Reaxa LaPCat$^{\mathrm{TM}}$ Perovskite Catalyst User Guide
(July 2006)

Contents:

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LaPCat^{TM} Perovskites as Catalysts

Perovskites are a class of inorganic compounds with the general structure ABO_3. A wide variety of metals are tolerated for *A* and *B* including mixtures of several elements.
Initially used as autocatalysts, certain perovskites also efficiently catalyse organic reactions at very low catalyst loadings.[1-4] The small amount of precious or active metal in the perovskite implies very high turnover numbers. Furthermore the catalysts are readily removed by filtration, are recyclable and lead to extremely low leaching into solution making perovskites an attractive alternative to homogeneous catalysis. Perovskites are compatible with microwave conditions and tolerate most substrate functional groups.

Catalyst Formulation and Physical Data

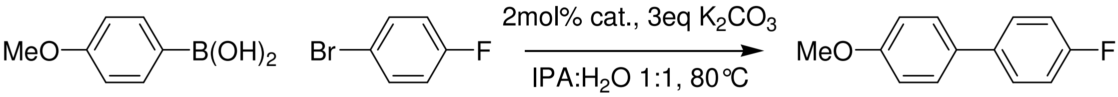
This LaPCat^{TM} test kit contains a representative range of perovskites prepared by Reaxa's partner which have been shown to be applicable in a wide range of organic reactions and coupling.

Catalyst	*Formulation*	*Formula Weight*	*Pd (wt%)*	*Cu (wt%)*	*Surface Area (m^2/g)*	*Mean Particle Size (µm)*
FP2	$LaFe_{0.95}Pd_{0.05}O_3$	245.29	2.169	-	5.5	41.1
FP8	$LaFe_{0.80}Pd_{0.20}O_3$	252.87	8.417	-	5.7	3.3
CoP	$LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$	246.46	2.159	-	3.4	4.0
CuP	$LaFe_{0.57}Cu_{0.38}Pd_{0.05}O_3$	248.21	2.144	8.20	12	3.7
CoCu	$La_{0.9}Ce_{0.1}Co_{0.60}Cu_{0.40}O_3$	247.81	-	8.64	7.9	5.4
YBCu	$YBa_2Cu_3O_7$	666.22	-	24.1	0.3	10.6

Suzuki Reactions

Catalyst Choice

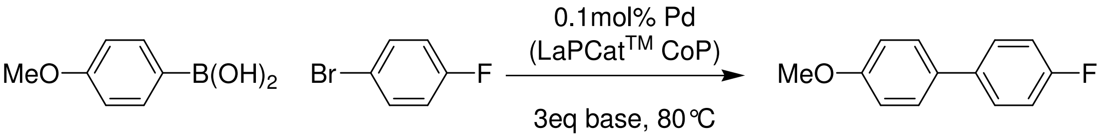
The full range of LaPCat^{TM} perovskites were examined for application in the Suzuki coupling. The results in a standard test reaction showed quantitative conversions within an hour using any of the palladium containing catalysts. Extremely low palladium loadings of as little as 0.1 mol% Pd (corresponding to *perovskite* loading of 2 mol% due the low precious metal content of these materials) were employed. The palladium free perovskites or no catalyst gave no conversion following overnight reactions.



	LaPCat^{TM}	*Time (h)*		*Conversion (%)*
1	FP2	1	-	100
2	FP8	1	-	100
3	CoP	1	-	100
4	CuP	1	-	100
5	CoCu	-	22	0
6	YBCu	-	22	0
7	no catalyst	-	22	7

Bases

Three common bases used in Suzuki reactions were applied in the perovskite catalysed standard reaction, using LaPCat^{TM} CoP as the catalyst.

