

Pd EnCat™ Experimental Guide

General Description

The Pd EnCat™ range of catalysts represent a versatile family of heterogeneous microencapsulated palladium catalysts offering many of the benefits of homogeneous catalysts with the ease of handling and recycle potential of heterogeneous catalysts. Low metal contamination of product and waste stream is a salient feature of this technology. In addition, efficiency and economy gains through recovery and recycling of catalyst are realized.

Grades of Pd EnCat™

Product No. Description

64,472-2	Pd EnCat™ 40 (0.4 mmol/g) palladium acetate, microencapsulated in polyurea matrix.
64,471-4	Pd EnCat™ 30 (0.4 mmol/g) palladium acetate, microencapsulated in polyurea matrix.
64,470-6	Pd EnCat™ TPP30 (0.4 mmol/g) palladium acetate and triphenyl phosphine, microencapsulated in polyurea matrix at 1/0.8 Pd/TPP.
64,469-2	Pd EnCat™ TOTP30 (0.4 mmol/g) palladium acetate and tri- <i>o</i> -tolylphosphine, microencapsulated in polyurea matrix at 1/0.5 Pd/TOTP.
65,869-3	Pd EnCat™ BINAP30 (0.4 mmol/g) palladium acetate and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, microencapsulated in polyurea matrix at 1/0.25 Pd/BINAP.
65,366-7	Pd(0) EnCat™ NP30 (0.4 mmol/g) nano particulate palladium(0), microencapsulated in polyurea matrix.

*Average bead size for all standard products is in the range 75–250 micron.

Pd EnCat™ 30 is a more porous version of Pd EnCat™ 40 with improved accessibility for substrates. Generally, Pd EnCat™ 30 exhibits improved kinetics while maintaining the mechanically robust nature of Pd EnCat™ 40 under similar conditions. Pd EnCat™ TPP30, TOTP30, and BINAP30 contain co-encapsulated ligands, triphenylphosphine, tri-*o*-tolylphosphine, and bis(diphenylphosphino)-1,1'-binaphthyl, respectively.

Reaction Types

- Suzuki Reactions
- Heck Reactions
- Stille Reactions
- Carbonylation Reactions
- Transfer Hydrogenation Reactions
- Hydrogenation Reactions

Solvent Selection

Bi-phasic solvent systems (e.g., toluene/water) should be avoided due to agglomeration and precipitation of Pd EnCat™ at the aqueous/organic interphase. Most other polar and alcoholic solvents work well with Pd EnCat™, giving low levels of Pd leaching. Slightly increased palladium leaching is observed when coordinating solvents which can swell the polyurea matrix, such as *N,N*-dimethylacetamide (DMA) and *N,N*-dimethylformamide (DMF), are used particularly at temperatures >80 °C.

Solvent Leaching

Suspensions of Pd EnCat™ 40 and Pd EnCat™ 30 stirred at 80 °C in various solvents for 48 hours gave the following levels of palladium in the solvent phase:

Solvent	Pd EnCat™ 40		Pd EnCat™ 30	
	Pd (ppm)	% Leached	Pd (ppm)	% Leached
THF	1	0.15	4	0.31
Acetone	<1	<0.15	1	0.08
Ethanol	<1	<0.15	<1	<0.08
Acetonitrile	1	0.15	<1	<0.08
IPA	<1	<0.15	<1	<0.08
Toluene	<1	<0.15	<1	<0.08
Dioxane	1	0.15	<1	<0.08
Ethyl Acetate	<1	<0.15	<1	<0.08
DMF	7	1.08	5	0.39
DMA	6	0.93	3	1.01

Slightly higher levels of Pd leaching are typically seen for the products with co-encapsulated phosphine ligand.

Stability & Handling

Unlike other palladium catalysts, Pd EnCat™ is stable to storage and use in air. The catalyst may be weighed out on bench using normal methods. Although the catalyst is in free-flowing form, static charge may make weighing small quantities difficult; hence, plastic weighing boats should be avoided.

