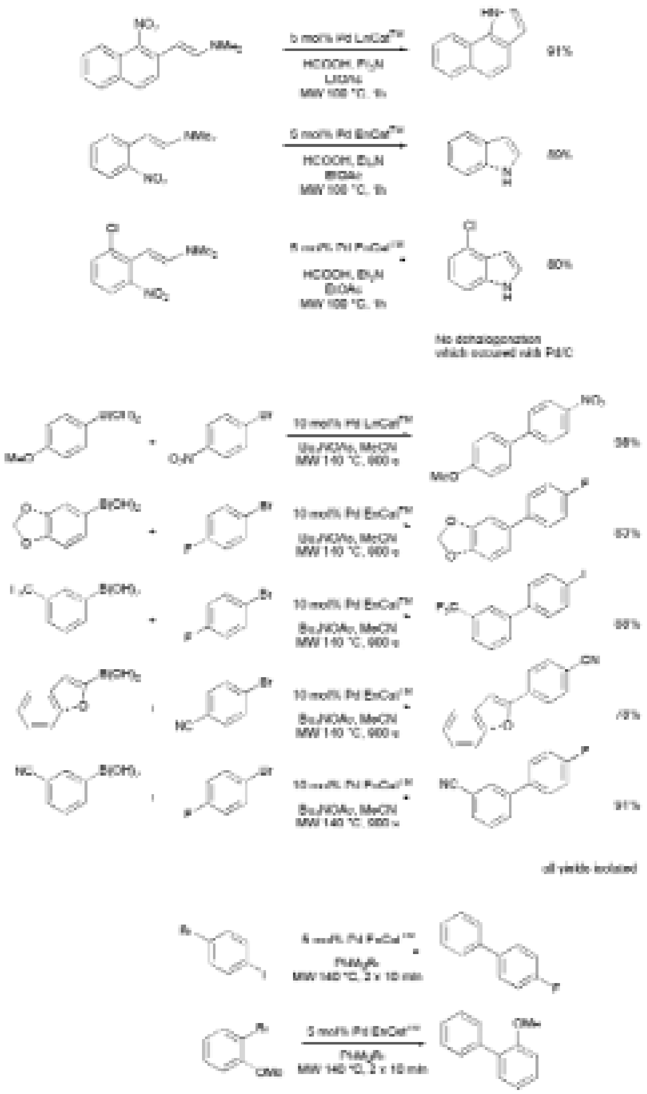


Figure 2

a stream of compressed air over the reaction tube during microwave irradiation. This cooling effect reduces the thermal energy in the mixture and allows a reaction to run at a lower bulk temperature for the same microwave energy input as without cooling. Side reactions and degradation of starting materials are thus often reduced.

MICROENCAPSULATED PALLADIUM

Difficulties in increasing the substrate range while keeping palladium levels to a minimum can be overcome by using microencapsulated palladium. The palladium EnCat™ range of catalysts represents a versatile family of microencapsulated palladium(II) and palladium(0) catalysts offering many of the benefits of homogeneous catalysts, but with the ease of handling and recycle potential of heterogeneous catalysts. Very low metal contamination of product and waste stream has been demonstrated with this technology under conventional conditions (7).

The key feature of the polyurea encapsulation approach is the ability of the microcapsules to retain the palladium by virtue of the ligating functionality of the polymer. Indeed, the reaction appears to occur within the pores of the resin bead, rather than the palladium leaching into solution to mediate the reaction.

Palladium EnCat™ has been shown to be compatible with microwave heating, and offers excellent conversion allied to compatibility with a wider range of functional groups. With microwave heating, it has been demonstrated being utilised within the Leimgruber-Batcho indole syntheses (nitro reduction) (8), and has also been applied to Suzuki and Kumada cross-coupling reactions (Figure 2). Interestingly, using the EnCat™ catalysts negates the requirement for additional co-ligands and avoids the use of sensitive palladium(0) catalyst in facilitating the Kumada reaction. Indeed, this is being discovered as quite a general occurrence for many additional palladium-mediated transformations.

In addition, the synergistic benefits in terms of increased yields, higher purities and simple work-up procedures derived from the use of the Pd EnCat™ with microwave-induced heating techniques are permitting access to many previously unattainable molecular assemblies. Reactions that were historically problematic, or substrate combinations that represented inferior yielding transformations, are now possible through the adoption of these two complementary technologies.

PEROVSKITES

Another synthetically useful form of immobilised palladium, again with extremely low leaching characteristics, are the Pd doped Perovskites which have recently been introduced to the industry (9). These materials have been shown to be very active in palladium-catalysed reactions, with the catalytic levels of palladium very low (typically 0.05 mol%).

Again, use of microwave heating broadened the range of substrates capable of undergoing Suzuki reaction, and allowed the coupling of aryl chlorides in a ligand-free

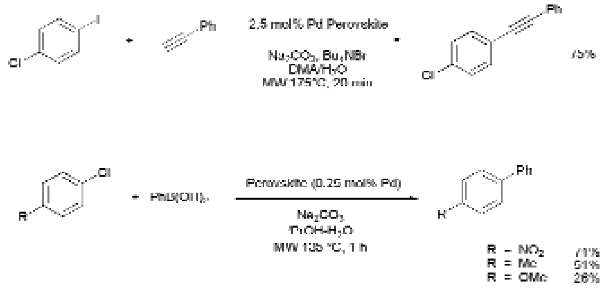


Figure 3

system (Figure 3). Their use in the Sonogashira and Ullmann reactions has also been demonstrated (10). These early results show Perovskites to be extremely useful and versatile catalysts. Further optimisation and extension of the described chemistries of these systems is underway.

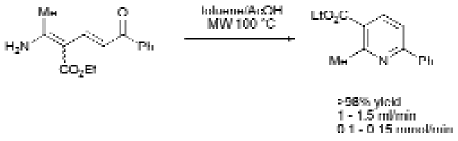
FLOW REACTORS

Microwave chemistry is ideal for adoption into a flow process, since the reaction times (and therefore residency times in the reactor) are short. Such methods open up the possibility of carrying out reaction sequences in an automated flow system, with in-line clean-up and purification. As with microreactor technology, such systems can be 'scaled-out' to approach the processing requirements for manufacture, without the need for further optimisation.

Progress towards such systems is underway and will be an area of increased development activity over the next few years. In recent work, the Discover® reactor (CEM) has been equipped with a 10ml vessel adapted to allow reagents to be pumped up through a packed bed with laminar flow through the channels of the packing material (11). The Bohlmann-Rahtz pyridine synthesis (condensation) was exemplified in the apparatus, using sand as the packing agent (Figure 4).

A non-benign packing agent could potentially be utilised in this system, such as an immobilised reagent or catalyst.

Figure 4



A (non-microwave) continuous flow arrangement with Pd EnCat™ has been already demonstrated by Holmes and Ley (12). Additional work is soon to be published that describes the extension of this approach to a microwave heated EnCat™ packed-bed flow reactor system.

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