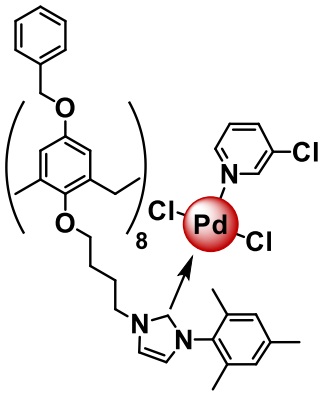
Supported catalysts for fine chemistry

NOVECAL is a French company specialized in the design and synthesis of cyclic oligomers, and of related supported catalysts. Our palladium-NHC catalysts show excellent efficiency in Suzuki C-C and Buchwald-Hartwig C-N cross coupling reactions along with a low metal leaching inside products after filtration. We are currently developing rhodium-phosphine supported catalysts for hydrogenation, cobalt-salen supported complexes for the opening of epoxides, and copper-phosphine supported complexes for C-X couplings.

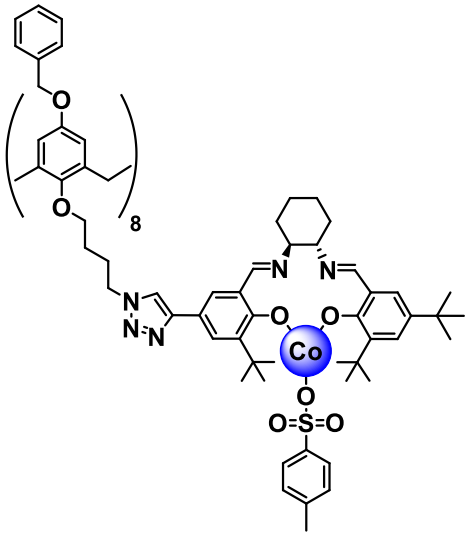
We also offer our expertise in various fields of catalysis:

- Cost optimization (catalysts screening and loading optimization, study and optimization of process parameters…)
- Custom catalysts heterogenization
- Realization and optimization of challenging reactions

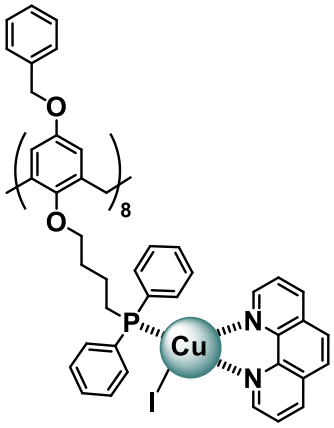
Structure of NOVECAL catalysts



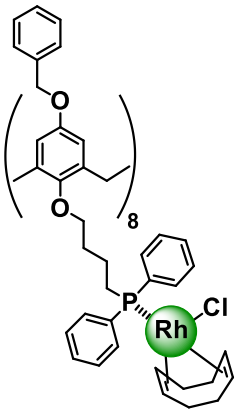
NOVECAT G1-01
Suzuki coupling



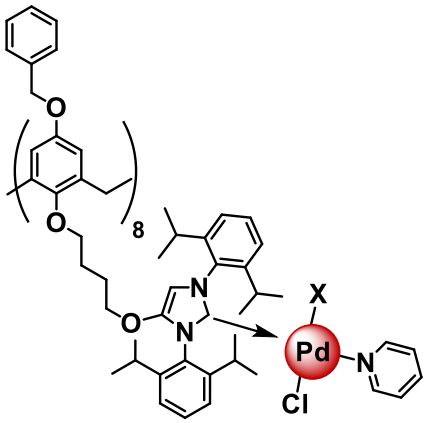
NOVECAT Co-01
Asymetric epoxide opening



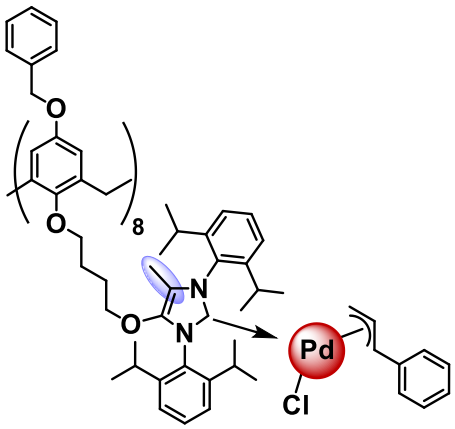
NOVECAT Cu-01
C-X Coupling



NOVECAT Rh-01
Hydrogenation reaction



NOVECAT G2
Suzuki coupling with challenging aryl halides

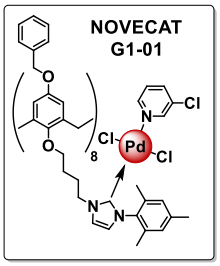


NOVECAT G3-01
Buchwald coupling with challenging substrates

General properties of NOVECAL catalysts

- Efficient at low catalytic loading
- Low metal leaching after simple filtration
- Robust structure, including high and reproducible metal content
- Air stable and easy to handle
- Compatible with diluted or concentrated reaction mixtures
- Soluble in polar solvents >> easy washing of the process equipment