For ease of handling, the Pd(0) EnCat™ 30NP is supplied as a water wet free-flowing solid. It may be necessary to remove the water from the catalyst just prior to use. To remove water, Pd(0) EnCat™ 30NP can be washed thoroughly on a sinter with ethanol or IMS followed by a single wash with the reaction solvent of choice.

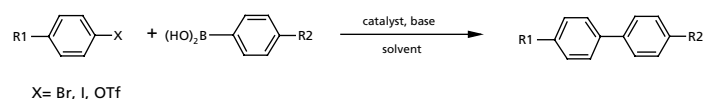
Recyclability

Pd EnCat™ has also shown good recyclability and may be reused multiple times without significant loss in activity. Also because of low metal leaching from beads, the residual palladium content remains fairly constant after each recycle. Specific examples of recyclability of Pd EnCat™ are described on the following pages.

Suzuki Reactions with Pd EnCat™

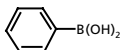
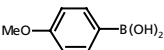
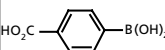
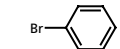
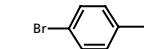
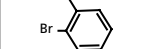
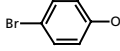
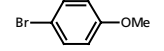
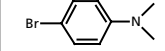
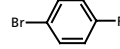
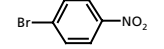
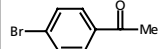
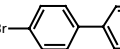
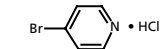
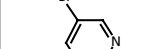
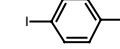
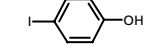
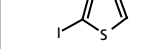
Suzuki Reaction

Suzuki reactions involve the coupling of organoboron compounds with alkyl, aryl, and alkenyl halides or triflates. A wide range of electron-rich (deactivated) and electron-poor (activated) substrates have been used with various grades of Pd EnCat™, achieving good conversions to product.



Substrates

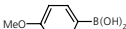

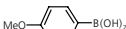

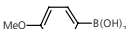

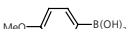

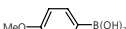

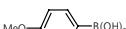

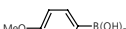

The table below summarizes examples of the substrates which have been successfully coupled in high yields using Pd EnCat™.

Boronic Acids			
Aryl Halides			
			
			
			
			

Catalyst Selection

For activated Suzuki coupling substrates, adequate conversions are often achieved through use of Pd EnCat™ 30 without addition of an activating phosphine ligand. For more difficult couplings (e.g., electron rich aryl bromides), the use of a Pd EnCat™ catalyst with a co-encapsulated phosphine ligand or alternatively the post addition of an activating ligand to the reaction is recommended. In particular, Pd EnCat™ BINAP30 often gives the best balance of yield and conversion rate, and also gives the lowest Pd and P contamination.

The following table summarizes coupling results with Pd EnCat™ BINAP30 catalyst with more demanding electron rich aryl bromides. High yields, low Pd contamination of crude product, and relatively low P contamination are observed.

Reaction	Boronic Acid	Aryl Halide	% conversion		Residual Metal	
			4 hours	21 hours	Pd/ppm	P/ppm
1			75	>99	2	30
2			36	50	3	38
3			65	97	5	47
4			79	>99	2	34
5			95	98	6	50
6			99	92	9	49
7			95	96	4	64

Base Selection

Pd EnCat™ can be used effectively with a wide selection of inorganic and organic bases such as sodium carbonate, potassium carbonate, potassium phosphate, cesium carbonate, potassium fluoride, and tetra-butylammonium salts.

Ligand Selection

When using Pd EnCat™ 40 and Pd EnCat™ 30, addition of ligands to the reaction mixtures may be necessary to get acceptable reaction rates. It is recommended to initially try ligand-to-metal ratios of <1/1 molar equivalents (ratios of P/Pd of 0.1/1 can be very effective). Because of the lower porosity of the Pd EnCat™ 40, it is necessary to allow approximately 1–2 hours contact time for a bulky phosphine ligand to diffuse through the matrix to activate the catalyst. If all the reagents are added from the beginning, there is in effect, an induction period before the reaction proceeds.