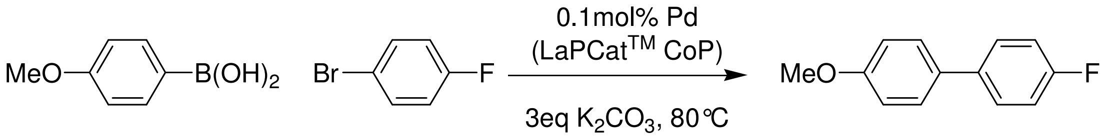


	Solvent	*Base*	*Conversion (%)*			
			1h	*3h*	*5h*	*22h*
1	IPA/H_2O 1:1	K_2CO_3	100%	-	-	-
2	IPA/H_2O 1:1	Cs_2CO_3	100%	-	-	-
3	IPA/H_2O 1:1	K_3PO_4	100%	-	-	-

Quantitative conversions were rapidly attained with each base, showing another potential for optimisation with perovskite catalysts.

Solvents

A range of common Suzuki solvents have been screened, showing a wide compatibility with perovskites in this reaction.

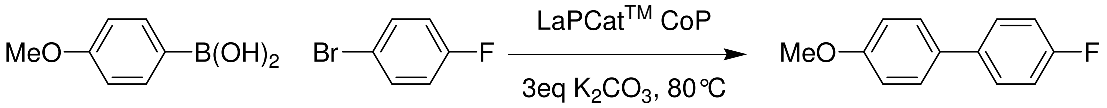


	Solvent	Solvent:Aqueous	Conversion (%)			
			1h	3h	5h	22h
1	IPA	1:1	92	100	100	100
2	Dioxane	1:1	99	100	100	100
3	MeCN	1:1	29	12	41	100
4	DME	1:1	-	-	-	82
5	THF	1:1	-	-	-	92
6	DMF	1:1	-	-	-	87
7	Toluene	1:1	-	-	-	12
8	IPA	2:1	-	-	-	100
9	Dioxane	2:1	-	-	-	100
10	DME	2:1	-	-	-	37
11	IPA	4:1	-	-	-	100

The reaction showed tolerance to changes in the proportion of the aqueous phase and gave quantitative or high conversion after 22 hours in all but toluene. Where tested, the time to reach complete reaction was in fact much quicker with most solvents.

Catalyst Loading

The required quantity of catalyst was probed by performing the standard Suzuki coupling at three different palladium loadings. Effective catalysis was demonstrated down to 0.01 mol% Pd (0.25 mol% LaPCat^{TM}).



	LaPCat™	*Loading (mol% Pd)*	*Solvent*	*Yield after 22 h (%)*
1	CoP	0.1	IPA/H_2O	100[a]
2	CoP	0.05	IPA/H_2O	87[b]
3	CoP	0.012	IPA/H_2O	93[b]
4	FP2	0.005	IPA/H_2O	85[b]

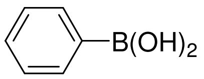
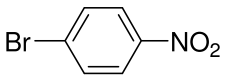
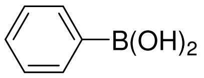
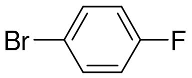
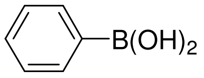
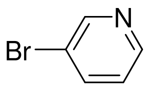
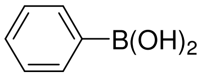
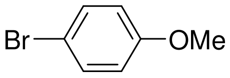
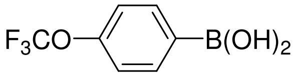
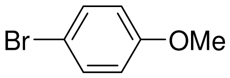
[a] Conversion by HPLC; [b] Isolated yield

