

A New Series of Catalysts for Deprotection Reactions



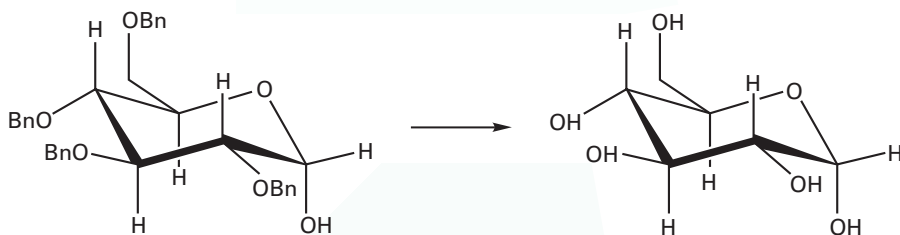
Johnson Matthey
Catalysts

In the manufacture of pharmaceuticals and fine chemicals there is often a requirement for a protection strategy to minimize possible side reactions during a synthesis. Small, easily removed protection, available for a range of functional groups, is highly desired. One such easily removed protection is derived from the facile catalytic hydrogenolysis of benzylic groups. An analysis of the published medicinal chemical routes shows that over 1000 drug syntheses currently use this type of protection. The classic functional groups requiring protection are alcohols, acids and amines.

O-Debenzylation

Simple cleavage of these protecting groups is critical. Cleavage by catalytic hydrogenation can be performed with good selectivity under mild conditions using a heterogeneous Palladium on Carbon (Pd/C) catalyst in the presence of hydrogen gas or a hydrogen transfer agent, e.g. ammonium formate or isopropanol. Efficient removal depends on selection of the most active and selective catalyst, and an optimized set of reaction conditions. For Johnson Matthey Catalysis and Chiral Technologies, this need has led to the development of a range of more active and selective catalysts for the O-debenzylation of benzyl protected alcohols and acids.

DEBENZYLATION OF 2,3,4,6-TETRA-O-BENZYL-D-GLUCOPYRANOSE



Reaction Conditions

Temperature: 25°C

Pressure: 3 bar

Catalyst Loading: 5% wrt substrate for 5% Pd/C catalysts

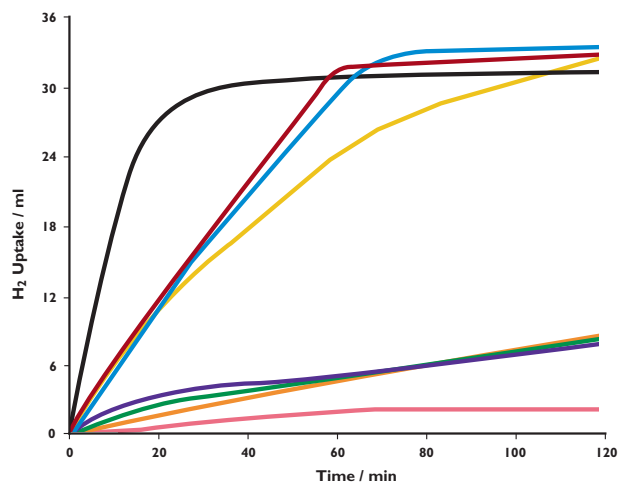
Screening: Argonaut Endeavor 8 x 10 ml reactor system

Reaction Monitoring: H₂ uptake, GC and/or HPLC

Catalyst Activity and Selectivity

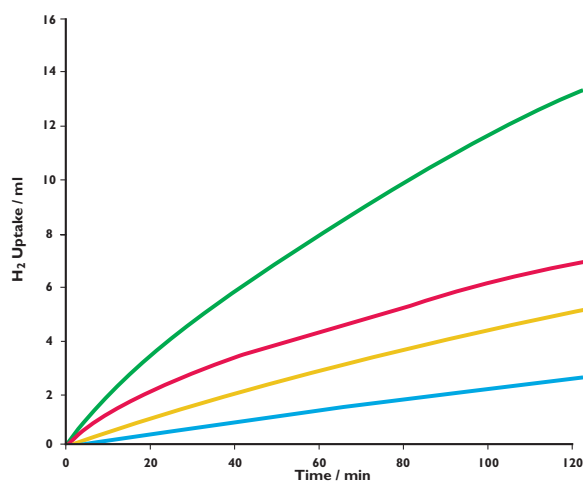
A wide range of 5% Pd/C and 10% Pd/C catalysts were screened under the standard reaction conditions. A number of catalysts were found to be more active than a current 10% Pd/C commercial catalyst standard. For the most active Pd/C catalysts, the reaction proceeded with complete conversion to the fully debenzylated product. For catalysts exhibiting slower reaction rates, partially debenzylated intermediates were observed.

