



Pd(II) EnCat™ Experimental User Guide

MAY 2006



Contents		Page
Introduction		3
Commercially Available Pd (II) EnCat™ Products		3
Pictorial of Pd EnCat™ Products		3
Tailored Catalysts		4
Development Catalysts		4
Metal Recovery		4
GMP Grade		4
General		5
Appearance and Characteristics		5
Reaction Solvent Selection		6
Solvent/ Catalyst Leaching Experiments		6
Catalyst Recovery and Recycling		6
Storage and Handling		6
Chemical Reactions Using Pd EnCat™ Catalysts		7
Heck Coupling		7
Substrates		7
Base		7
General Experimental		7
Specific Heck Reaction Systems		8
Comparison of Pd (II) EnCat™ in Heck Reaction of <i>n</i> -Butyl Acrylate		8
Comparison of Pd (II) EnCat™ in Heck Reaction of <i>tert</i> -Butyl Acrylate		8
Suzuki Coupling		10
Catalyst Selection		10
Substrates		10
Base		11
Ligands		11
Reaction Kinetic Studies for Suzuki with Added Triphenylphosphine		11
Catalyst Recycling		11
Example of Pd(II) EnCat™ 40 or 30 Recycle in Suzuki Coupling:		12
Reaction Kinetic Studies		12
Comparison of Pd (II) EnCat™ in the Suzuki Coupling of 2-Bromo- <i>p</i> -xylene		13
Use of Pd(II) EnCat™ BINAP30 in Suzuki Reactions		14
General Experimental		14
Reaction Kinetics of Pd (II) EnCat™ BINAP30 in Standard Screening Reaction		15
Reactions under Mild or (Semi) Continuous Conditions with Homogeneous Bases		15
Results of Using Pd(II) EnCat™ 40 in the Presence of Tetra-butylammonium Bases		16
Results Using Pd(II) EnCat™ 30 in the Presence Tetrabutylammonium Bases		16
Boronate Ester Suzuki Coupling Using Pd(II) EnCat™ 30		17
Microwave Assisted Suzuki Couplings		17
Procedure Using Pd(II) EnCat™ 40		18
Specific Examples		18
Experimental Conditions		19
Continuous Flow Suzuki Reactions		20
		21
Stille Reactions		
Using Pd(II) EnCat™ 30 and 40		21
Catalyst Recovery and Reuse		21
		22
Carbonylation Reactions		
Using Pd(II) EnCat™ 30 and 40		22
		23
References		

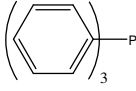
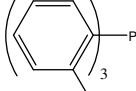
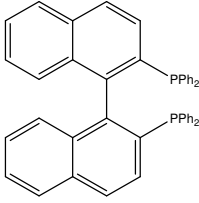


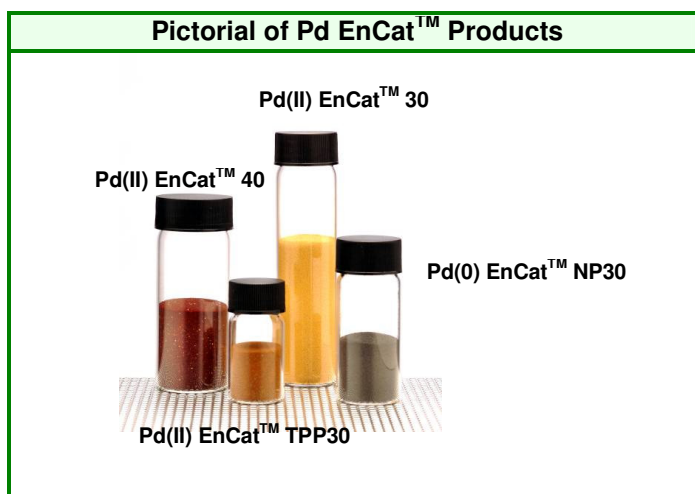
Introduction

Reaxa's palladium EnCat™ range of catalysts represent a versatile family of heterogeneous microencapsulated palladium(II) and palladium(0) catalysts (-see separate User Guide for Pd(0) EnCat™ products) 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 particular feature of this technology.

Commercially Available Pd (II) EnCat™ Products*

Commercially available products are shown in the table below. The product range is also available from Sigma-Aldrich as a Catalyst Screening Toolkit (Pd EnCat™ Kit, Catalogue No. 666335, www.sigma-aldrich.com).

Product	Aldrich Cat. No.	Pd Content % w/w	Pd loading mmol/g	P loading mmol/g	Co-encapsulated ligand
Pd(II) EnCat™ 30	64,471-4	4.3	0.40	-	None
Pd(II) EnCat™ 40	64,472-2	4.6	0.43	-	None
Pd(II) EnCat™ TPP30	64,470-6	4.7	0.44	0.30	
Pd(II) EnCat™ TOTP30	64,649-2	4.7	0.44	0.20	
Pd(II) EnCat™ BINAP30	65,869-3	4.7	0.44	0.22	
Pd EnCat™ Kit	666335				





Tailored Catalysts

Based on extensive experience in encapsulation technology, Reaxa scientists are positioned to offer custom development programmes to microencapsulate specific homogeneous catalysts of interest to the customer.

Catalyst modification takes into account process optimisation which can be achieved through manipulation of variables such as ligand type, porosity, crosslink density, matrix components, and metal and ligand loading.

Development Catalysts

The Pd EnCat™ product range is continually under development by Reaxa scientists. A range of development catalysts can be made available to clients for evaluation on studies.

For details of available catalysts please enquire at info@reaxa.com.

Pd(II) EnCat™ polyTPP30 is the latest development product offering significantly reduced Pd and phosphine leaching over existing products and excellent catalytic activity.

Metal Recovery

For all Pd EnCat™ catalysts the value of the metal may be recuperated by incineration of the catalyst after use. Reaxa is also pleased to offer through partnership with Umicore, (www.umicore.com) complete metal management solutions.

GMP Grade

Regulatory support files are available upon request (info@reaxa.com) for each of the Pd EnCat™ products to support their use in GMP pharmaceutical manufacturing.



