



Johnson Matthey Catalysts

Catalysis & Chiral Technologies

FibreCat® Anchored Homogeneous Palladium Catalysts for Cross Coupling

The use of palladium in homogeneous catalysts for cross coupling reactions is steadily increasing in pharmaceutical processes. However, these systems continue to present a notable concern over potential metal contamination with palladium in the product. To address these concerns, Johnson Matthey has developed a new line of tunable, polymer supported palladium catalysts of electron rich and bulky monodentate and bidentate ligands that provides:

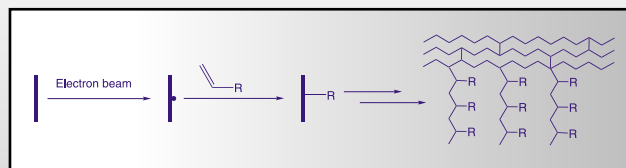
- Ease of separation
- Selectivity
- Recyclability
- Negligible metal leaching

Fibre vs. Bead Technology

In contrast to traditional bead technology where swelling is required for the diffusion of the substrate to interact with the reactive sites, the functional groups of the FibreCat catalysts are located at the exterior of the fiber, allowing ready access to the substrate for increased activity and selectivity.

FibreCat Structure

FibreCat is a patented technology, wherein the polymer backbone is produced commercially by graft copolymerization of polypropylene, with functionalized monomers under electron beam irradiation conditions.



Active sites (red) on a traditional bead vs. fiber



FibreCat Palladium Series

The Palladium FibreCat series was developed specifically for C-C coupling reactions. The design of these catalysts allows them to be tuned in three ways by changing:

1) The palladium precursors 2) The ligand on the support 3) The ligand on the metal

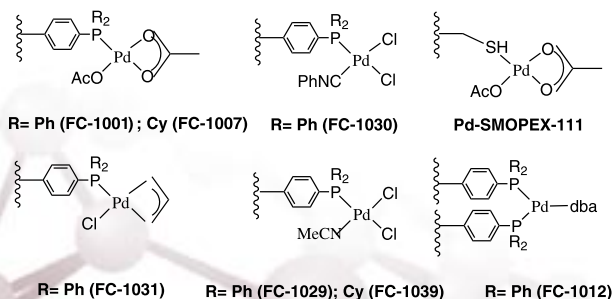
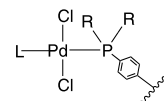


Figure 1. Examples of First Generation FibreCats for Routine Substrates Such as Ar-I and Ar-Br.



FC-1032-1048

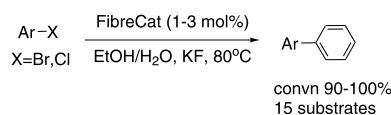
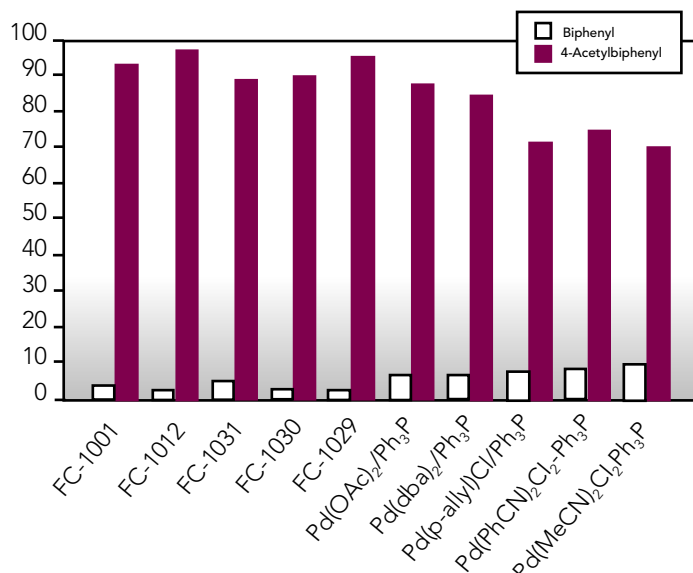
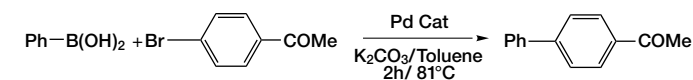


Figure 2. Basic Structure of Second Generation FibreCats (FC1032-1048) Designed for Challenging Substrates

Suzuki & Heck Coupling of Aryl Bromides

The Pd-FibreCats below have shown to be effective in the coupling of a variety of aryl bromides, in terms of selectivity, activity and low leaching with respect to the homogeneous systems. Pd-SMOPEX-111 demonstrated good activity for both Heck and Suzuki coupling of simple aryl bromides.

