Pd(0) EnCat^{TM} 30NP

Hydrogenation & Transfer Hydrogenation User Guide

Reaxa Ltd, Hexagon Tower, Blackley, Manchester M9 8ZS, UK
T: +44 (0)161 721 2202; F: +44 (0)161 721 2005; E: info@reaxa.com; W: www.reaxa.com

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Introduction

Commercially available (www.sigmaaldrich.com), Pd(0) EnCat™30NP is a new microencapsulated heterogeneous hydrogenation catalyst offering key advantages over existing products.

Reductive transformations catalysed by Pd(0) EnCat™30NP include aryl ketones, aldehydes and epoxides to corresponding alcohol; nitro arenes and aryl nitriles to corresponding amine; alkenes and alkynes to corresponding alkane; debenzylation of aryl benzyl ethers, benzyl esters and benzyl amines; and reductive aminations.

General characteristics of the catalyst include a Pd metal content of 4.3 w/w%, Pd loading of 0.35-0.43 mmol/g and an average particle size range of 100-350µm.

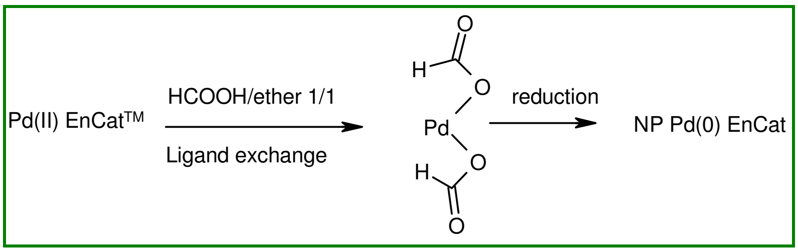
Benefits of Pd(0) EnCat™30NP include:

- Safety - non pyrophoric
- Simple and easy removal of catalyst from reactor
- Very low metal contamination of product
- No Pd(0) contamination of reactor vessel
- Excellent catalyst recyclability
- Highly chemo selective under both hydrogen & transfer hydrogenation conditions
- Excellent batch to batch activity
- No license required

For ease of handling the Pd(0) EnCat™ 30NP is supplied as a water-wet free flowing solid. In some cases, it may be necessary to remove the water from the catalyst just prior to use and this is best achieved by washing the catalyst several times with a water miscible solvent.

Preparation and Characteristics of the Catalyst

Pd(0) EnCat™ 30NP is obtained by the reduction of Pd(II) EnCat™ 30 with formic acid. The postulated mechanism is shown below; the polyurea-coordinated $Pd(OAc)_2$ undergoes anionic ligand exchange with formate to form a palladium diformate complex. This complex then undergoes decarboxylation, followed by loss of H_2 to form Pd(0). The latter is deposited as fine nanoparticules within the polyurea matrix.



Pd particles <2nm (approx 10 atoms)
Nano structure stabilised by polyurea matrix

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'NP' in Pd(0) EnCat^{TM} 30NP denotes the 'nano-particulate' nature of the Pd(0) particles stabilised within the EnCat^{TM} polyurea matrix. In fact the palladium(0) particles are mostly smaller than 2nm in diameter with further evidence for highly ordered areas corresponding to the preferred Pd cubic close packed cell structure (see Figure). It has been suggested in the literature[(1)] that the superior activity of this catalyst versus Pd/C may be due to both the small size of the palladium nanoparticles and because the Pd(0) metal centre is more electron rich.[(2)]

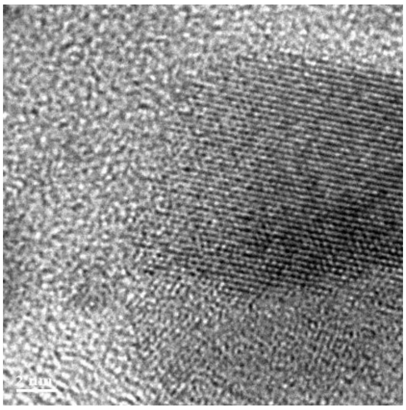

Figure 1. Transmission electron micrograph (TEM) of sliced Pd(0) EnCat^{TM} 30NP microcapsules

Experimental Method for Removing Water from the Catalyst Prior to Use

For ease of handling, Pd(0) EnCat^{TM} NP30 is typically supplied as a water-wet solid with water content 45% w/w. It may be necessary to remove the water from the catalyst just prior to use. To remove water content, the product should be washed thoroughly on a sinter with ethanol or IMS, followed by a single wash with the reaction solvent of choice.

