

# A New Series of Catalysts for Deprotection Reactions



## Johnson Matthey Catalysts

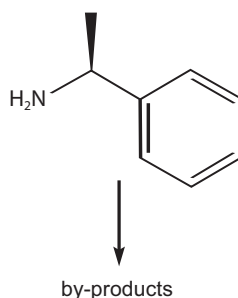
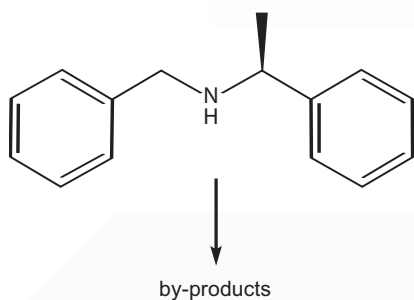
Very often, synthetic organic chemists are required to protect reactive functional groups such as hydroxy and amino groups to minimise the side reactions during a synthesis. Many protecting groups have been designed to allow cleavage by catalytic hydrogenation and can be performed with good selectivity, typically under mild conditions, using a palladium/carbon catalyst in the presence of hydrogen gas or a hydrogen-transfer agent, e.g. ammonium formate, IPA. One of the most robust deprotection catalysts is Pearlman's, 20% Pd(OH)<sub>2</sub>/C, a well established standard for N-debenzylation. However, a major drawback of this catalyst is the cost associated with the significantly high palladium metal loading. Many users have invested considerable resources to find more economical alternatives.

## N-Debenzylation

As part of our **Catalyst Innovation Program**, Johnson Matthey has recently developed a line of catalysts specifically for deprotection reactions. This series has been optimised to provide improved catalytic activity and/or selectivity with palladium metal loadings as low as 5%. These catalysts are designed to work at low pressure and moderate temperatures.

Debenzylation of *N*-benzyl-*N*- $\alpha$ -methylbenzylamine represents the first in a series of reviews presented by the Heterogeneous Catalyst Development Team of Johnson Matthey.

### DEBENZYLATION OF *N*-BENZYL-*N*- $\alpha$ -METHYLBENZYLAMINE



### Reaction Conditions

Temperature: 50°C

Pressure: 3 bar

Screening - HEL Chemscan 8x15 ml Hastelloy reactor system.

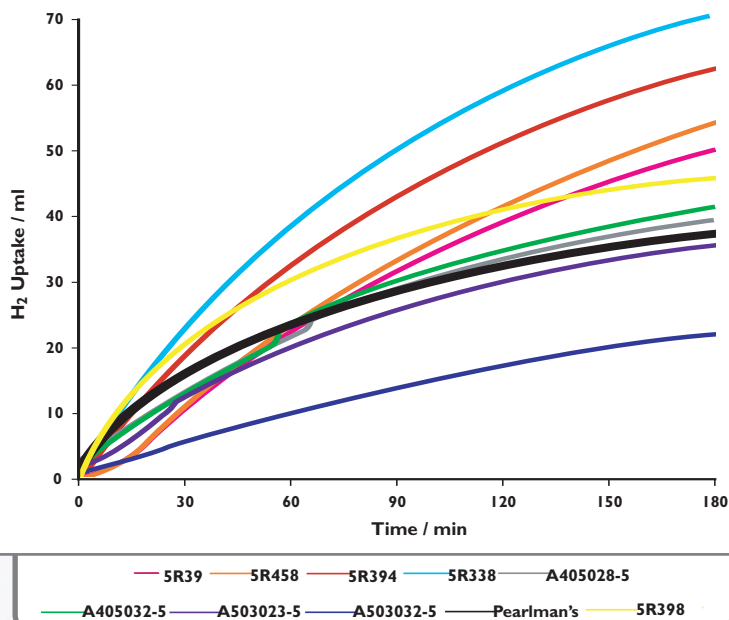
Reaction-profiling - Buchi 100 ml stainless steel autoclave.