Suzuki coupling of p-bromoacetophenone using Pd-Fibre-Cat vs their respective homogeneous systems



Colacot, et.al., Organometallics **2002**, 21, 3301

Heck coupling of Ar-Br using Pd-SMOPEX-111

Entry	Substrate	Product	Yield	Pd Leaching
1			80%	4.0 PPM
2			70%	4.8 PPM
3			80%	4.9 PPM
4			77%	5.8 PPM
5			87%	8.7 PPM
6			80%	4.9 PPM

Reaction conditions: 10 mmol of substrate, 13 mmol of Heck acceptor, 0.8 g of Pd-Smopex (2.5 wt % of Pd with respect to the substrate), 10 mL of NMP, 118°C, 16-24 h.

Prasad, et.al., Org. Process Res. Dev., **2007**, 11, 769-772

Suzuki Coupling of Aryl Chlorides

To our knowledge there are very few examples of supported catalysts available for Suzuki coupling of aryl chlorides. For challenging substrates, such as electron-rich aryl bromides and chlorides, the first generation FibreCats were tuned in such a way to induce more electron density and bulkiness onto the palladium.

New Palladium FibreCat Catalysts

R	L	CAS#	%Pd	code
Ph	t-Bu ₃ P	960620-60-4	4.47	FC-1032
	Q-Phos	1073550-94-3	6.34	FC-1033
	PhP(t-Bu) ₂	1073551-04-8	4.62	FC-1034
	Dppf	1073551-09-3	4.64	FC-1035
	BINAP	1073551-11-7	4.85	FC-1036
	Dippf	1073551-12-8	5.23	FC-1037
	(Me ₂ NC ₆ H ₄)P(t-Bu) ₂	1073551-14-0	4.37	FC-1034A
Cy	MeCN	1073549-97-9	9.61	FC-1039
	t-Bu ₃ P	1073551-16-2	5.76	FC-1042
	Q-Phos	1073551-18-4	6.61	FC-1043
	PhP(t-Bu) ₂	1073551-20-8	6.48	FC-1044
	Dppf	1073551-23-1	5.61	FC-1045
	BINAP	1073551-49-1	6.63	FC-1046
	Dippf	1073552-02-9	7.47	FC-1047
	(Me ₂ NC ₆ H ₄)P(t-Bu) ₂	1073552-38-1	4.43	FC-1048

Relative superior activity of FC-1034A & FC-1042



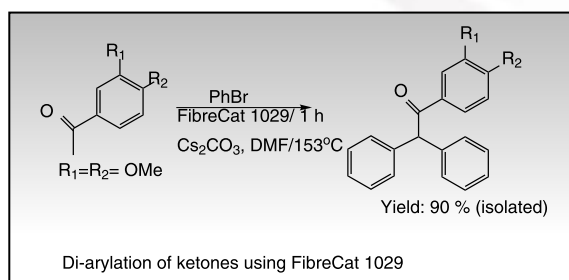
catalyst	entry	loading	time	yield
FC-1032	1	2 mol%	8	11
	2	3 mol%	15	70
FC-1039	3	2 mol%	8	25
	4	3 mol%	15	36
FC-1042	5	2 mol%	8	41
	6	3 mol%	15	100 (93) ^a
FC-1029	7	2 mol%	8	16
	8	3 mol%	15	16
Pd-Smopex 111	9	2 mol%	8	--
	10	3 mol%	15	6
FC-1034	11	2 mol%	8	59
	12	3 mol%	15	100 (92) ^a
a.) isolated yield	13b	3 mol%	4	100 (94)
b.) KF was used as a base				

Colacot, et.al., Organometallics, **2008**, 27, 5605-5611

α -Arylation with Aryl Bromides

FibreCat 1007 and 1029 were used for the stereoselective mono- and diarylation of ketones. The arylated products were isolated in very good yield and selectivity. The α,α -diarylated products result from acetophenone, resemble Tamoxifen, an adjuvant drug used for the treatment of estrogen receptor-positive breast cancer.