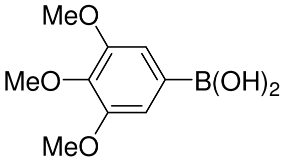
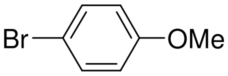
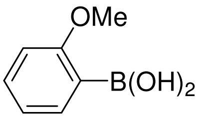
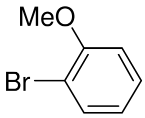
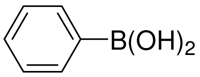
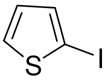
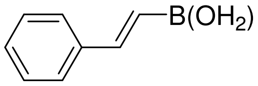
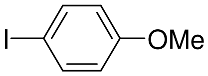
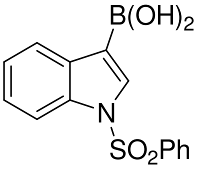
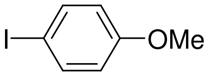
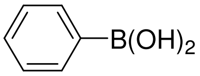
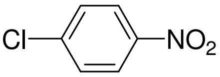
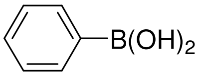
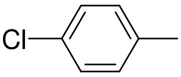
Metal Leaching

Previous work[2] has shown extremely low palladium levels in the crude reaction products. ICP analysis gave Pd contents ranging from 0.5-2.4 ppm (compared to 0.3 ppm Pd in the starting materials).

Substrates

Numerous boronic acids and esters have been successfully coupled with aryl bromides, iodides and chlorides.[2,3] Aryl iodides showed success in a few instances where bromides failed (eg vinyl boronic acids or sulphur containing compounds). In some cases the addition of tetra-*n*-butylammonium bromide (TBAB) gave improved yields. The less reactive aryl chlorides required microwave heating to give good yields for activated substrates only. A selection of substrates is shown below.

	Boronic Acid	*Halide*	*Time (h)*[a]	*Yield (with TBAB)*
1			10	92 (95)
2			3	91
3			18	85
4			0.5	95
5			18	95

6			18	60 (95)
7			1	89
8			18	61 (89)
9			18	92
10			18	70 (70)
11			1[b]	71
12			1[b]	51

[a] Standard conditions: LaPCat™ CoP (0.1 mol% Pd), 3 eq K_2CO_3, 1:1 IPA/water, 80℃.

[b] Microwave conditions: LaPCat™ CoP (0.25 mol% Pd), 3 eq Na_2CO_3, 1:1 IPA/water, 135℃.

Experimental

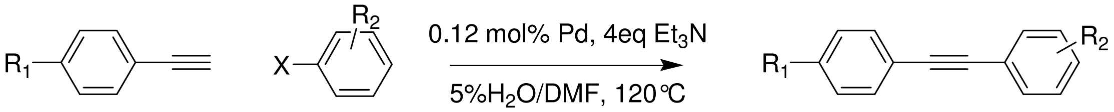
Typical Suzuki Coupling Procedure

1-Bromo-4-fluorobenzene (1.64 ml, 0.015 mol) and benzene boronic acid (2.19 g, 0.018 mol) were dissolved in IPA (40 ml) and aqueous potassium carbonate (6.2 g, 0.045 mol in 40 ml water). The reaction mixture was flushed with nitrogen, LaPCat™ FP2 catalyst (3.7 mg, 0.005 mol% Pd) was added and heated at 80 ℃ for 18h. The reaction mixture was cooled, diluted with EtOAc (100 ml) and filtered through a celite plug. The organic phase was separated and washed with water (100 ml), extracting the aqueous with EtOAc. The combined organic layers were dried over $MgSO_4$, solvents removed and purified by flash column chromatography to yield biphenyl product (2.1 g, 85%).

Sonogashira Reactions

Catalyst Choice

At present only selected perovskites have been extensively used in the Sonogashira reaction.[4] Good results have been obtained using palladium only LaPCat™ CoP and palladium/copper LaPCat™ CuP.