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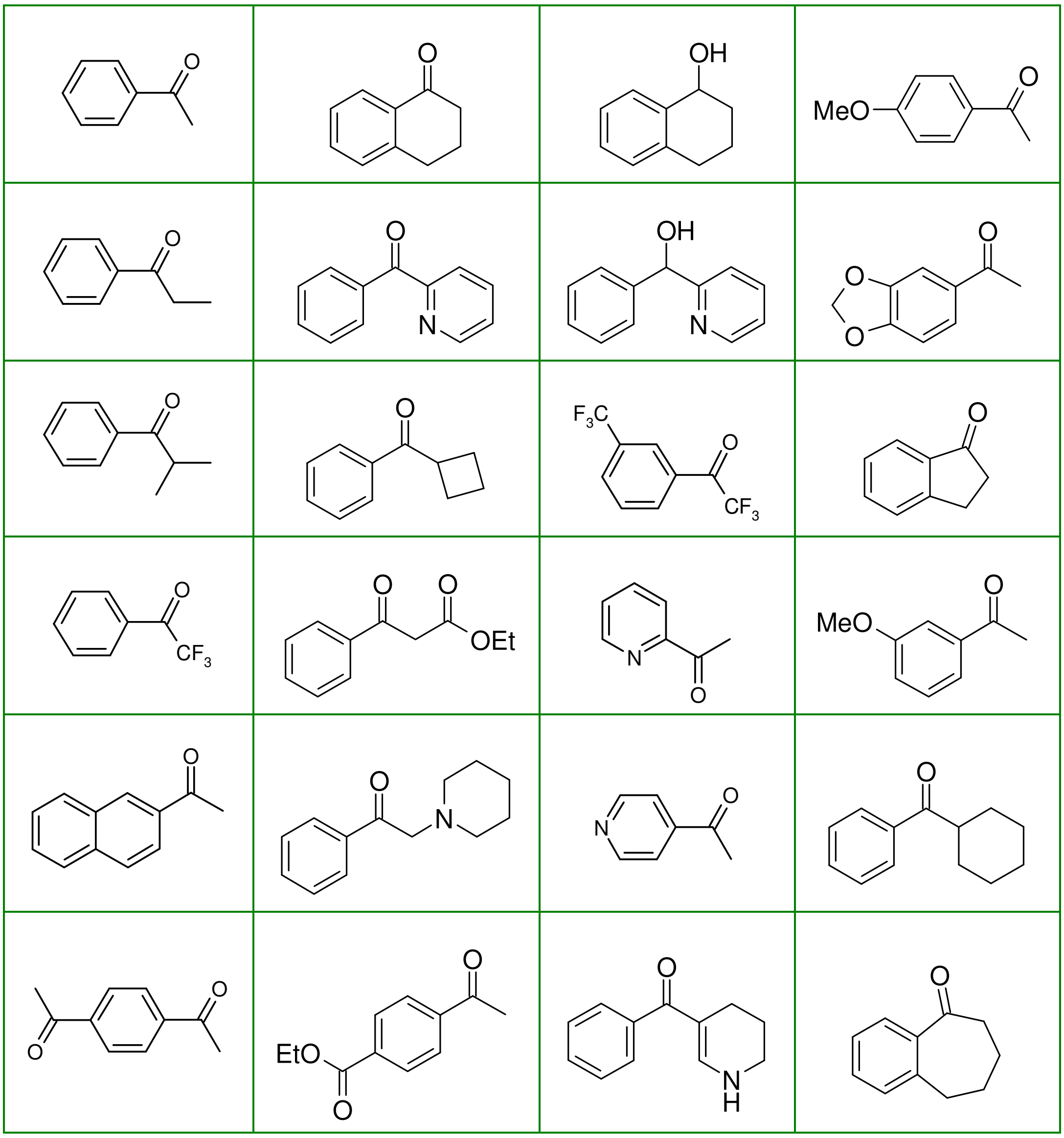
Transfer Hydrogenation Reactions

- **Aromatic Ketones**

Pd(0) EnCat™ 30NP can be used as an alternative to Pd/C for the reduction of aryl ketones.[3] Examples of successfully reduced substrates are tabulated below:



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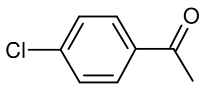
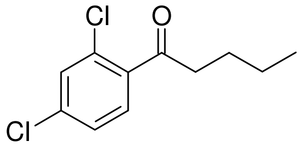
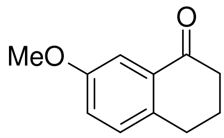
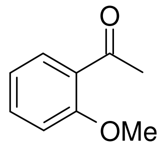
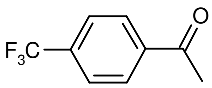
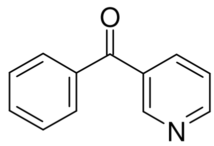
			
			

Experimental Conditions*:* 10 mol% Pd(0) EnCat^{TM} 30NP, 5 molar equiv. Et_3N, 5 molar equiv. HCOOH, EtOAc, 24°C

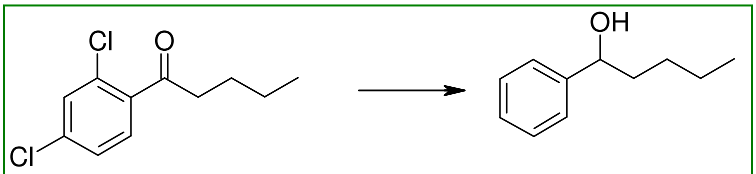
After filtration and evaporation, the residues are taken up in organic solvent and treated with water followed by filtration through a phase-separation plate. In many cases pure products are obtained (as analysed by GC and NMR).

Optimisation experiments of catalyst loading and reagent stoichiometry have indicated that efficient conversions of acetophenone can be obtained with <2 mol% Pd(0) EnCat^{TM} 30NP and two equivalents of formic acid and triethylamine.

Very hindered or electron-rich aromatic ketones are unreactive or slower to reduce. Biaryl ketones, such as benzophenone, have shown significant amounts of over-reduction to the corresponding methylene compounds. 2-Acyl pyridines have been reduced to the corresponding alcohol whereas 3-acyl pyridines are reduced to tetrahydropyridines.

- ### Aryl Chlorides

Aromatic halides (except fluorine) are rapidly reduced, for example 1-pentoyl-2,4-dichlorobenzene gives pure alpha-methyl benzyl alcohol providing a very mild method for the dechlorination of aromatic substrates.