Di-arylation of ketones using FibreCat 1029



F. Churrucá et al., *Tetrahedron*, **2004**, 60, 2393–2408

F. Churrucá et al., *Tetrahedron Lett.*, **2003**, 44, 5925–5929

Leaching and Recyclability

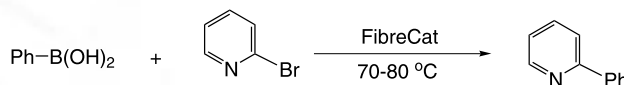
An ideal supported homogeneous catalyst should demonstrate its application for higher activity without undergoing any leaching and therefore give very good recyclability. Johnson Matthey has performed several studies in this area, summarized in the tables below. Subsequent studies report the re-usability of FC-1029 for five times in the α -arylation of a ketone, by simple treatment of the catalyst.

Recycling of catalysts used in the coupling of 4-bromoanisole with phenyl boronic acid in EtOH-H₂O solvent and K₂CO₃ base at 70°C for 4 h

catalyst	loading	cycle	yield (isol)	leaching
FC-1032	1 mol%	1	100 (94)	<1 ppm
		2	100 (92)	<1 ppm
		3	100 (93)	5 ppm
		4	95 (87)	10 ppm
FC-1039	0.5 mol%	1	100 (93)	<1 ppm
		2	98 (91.5)	<1 ppm
		3	94 (88)	1 ppm
		4	16	20 ppm
FC-1029	0.5 mol%	1	100 (94)	0 ppm
		2	100 (91)	<1 ppm
		3	92 (88)	1 ppm
		4	26	30 ppm
Pd Smopex 111	1 mol%	1	100 (92)	not detected
		2	100 (91)	<1 ppm
		3	77 (65)	1 ppm
		4	5	65 ppm

Colacot, et al., *Organometallics* **2002**, 21, 3301

Recycling of the catalysts used in the reaction of 2-bromopyridine with PhB(OH)₂ in toluene as solvent and K₂CO₃ for 15 h

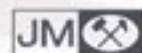


catalyst	loading	cycle	yield (1501)	leaching
FC-1032	3 mol%	1	100 (92)	<1 ppm
		2	90 (82)	<1 ppm
		3	60	<1 ppm
		4	58	<1 ppm
FC-1042	3 mol%	1	100 (92)	<1 ppm
		2	100 (94)	<1 ppm
		3	91 (82)	<1 ppm
		4	82	<1 ppm
FC-1034A	3 mol%	1	100 (94)	<1 ppm
		2	100 (91)	<1 ppm
		3	100 (91)	<1 ppm
		4	96 (88)	<1 ppm

Colacot, et al., *Organometallics* **2002**, 21, 3301

The Palladium FibreCat family is a unique class of polymer-supported systems useful for various coupling reactions, and works as a cost effective process technology, especially for aryl bromides.

The ability to tune FibreCat makes it a very practical catalyst system for various substrates with palladium leaching in the acceptable range for API even under relatively drastic conditions, irrespective of the number of recycles.

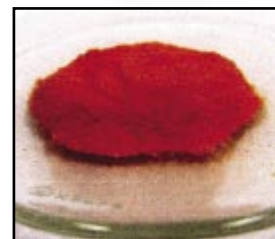


Johnson Matthey Catalysts

Catalysis & Chiral Technologies

Applications Table

Reaction Type	Substrate	Catalyst
Heck	aryl iodides & aryl bromides	Pd-SMOPEX-111
Suzuki	neutral aryl bromides	FC-1032, FC-1029, FC-1031
	aryl iodides & activated aryl bromides	FC-1029, Pd-SMOPEX-111, FC-1001, FC-1035
	aryl triflates & unactivated aryl bromides	FC-1032, FC-1034, FC-1035, FC-1034A
	activated aryl chlorides	FC-1032, FC-1034, FC-1037
	unactivated aryl chlorides	FC-1034A, FC-1042, FC-1048, FC-1044
Carbonylation	aryl iodides and bromides	FC-1032, FC-1034A, FC-1035
α -arylation	aryl bromides	FC-1029, FC-1032, FC-1007, FC-1035



FC-1037

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