General

Appearance and Characteristics

- Average bead size range for all standard products is 75-250 micron
- Beads are highly cross-linked and do not swell in most common organic solvents
- EnCat™ beads are generally mechanically robust
- The metal is homogeneously distributed throughout the bead
- No special storage conditions are required

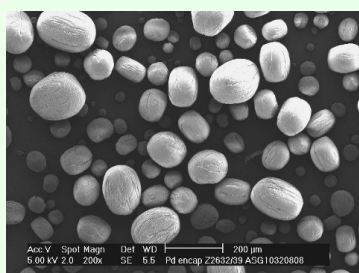


Fig 1 SEM image of Pd EnCat™ beads

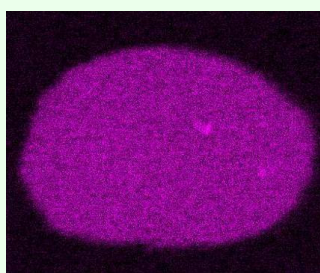


Fig 2 TEM image showing metal distribution

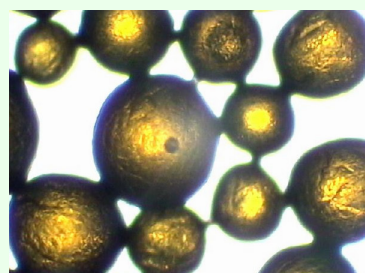


Fig 3 Optical microscope image of Pd EnCat™ beads

Notes:

Pd(II) EnCat™ 30 is a more porous version of Pd (II) EnCat™ 40 with improved accessibility for substrates.

*Pd(II) EnCat™ TPP30, TOTP30 and BINAP30 contain co-encapsulated ligands, triphenylphosphine, tri-*o*-tolylphosphine and bis(diphenylphosphino) -1,1'-binaphthyl, respectively.*

The ligand to palladium level is selected by extensive optimisation of the activity of the catalyst in Suzuki reactions.



Reaction Solvent Selection

Bi-phasic solvent systems (e.g. toluene/water) should be avoided as agglomeration and precipitation of Pd(II) EnCat™ at the aqueous/organic interface can occur with the catalyst adhering loosely to the reactor walls.

Most other polar and alcoholic solvents work well with Pd(II) EnCat™ giving low levels of Pd leaching. Slightly increased palladium leaching is observed when coordinating solvents, which can swell the polyurea matrix, are used. Typical examples are *N,N*-dimethylacetamide (DMA) and *N,N*-dimethylformamide (DMF), where increased leaching occurs at temperatures >80°C.

Solvent/ Catalyst Leaching Experiments

Suspensions of Pd(II) EnCat™ 40 or Pd(II) EnCat™ 30 (0.3g) were stirred at 80°C in various solvents (10 ml) at 80°C for 48 hours. The following levels of palladium were detected in the solvent phase:

Solvent	Pd(II) EnCat™ 40		Pd(II) 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

Catalyst Recovery and Recycling

Pd(II) EnCat™ 30 and Pd(II) EnCat™ 40 catalysts can be recycled, and examples are included within this document to demonstrate catalyst recovery and re-use without significant loss in activity.

Storage and Handling

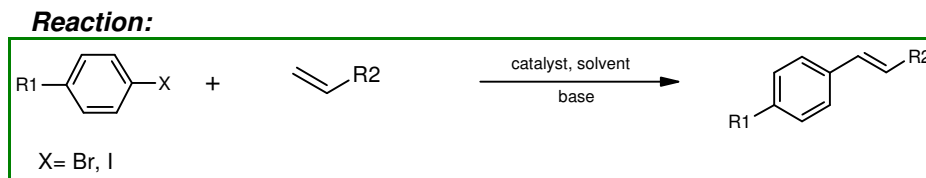
Unlike other palladium catalysts, Pd(II) EnCat™ is stable to storage and use in air. The catalysts may be weighed out on the bench using normal methods. It should be noted that as the catalysts are in free-flowing form, static charge may make weighing small quantities tricky; hence plastic weighing boats should be avoided.



Chemical Reactions Using Pd EnCat™ Catalysts

Heck Coupling

Heck reactions involve the coupling of olefins with alkyl, aryl and alkenyl halides¹. 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 product².



Substrates

The following table summarises some of the substrates, which have been successfully coupled in high yield using Pd EnCat™ catalysts:

Olefin			
Aryl halides			

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

Base

Pd EnCat™ can be used effectively with a wide selection of organic and inorganic bases such as tetra-butylammonium acetate, tetra-butylammonium bromide, potassium carbonate and caesium carbonate. In general, higher levels of conversions were achieved using organic bases (see later sections).

General Experimental

The olefin substrate (1.2 mmol, 1.2eq) was dissolved in toluene (5ml) and tetra-n-butylammonium acetate (2.4 mmol, 2.4 eq) was added. 0.4mmol/g Pd EnCat™ (0.12g, 5 mol%) was added followed by the aryl halide (1 mmol, 1 eq) and the mixture agitated for up to 48 hours at 100°C. The mixture was then cooled to room temperature and filtered through a sintered funnel. The filtrate was concentrated under reduced pressure to afford

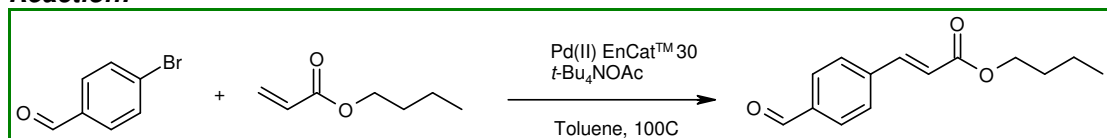


the oily cinnamate product. The residual palladium content in the crude product was determined by ICP analysis. Typically, levels of palladium of <90ppm (generally 30-60ppm) and phosphorus levels of <120ppm (where applicable) were detected in the crude products.

Specific Heck Reaction Systems

Comparison of Pd (II) EnCat™ in Heck Reaction of *n*-Butyl Acrylate

Reaction:



In a 25ml reaction tube, *n*-butyl acrylate (0.15g, 1.2 mmol) was dissolved in toluene (5 ml) and tetrabutylammonium acetate (0.72g, 2.4 mmol) added. Pd EnCat™ (0.12g, 5 mol%) was added to the mixture followed by 4-bromobenzaldehyde (0.19g, 1 mmol). The contents of the reaction tube were stirred at 100°C for 48 hours.