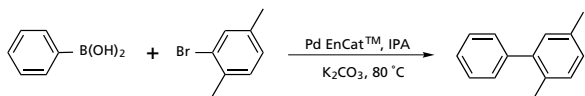
Experimental Conditions

aryl halide (1 eq.), boronic acid (1.5 eq.) Pd EnCat™ (3 mol%), base (3 eq.), IPA, 80 °C

After simple filtration and concentration of the organic layer, palladium levels of <30 ppm (generally 5–10 ppm) and phosphorus levels of <80 ppm (where applicable) were detected in the crude products.

Representative Experimental

Suzuki Coupling of Phenylboronic Acid with 2-Bromo-*p*-xylene

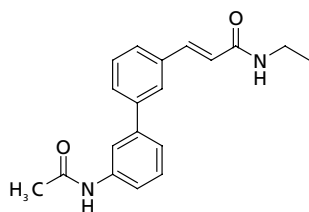
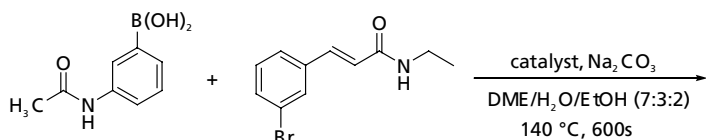


Phenylboronic acid (0.18 g, 1.5 mmol) was dissolved in 2-propanol (9.5 mL) in a 25-mL reaction tube, and to this potassium carbonate (0.41 g, 3 mmol) in water (0.5 mL) was added. 0.4 mmol/g Pd EnCat™ (0.07 g, 3 mol %) was then added followed by 2-bromo-*p*-xylene (0.19 g, 1 mmol) and the mixture agitated for 30 hours at 80 °C. The mixture was then cooled to room temperature and filtered through a sintered funnel. The organic layer was then concentrated under reduced pressure to afford the biaryl product. The residual palladium content in the crude product was determined by ICP analysis.

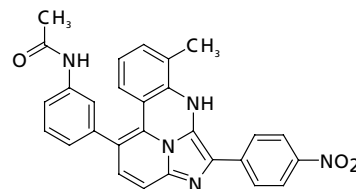
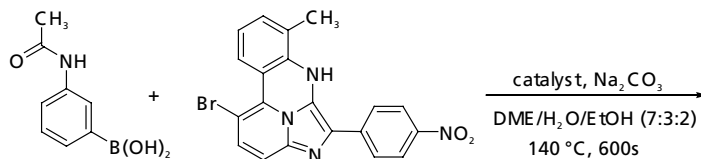
Microwave Conditions

Pd EnCat™ has been shown to be highly effective at catalyzing reactions under microwave heating.

Workers at Biotage have successfully demonstrated the use of various Pd EnCat™ catalysts in microwave assisted Suzuki couplings.¹



Catalyst (0.0125 eq.)	Ligand (0.025 eq.)	Yield (%) (LCMS)
Pd EnCat™ 40	-	17
Pd EnCat™ 30	-	28
Pd EnCat™ 40	Ph ₃ P	74
Pd EnCat™ 30	Ph ₃ P	99
Pd EnCat™ TPP30	-	77
Pd EnCat™ TOTP30	-	93



Catalyst (0.0125 eq.)	Ligand (0.025 eq.)	Yield (%) (LCMS)
Pd EnCat™ 40	-	84
Pd EnCat™ 30	-	89
Pd EnCat™ 40	Ph ₃ P	99
Pd EnCat™ 30	Ph ₃ P	97
Pd EnCat™ TPP30	-	92
Pd EnCat™ TOTP30	-	78

Experimental Conditions

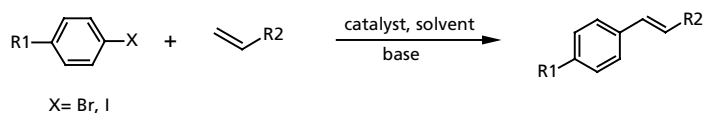
The microwave-assisted Suzuki reactions were performed on an Emrys Liberator™ from Biotage.

The reactions were performed at 0.2 mmol scale using 1.5 equivalents of base and boronic acid. The reactants were suspended in 1 mL of solvent mixture and subjected to microwave heating for 600 s at 140 °C with stirring in a 0.5–2 mL process vial. After the reaction, the reaction mixtures were cooled to room temperature and filtered. The filtrates were then analyzed by LCMS.

