

A New Series of Catalysts for Deprotection Reactions



Johnson Matthey
Catalysts

Removal of Benzyloxycarbonyl (Cbz) Protecting Groups via Hydrogenation

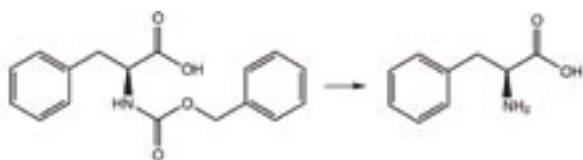
In the manufacture of pharmaceuticals and fine chemicals there is often a requirement for a protection strategy to minimize possible side reactions during a synthesis. Benzylic protecting groups are widely employed. The classic functional groups requiring protection are alcohols, acids and amines. Simple 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.

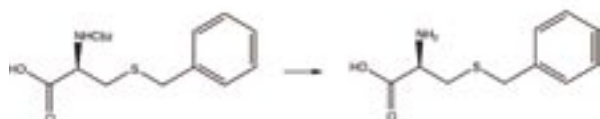
Efficient deprotection depends on the selection of the most active and selective catalyst, and an optimized set of reaction conditions. For Johnson Matthey Catalysis and Chiral Technologies, this need has led to the development of a range of more active and selective catalysts for the removal of benzyloxycarbonyl (Cbz) protecting groups via gas phase hydrogenation.

Deprotection Model Reactions

The deprotection of N-benzyloxycarbonyl-L-phenylalanine and N-benzyloxycarbonyl-S-benzyl-L-cysteine were selected and investigated.



N-benzyloxycarbonyl-L-phenylalanine



N-benzyloxycarbonyl-S-benzyl-L-cysteine

Reaction Conditions:

N-benzyloxycarbonyl-L-phenylalanine:

Temperature: 25°C

Pressure: 3 bar H₂

Catalyst Loading: 2% wrt substrate for 5% Pd/C catalysts

Reaction Time: 1.5 hours

Screening: Argonaut Endeavor 8 x 10 ml reactor system

Reaction Monitoring: GC and/or HPLC

N-benzyloxycarbonyl-S-benzyl-L-cysteine:

Temperature: 30°C

Pressure: 3 bar H₂

Catalyst Loading: 2% wrt substrate for 5% Pd/C catalysts

Reaction Time: 10 hours

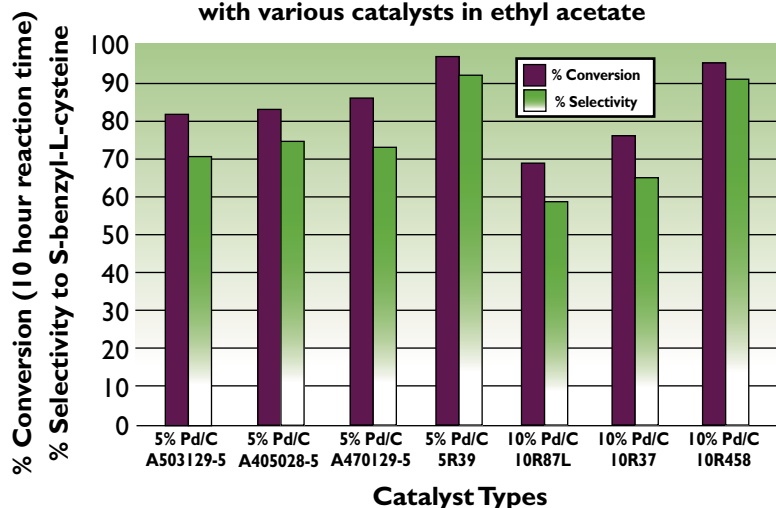
Screening: HEL Chemsan 8 x 15 ml reactor system

Reaction Monitoring: GC and/or HPLC

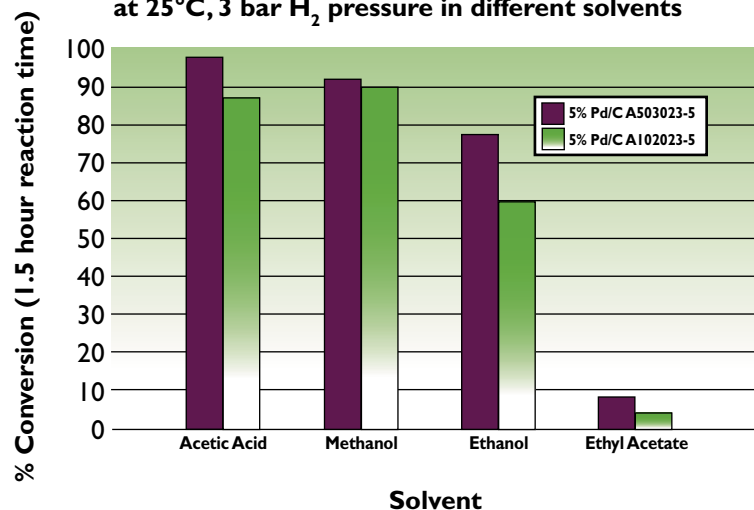
Catalyst Activity and Selectivity

A wide range of 5% Pd/C, 5% Pd/Al₂O₃ and 10% Pd/C catalysts were investigated under the standard reaction conditions for each reaction. It was not possible to accurately follow the course of either reaction by hydrogen uptake as for the removal of a Cbz protecting group 1 mole of carbon dioxide is generated for each mole of hydrogen consumed. For the L-phenylalanine reaction, the most active Pd/C catalysts proceeded with complete conversion and high selectivity to the deprotected product. For the L-cysteine substrate, the most active Pd/C catalysts proceeded with complete conversion and selective removal of the N-benzyloxycarbonyl protecting group. Minor amounts of by-products arising from S-debenzylation were observed in some cases.