The mixture was analysed at regular intervals to measure % conversion (see graph below), after which it was cooled and the beads filtered off. The filtrate was concentrated under vacuum to yield the oily cinnamate product.

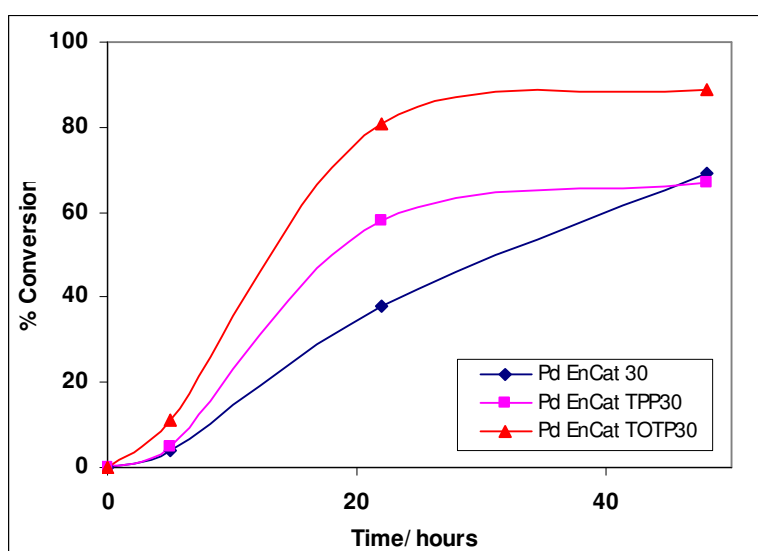
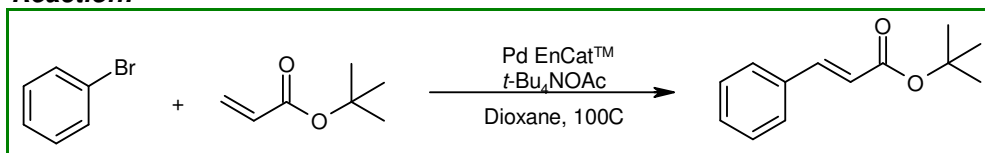


Fig 4 Comparison of Pd (II) EnCat™ in Heck reaction of *n*-butyl acrylate

Comparison of Pd (II) EnCat™ in Heck Reaction of *tert*-Butyl Acrylate

Reaction:



In 25ml reaction tube, *tert*-butyl acrylate (0.15g, 1.2 mmol) was dissolved in dioxane (5 ml) and tetra-butylammonium acetate (0.72g, 2.4 mmol) added. Pd EnCat™ 30 (0.12g, 5 mol%) was then added to the mixture followed by 4-bromobenzene (0.19g, 1 mmol). The contents of the reaction tube were stirred at 100°C for 48 hours. The mixture was analysed at regular intervals to measure % conversions (see graph below), after which it was cooled



and the beads filtered off. The filtrate was concentrated under vacuum to yield the oily cinnamate product. The reaction was repeated under the same conditions using Pd EnCat™ BINAP30 giving the following results:

Results:

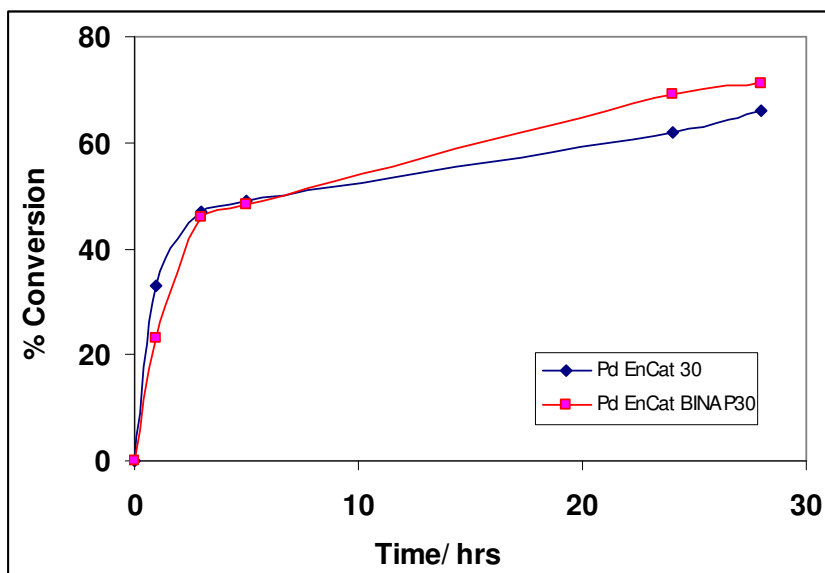
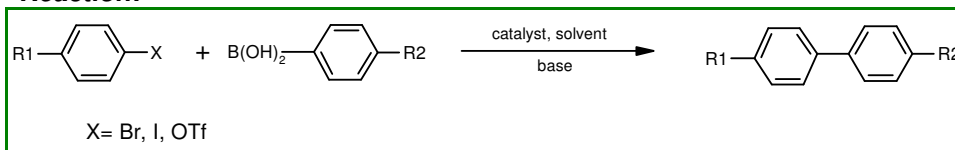


Fig 5 Comparison of Pd (II) EnCat™ in Heck reaction of *tert*-butyl acrylate



Suzuki Coupling

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(II) EnCat™ catalysts achieving good conversions to product².

In general, palladium levels of <30ppm (generally 5-10ppm) and phosphorus levels of <80ppm (where applicable) were detectable in the crude products.

Catalyst Selection

In order to select the best Pd(II) EnCat™ catalyst for a particular Suzuki coupling it is recommended screening several of the standard grades including Pd(II) EnCat™ 30, Pd(II) EnCat™ TPP30, Pd(II) EnCat™ TOTP30 and Pd(II) EnCat™ BINAP30. If the Pd(II) EnCat™ 30 catalysed reaction is slow then screening of separately added phosphine ligands (TPP, BINAP etc) is recommended.

In general, 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 with, for example, electron rich aryl bromides, a Pd EnCat™ grade with a co-encapsulated phosphine ligand or post addition of activating ligand to Pd EnCat 30 may be required.