Suzuki cross-coupling reaction with NOVECAT G1



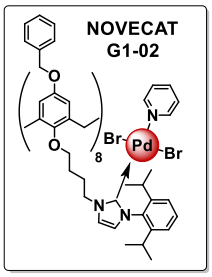
Ar_1-Br + $(HO)_2B$-Ar_2 → Ar_1-Ar_2

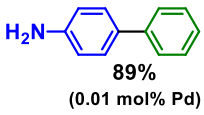
1 eq 1.5 eq

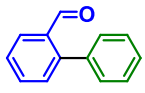
NOVECAT G1 (X mol% Pd)

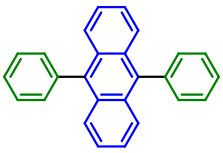
K_3PO_4, EtOH, 80 °C, 2 h

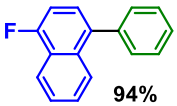
C = 0.25 - 0.5 M

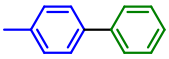


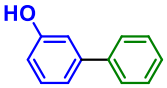

89%
(0.01 mol% Pd)

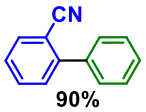

87%
(0.5 mol% Pd)


97%
(0.2 mol% Pd)


94%
(0.05 mol% Pd)


77%
(0.001 mol% Pd)
mole scale


88%
(0.5 mol% Pd)


90%
(0.1 mol% Pd)
Pd leaching : **3 ppm**

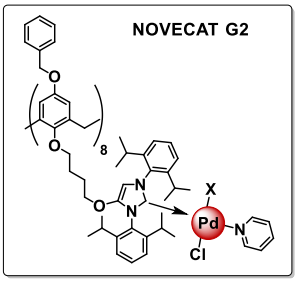
For publications on those results, see: a) *Dalton Trans.* **2018**, *47*, 13843; b) *React. Chem. Eng.* **2020**, *5*, 1509.

Suzuki cross-coupling reaction with NOVECAT G2

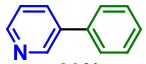
Ar_1-X + $(HO)_2B$-Ar_2 → Ar_1-Ar_2

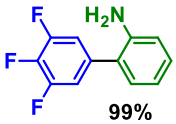
NOVECAT G2 (X mol% Pd)

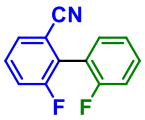
K_3PO_4, EtOH, 80 °C, 2 h

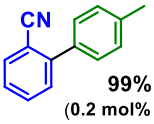


Preparation of pharmaceutical key intermediates from aryl bromides:

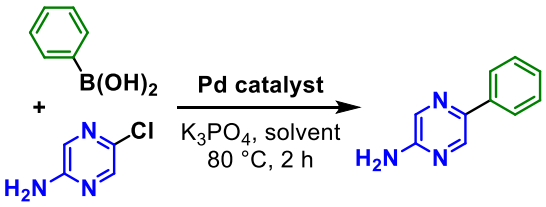

89%
(0.1 mol% Pd)
Pd leaching : **10 ppm**


99%
(0.2 mol% Pd)
Fluxapyroxad intermediate


95%
(0.5 mol% Pd)
Selective $GABA_A$ agonist intermediate


99%
(0.2 mol% Pd)
Valsartan intermediate

Comparison of Pd catalysts with functionalized aryl chlorides:



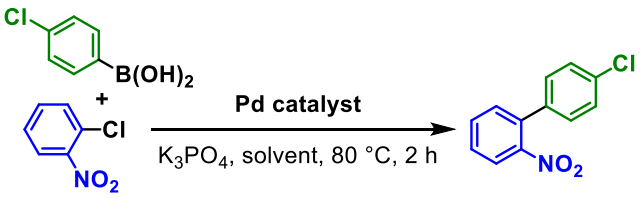
1 mol% **NOVECAT G2** : **94%**

1 mol% **$Pd(OAc)_2$/XPhos** : **87%**

1 mol% **Pd/C** : **0%**

1 mol% **$Pd(PPh_3)_4$** : **4%**

Intermediate of a highly selective drug candidate for obesity treatment



0.5 mol% **NOVECAT G2** : **88%** (Pd leaching : **31** ppm)