	R_1	*R_2*	*LaPCat™*	*Time (h)*	*Yield (%)*
1	H	4-Me	FP2	22	11
2	H	4-Me	FP8	22	10
3	4-MeO	4-COMe	CoP	16	96
4	4-MeO	4-COMe	CuP	16	86
5	H	4-Me	CoCu	22	5
6	H	4-Me	YBCu	22	22

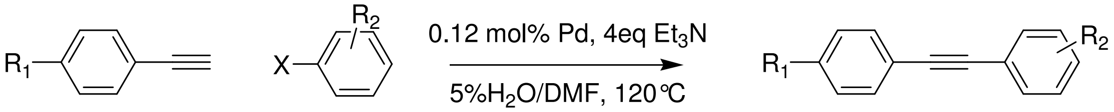
Comprehensive testing of the full LaPCat™ range in the Sonogashira reaction is in progress.

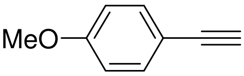
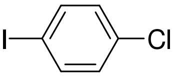
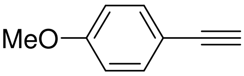
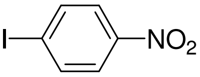
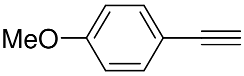
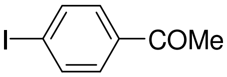
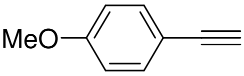
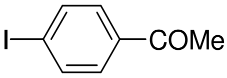
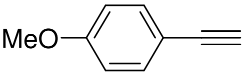
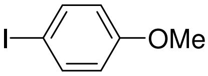
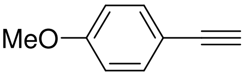
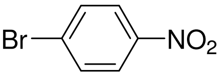
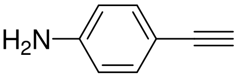
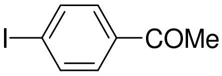
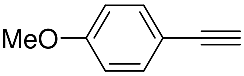
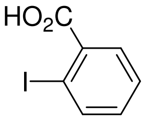
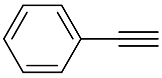
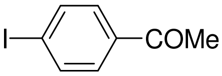
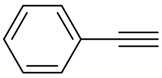
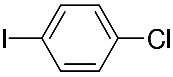
Bases and Solvents

Sonogashira reactions with perovskites have been shown to be effective in aqueous DMF and DMA as solvent, using triethylamine as base.

Substrates

A range of halides and selected acetylenic compounds have been used in the Sonogashira coupling.[4] Exploring the use of perovskite catalysts in these reactions has suggested that optimisation of yields can often be achieved by varying the perovskite used.



	Acetylene	*Halide*	*Solvent*	*LaPCat™*	*Yield*
1			DMF	CuP	71
2			DMF	CuP	96
3			DMF	CoP	96
4			DMF	CuP	86
5			DMA	CuP	47
6			DMA	CuP	71
7			DMF	CuP	84
8			DMF	CuP	52
9			THF	CuP	54[a]
10			Neat	CuP	75[b]

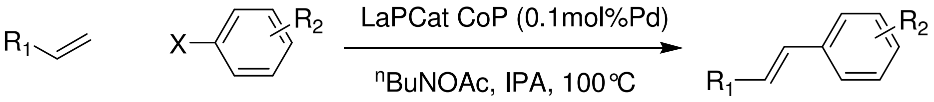
[a] 0.2 mol% Pd, 1.1 eq acetylene, 3 eq BuN_4OAc, THF, 60 °C, 20 h.

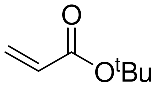
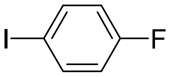
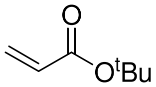
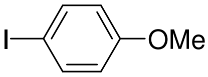
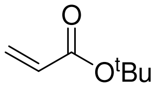
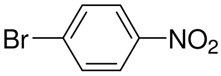
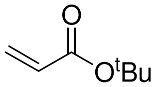
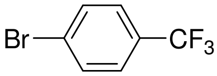
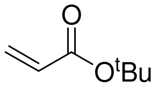
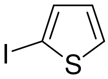
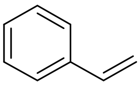
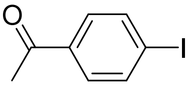
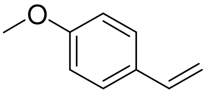
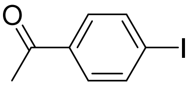
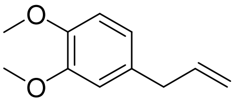
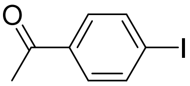
[b] Microwave conditions: 1 eq aryl iodide, 0.12 mol% Pd, 2.2 eq acetylene, 2 eq Na_2CO_3, 1 eq TBAB, MW, 175 °C, 20 min.