Substrates

The following table shows a selection of the substrates which have been successfully coupled in high yield using Pd(II) EnCat™ catalysts:

Boronic acids			
Aryl halides			

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

Base



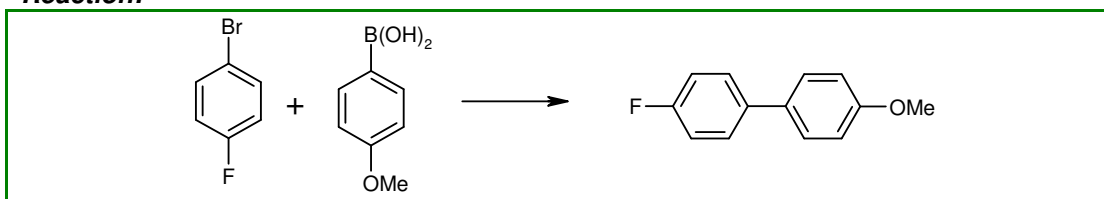
Pd(II) EnCat™ can be used effectively with a wide selection of inorganic and organic bases such as sodium carbonate, potassium carbonate, potassium phosphate, caesium carbonate, potassium fluoride and tetra-butyl ammonium salts (see later section).

Ligands

In many cases it is not necessary to add ligands to Pd(II) EnCat™ 40 and Pd(II) EnCat™ 30 catalysed reactions as activity is often sufficiently high. However, if the reaction rate is slow it is recommended to initially try ligand to metal ratios of <1/1 molar equivalents (ratios of Pd/P of 1/0.1 can be very effective).

Reaction Kinetic Studies for Suzuki with Added Triphenylphosphine

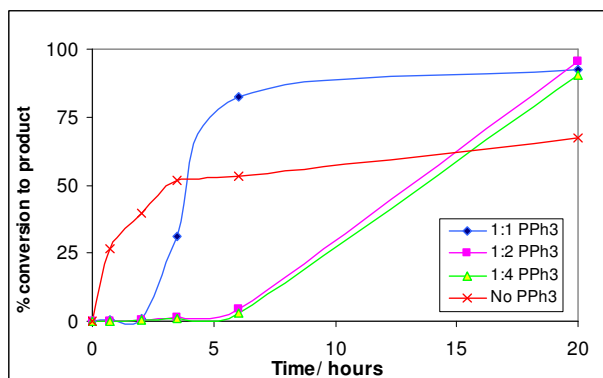
Reaction:



Conditions: 3 mol% Pd, K₂CO₃, 80°C, IPA

Results:

Pd(II) EnCat™ 40 with post added TPP



Pd(II) EnCat™ 30 with post added TPP

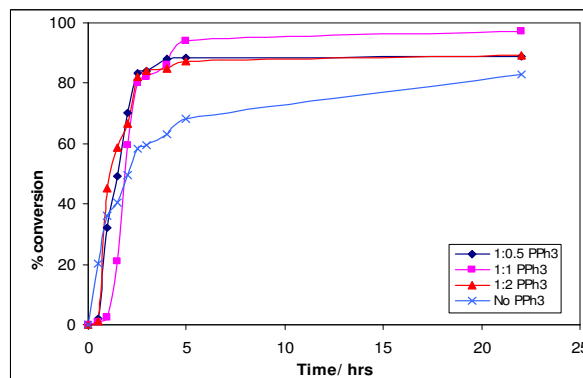


Fig 6. Reaction kinetics of Suzuki reaction with added triphenylphosphine

Due to the lower porosity of the Pd(II) EnCat™ 40 it is necessary to allow approx 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 (note that this is not the case for the more porous Pd(II) EnCat™ 30 catalyst).

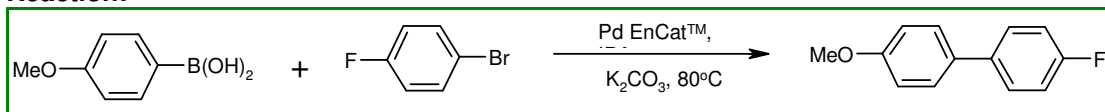
Catalyst Recycling

Pd(II) EnCat™ 30 and 40 have shown good recycle properties and may be re-used several times without significant loss in activity. Also due to low metal leaching from beads, the residual palladium content remains fairly constant after each recycle.



Example of Pd(II) EnCat™ 40 or 30 Recycle in Suzuki Coupling

Reaction:



4-Methoxyphenylboronic acid (0.23g, 1.5 mmol) was dissolved in 2-propanol (9.5ml) and potassium carbonate (0.41g, 3 mmol) in water (0.5ml) added. 0.4mmol/g Pd(II) EnCat™ 40 (0.07g, 3 mol %) was then added followed by 4-bromofluorobenzene (0.18g, 1 mmol) and the mixture agitated for 21 hours at 80°C. The mixture was cooled to room temperature and filtered through a sintered funnel. The filtrate was concentrated under reduced pressure to afford the biaryl product.

The Pd EnCat™ beads were washed on the filter with water (2x) followed by 2-propanol (5x) before being re-used in a Suzuki coupling reaction (the beads may also be washed further with the reaction solvent of choice prior to re-use).

Results:

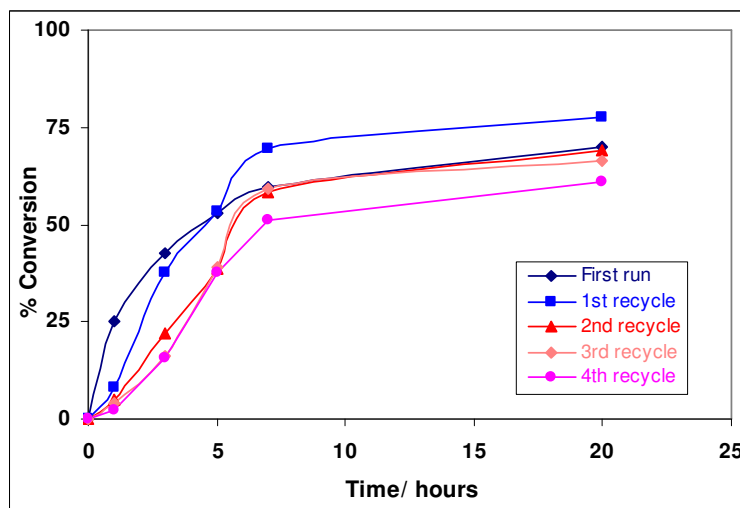
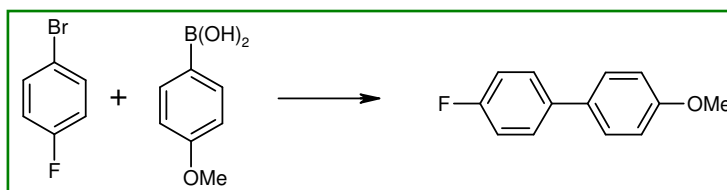


Fig 7 Recycling of Pd (II) EnCat™ 40 catalyst

Reaction Kinetic Studies



Kinetic studies of the above simple Suzuki coupling reaction demonstrate the activity differences between the standard products without the addition of extra activating ligand (see graph below, Fig 8). The resulting crude products contained Pd and P levels at <10ppm and <20ppm, respectively. It is recommended to start with catalyst levels at between 2 to 5 mol% Pd on substrates although it may well be possible to significantly reduce this level with optimisation.

