Progress in nano and flow chemistry reshaping the production of fine chemicals and drugs

BIOMATERIALS & NANOMATERIALS

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Due to low turnover numbers, leaching of the metal and quick catalyst deactivation, industry -- eminent colleagues wrote in a presigious journal in early 2016 -- would not use immobilized transition metal complexes as catalysts (1).
Joint progress in flow chemistry and in the application of nanochemistry to catalyst making, however, is actually reshaping the way the fine and the pharmaceutical industries produce the active substances for which they exist.
Writing in a recent issue of OPRD, a team of academic and industrial chemists based in Germany and in the UK, lately provided a nice example (2).

(Rh/(*S*,*S*)-EthylDuphos) immobilized on composite support enabling the scale-up of asymmetric hydrogenation of an enamide under flow

The team used an heterogenized Rh chiral metal complex (Rh/(*S*,*S*)-EthylDuphos) to mediate the asymmetric hydrogenation of an enamide under flow on kilogram scale with constant high single-pass conversion (>95.0%) and enantioselectivity (>98.6% ee).
They identified and optimized the (nanochemistry) factors affecting the long-term catalyst stability and enantioselectivity so that catalyst leaching in the product was reduced to < 1 ppm, while obtaining a virtually metal-free product stream with a space time yield of up to 400 g L^{-1} h^{-1} (1 kg of enamide fully hydrogenated in 18 h) meeting at the same time product purity and green chemistry requirements, as downstream purification is no longer required while the expensive catalyst is smoothly reused.

In further detail, the catalyst was anchored on a commercially available composite of phospho tungstic acid and alumina as the support, previously dehydroxylated at 200 °C under vacuum with regular argon flushes. It is enough to pump an ethanol solution of the organometallic Rh^+ catalytic species, through a rubular reactor containing the dehydroxylated support, to entrap it by ion exchange (Figure 1), and obtain a solid catalyst of exceptional robustness. The asymmetric hydrogenation of 1 kg of the enamide dissolved in THF (0.11 g/mL), delivered at 9 mL/min, was carried out at 25 °C and 10 bar, with H_2 supplied at 870 mL/min (molar ratio H_2: substrate = 6.75) via a mass flow controller.

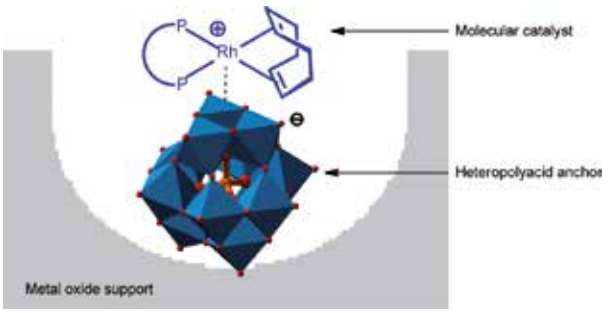

Figure 1. Augustine's anchoring of the Rh+ molecular catalyst to alumina used as solid support via phosphotungstic acid as heteropolyacid linker
(Reproduced from Ref.2, with kind permission).

SiliaC*at* DPP-Pd mediating cross-coupling reactions of fundamental industrial relevance under flow

Many other companies are pursuing the same approach, using different supported catalysts. Alcázar and his team at another pharmaceutical company in co-operation with academic scholars in Spain, use sol-gel entrapped molecular catalysts (SiliaC*at* DPP-Pd) to mediate under flow cross-coupling reactions of fundamental industrial relevance (3). Again, the continuous reaction over the solid catalyst does not require catalyst separation from the product, drastically reducing solvent utilization, while providing increased yields of valued products at a much faster rate than in the homogeneously catalyzed process in a batch reactor.

Due to the low metal leaching (30 ppb), the catalyst could be used in more than 30 reactions and for more

than 8 h of continuous Suzuki-Miyaura cross-coupling reaction between (4-methoxyphenyl)boronic acid and 1-bromo-2-methylbenzene over 1 g of fresh catalyst kept in the reaction cartridge, without a noticeable decrease in reactivity (Figure 2).

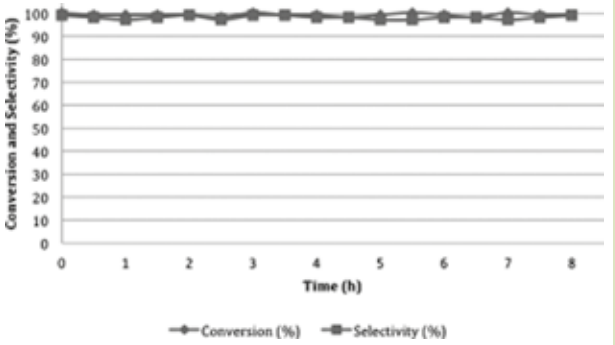

Figure 2. Suzuki-Miyaura cross-coupling reaction between (4-methoxyphenyl)boronic acid and 1-bromo-2-methylbenzene mediated by SiliaCat DPP-Pd for 8 h (Reproduced from Ref.3, with kind permission).

Showing the versatility of the method, furthermore, different halides or pseudo-halides and organoboron compounds could be used without having to modify the standard procedure.

Several other new generation catalytic materials exist that have been successfully applied to organic syntheses under flow of significant industrial relevance, very often as the outcome of scientific cooperation between academic and industrial researchers.

In brief, the economic, technical and environmental advantages are so numerous that chemical companies lately started to use flow chemistry in their pharmaceutical production plants (4). The next step will be to move from homogeneously to heterogenously catalyzed processes. It will happen.

What remains to be done is to merge nano-, flow and green chemistry education in the renewed curriculum of chemistry students across the world teaching them in a practical way how to harness the advantages of new chemical science and technology (5).

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Corning® Advanced-Flow™ Reactors (AFR) launches Lab Reactor System

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