Johnson Matthey

Technical brief

ETA3™ pi-allyl palladium complexes



Pi-allyl palladium precatalysts for cross-coupling



Simplifying cross-coupling reactions with precatalyst technologies

Palladium catalysed cross-coupling reactions are a ubiquitous methodology in the chemist's toolbox for constructing small molecules with a variety of industrial and human health applications.

Due to the high reactivity and sensitivity of the catalytically active Pd complexes, stable precatalysts that can generate the active Pd catalyst in the reaction mixture are highly desirable. Over the past several decades, many air and moisture-stable precatalyst technologies have been designed to deliver these highly active low-valent palladium species in a facile and highly efficient manner (Figure 1).

Key benefits

Unmatched ligand scope
Enables the wide use of bulky, electron-rich phosphine ligands.

Cleaner activation chemistry
Produces benign byproducts (ether and alkenes), unlike Buchwald palladacycles.

Superior performance
High efficiency and reliability across a broad range of cross-coupling reactions.

History of palladium precatalyst development

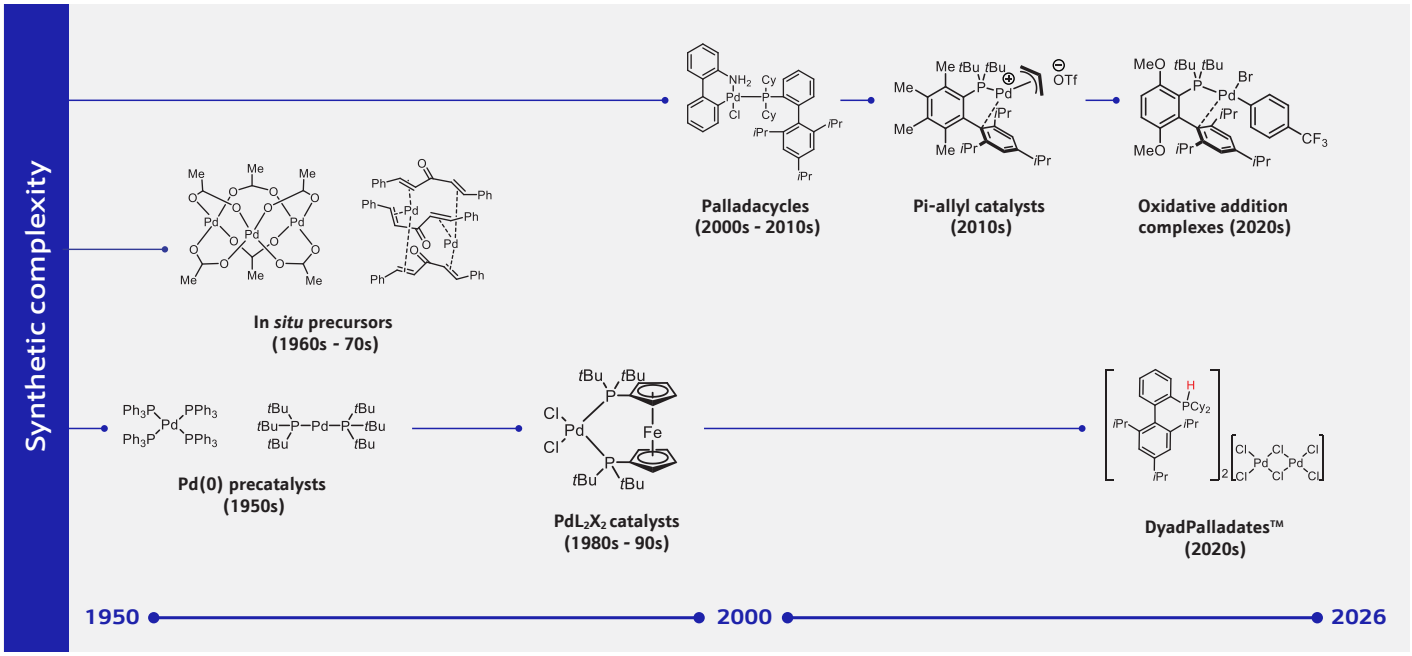


Figure 1. Examples of commonly used phosphine-ligated precatalysts.



State-of-the-art ligand technology revolves around bulky, sterically complex, and electron-rich monophosphines along with NHC ligands developed by Nolan, Hartwig, Buchwald, Beller, and others. Precatalysts that enable the rapid and efficient formation of active catalysts containing these privileged ligands offer tremendous value to the chemical industry. Examples of notable precatalyst technologies include NHC-ligated PEPPSI™ precatalysts (Organ), palladacycle precatalysts (Buchwald), and ETA3™ pi-allyl precatalysts. Pi-allyls come in two general types that include NHC ligands (Nolan) and phosphine ligands (Johnson Matthey / Shaughnessy).