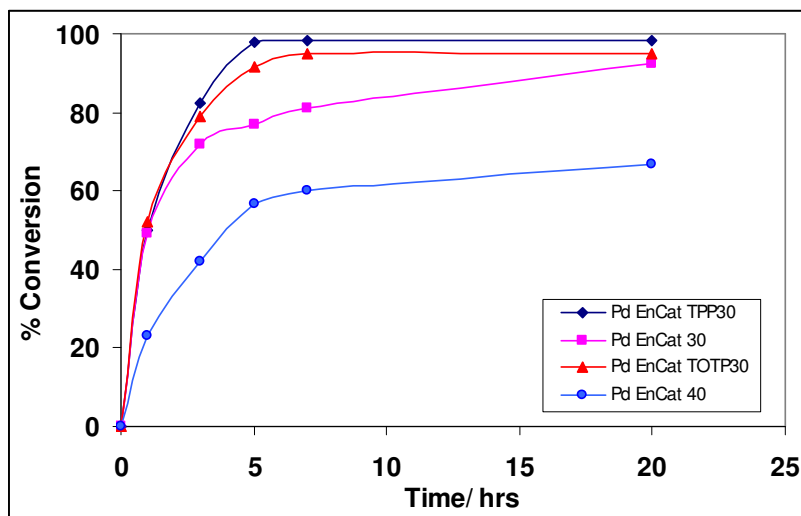
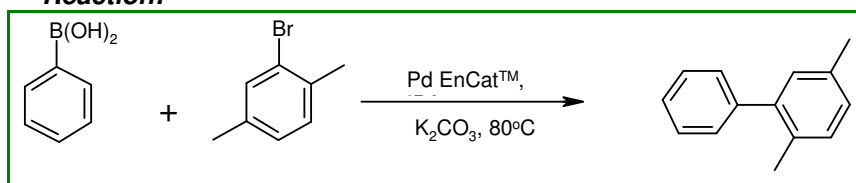
**Results:**

Fig 8 Reaction kinetics of Pd (II) EnCat™ grades
Conditions: 3 mol% Pd EnCat™, K₂CO₃, 80°C, IPA/W (20:1).

Comparison of Pd (II) EnCat™ in the Suzuki Coupling Reaction of 2-Bromo-*p*-xylene

Reaction:

Phenylboronic acid (0.18g, 1.5 mmol) was dissolved in 2-propanol (9.5ml) in a 25ml reaction tube, and potassium carbonate (0.41g, 3 mmol) in water (0.5ml) added. Pd(II) EnCat™ (0.07g, 3 mol%) was added followed by 2-bromo-*p*-xylene (0.185g, 1 mmol) and the stirred mixture heated to 80°C. for 21 hours. Aliquots of the mixture were analysed at regular intervals to determine % conversions (see fig 9).

After 21 hours the mixture was cooled to room temperature and filtered through a sintered funnel. The organic layer was concentrated under reduced pressure to afford the biaryl product.

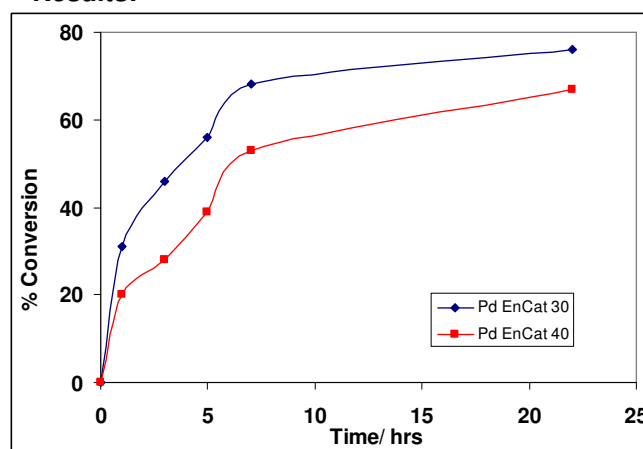
Results:

Fig 9 Comparison of Pd (II) EnCat™ in Suzuki reaction of 2-bromo-*p*-xylene



Use of Pd(II) EnCat™ BINAP30 in Suzuki Reactions

General Experimental

The boronic acid (1.5 mmol, 1.5eq) was dissolved in isopropanol (4.5ml) and potassium carbonate (3 mmol, 2 eq) in water (0.5ml) added. Pd EnCat™ (0.07g, 3 mol%, 0.4 mmol/g Pd) was added followed by the aryl halide (1 mmol, 1 eq) and the mixture agitated for 21 hours at 80°C. The reaction was sampled and analysed at 4 and 21 hours by GC-MS. The mixture was then cooled to room temperature and filtered through a sintered funnel. The filtrate was then concentrated under reduced pressure to afford the biaryl product. The residual palladium content in the crude product was determined by ICP analysis.

The following tables summarise coupling results using Pd(II) EnCat™ BINAP30 catalyst on demanding electron rich aryl bromides.

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

Note: high yields, low Pd contamination of crude product and relatively low P contamination.

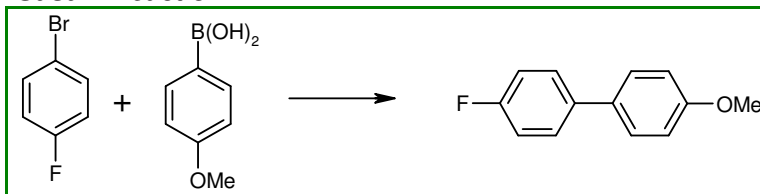
The Table below compares Pd(II) EnCat™ BINAP30 yields at 21 hours with those of other EnCat™ products.