Experimental Conditions: 10 mol% Pd(0) EnCat^{TM} 30NP, 5 molar equiv. Et_3N, 5 molar equiv. HCOOH, EtOAc, 24°C

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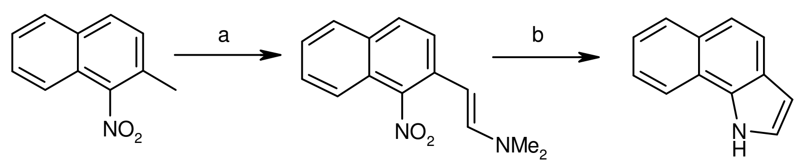
- **Aromatic Nitro Compounds**

Pd(0) EnCat™ 30NP is an effective catalyst for the reduction aromatic nitro compounds and its use has been reported in the reductive cyclisation of Leimgruber-Batcho derived enamine derivatives to form the corresponding indoles.**[4]**

Leimgruber-Batcho Indole Synthesis



Experimental Conditions: a. Microwave heating, DMF, Lewis acid. b. 6 mol% Pd(0) EnCat™ 30NP, EtOAc, HCOOH, NEt_3, 24°C, 24 hours or 6 mol% Pd(0) EnCat™ 30NP, EtOAc, HCOOH, NEt_3, microwave heating, 120°C, 2 hours

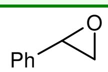
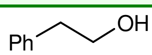
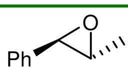
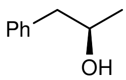
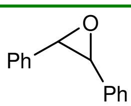
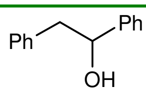
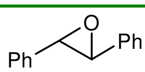
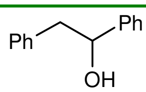
- **Aromatic Epoxides**

The reductive ring-opening of epoxides to the corresponding alcohols in the presence of a hydrogen donor is an important chemical transformation. Pd(0) EnCat™ 30NP is a highly efficient transfer hydrogenation catalyst for this transformation.

Benzylic epoxides can be reduced in high yield under mild transfer hydrogenation conditions with Pd(0) EnCat™ NP30 and formic acid and triethyl amine.[5] In all cases the epoxide is opened regio and stereoselectively at the benzylic carbon e.g. enantiomerically pure trans-methylstyrene oxide gave the corresponding alcohol with complete retention of the stereochemistry.

Over-reduction of the alcoholic C-O bond is not observed at a detectable level even with prolonged reaction times demonstrating a clear advantage of particulate Pd(0) EnCat™ 30NP over Pd/C in terms of chemoselectivity.

Examples of successfully reduced benzylic epoxides are tabulated below:[6]

Substrate	Product
	
	
	
	

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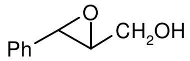
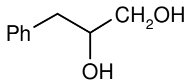
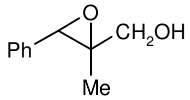
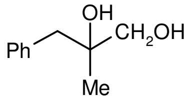
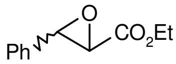
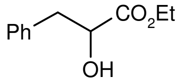
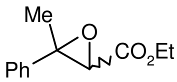
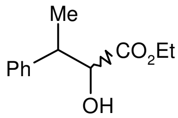
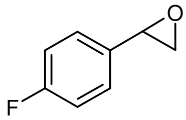
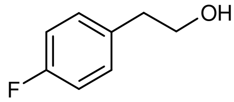
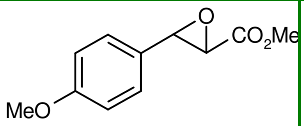
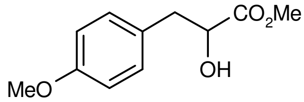
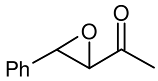
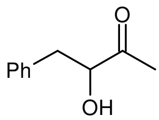
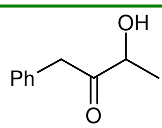
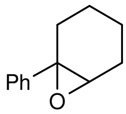
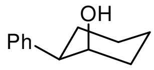
Substrate	Product
	
	
	
	
	
	
	 6:1 
	

Experimental Conditions: Epoxide (0.5 mmol), Pd(0) EnCat™ 30NP (5 mol%), 0.75 ml EtOAc, HCOOH (4 equiv.), NEt_3 (4 equiv.) 23°C, time 2 to16 hours

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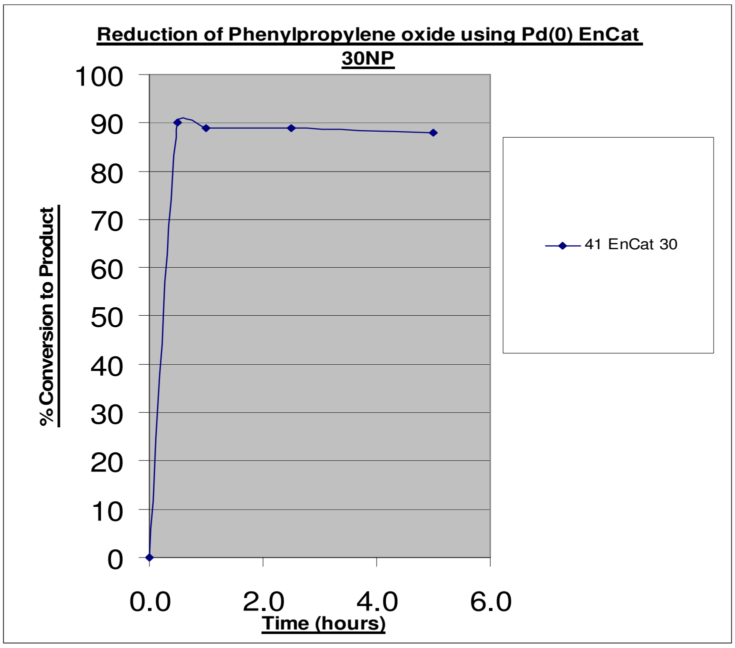
Example Experimental Conditions For the Reduction of 1-Phenylpropylene Oxide

In a 100 ml round bottom flask, 1-phenylpropylene oxide (0.75g, 5.6 mmol), formic acid (1.03g, 22.4 mmol), triethylamine (2.26g, 22.4 mmol), and Pd(0) EnCat™ 30NP (5 mol%), were stirred with ethyl acetate (29 ml) at room temperature for 5 hours. The reaction was monitored at regular intervals by HPLC after which the mixture was filtered and the beads washed with ethyl acetate. The filtrate was concentrated with work up and the crude product analysed for Pd content.