### Catalyst Activity

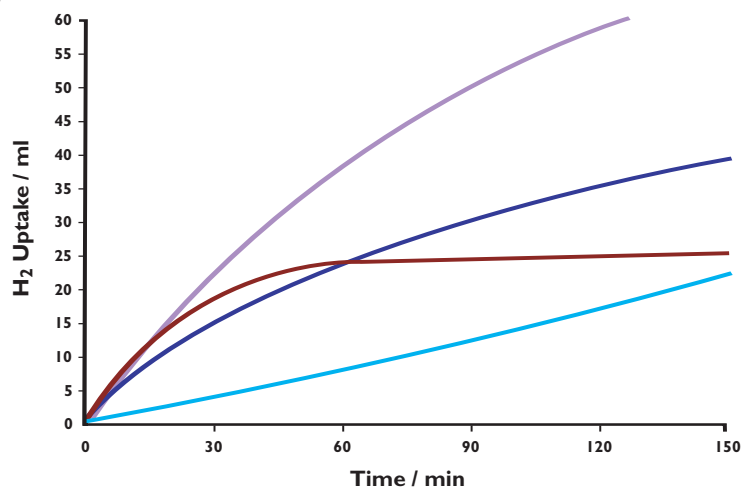
Johnson Matthey has developed a range of "eggshell" 5% Pd catalysts which are considerably more active and selective than the Pearlman's standard. Important catalyst properties considered in this work include support type, active metal precursor, metal location, particle size and pH.

The results of testing this new series in the debenzylation reaction are shown in the graph. Types 394 and 338 clearly show superior activity and selectivity, with the majority of the new generation catalysts outperforming Pearlman's. The structure of the substrate also plays an important role in determining the activity and selectivity of any debenzylation reaction. This is why Johnson Matthey offers a range of catalysts designed to achieve optimal performance.

### Hydrogenation of *N*-benzyl-*N*- $\alpha$ -methylbenzylamine at 50°C, 3 bar hydrogen pressure with various catalysts in EtOH



## Hydrogenation of *N*-benzyl-*N*- $\alpha$ -methylbenzylamine using 5R338 catalyst



— 5R338 in EtOH — 5R338 in EtOAc — 5R338 in AcOH — 5R338 in THF

## Solvent Effect

Solvent choice is critical when deprotecting amine groups because the free amine products are well known to strongly adsorb at active sites, inhibiting or even completely poisoning the catalyst. The dramatic effect of solvent is clearly shown in the figure for our most active *N*-debenzylation catalyst, 5R338. Gradual slowing occurs in ethanol and ethyl acetate, and premature cessation occurs in THF, despite very good initial kinetics. Use of an acidic solvent or adding strong acid to protonate the amine products generally serves to prevent the inhibition. This is seen in glacial acetic acid, but the overall rate is dramatically slowed.

Clearly, a variety of solvents must be screened in the optimisation of any catalytic *N*-debenzylation reaction.

## Summary

### Results

- Newly developed and optimised catalysts provide a variety of excellent catalyst options
- Initial reaction rates are generally higher in ethanol and ethyl acetate. Acetic acid gives slower rate but no product inhibition as the reaction proceeds
- Hydrogenolysis of less bulky benzyl group occurs with high selectivity under our conditions
- Increase of temperature from 50 to 70°C increases the rate by a factor of 3
- The reaction works well at low pressures

### Recommendations

Catalyst:	5% Pd/C types 39, 394, 338, A405028-5, A405032-5 and A503130-5
Solvent:	Alcohols (+H <sup>+</sup> ), ethyl acetate, acetic acid
Temperature:	30 - 100°C
Pressure:	1 - 10 bar
Catalyst loading:	2 - 10% wrt substrate

## Screening & Optimisation

Heterogeneous Platinum Group Metal catalysts are used extensively in the pharmaceutical and fine chemical industries due to their ease of separation, high activity and selectivity. However, the performance of these catalysts depends on a myriad of variables. Varying factors such as active metal, precursor, support, metal location, particle size, pH and pore size distribution can have a significant impact on catalyst performance. Identifying the best combination of these factors for each specific application remains a major challenge in catalytic route development.

Johnson Matthey offers a novel approach to facilitate this process through our **Knowledge Based Screening (KBS)** service. With one of the most diverse portfolios of catalysts and decades of experience in catalysis, we provide screening services for the identification of optimal catalysts as well as process optimisation services in all aspects of the design and operation of catalytic processes.

To learn more about our services and new line of debenzylation catalysts, please contact our scientists:

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