Reaction	Pd EnCat™ 40	Pd EnCat™ TPP30	Pd EnCat™ TOTP30	Pd EnCat™ BINAP30
1	55	74	76	>99
2	27	15	2	50
3	68	61	100	97
4	53	76	91	>99



Reaction Kinetics of Pd(II) EnCat™ BINAP30 in Standard Screening Reaction

Suzuki Reaction:



Conditions: 3 mol% Pd EnCat, 80°C, IPA/W 20/1, potassium carbonate

Results:

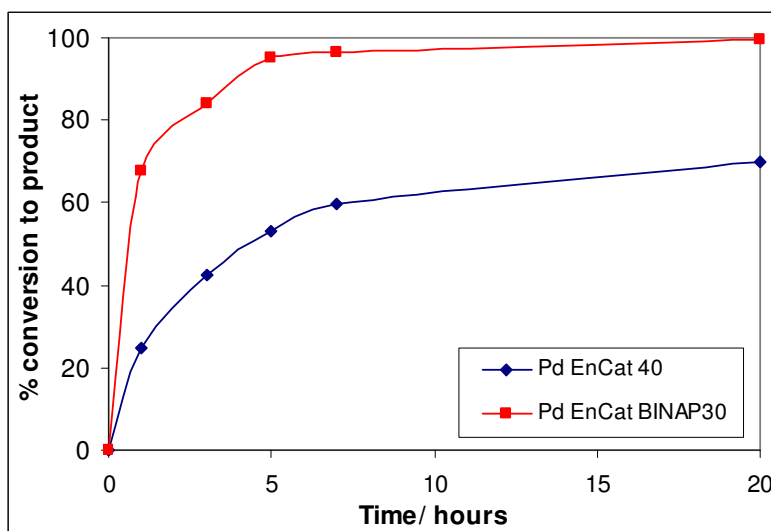


Fig 10 Reaction Kinetics of Pd (II) EnCat™ BINAP30

Reactions under Mild or (Semi) Continuous Conditions with Homogeneous Bases

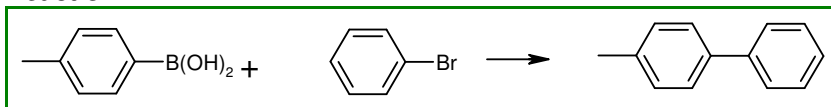
Homogeneous tetra-butylammonium salts can be used to carrying out Suzuki reactions using Pd(II) EnCat™ 40 or Pd(II) EnCat™ 30 under mild conditions with just stoichiometric quantities of base³.

Suzuki reactions proceed in high yield (see Table below) in toluene-methanol (9:1, v:v) in the presence of stoichiometric quantities of ⁿBu₄NOAc, ⁿBu₄NOH (1M in MeOH), ⁿBu₄NOMe (20% w/v in MeOH) and ⁿBu₄NF (1M in THF). At 110°C and in the presence of Pd(II) EnCat™ 40, each of the four ⁿBu₄NX salts are extremely effective at facilitating the cross-coupling of bromobenzene and p-tolylboronic acid giving rise to 4-methylbiphenyl in near quantitative yields (see Table below, entries 1-4). At 40°C high coupling yields are obtained with the use of ⁿBu₄NOH and good yields with ⁿBu₄NOMe and ⁿBu₄NF. The higher coupling yields observed for the ⁿBu₄NX (X = OH, OMe and F) relative to that seen with ⁿBu₄NOAc may be attributed to the strongly nucleophilic nature of the hydroxide, methoxide and fluoride anions, which facilitates the transmetallation process.



Results of Using Pd(II) EnCat™ 40 in the Presence of Tetra-butylammonium Bases

Reaction:



Conditions: 0.4 mol% 0.4 Pd(II) EnCat™ 40, MeOH-MePh (1/9), ${}^n\text{Bu}_4\text{NX}$ (1 mmol), PhBr (1 mmol), MePhB(OH)₂ (1 mmol)

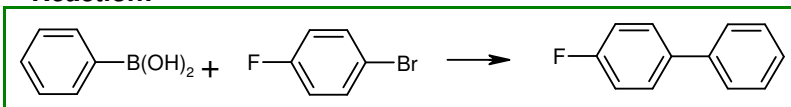
Table of Results:

Entry	Temp (°C)	${}^n\text{Bu}_4\text{NX}$	Yield (%)
1	110	X = OAc	98
2	110	X = OH	98
3	110	X = OMe	98
4	110	X = F	97
5	40	X = OAc	59
6	40	X = OH	85
7	40	X = OMe	74
8	40	X = F	76

Similarly, tetra-butylammonium bases can be used with the more porous Pd(II) EnCat™ 30. Results in the table below for the Suzuki coupling of 4-bromofluorobenzene and phenyl boronic acid in isopropyl alcohol at 70°C show high yield in less than 30 minutes in all cases except for with ${}^n\text{Bu}_4\text{F}$ as base. In addition the crude products contained 20 to 50ppm of palladium (ICP analysis). The high speed of these reactions and the low extent of catalyst leaching suggest that this system could be appropriate for a continuous flow Suzuki application.

Results Using Pd(II) EnCat™ 30 in the Presence Tetrabutylammonium Bases

Reaction:



Conditions: 3 mol% 0.4 Pd(II) EnCat™ 30, IPA, ${}^n\text{Bu}_4\text{NX}$ (3 mmol), FPhBr (1 mmol), PhB(OH)₂ (1.5 mmol), 70°C.