Hydrogenation of N-benzyloxycarbonyl-S-benzyl-L-cysteine at 30°C, 3 bar H₂ pressure with various catalysts in ethyl acetate



Hydrogenation of N-benzyloxycarbonyl-L-phenylalanine at 25°C, 3 bar H₂ pressure in different solvents



Solvent Effects

Solvent choice is critical for any deprotection reaction. A series of commonly employed solvents (methanol, ethanol, ethyl acetate and acetic acid for the L-phenylalanine substrate; ethanol, ethyl acetate, acetic acid and solvent mixtures for the L-cysteine substrate) were screened for each reaction under standard reaction conditions using a number of top performing catalysts. For the L-phenylalanine reaction, reaction rates were fastest in acetic acid and methanol, and significantly slower in ethanol and ethyl acetate. For the L-cysteine reaction, reaction rates were fastest in ethyl acetate and an ethyl acetate/acetic acid solvent mixture, and significantly slower in ethanol and acetic acid.

Reaction Temperature, Pressure and Catalyst Loading

For each reaction, a range of reaction temperatures (25, 30, 50°C), pressures (3, 5 bar H₂), catalyst percent metal (5, 10% Pd) and catalyst loadings (1, 2, 5, 10 wt/wt%) were investigated. The trends were in general as would be expected. For the L-phenylalanine reaction, increased catalyst loadings increased reaction rate; decreased catalyst loadings decreased reaction rate. Increasing the reaction temperature from 25 to 50°C increased the reaction rate by

approximately a factor of 3. For the L-cysteine reaction, increased reaction temperature, pressure and catalyst loading increased reaction rate but decreased selectivity to the desired S-benzyl-L-cysteine product. At equal metal loadings little rate or selectivity differences were observed between equivalent 5% and 10% Pd/C catalysts for either reaction. 10% Pd/C catalysts did offer the advantage of reducing the physical catalyst charge by 50%.

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 be evenly dispersed throughout the

support structure (a standard or uniform catalyst). Deposited metal may be either in a reduced or unreduced form. For both the N-benzyloxycarbonyl-L-phenylalanine and N-benzyloxycarbonyl-S-benzyl-L-cysteine deprotection reactions, eggshell reduced and unreduced catalysts performed better than uniform catalysts. Carbon supported catalysts performed better than those on alumina supports.

Summary

Facile cleavage of benzyloxycarbonyl protecting groups can be easily achieved by catalytic hydrogenation using heterogeneous Pd/C catalysts at low temperature with low catalyst loadings. 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, hydrogen pressures, temperatures, and catalyst loadings should be evaluated to arrive at an optimized set of reaction conditions. This need is exemplified by the large solvent effects seen in both of the above discussed model reactions.

Screening and 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 broad experience in catalysis, we provide screening services for the identification of optimal catalysts; and the optimization, design and operation of catalytic processes.

Recommendations:

N-benzyloxycarbonyl-L-phenylalanine deprotection:

Catalyst: 5% Pd/C A405023-5, A503038-5, A503129-5 and 5R394

Solvent: Acetic acid, Methanol

Temperature: 25 - 50°C

Pressure: 2 – 5 bar

Catalyst Loading: 1 to 5% wrt substrate

N-benzyloxycarbonyl-S-benzyl-L-cysteine selective Cbz deprotection:

Catalyst: 5% Pd/C A405129-5 and 5R39; 10% Pd/C A402032-10, A402129-10 and 10R458

Solvent: Ethyl acetate, Ethyl acetate/Acetic acid

Temperature: 25 - 50°C

Pressure: 2 – 5 bar

Catalyst Loading: 2 to 10% wrt substrate

For copies of additional technical flyers on Deprotection Reactions, please contact us at inquiries@jmus.com

Technical Contacts:

USA and Asia

Dr. Robert McNair
Tel: +1 856 384-7176
Email: mcnairj@jmus.com

Europe

Dr. Steve Hawker
Tel: +44 1763 253 447
Email: steve.hawker@matthey.com

India

Nitin Patil
Tel: +91 22 27 401 710
Email: nitin.patil@matthey.com

www.jmcatalysts.com/pharma

Deprotection and Debenzylation Catalyst Kit



Johnson Matthey Catalysts

As part of our **Catalyst Innovation Program**, Johnson Matthey has recently developed a range of more active and selective catalysts with reduced metal loadings designed for the O-debenzylation of benzyl protected alcohols and acids, N-debenzylation of amines and amides and Cbz (carbamate) type protection of amines.

Kit includes 5 grams of the following catalysts:



- 5% Pd/C 5R39
- 5% Pd/C 5R338
- 5% Pd/C 5R394
- 5% Pd/C A405028-5
- 5% Pd/C A405032-5
- 5% Pd/C A503129-5
- 10% Pd/C A402028-10
- 10% Pd/C A501023-10
- 10% Pd/C 10R39
- 20% Pd/C 20R91

To view our complete series of Deprotection flyers, visit www.jmcatalysts.com/pharma. Click on the link for literature.

Kits are available for purchase through Johnson Matthey Catalysis and Chiral Technologies

Please contact your local sales representative for additional details or email us at inquiries@jmusa.com.