Heck Reactions with Pd EnCat™

Heck Reaction

Heck reactions involve the coupling of olefins with alkyl, aryl, and alkenyl halides. A wide range of electron-rich (deactivated) and electron-poor (activated) substrates have been coupled with various grades of Pd EnCat™ achieving good conversions to product.



Substrates

The table below summarizes examples of the substrates, which have been successfully coupled in high yields using Pd EnCat™ catalysts.

Olefins			
Aryl Halides			

Base Selection

Pd EnCat™ can be used effectively with a wide selection of organic bases such as tetra-butylammonium acetate, tetra-butylammonium bromide, and some inorganic bases such as potassium carbonate and cesium carbonate. However, higher levels of conversions were generally achieved with the organic bases.

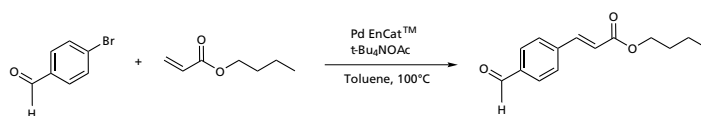
Experimental Conditions

aryl halide (1 eq.), alkene (1.2 eq.), Pd EnCat™ (5 mol%), base (2.4 eq.), Toluene/Dioxane, 100 °C

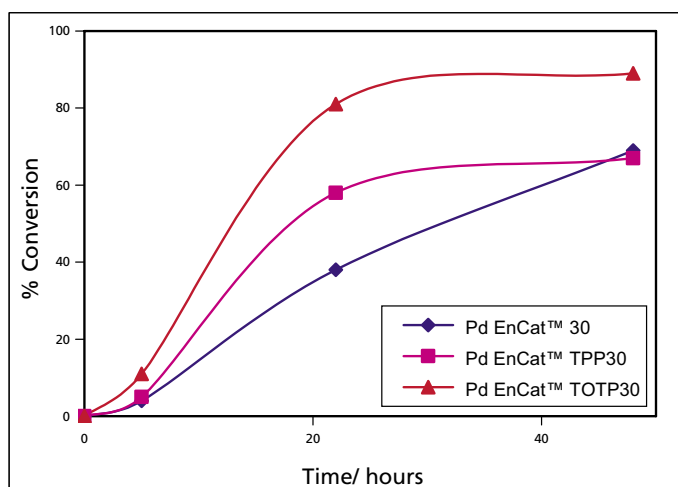
After simple filtration and concentration of the organic layer, palladium levels of <90 ppm (generally 30–60 ppm) and phosphorus levels of <120 ppm (where applicable) were detected in the crude products.

Representative Experimental

Heck Coupling of 4-Bromobenzaldehyde with *n*-Butyl Acrylate



In a 25-mL reaction tube, *n*-butyl acrylate (0.15 g, 1.2 mmol) was dissolved in toluene (5 mL) and to this tetra-butylammonium acetate (0.72 g, 2.4 mmol) was added. Pd EnCat™ (0.12 g, 5 mol%) was then added to the mixture followed by 4-bromobenzaldehyde (0.19 g, 1 mmol). The contents of the reaction tube were stirred and heated at 100 °C for 48 hours. The mixture was analyzed at regular intervals, after which it was cooled and the beads filtered off. The filtrate was concentrated under vacuum to yield the oily cinnamate product. The residual palladium content in crude product was determined by ICP analysis.

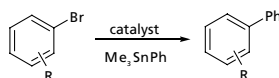


Stille Reactions with Pd Encat™

Stille Reaction

Stille reactions involve the coupling of organotin compounds with aryl and alkenyl halides or triflates.

Pd Encat™ 40 and 30 can be used to catalyze Stille couplings with both electron-rich (deactivated) and electron-poor (activated) substrates in good to excellent yields.



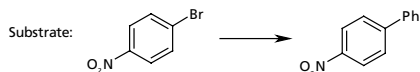
R	Yield (%)
<i>p</i> -NO ₂	99
<i>p</i> -OMe	88
<i>p</i> -F	82
<i>o</i> -OMe	74

Experimental Conditions

Pd Encat™ 40 (2.5 mol%), Me₃SnPh, ⁿBu₄NOAc, IPA-MePh (1:1), 90 °C.