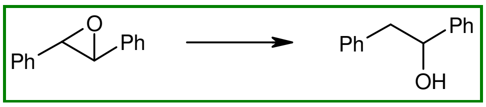
Hydrogenolysis of methyl styrene oxide with Pd(0) EnCat™ 30NP proceeds to virtually quantitative conversion of the anticipated product within 30 minutes. Furthermore, the catalyst can be readily recovered and recycled. Following catalyst removal and solvent evaporation, the product contains less than 5ppm of palladium by ICP analysis.



- **Catalyst Recyclability: Case Study 1**

The catalyst can be recovered by simple filtration and re-used without loss of activity. The level of palladium in the reaction following filtration of the catalyst is typically below 1ppm (ICP).

The Table below illustrates how the catalyst can be recycled through >10 successive hydrogenolysis reactions and in each case excellent isolated yields of product are obtained.(2)



Experimental Conditions: 0.5 mmol epoxide, 5 mol % Pd(0) EnCat™ 30NP, 4 equiv. Et_3N, 4 equiv. HCOOH , 0.75 mL EtOAc

Run	1	2	3	4	5	6	7	8	9	10
Time (h)	5	3	3	3	5	3	5	5	5	5
Yield (%)	99	91	76	96	92	93	98	97	97	92

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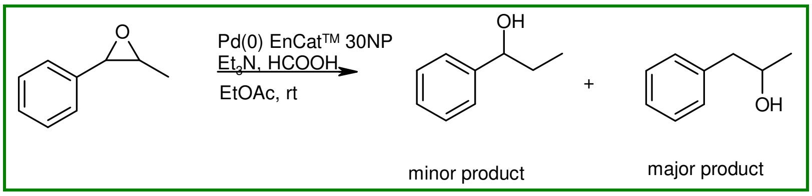
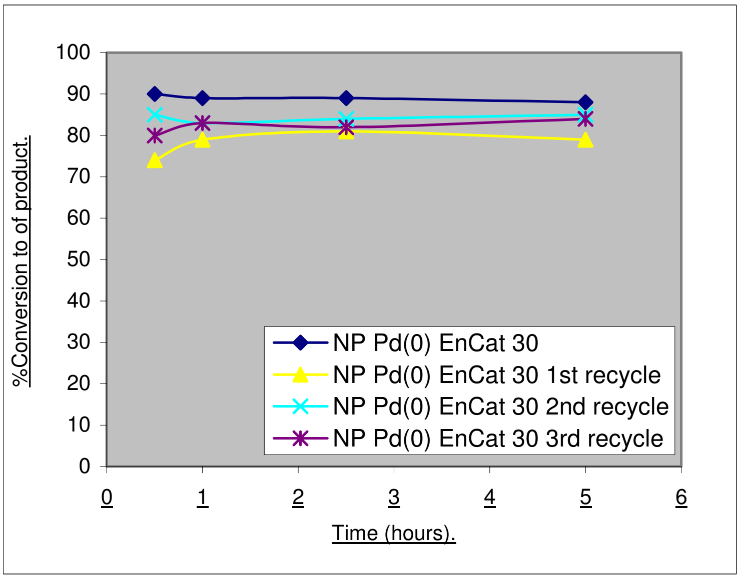
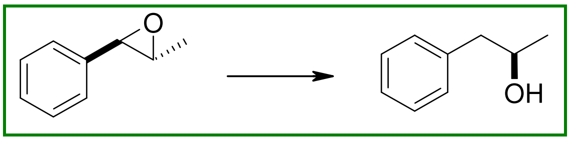
- **Catalyst Recyclability: Case Study 2**

The recovered Pd(0) EnCat™ 30NP beads were washed with IMS (5x) on a filter plate followed by ethyl acetate (or reaction solvent of choice) before being re-used without drying.





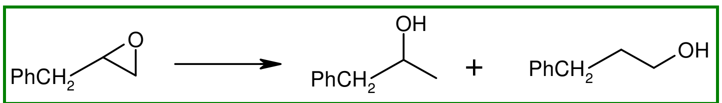
- **Stereoselective Reduction of Aromatic Epoxides**



Experimental Conditions: 5 mol% Pd(0) EnCat™ 30NP, EtOAc, 4 equiv. HCOOH, 4 equiv. NEt_3, 23°C, 26 hours

- **Terminal Epoxides**

Regioselective reduction of terminal epoxides is a particularly attractive route to substituted alcohols. Under transfer hydrogenation conditions the reaction was found to be very slow, however, under conventional hydrogenation conditions a good yield of the secondary alcohol was obtained.(6)



Experimental Conditions: 5 mol% Pd(0) EnCat™ 30NP, methanol, H_2 (40 atm), 23°C, 19 hours

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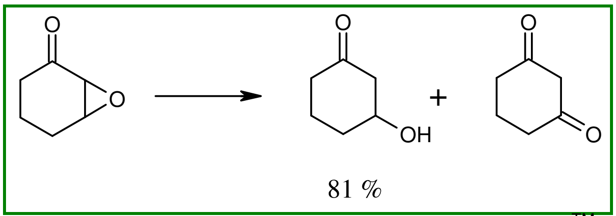
- **α,β–Epoxy Ketones**

Pd(0) EnCat™ 30NP reductive cleavage of α,β–epoxy ketone gives the corresponding β-hydroxy ketone in good yield where NMR analysis indicated that the main side product formed was the diketone.