Of these various precatalyst technologies, Johnson Matthey's proprietary ETA3™ pi-allyl phosphine precatalysts offer best-in-class ligand scope, quantitative catalyst generation, and superior reactivity for a wide range of cross-coupling applications.

Precatalyst technologies

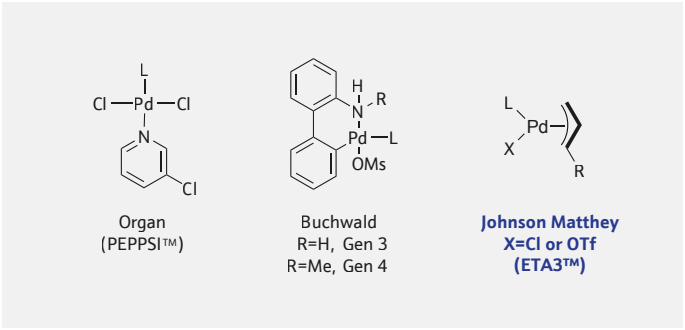


Figure 2. Modern precatalyst technologies widely used in industrial applications.

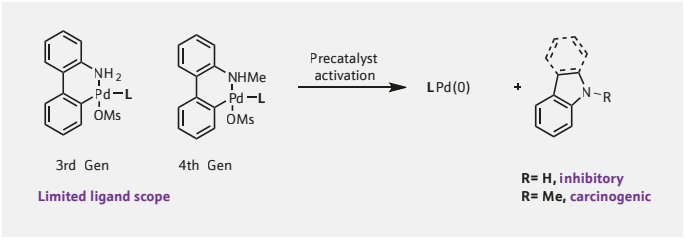
ETA3™ pi-allyl precatalysts activate under facile conditions with innocuous byproduct formation

Monoligated Pd(0) complexes are highly reactive catalytic intermediates widely accepted as the key species that drive challenging cross-coupling reactions.

A key criterion for the use and efficiency of a given precatalyst technology relies on the activation mechanism that delivers the active monoligated Pd(0) complex as well as the byproducts that result from this activation. Both Buchwald palladacycle and pi-allyl based catalysts are readily activated under basic and nucleophilic conditions.

However, initiation of Buchwald palladacycles forms organic byproducts associated with the aminobiphenyl backbone of the Buchwald scaffold, such as carbazoles and biaryl C-H coupling adducts[1]. These byproducts have notable implications for catalyst performance and may generate impurities that are: (1) dependent on the ligand used, (2) challenging to purge downstream and (3) problematic from a safety or regulatory standpoint. In contrast, activation of ETA3 pi-allyl precatalysts typically results in innocuous ether or alkene byproducts that do not interfere with productive catalysis[2].

Buchwald Palladacycles



Johnson Matthey ETA3™

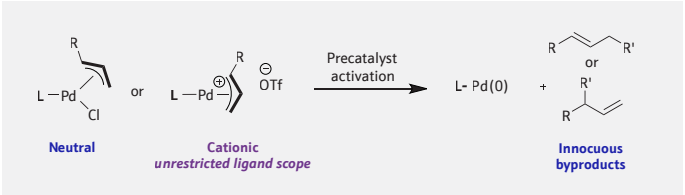


Figure 3. Snapshot comparison of Buchwald palladacycle and Johnson Matthey ETA3 pi-allyl precatalyst technologies.



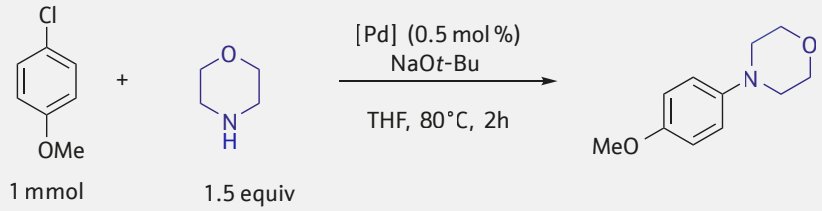
ETA3™ pi-allyl technology enables best-in-class ligand compatibility and screening flexibility

Johnson Matthey's ETA3 pi-allyl catalyst technology offers the largest and most diverse scope of phosphine ligands when compared to other precatalyst technologies.