Results:

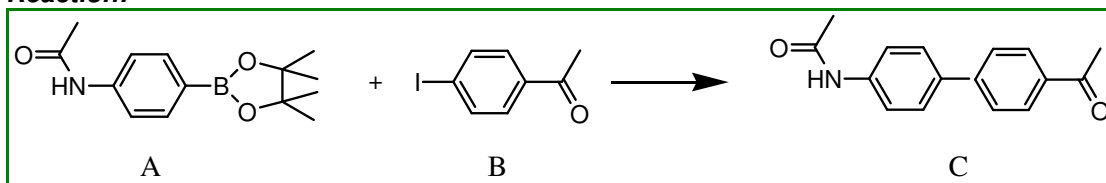
${}^n\text{Bu}_4\text{NX}$	Yield at 30 minutes (%)	Yield at 60 minutes (%)
X = OAc	84	84
X = OH	92	92
X = OMe	80	80
X = F	8	23



Boronate Ester Suzuki Coupling Using Pd(II) EnCat™ 30

Arylboronic esters are another important class of substrates often utilised in Suzuki coupling reactions. These compounds are particularly stable under reaction conditions and side products often resulting from deboronation of boronic acid substrates are avoided. Pd (II) EnCat™ has also shown to be an effective catalyst for the coupling reaction of these types of substrates:

Reaction:



Conditions: 3mol% Pd EnCat™ 30, Base 1.5mmol, **A** 0.6mmol, **B** 0.5mmol, solvent 5 ml, temperature 80°C

Results:

Solvent	Time (h)	Base	% Composition (by ¹ H NMR)		
			A	B	C
Dioxane	7	K ₂ CO ₃	No reaction		
Dioxane	16	K ₃ PO ₄	40	30	30
IPA/W 19/1	16	K ₂ CO ₃	20	0	80

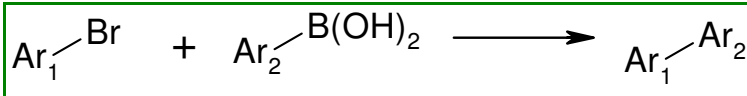
Microwave Assisted Suzuki Couplings

Pd(II) EnCat™ has been shown to be highly effective at catalysing reactions under microwave heating. The following examples below demonstrate use of Pd(II) EnCat™ 40 in the microwave-promoted synthesis of a biaryl library from a diverse set of boronic acids and aryl halides.^{4,5} Optimal conditions were found to be 5 mol% Pd(II) EnCat™ 40, tetrabutylammonium acetate (1 equiv.), aryl bromide (1.5 equiv.), boronic acid (1.0 equiv) in acetonitrile at 150°C in microwave for 960 seconds. These conditions were optimised against substrate reactivity in order to generate robust general conditions in a Personal Chemistry Synthesiser microwave reactor.



Procedure Using Pd(II) EnCat™ 40

Reaction:



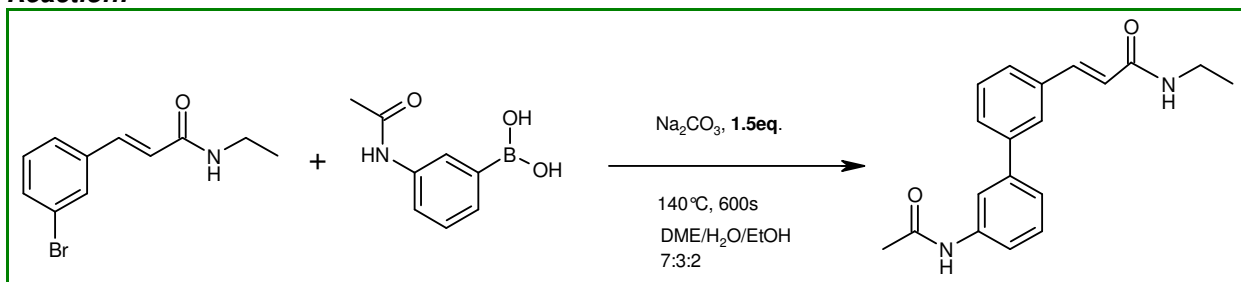
Conditions: 5 mol% Pd(II) EnCat™ 40, Bu₄NOAc, 1 equiv. Ar₁Br, 1.5 equiv. Ar₂B(OH)₂, CH₃CN, 150°C, microwave, 960 sec.

General: Prior to reaction, the base (tetra-*n*-butylammonium acetate) was dispensed in acetonitrile. Following the reaction, the mixture was cooled and the microencapsulated catalyst filtered off prior to purification. Alternatively, the reaction mixture can be applied to a disposable chromatography cartridge and purified directly.

Specific Examples

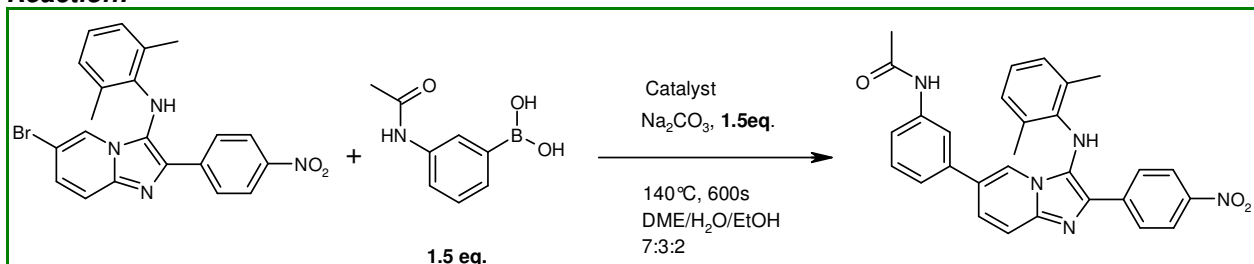
Scientists at Biotage (www.biotage.com) have successfully demonstrated the use of various Pd EnCat™ catalysts in microwave assisted Suzuki couplings⁶:

Reaction:

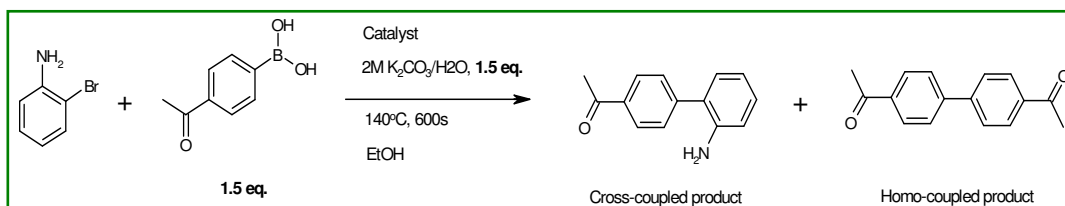


Results:

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

**Reaction:****Results:**

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

Reaction:**Results:**

Catalyst 0.0125eq.	Yield Product % LCMS	Yield Homocoupled % LCMS
PdCl ₂ (PPh ₃) ₂	66	0
Pd(II)EnCat™ TPP30	62	14
Pd(II)EnCat™ TOTP30	76	0

Experimental Conditions

The microwave-assisted Suzuki reactions were performed on an Emrys Liberator™ (www.biotage.com). The experimental conditions had previously been optimised for reactions using a conventional soluble catalyst (PdCl₂(Ph₃P)₂) and were directly applied to the reactions with the Pd EnCat™ catalysts. Reactions were performed at 0.2 mmol scale using 1.5 equivalents of base and boronic acid. The reactants were suspended in 1mL of solvent mixture and subjected to microwave heating for 600s 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 analysed by LCMS.