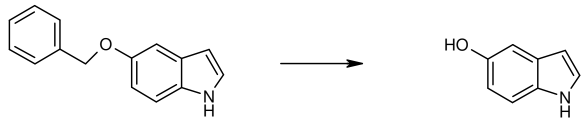
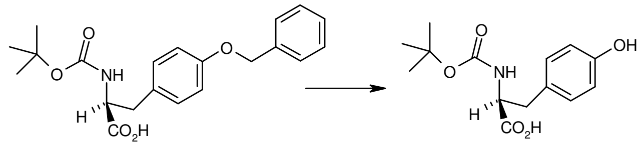
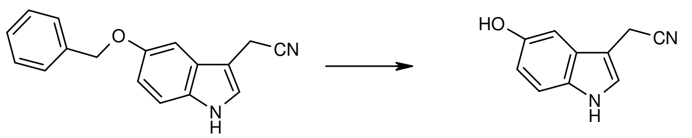
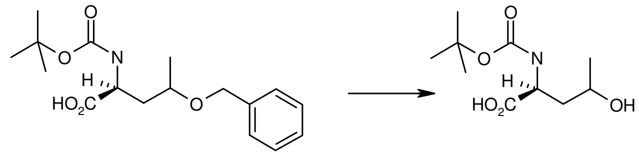


Experimental Conditions: 5 mol% Pd(0) EnCat™ 30NP, 0.5 mmol epoxide, 0.75mL EtOAc, 4 equiv. HCOOH, 4 equiv. NEt_3, 23°C, 26 hours

- **O-Debenzylation under Transfer Hydrogenation Conditions**

Under transfer hydrogenation conditions we have observed efficient debenzylation of O-aryl benzyl ethers but we have not observed debenzylation of alkyl benzylethers, Z groups, or benzyl amines.

The selection of hydrogen donor is important. Cyclohexene is preferred for debenzylations but no reaction takes place in the absence of acetic acid. Formic acid was not an efficient donor for the debenzylation reaction.

Reaction	Conversion (%)
	quantitative
	86%
	quantitative
	No reaction

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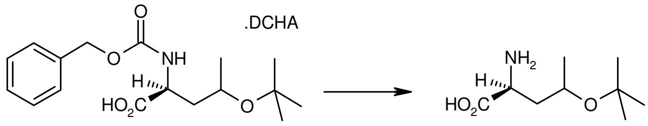
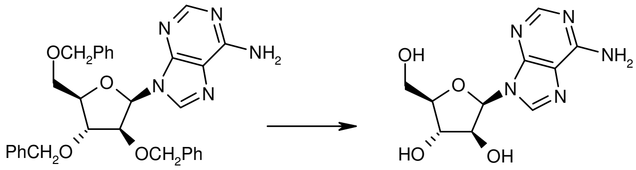
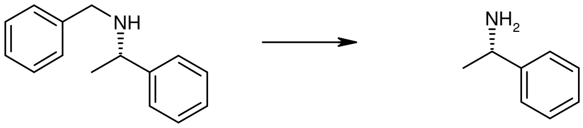
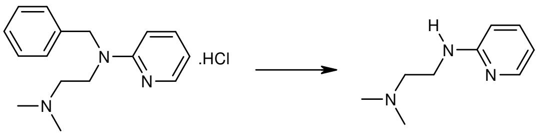
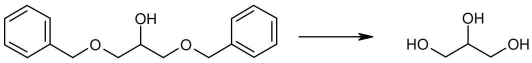
-table continued

Reaction	Conversion (%)
	No reaction
	No reaction
	No reaction
	No reaction
	No reaction

Experimental Conditions

Before use, Pd(0) EnCat™ 30NP (0.55g, 10mol%) was washed thoroughly with ethanol to remove water (supplied as a water wet solid with water content 45%w/w).

To 5-benzyloxyindole (0.22g, 1 mmol) in cyclohexene (9.1ml, 90mmol) pre-washed Pd(0) EnCat™ 30NP was added. Ethanol (5 ml) and acetic acid (1ml, 6%v/v) were added to the reaction mixture which was then heated at 85°C until the reaction was judged to be completed (TLC). Samples were analysed by RP-HPLC which showed that after 20 hours reaction 5.5% of 5-benzyloxyindole remained and after 38 hours 1.4% of 5-benzyloxyindole remained with the only other peak being the hydroxyindole product.

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Hydrogenation Reactions

Hydrogenation reaction examples using Pd(0) EnCat™30NP are sub-sectioned below. In all cases exceptionally low levels of Pd contamination (<1ppm) was detected in the crude product.

- **Chemoselective Hydrogenation of Aryl Aldehydes and Aryl Ketones**

We have observed that arylketones and arylaldehydes can effectively be reduced using Pd(0) EnCat™ 30NP under conventional catalytic hydrogenation conditions of H_2 (atmospheric pressure) with good selectivity and conversions.

The results of different conditions for the carbonyl reduction of 4-methoxybenzaldehyde and 4-methoxyacetophenone are summarized in the proceeding table.

When Pd/C was used, the over-reduced product was quantitatively obtained (entries 7 and 8).

Using palladium on different supports with lower surface area than carbon, such as $CaCO_3$ or Al_2O_3 (entries 4 and 5) a mixture of benzylic alcohol and over-reduced product was found. A much better selectivity was achieved when using Pd(0) EnCat™ 30NP. In this case, the corresponding alcohol was obtained in 94%-95% conversion (entries 1, 2, and 3).