Due to steric constraints around the aminobiphenyl backbone, G3 and G4 Buchwald palladacycles do not form clean, single-component complexes with highly bulky, electron-rich biaryl ligands. Also, these complexes can often be air-sensitive or thermally unstable in solution. By comparison, ETA3 pi-allyl precatalysts possess the ability to readily access a cationic metal centre with a dissociated counteranion, opening an additional coordination site around the metal centre.

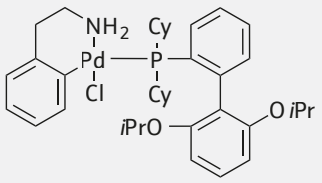
This additional coordination site enables the synthesis of air-stable pi-allyl complexes containing a diverse array of highly bulky and electron-rich phosphine ligands (both monodentate and bidentate). Having access to a large library of well-defined precatalysts containing privileged phosphine ligands can deconvolute variation due to precatalyst activation in high-throughput and miniaturised screening workflows.

Applications and performance

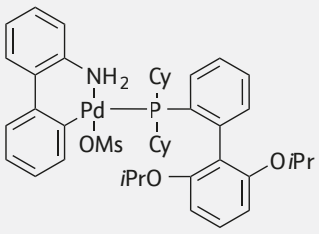


Pd Source	Iso.yield (%)
1	66
2	5
3	87
3[a]	5

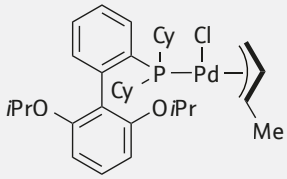
[a]0.5 mol% carbazole added.



1
RuPhos Pd G1



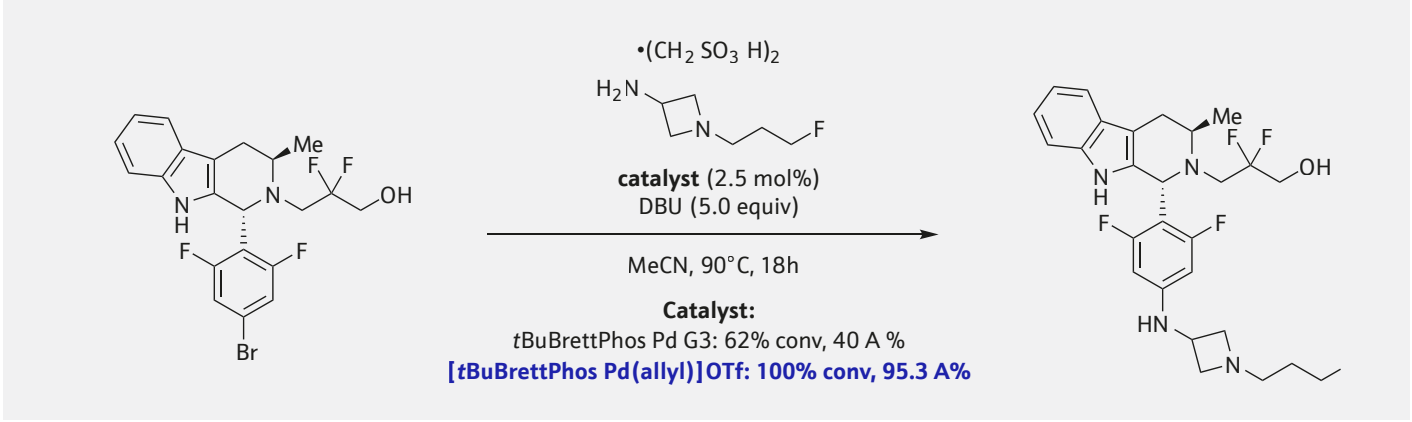
2
RuPhos Pd G3



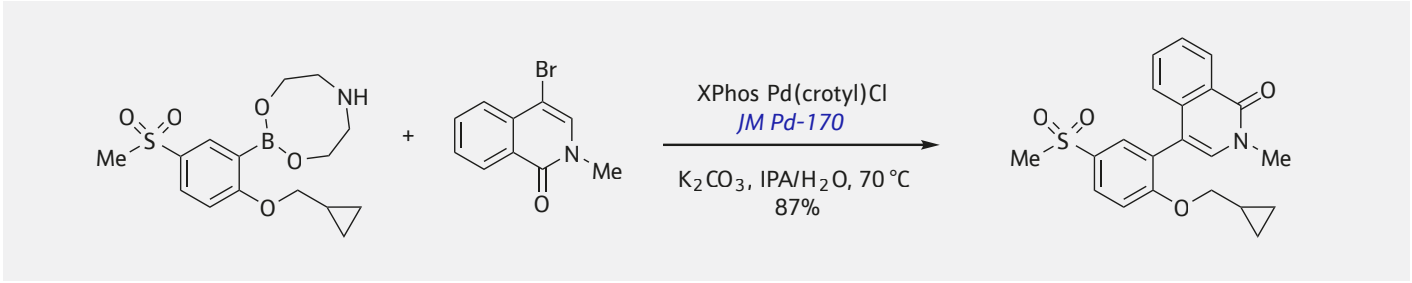
3
RuPhos Pd(crotyl)Cl

Scheme 1. Comparison of RuPhos containing precatalysts in the coupling of 4-chloroanisole with morpholine. RuPhos Pd(crotyl)Cl (3) provided superior yields in comparison to all Buchwald palladacycles tested.[3]