Catalysts Recycle

The catalyst (Pd Encat™ 40) can be recovered and re-used as shown below for a series of sequential Stille reactions with 4-nitrobromobenzene; all the reactions proceed to completion giving near quantitative yield of the product. A progressive increase in reaction time was observed indicating that some of the more accessible metal may have been removed during the reaction or solvent washing, following recovery of the catalyst.



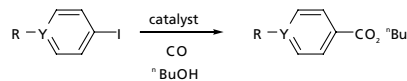
Run	1	2	3	4
Yield (%)	99	98	99	97
Time/h	3	4.5	12	24

Carbonylation Reactions with Pd Encat™

Carbonylation Reaction

Carbonylation reactions involve the addition of carbon monoxide to aryl and alkenyl halides or triflates. In the presence of alcoholic solvents, the corresponding esters are formed from the carbonylation reaction.

Pd Encat™ 40 and 30 can be used to catalyze the addition of carbon monoxide to aryl iodides to give substituted aryl esters in high yields.



R	Y	Yield (%)
Me	C	89
OMe	C	99
COMe	C	95
–	N	93

Experimental Conditions

Pd Encat™ 40 (3 mol%), Et₃N, ⁿBuOH, 90 °C, 16 h.

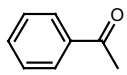
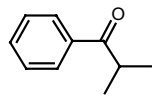
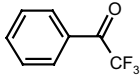
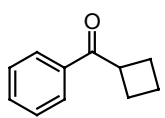
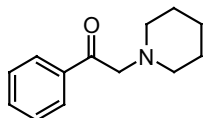
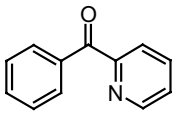
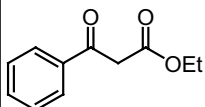
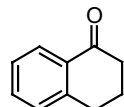
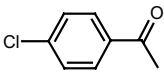
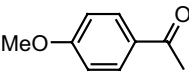
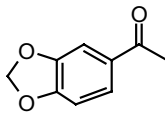
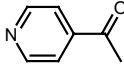
The catalyst was simply removed by filtration, followed by solvent evaporation. The crude products were found to contain approximately 80 ppm of Pd (wt/wt) corresponding to about 1% leaching of palladium from the microcapsules.

Transfer Hydrogenation Reactions with Pd(0) EnCat™ 30NP

Transfer Hydrogenation of Aromatic Ketones²

Pd(0) EnCat™ NP30 can be used as an alternative to Pd/C for the reduction of aryl ketones. Pd(0) EnCat™ 30NP is much safer and easier to handle than Pd/C. The larger particle size greatly facilitates filtration from the reaction mixture. The catalyst also has shown no tendency to be pyrophoric; hence the recovery of the used catalyst is further simplified.

Examples of Successfully Reduced Substrates

Experimental Conditions

Pd(0) EnCat™ 30NP (10 mol%), Et₃N (5 eq.), HCOOH (5 eq.), EtOAc, 24 °C.


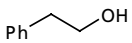
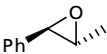
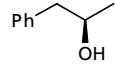
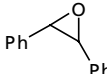
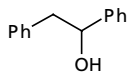
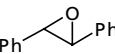
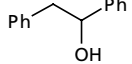
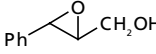
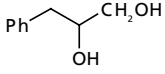
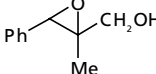
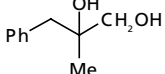
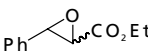
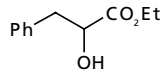
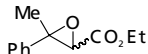
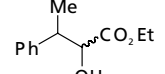
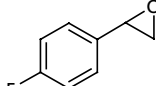
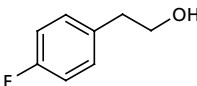
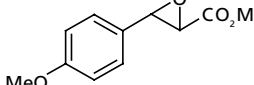
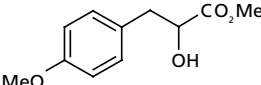
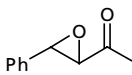
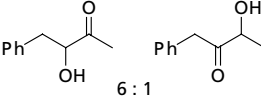
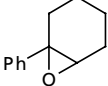
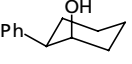
After filtration and evaporation, the residues in solvent are treated with water and filtered through a phase-separation plate. In many cases, pure products were obtained as analyzed by GC and NMR. Optimization experiments of catalyst loading and reagent stoichiometry indicated that efficient conversions could be obtained with acetophenone down to <2 mol% Pd(0) EnCat™ 30NP and only two equivalents of formic acid and triethylamine.