It is known that the use of non-protic solvents like ethyl acetate can avoid the over-reduction of aryl aldehydes but in our experiments the same selectivity was obtained in ethanol and ethyl acetate. We have observed minor differences in reactivity between water wet or solvent pre-washed EnCat™. Solvent pre-washed catalyst is slightly less active and so more selective, giving less of the over-reduced side product (entry 3).

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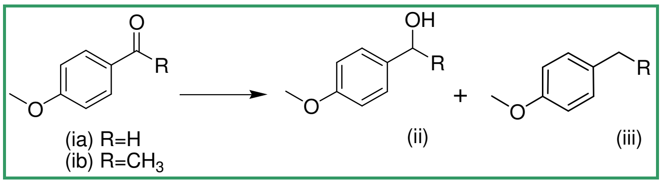
Table: Pd(0) EnCat™ 30NP-catalyzed hydrogenolysis of aryl ketones and aldehydes. Comparison with other Pd catalysts[a]



Entry	Method	R	Solvent	Conversion [b]	
				(ii)%	(iii)%
1	H_2, Pd(0) EnCat™ 30NP	H	EtOH	94	6
2	H_2, Pd(0) EnCat™ 30NP	H	AcOEt	94	6
3	H_2, Pd(0) EnCat™ 30NP pre-washed with EtOH	H	EtOH	95	5
4	H_2, 5% Pd/$CaCO_3$ [c]	H	EtOH	63	37
5	H_2, 5% Pd/Al_2O_3 [d]	H	EtOH	45	55
6	H_2, 10% Pd/C Engelhard [e]	H	EtOH	13	84
7	H_2, 5% Pd/C Aldrich [f]	H	EtOH	---	100
8	H_2, 5% Pd/C J.Matthey [g]	H	EtOH	---	100
9	H_2, Pd(0) EnCat™ 30NP	CH_3	EtOH	100	---
10	HCO_2H, Et_3N, Pd(0) EnCat™ 30NP, 40h	CH_3	AcOEt	54[h]	---

[a] *Reaction conditions*: H_2 Balloon or HCO_2H/Et_3N, 10 mol% Pdcatalyst, r.t., 16 hours. Pd(0) EnCat™ 30NP is supplied as a water wet solid with water content 45% w/w. All NMR data were in agreement with the literature; [b] Conversions calculated by ^1H NMR; [c] unreduced dry ESCAT 1371 Engelhard; [d] reduced, dry ESCAT 1241 Engelhard; [e] 10% Pd/C Engelhard C3645 Aldrich ref. 520888, 3% of aldehyde is observed; [f] 5% Pd/C Aldrich ref. 205680; [g] 5% Pd/C Johnson Matthey ref. 113026; [h] see Pears D.A.; Smith S.C. *Aldrichimia Acta* **2005** , *38*, 24

In the case of 4-methoxyacetophenone the same excellent selectivity was achieved and the alcohol was obtained in 100% conversion when using Pd(0) EnCat™ 30NP under our standard conditions (entry 9). It is worthwhile mentioning that, as we expected, transfer hydrogenation conditions did not work efficiently for this electron rich aromatic system (entry 10).

Experimental Conditions

Typically reactions were performed at a scale of 1 mmol of substrate. The amount of wet catalyst required was weighed and then washed with the solvent in which the reaction was to take place.

The substrate was dissolved in 10 ml of EtOH and 10 mol% of the catalyst was added. The mixture was degassed twice under vacuum (using a water pump) refilling with hydrogen each time. The reaction mixture was left at room temperature overnight connected to a double layer balloon of hydrogen. The catalyst was then filtered off, washed with EtOH, and the filtrated

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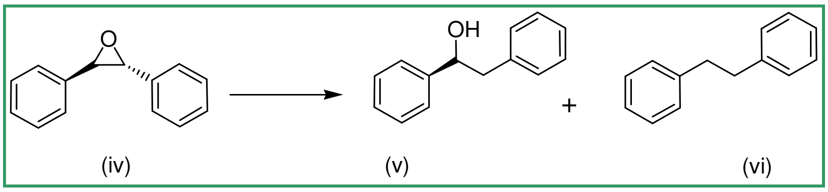
concentrated to give a crude product which was submitted for ^{1}H-NMR analysis to determine the conversion.

- **Chemoselective Hydrogenation of Aryl Epoxides**

As a model for the hydrogenolysis of aromatic epoxides we chose *trans*-stilbene oxide, for which similarly encouraging results were obtained (see Table below). Here the same problem of over-reduction is encountered if the right catalyst and conditions are not used. This is the case when using Pd/C, with 100% conversion to the over-reduced product (entry 3). However, the use of Pd(0) EnCat™ 30NP as supplied gives the benzylic alcohol in 93% conversion (entry 1) which is improved to a conversion of 96% when the catalyst was pre-washed with ethanol (Table, entry 2). In this case, transfer hydrogenation conditions using ammonium formate as a source of hydrogen works equally well (entry 4 in Table 2).

Table:. Pd(0) EnCat™ 30NP-Catalysed Hydrogenolysis of trans-stilbene oxide. Comparison with other Pd catalysts [a]



Entry	Method	Solvent	Conversion	
			(v)%	(vi)%
1	H_2, Pd(0) EnCat™ 30NP	EtOH	93	7
2	H_2, Pd(0) EnCat™ 30NP pre-washed with EtOH	EtOH	96	4
3	H_2, 5% Pd/C Aldrich[c]	EtOH	---	100
4	HCO_2NH_4, Pd(0) EnCat™ 30NP	MeOH/H_2O	98	2

[a] Reaction conditions: H_2 Balloon or HCO_2NH_4, 10 mol% catalyst, r.t., 16 hours. Pd(0) EnCat™ 30NP is supplied as a water wet solid with water content 45% w/w. All NMR data were in agreement with the literature; [b] Conversions calculated by ^{1}H NMR; [c] 5% Pd/C Aldrich ref. 205680.