Hydrogenation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose at 25° C, 3 bar hydrogen pressure with various Pd/C catalysts in THF



— A470129-10 — 10R39 — A405130-5 — A470129-5
— 10R338 — A402032-10 — A001023-10 — Commercial Standard

Hydrogenation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose at 25°C, 3 bar hydrogen pressure using 5% Pd/C A405130-5 in different solvents



— THF — Ethyl Acetate — Ethanol — Acetic Acid

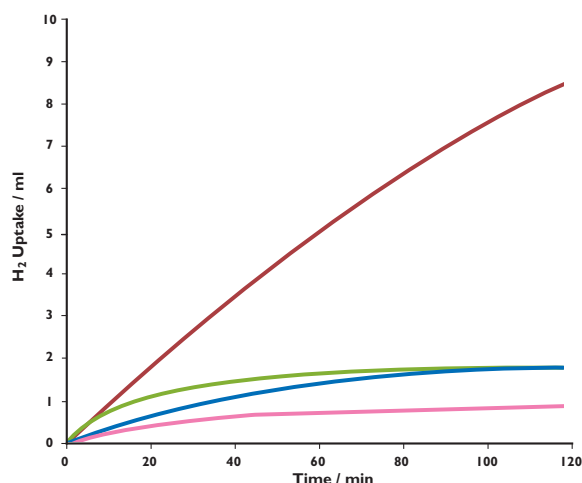
Solvent Effects

Solvent choice is critical for any debenzylation reaction. A series of commonly employed solvents, THF, ethanol, ethyl acetate, and acetic acid were screened under standard reaction conditions using a number of top performing catalysts. Reaction rates were fastest in THF, slightly slower in ethanol and ethyl acetate, and slowest in acetic acid. For less active catalysts, ethanol was a poor solvent choice due to limited substrate solubility.

Catalyst Design Effects

A number of catalyst design variables were investigated. The performance of a Pd/C catalyst is affected by the nature of the underlying carbon support, the size and location of the deposited metal particulates, the active metal precursor, the metal oxidation state and the method of catalyst preparation. Metal particulates can be made to distribute preferentially at the exterior surface of the support (an eggshell or surface loaded catalyst) or to be evenly dispersed throughout the support structure (a standard or uniform catalyst). Deposited metal may be either in a reduced or unreduced form. For the O-debenzyl reaction, eggshell unreduced catalysts performed better than uniform and/or reduced catalysts.

Hydrogenation of 2,3,4,6-tetra-O-benzyl-D-glucopyranose at 25°C, 3 bar hydrogen pressure with 5% Pd/C catalysts of different design in ethyl acetate



— Eggshell Unreduced — Uniform Reduced
— Uniform Unreduced — Eggshell Reduced

Summary

Results

Facile cleavage of O-benzyl protecting groups can be easily achieved by catalytic hydrogenation using heterogeneous Pd/C catalysts at low temperature and pressure, with low catalyst loadings and low catalyst weight percent metal. It is important to investigate a number of catalyst types for each specific application – not all Pd/C catalysts should be considered equal. A variety of solvents, temperatures, pressures, and catalyst loadings should be evaluated to arrive at an optimized set of reaction conditions.

Recommendations

Catalyst: 5% Pd/C A470129-5 and A405130-5;
10% Pd/C 10R39 and A470129-10
Solvent: THF, ethyl acetate, ethanol
Temperature: 25 - 50°C
Pressure: 1 - 10 bar
Catalyst loading: 2 - 10% wrt substrate

Screening & Optimization

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; and the optimization, 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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