

# A New Series of Catalysts for Deprotection Reactions



Johnson Matthey  
Catalysts

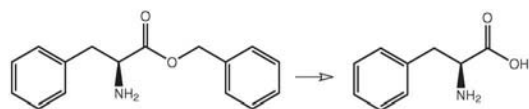
## Transfer Hydrogenation

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. The use of a hydrogen donor rather than gas phase hydrogen has many processing advantages including: 1) no pressure equipment

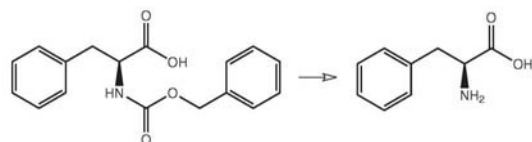
requirement, 2) no need for H<sub>2</sub> storage, delivery systems or gas measurement, 3) the use of standard vessels and equipment, and 4) potential chemoselectivity advantages (e.g. deprotection in the presence of an aryl chloride). Efficient deprotection using hydrogen donors depends on the selection of the most active and selective catalyst, and an optimized set of reaction conditions. To address this need, Johnson Matthey Catalysis and Chiral Technologies has recently developed a range of more active and selective catalysts for the removal of benzyl (Bn) and benzyloxycarbonyl (Cbz) protecting groups via transfer hydrogenation.

## Deprotection Model Reactions

The following reactions were selected and investigated:



**O-benzyl-L-phenylalanine**



**N-benzyloxycarbonyl-L-phenylalanine**

### Reaction Conditions:

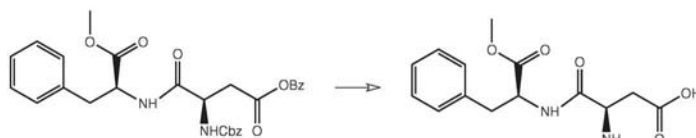
**Temperature:** Solvent reflux or 50°C

**Pressure:** Atmospheric N<sub>2</sub>

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

**Screening:** Radley Carousel 12 x 30 ml reactor system

**Reaction Monitoring:** GC and/or HPLC



**O-benzyl-N-benzyloxycarbonyl-L-aspartame**

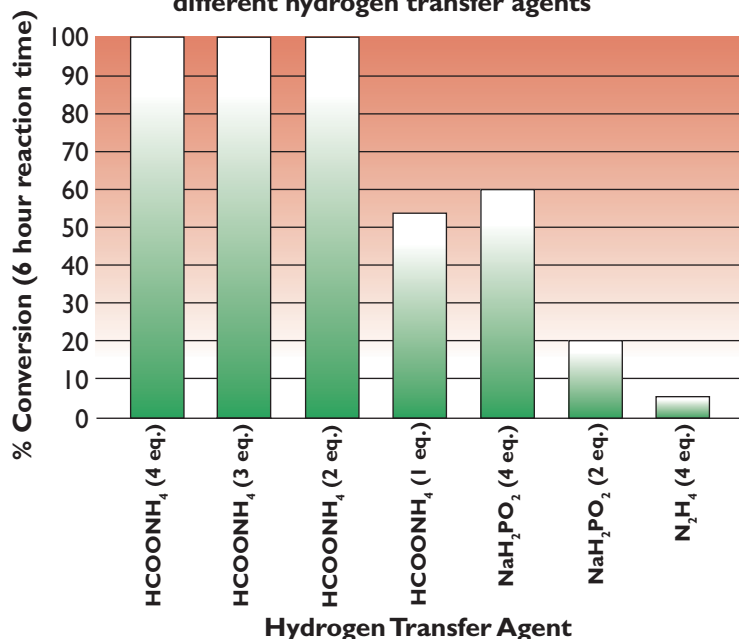
## Catalyst Activity and Selectivity

A wide range of 5% Pd/C, 10% Pd/C, and 20% Pd/C catalysts were investigated under the standard reaction conditions for each reaction. For both L-phenylalanine reactions, the most active Pd/C catalysts proceeded with complete conversion to the fully deprotected product. For L-aspartame, depending on catalyst and solvent choice, removal of both the benzyl and benzyloxycarbonyl protecting groups, or selective removal of either the benzyl or the benzyloxycarbonyl protecting group could be affected. Different and/or beneficial reaction selectivity can be observed during catalytic hydrogenation using a hydrogen transfer agent instead of hydrogen gas.

## 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 the O-benzyl-L-phenylalanine deprotection, eggshell reduced catalysts performed better than uniform and/or unreduced catalysts. Catalysts on acidic carbon supports performed best for the N-benzyloxycarbonyl-L-phenylalanine deprotection reaction. Eggshell reduced and unreduced catalysts performed better than uniform catalysts for the O-benzyl-N-benzyloxycarbonyl-L-aspartame deprotections.

### Hydrogenation of N-benzyloxycarbonyl-L-phenylalanine at 50°C in MeOH solvent using 5% Pd/C 5R394 with different hydrogen transfer agents



## Solvent and Hydrogen Transfer Agent Effects

Solvent and hydrogen transfer agent choices are critical for any deprotection reaction. A series of commonly employed solvents (methanol, ethanol, ethyl acetate, THF and/or water) and hydrogen transfer agents (ammonium formate, sodium hypophosphite hydrate, hydrazine hydrate) were screened for each reaction under standard reaction conditions using a number of top performing catalysts. Reaction rates were fastest in methanol and ethanol using two or more molar equivalents of ammonium formate. Typically more than one equivalent of a hydrogen donor is required as some decomposition of the transfer agent over the catalyst occurs.

## Recommendations

### Conditions

Solvent: Methanol, ethanol

Temperature: 25-50°C

Hydrogen Transfer Agent: Ammonium formate (≥2 equiv.)

Catalyst Loading: 2 to 10% wrt substrate

### Catalysts

#### O-benzyl deprotection:

Catalyst: 10% Pd/C A501023-10, A501129-10 and A101023-10

#### N-benzyloxycarbonyl deprotection:

Catalyst: 5% Pd/C A405032-5, A102129-5 and 5R394; 10% Pd/C 10R338 and 10R487

#### Concomitant O-benzyl and N-benzyloxycarbonyl deprotection:

Catalyst: 5% Pd/C A405032-5, A503129-5; 10% Pd/C 10R338; and A402032-10

## Summary

Facile cleavage of benzyl or benzyloxycarbonyl protecting groups can be easily achieved by catalytic hydrogenation using heterogeneous Pd/C catalysts at low temperature with low catalyst loadings via transfer hydrogenation. 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 transfer agents, temperatures, and catalyst loadings should be evaluated to arrive at an optimized set of reaction conditions.

## Screening & Optimization Services

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.

To learn more about our services and new line of deprotection catalysts please contact:

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