Experimental Conditions

Typically reactions were performed at a scale of 1 mmol of substrate. The amount of wet catalyst required was weighed and then washed with the solvent in which the reaction was to take place. The substrate was generally dissolved in 10 ml of EtOH, 10 mol% of the catalyst was added and the mixture degassed twice under vacuum (using a water pump) and refilling with hydrogen each time. The reaction mixture was left at room temperature overnight connected to a double layer balloon of hydrogen. The catalyst was then filtered off, washed with EtOH, and the filtrate concentrated to give crude product

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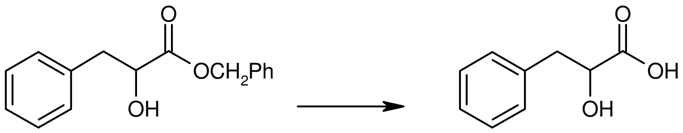
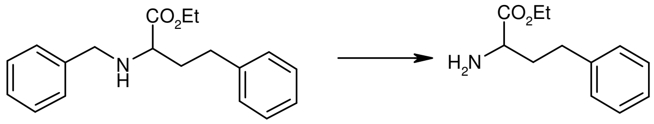
Debenzylation Reactions

Pd(0) EnCat™ 30NP can be an efficient catalyst for the selective reductive hydrogenation of aryl benzyl ethers, benzyl esters, and benzyl amines leaving other sensitive groups intact.

Alkyl benzyl ethers, are not reduced under hydrogen balloon with Pd(0) EnCat™ 30NP.

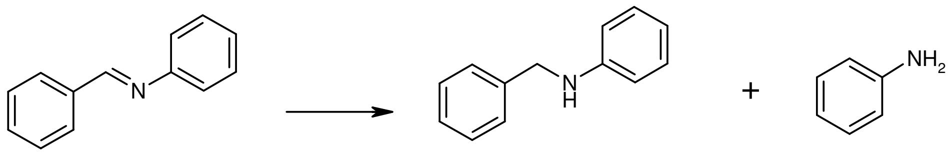
Reaction	Conversion (%)
	100
	100
	100

Experimental Procedure

All reactions were performed at a scale of 1 mmol of substrate. The substrate was dissolved in 10 ml of EtOH, 10 mol% of the catalyst (water wet) was added and the mixture degassed twice under vacuum (using a water pump) and replacing each time the vacuum by hydrogen. The reaction mixture was left at room temperature overnight connected to a double layer balloon of hydrogen. The catalyst was then filtered off and washed with EtOH. The filtrate was concentrated to give a crude product, which was submitted for ^{1}H-NMR analysis to determine the conversion.

- **Aryl Imine Reduction under Hydrogen Balloon**

Hydrogenation of aryl imines in the presence of Pd(0) EnCat™ 30NP and under hydrogen balloon conditions leads to some cleavage of the C-N bond. Best yields of the secondary amine were obtained when the catalyst was solvent washed to remove water before use.



A **B** **C**

Method	Conversion (%)	
	B	C
Pd(0) EnCat™ 30NP (10 mol%), used water wet Hydrogen balloon, CH_3CN, RT, 16 hours	69	31
Pd(0) EnCat™ 30NP (10 mol%), pre washed with EtOH Hydrogen balloon, CH_3CN, RT, 16 hours	89	11

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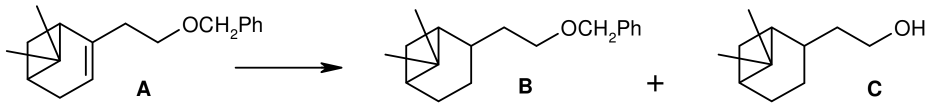
- **Hydrogenation of Alkenes in the Presence of Alkylbenzyl Ethers**

A potentially interesting application of Pd(0) EnCat^{TM} 30NP is the selective reduction of double bonds in the presence of sensitive alkylbenzyl ethers under hydrogenation conditions.



Method	Conversion (%)		
	A	B	C
Pd(0) EnCat^{TM} 30NP (10 mol%), used water wet Hydrogen balloon, EtOH, RT, 16 hours	—	86	14
Pd(0) EnCat^{TM} 30NP (10 mol%), used water wet Hydrogen balloon, EtOH, 76°C, 16 hours	—	65	35
Pd(0) EnCat^{TM} 30NP (10 mol%) HCO_2NH_4, RT, water, MeOH, 16 hours	64	36	—
Pd(0) EnCat^{TM} 30NP (10 mol%), pre washed with EtOH Hydrogen balloon, RT, EtOH, 16 hours	18	82	—
Pd(0) EnCat^{TM} 30NP (10 mol%), used water wet Hydrogen balloon, EtOAc, RT, 16 hours	40	60	—
5% Pd/C (10 mol%) Hydrogen balloon, RT, EtOAc, 16 hours	—	—	100