Again, work is in progress to extend to range of solvents and substrates applied in this reaction, as is the use of microwave conditions.

Heck Reactions

So far, LaPCat^{TM} CoP has been predominantly investigated in Heck couplings, though the other palladium containing catalysts have also shown activity. A relatively limited range of substrates has been screened. However, for the various aryl halides used, good yields were obtained with t-butyl acrylate[5] and acceptable yields with other alkenes.



	Alkene	*Halide*	*Time (h)*	*Yield (%)*
1			6	95
2			6	99
3			18	70
4			6	90
5			18	51
6			18	59
7			18	56
8			18	73

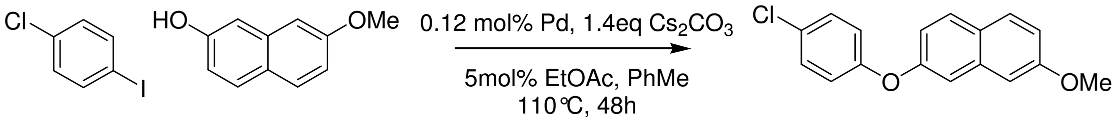
Work is in progress to extend the scope of perovskites in the Heck reaction.

Ullmann Reactions

Perovskites have been applied to a wide variety of substrate in the Ullmann coupling to produce ethers and thioethers. Copper containing perovskites were found to be successful.

Catalyst Choice

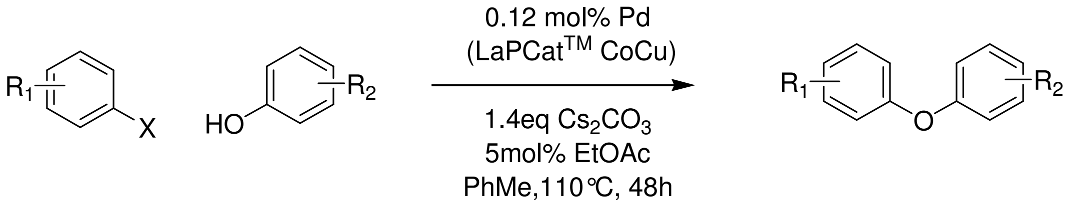
Using a standard reaction, copper containing perovskites were found to be successful.[4]

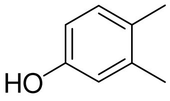
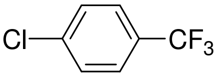
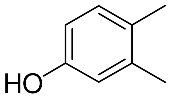
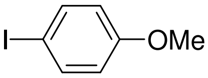


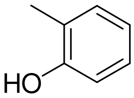
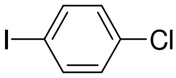
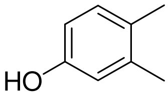
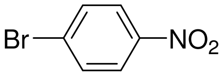
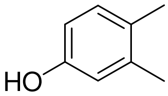
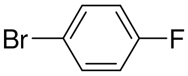
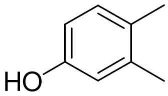
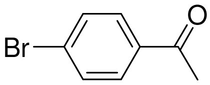
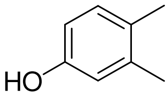
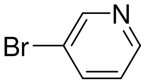
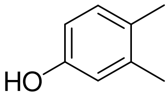
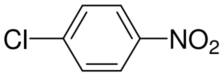
	LaPCat^{TM}	*Time (h)*	*Yield (%)*
1	FP2	-	-
2	FP8	-	-
3	CoP	-	-
4	CuP	48	65
5	CoCu	48	82
6	YBCu	48	73