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

Transfer Hydrogenation Reduction of Benzylic Epoxides²

Benzylic epoxides can be reduced in high yield under mild transfer hydrogenation conditions with Pd(0) EnCat™ 30NP and formic acid, and triethylamine. In all cases the epoxides are opened regio- and stereoselectively at the benzylic carbon. With enantiomerically pure *trans*-methylstyrene oxide, the alcohol was formed with complete retention of stereochemistry.

Examples of Successfully Reduced Benzylic Epoxides

Substrate	Product
	
	
	
	
	
	
	
	
	
	
	
	

Experimental Conditions

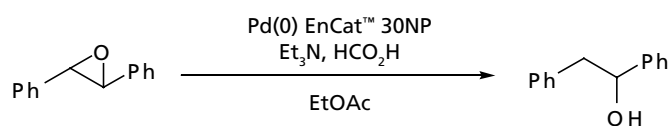
epoxide (0.5 mmol), Pd EnCat™ 30NP (5 mol%), HCOOH (4 eq.), NEt₃ (4 eq.), EtOAc, 23 °C.

The above reductions proceed in significantly higher yield than with Pd/C catalysts and over-reduction of the alcoholic C–O bond is not observed at a detectable level even with prolonged reaction times and this illustrates a clear advantage over Pd/C in terms of chemoselectivity.

Catalyst Recycle

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 the detection limit of the inductively coupled plasma analysis (ICP).

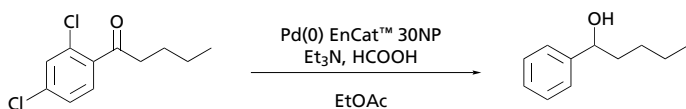
The example below illustrates how the catalyst can be recycled through >10 successive hydrogenolysis reactions and in each case, excellent isolated yields of product are obtained.³



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

Dechlorination of Aromatic Halides

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 dechlorination of aromatic substrates.

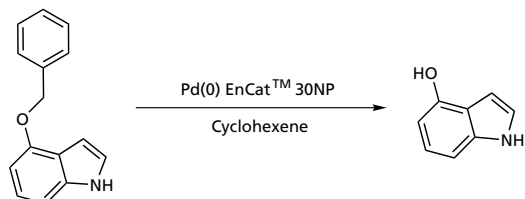


Experimental Conditions

Pd(0) EnCat™ 30NP (10 mol%), Et₃N (5 eq.), HCOOH (5 eq.), EtOAc, 24 °C.

Debenzylation of O-Benzyl Ethers

Pd(0) EnCat™ NP30 can also be utilized for the debenzylation of O-benzyl ethers.



Experimental

To 5-benzyloxyindole (0.22 g, 1 mmol) in cyclohexene (9.1 mL, 90 mmol) was added the pre-washed Pd(0) EnCat™ 30NP. Ethanol (5 mL) and acetic acid (6 mg, 0.1 mmol) were added to the reaction mixture which was then heated at 85 °C until the reaction was complete (monitored by TLC). Samples were also analyzed on a RP-HPLC.

Hydrogenation Reactions with Pd EnCat™ 40

Hydrogenation Reactions

The hydrogenation experimental work presented in this section is all based on active catalyst formed by the pre-reduction of Pd EnCat™ 40 with hydrogen.