Workers at Cambridge University have more recently described the design, optimisation and development of a Suzuki cross-coupling protocol mediated by Pd(II) EnCat™ 30⁷. Direct, focussed microwave heating, whilst applying an external cooling source, enabled a



lower than normal bulk temperature to be maintained leading to significant improvements in overall yield and purity of the reaction products. This technique was applied in both batch mode for classical library preparation and in continuous flow applications producing multi-gram quantities of product.

Continuous Flow Suzuki Reactions

A number of reports have suggested that Pd(II) EnCat™ catalysts can be used to facilitate continuous flow Suzuki reactions under mild conditions by passing reagents over a bed of catalyst packed in a column. Best results have been achieved with Pd(II) EnCat™ BINAP30. It is advised that an inert atmosphere be maintained over the catalyst and that the reaction mixture be fully homogeneous. Further information can be provided by writing to info@reaxa.com.

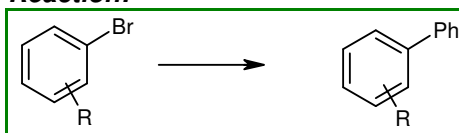


Stille Reactions

Using Pd(II) EnCat™ 30 and 40

Pd(II) EnCat™ 30 and 40 can be used to catalyse Stille couplings in good to excellent yield (Table).²

Reaction:



Conditions: 2.5 mol% 0.4 Pd(II) EnCat™ 40, IPA-MePh (1/1), ^tBu₄NOAc, Me₃SnPh, 90°C.

Results:

Transformation	Yield (%)
R = p-NO ₂	99
R = p-OMe	88
R = p-F	82
R = o-OMe	74

Catalyst Recovery and Reuse

The catalyst can be recovered and re-used as indicated in the table below for a series of sequential Stille reactions with 4-nitrobromobenzene. All reactions proceed to completion giving near quantitative yield of product. A progressive increase in reaction time was observed which may be indicative of some of the more accessible metal being removed during the reaction work-up 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

Substrate: Conditions: 2.5 mol% 0.4 Pd(II) EnCat™ 40, IPA-MePh (1/1), ^tBu₄NOAc, Me₃SnPh, 90°C

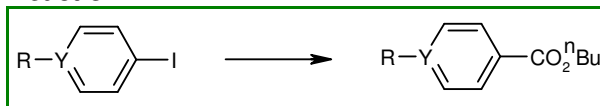


Carbonylation Reactions

Using Pd(II) EnCat™ 30 and 40

Pd(II) EnCat™ 40 and 30 can be successfully used to catalyse the addition of carbon monoxide to aryl iodides to give substituted aryl esters in high yield (see Table below).²

Reaction:



Conditions: 3 mol% Pd(II) EnCat™ 40, ⁿBuOH, Et₃N, CO, 16h, 90°C.

Results:

Transformation	Y	Yield (%)
R = Me	C	89
R = OMe	C	99
R = COMe	C	95
-	N	93

Note: In the experimental procedure, the catalyst was simply removed by filtration. Following evaporation of the filtrate, the crude products were found to contain approximately 80 ppm of Pd (wt/wt) corresponding to about 1% leaching of the palladium from the microcapsules.



References

- (1) Heck, R.F., *J. Am. Chem. Soc.*, **1968**, *90*, 5518.
- (2) **Polyurea-encapsulated palladium(II) acetate: a robust and recyclable catalyst for use in conventional and supercritical media**, Steven V. Ley, Ramarao, C., Gordon, R.S., Holmes, A.B., Morrison, A.J., McConvey, I.F., Shirley, I.M., Smith, S.C., Smith, M.D.; *Chemical Communications* 2002, 10, 1134-1135.
- Encapsulation of palladium in polyurea microcapsules**, Chandrashekar Ramarao, Steven V. Ley Stephen C. Smith, Ian M. Shirley, Nathalie DeAlmeida, *Chemical Communications* 2002, 10, 1132-1133.
- Polyurea-Encapsulated Palladium Catalysts: The Development and Application of A New Versatile Immobilised Homogeneous Catalyst Technology**, Pears, D. A., Smith S. C.; *Aldrichimica Acta*, 2005, 8(1), 23-34
- Investigating Pd EnCat catalysts**, Braodwater, S.J.; McQuade, D.T.; *J. Org. Chem.*, 2006, 71, 2131.
- Gil-Moltó, J., Karlström, S., Nàjera, C.; *Tetrahedron*, **2005**, 61, 12168
- (3) **Efficient batch and continuous flow Suzuki reactions under mild conditions, catalysed by polyurea-encapsulated palladium(II) acetate and tetra-n-butylammonium salts**, Lee, C.K.Y., Holmes, A.B., Ley, S.V., McConvey, I.F., Al-Duri, B., Leeke, G.A., Santos, R.C.D., Seville, J.P.K.; *Chemical Communications* **2004**, in press.
- (4) Smith, S.C.; Lecture Given at the Combinatorial Gordon Conference, Queens College Oxford, 23rd-27th August **2004**
- (5) Smith, S.C.; Lecture Given at the RSC CombiChem Comes of Age Conference, Cambridge, 1-3rd July **2004**.
- (6) Pilotti, P., Lundin, R.; Biotage, unpublished results and used with permission, Feb-05
- (7) **Microwave-Assisted Suzuki Coupling Reactions with an Encapsulated Palladium Catalyst for Batch and Continuous Flow Reactions**, Baxendale, I.R., Griffiths-Jones, C.M., Ley, S.V., Tranmer, G.K.; *Chem. Eur.*, **2006**, 4407-16