Substrates - Phenols

Using LaPCat^{TM} CoCu a range of substrates were tested using the standard reaction conditions in the Ullmann coupling.[4]



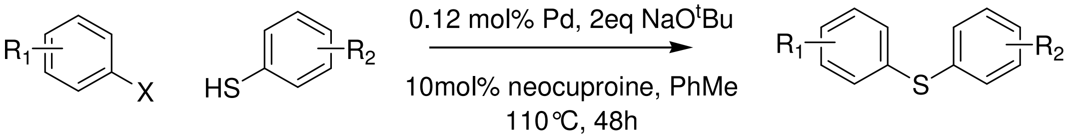
	Phenol	*Halide*	*Yield (%)*
1			90
2			78

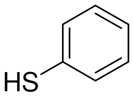
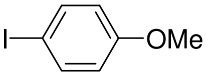
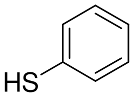
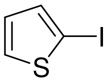
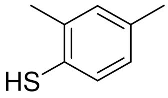
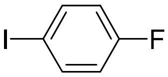
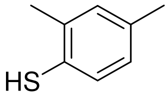
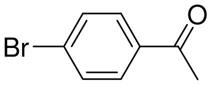
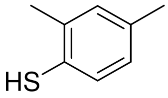
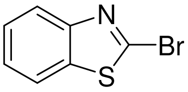
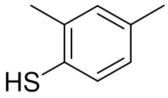
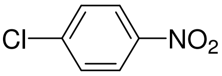
3			71
4			89
5			71
6			86[a]
7			74
8			46

[a] 25% isolated yield in the absence of EtOAc

Substrates – Thiophenols

The successful application of LaPCat™ CoCu to phenols was transferred to thiophenol generating a range of thioethers.[4]



	Thiophenol	*Halide*	*Yield (%)*
1			90
2			64
3			100[a]
4			99
5			78
6			100

[a] No conversion in the absence of neocuproine

Perovskite Removal

Due to the finely powdered form of LaPCat^{TM} perovskites, their effective removal from reaction mixtures is an important issue. On a small screening reaction scale, the use of 0.45 μm syringe filters has been found to be a simple and quick means of catalyst removal.

In larger scale reactions, use of filter aids has proved effective, especially Celite™, giving complete removal of the LaPCat^{TM} without excessive quantities required and good filtration speeds.

Any residual contamination of glassware following reaction can be easily cleaned up by stirring with 1N HCl aq at 60 ℃ for 1-2 hours.

References

1. S. V. Ley, M. D. Smith, C. Ramarao, A. F. Stepan, H. Tanaka; U.S. Pat. Appl. Publ., 2005, US 2005215804.
2. Palladium-Containing Perovskites: Recoverable and Reusable Catalysts for Suzuki Couplings. M. D. Smith, A. F. Stepan, C. Ramarao, P. E. Brennan, S. V. Ley; *Chem. Commun.*, 2003, 2652-3.
3. Heterogeneous or Homogeneous? A Case Study Involving Palladium-Containing Perovskites in the Suzuki Reaction. S. P. Andrews, A. F. Stepan, H. Tanaka, S. V. Ley, M. D. Smith; *Adv. Synth. Catal.*, 2005, **347**, 647-54.
4. Copper and Palladium-Containing Perovskites: Catalysts for the Ullmann and Sonogashira Reactions. S. Lohmann, S. P. Andrews, B. J. Burke, M. D. Smith, J. P. Attfield, H. Tanaka, K. Kaneko, S. V. Ley; *Synlett*, 2005, 1291-5.
5. A. F. Stepan, Degree of Postgraduate Studies Dissertation, University of Cambridge, 2004.