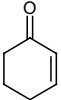
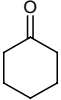
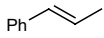
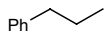
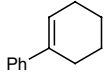
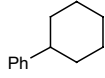
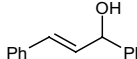
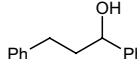
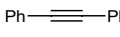
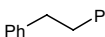
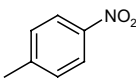
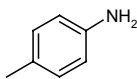
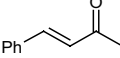
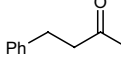
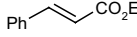
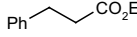
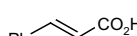
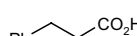
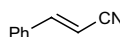
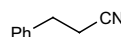
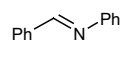
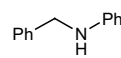
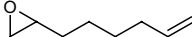
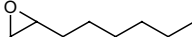
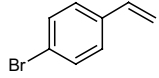
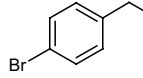
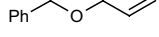
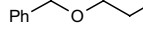
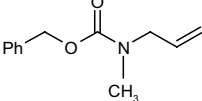
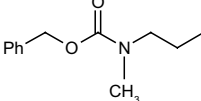
Initial studies by Ley revealed this catalyst to be effective in promoting hydrogenation of alkenes, alkynes, imines, and nitro functionalities (Table 1).⁴ Reactions were carried out under an atmosphere of hydrogen either in an autoclave or maintained by a hydrogen-filled balloon. Simple alkenes, alkynes, and aryl nitro groups are reduced at room temperature under an atmosphere of hydrogen (inflated balloon). Using cyclohexene as a test substrate, the catalyst could be recycled 20 times without any significant loss of activity. Reduction of electron-deficient alkenes is sluggish at room temperature and requires slightly elevated temperatures (60 °C). Reduction of imine (entry 11) requires use of high pressure (50 bar). Potentially labile groups such as alkyl epoxides, aryl halogens, and benzyloxy groups (entries 12, 13, and 14, respectively) remain unaffected even after being subjected to high pressures (up to 50 bar) and extended reaction times. However, the benzyloxycarbonyl group in entry 15 is cleaved under high pressure (50 bar) while performing the same reaction under an atmosphere of hydrogen (inflated balloon) gives the alkene reduced product in 93% isolated yield with the benzyloxycarbonyl group intact. All the crude products contain less than 10 ppm of palladium by ICP.

References

- (1) Pilotti, P.; Lundin, R.; Biotage, unpublished results and used with permission, February 2005.
- (2) Smith, S. C. Lecture Given at the Combinatorial Gordon Conference, Queens College Oxford, 23–27 August, 2004.
- (3) Ley, S. V.; Mitchell, C.; Pears, D.; Ramarao, C.; Yu, J.-Q.; Zhou, W. Recyclable Polyurea-Microencapsulated Pd(0) Nano-Particles: An Efficient Catalyst for Hydrogenolysis of Epoxides. *Org. Lett.* **2003**, *5* (24), 4665.
- (4) Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. Palladium Acetate in Polyurea Microcapsules: A Recoverable and Reusable Catalyst for Hydrogenations. *Synlett.* **2002**, *11*, 1843–1844.

For more detailed information on Pd EnCat™ products or to request your FREE Pd EnCat™ User Guide CD, please contact cdavis1@sial.com (USA) or your local Sigma-Aldrich office.

Table 1: Hydrogenation Reactions with Pd EnCat™ 40

Entry	Substrate	Product	Method ^a	Time (h) ^d
1			A	2
2			A	3
3			A	60
4			A	18
5			A ^b	18
6			A	18
7			B	3
8			B	5
9			B	3
10			B	5
11			C ^c	18
12			C	18
13			C	18
14			C	18
15			A	4 ^e

Notes

^a Method A: 5 mol% Pd EnCat™ 40, EtOH, r.t., H₂ (balloon); Method B: 5 mol% Pd EnCat™ 40, EtOH-MeCN (1:1), 60 °C, H₂ (balloon); Method C: 5 mol% Pd EnCat™ 40, EtOH, r.t., H₂ (50 bar). ^b EtOH-MeCN (1:1) used as solvent. ^c MeCN used as solvent. ^d Complete conversion to products by GC or LCMS. ^e 93% yield and 7% cleavage product.