0.5 mol% **$Pd(OAc)_2$/XPhos** : **88%** (Pd leaching : **1450** ppm)

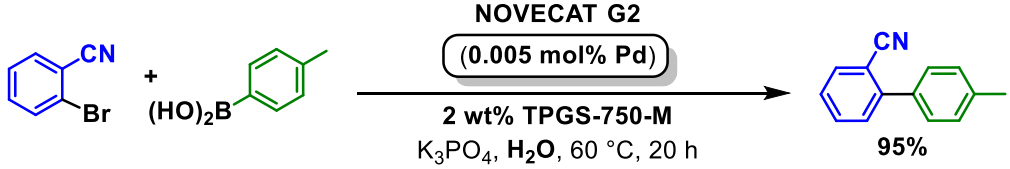
1 mol% **Pd/C** : **5%**

1 mol% **$Pd(PPh_3)_4$** : **29%**

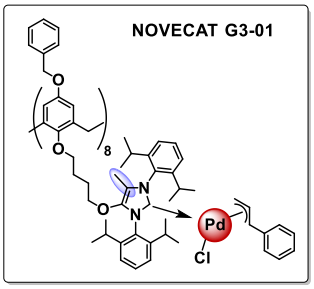
1 mol% **PEPPSI-IPr** : **68%**

Boscalid intermediate

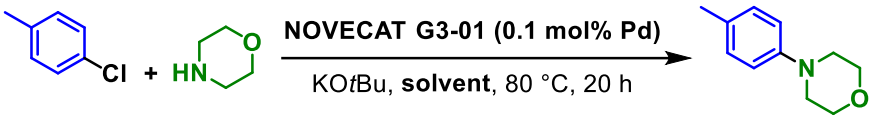
Synthesis of Valsartan intermediate in water using very low catalytic loading:



Buchwald-Hartwig C-N coupling

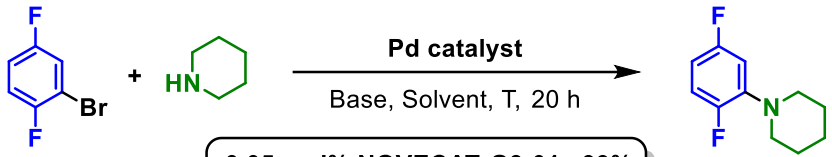


Screening of solvents with an aliphatic amine:



Solvent	Yield (%)	Pd content after filtration (ppm)
MeTHF	99	24.5
Dioxane	99	25
CPME	93	38
Methylcyclohexane (0.2 mol% Pd)	97	9
Toluene (0.2 mol% Pd)	99	43

Synthesis of a model intermediate for RORc Inhibitor GDC-0022:

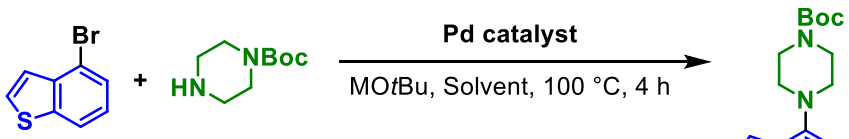


0.05 mol% NOVECAT G3-01 : 99%

2 mol% $Pd_2(dba)_3$/XantPhos : 58%

2 mol% $Pd_2(dba)_3$/XPhos : 49%

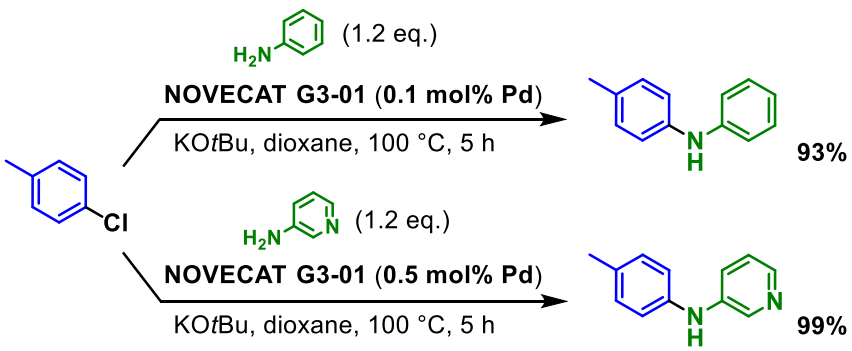
Preparation of Brexpiprazole's key intermediate:



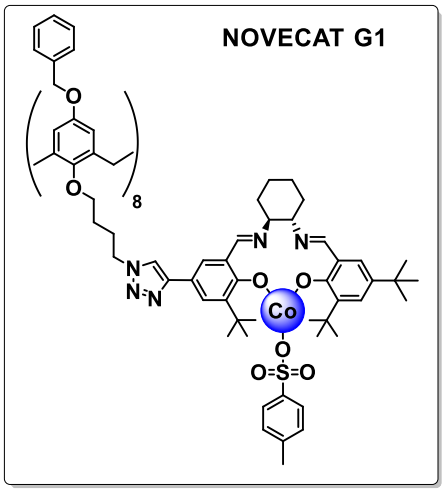
0.2 mol% NOVECAT G3-01 : 96% (Pd leaching : 8 ppm)

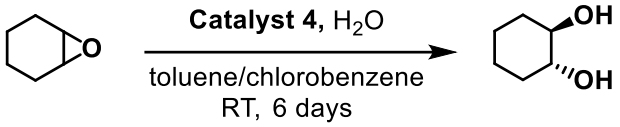
0.5 mol% $Pd_2(dba)_3$•$CHCl_3$/BINAP : 99% (Pd leaching : 520 ppm)

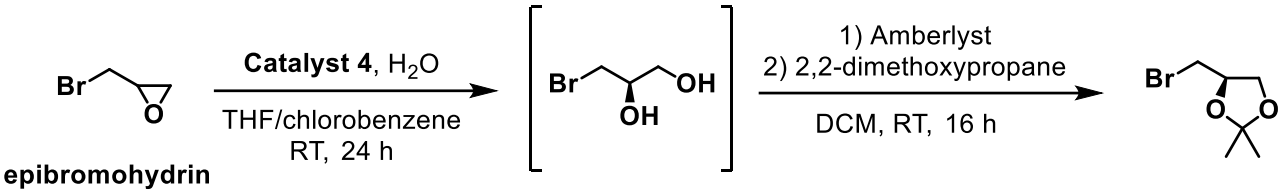
Coupling with aromatic amines:



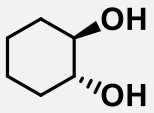
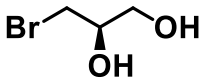
Asymmetric epoxide ring-opening



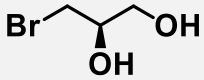




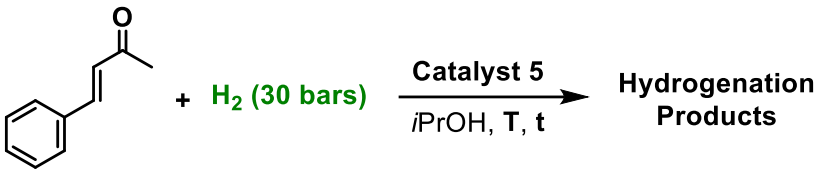
epibromohydrin

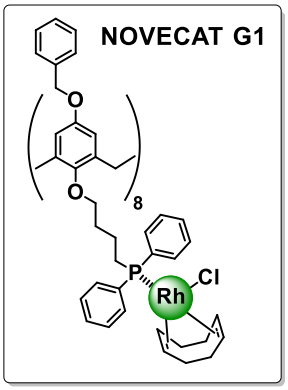
Product	Co (mol%)	Conversion (%)	e.e. (%)	$[Co]_{Product}$ (ppm)	Co eliminated (%)
	2	100	76	-	-
	1	100	94	0.7	99.98

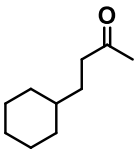
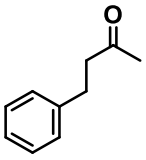
Recycling experiments performed on asymmetric epibromohydrin ring-opening:

Product	Cycles	Co (mol%)	Conversion (%)	e.e. (%)
	**Cycle 1**	2	100	94
	Cycle 2	2	100	94

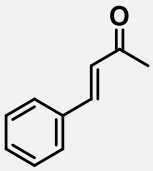
Hydrogenation reaction





Rh (mol%)	T (°C)	t (h)	Conversion (%)		
0.05	100	2	100	> 95%	
0.3	25	72	100		> 92%

Residual metal content inside products after filtration (leaching)

Substrate	Rh (mol%)	T (°C)	t (h)	Conversion (%)	Residual metal content (ppm)
	0.05	100	3	100	2.4
	0.3	25	49	98	6.2