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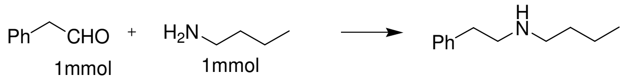
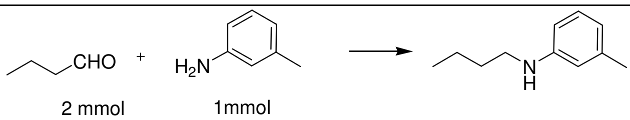
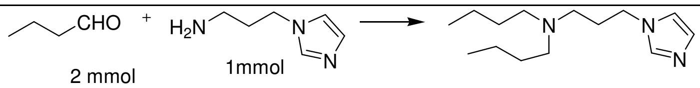
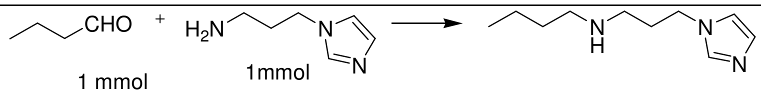
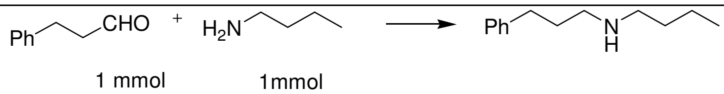
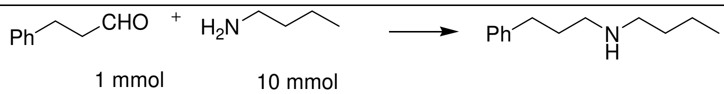
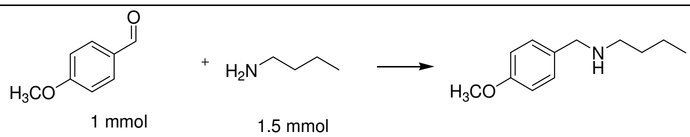
- **Reductive Amination with Selective Formation of Secondary or Tertiary Amines**

Reductive aminations proceed in good conversions with alkyl aldehydes and non benzylic alkyl or aryl amines. The ratio between mono-and dialkylated amine can be controlled by the number of equivalents of aldehyde used (see entries 3 and 4). An excess of amine does not inactivate the catalyst and give better conversions (entries 5 and 6). As we expected aryl aldehydes were partially reduced to the benzylic alcohol (entry 7).

Entry	Reaction	Conversion (%)
1		100 a
2		83 b
3		83 c
4		97 d
5		74 e
6		95 f
7		51 g

Experimental Conditions:10 mol% Pd(0) EnCat™ 30NP wet, EtOH, Hydrogen gas (balloon), r.t., 16h.
[a] Determined by 1HNMR [b] Determined by 1HNMR and GCMS + 4% dialkylation [c] Determined by 1HNMR and GCMS. No evidence of monoalkylated by GCMS [d] Determined by 1HNMR and GCMS
[e] Determined by 1HNMR and GCMS +22% dialkylation + 3% alcohol [f] Determined by 1HNMR and GCMS +1% dialkylation + 4% alcohol [g] Determined by 1HNMR and GCMS +40% benzylic alcohol + 9% toluene derivative (benzylic N)

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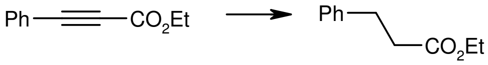
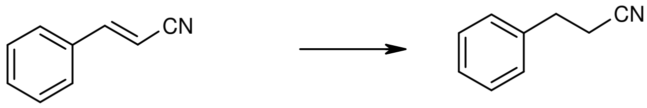
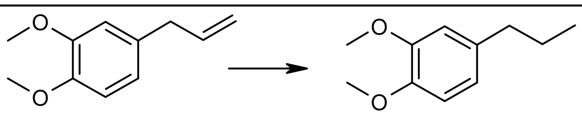
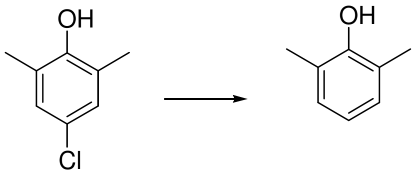
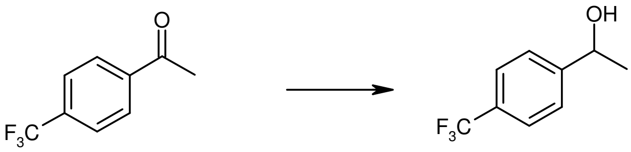
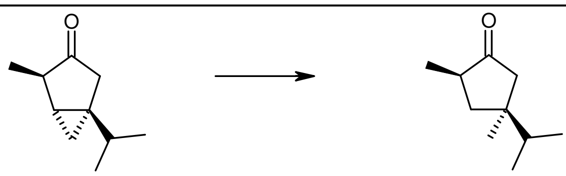
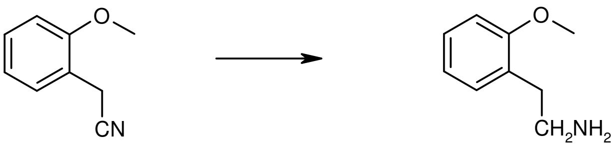
Miscellaneous

Pd(0) EnCat™ 30NP is an efficient catalyst for the reductive hydrogenation of alkenes, aryl chlorides and aryl alkynes. Alkyl nitriles and cyclopropanes are not reduced in the presence of Pd(0) EnCat™ 30NP under hydrogen balloon conditions.

Reaction[1]	Conversion (%)
	100
	100
	100
	67
	88
	No reaction
	No reaction

[1] H_2 balloon, Pd(0) EnCat™ 30NP (10 mol%) water wet, EtOH, r.t. overnight

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(3) Smith, S. C. Lecture Given at the Combinatorial Gordon Conference, Queens College Oxford, 23rd-27th August **2004**

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(6) **Recyclable polyurea-microencapsulated Pd(0) nano-particles: an efficient catalyst for hydrogenolysis of epoxides,** S.V. Ley, C. Mitchell, D. Pears, C Ramarao, J-Q. Yu, W. Zhou, *Org Lett.*, **2003**, 5 (24), 4665

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