Scheme 2. Use of Pd-175 in the synthesis of giredestrant, a selective ER degrader developed by the Roche group.[4]



Scheme 3. Suzuki coupling sequence using Pd-170 in development efforts towards BMS-986378.[5]

Find the right precatalyst for your project or process

The high flexibility of the ETA3 precatalyst platform allows easy integration of new and innovative phosphine ligands into Johnson Matthey's diverse catalyst portfolio.

Advanced generation Buchwald ligands designed for challenging amination reactions (EPhos, GPhos, and others) are now available at commercial scale.

Don't see the ligand you are looking for in our catalogue below, but want to try our best-in-class precatalyst technology?

Reach out to our team about custom synthesis of ETA3 precatalysts. Our team of experts can also help you choose the ideal catalyst to ensure optimal precious metal recovery in your process.



ETA3™ pi-allyl product list:

Product number	Description	CAS number	Mol weight	% Metal
Pd-110	$[PdCl(allyl)]_2$	12012-95-2	365.89	58.17
Pd-161	AmPhos Pd(crotyl)Cl	1334497-06-1	462.35	23.02
Pd-162	$P(tBu)_3$ Pd(crotyl)Cl	1334497-00-5	399.29	26.65
Pd-170	XPhos Pd(crotyl)Cl	1798782-02-1	673.7	15.8
Pd-171	RuPhos Pd(crotyl)Cl	1798781-96-0	663.62	16.04
Pd-172	SPhos Pd(crotyl)Cl	1798781-99-3	607.51	17.52
Pd-173	[BrettPhos Pd(crotyl)]OTf	1798782-11-2	847.36	12.56
Pd-174	[tBuXPhos Pd(allyl)]OTf	1798782-25-8	721.21	14.76
Pd-175	[tBuBrettPhos Pd(allyl)]OTf	1798782-15-6	781.26	13.62
Pd-176	[(R)-BINAP Pd(allyl)]Cl	879689-47-1	890.56	11.95
Pd-177	XantPhos Pd(allyl)Cl	879689-28-8	761.57	13.97
Pd-178	PCy_3 Pd(crotyl)Cl	307494-95-7	477.41	22.29
Pd-180	[BippyPhos Pd(allyl)]OTf	146558-62-0	803.19	13.25
Pd-181	$P(o\text{-}tolyl)_3$ Pd(crotyl)Cl	1385042-42-1	501.34	21.22
Pd-188	CyJohnPhos Pd(crotyl)Cl	692782-19-7	547.46	19.44
Pd-189	JohnPhos Pd(crotyl)Cl	1798782-05-4	495.38	21.48
Pd-191	[SPhos Pd(allyl)]OTf	1846557-10-5	707.09	15.05
Pd-214	$[Me_4tBuXPhos$ Pd(allyl)]OTf	1798782-29-2	777.32	13.69
Pd-215	[RockPhos Pd(allyl)]OTf	1798782-31-6	756.26	13.90
Pd-216	$[Me_3OMetBuXPhos$ Pd(allyl)]OTf	2924017-86-5	793.32	13.41
Pd-217	CPhos Pd(crotyl)Cl	3105698-81-2	669.65	15.89
Pd-218	[EPhos Pd(allyl)]OTf	3105698-83-4	831.37	12.80
Pd-219	[GPhos Pd(allyl)]OTf	3105698-85-6	833.34	12.77
Pd-220	[AlPhos Pd(allyl)]OTf	3055551-75-9	1111.63	9.57
Pd-221	[MorDalPhos Pd(crotyl)]OTf	3105698-87-8	760.2	14.00



References

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2. ACS Catal. **2015,** 5, 9, 5596-5606
3. J. Org. Chem. **2015,** 80, 13, 6794-6813
4. Org. Process Res. Dev. **2022,** 26, 568-582
5. Org. Process Res. Dev. **2022,** 26, 1458-1469

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Learn more about our ETA3™ precatalyst portfolio