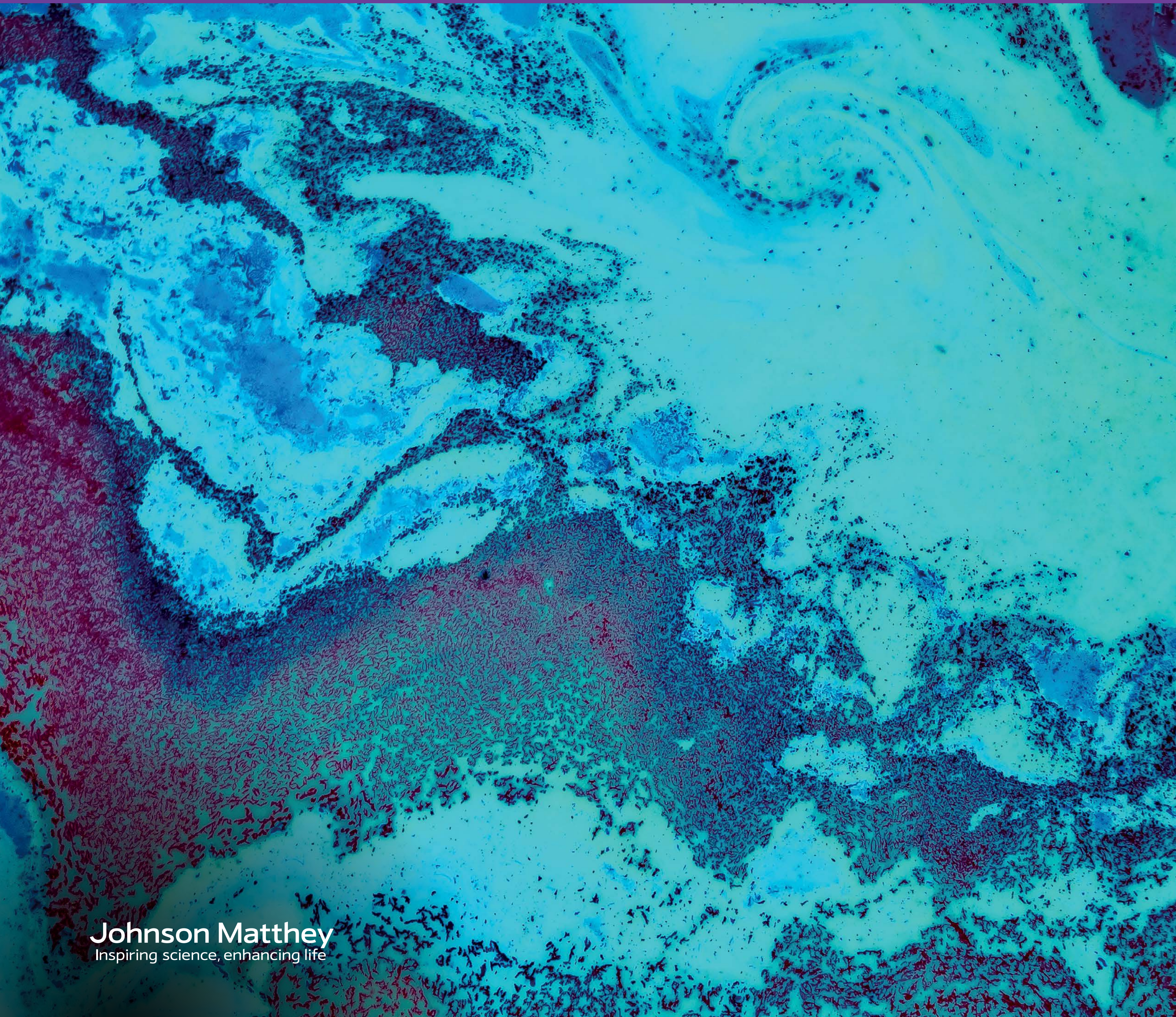
JM

# Technical Brief

## DyadPalladate™ pre-catalysts: Cross-coupling made simple



Johnson Matthey
Inspiring science, enhancing life

# Designed to deliver maximum value and enable sustainable success

Cross-coupling reactions have shown broad application in the pharmaceutical, agrochemical, electronics and fine chemicals industries. Of the various types of cross-coupling reactions, palladium-catalysed $sp^2$-$sp^2$ type Suzuki-Miyaura C-C and Buchwald-Hartwig C-N bond formations are the most common. Advances in this area have come from increasingly complex ligands, such as the dialkylbiarylphosphines (Buchwald-type ligands) and state-of-the-art pre-catalysts that deliver the active catalyst with ever-increasing efficiency.

As a cost-effective alternative to *in situ* and advanced cross-coupling systems, the DyadPalladate™ pre-catalysts exhibit comparable performance, simplifying product purification, and offering a sustainable alternative to traditional cross-coupling pre-catalysts.

## How can JM support your cross-coupling science?

Achieving success in the development of a sustainable catalytic process is a highly collaborative endeavour. Johnson Matthey (JM) is a committed innovator for cost-effective and sustainable chemistry focusing on catalyst performance. We believe in a flexible approach offering readily available options, as well as being open to explore custom catalyst solutions. With our strong reputation for reliable supply chain and global manufacturing capability, we can streamline your catalytic processes to maximise value and minimise catalyst cost contribution.

# *In situ* vs preformed pre-catalysts

Traditionally, pre-catalysts fall into two categories

## *In situ* pre-catalysts

- Formed in the reaction flask with free or acidified ligand
- Formed in the presence of other reagents

**Advances in this area:**

- Development of bulky and air-insensitive ligands (Buchwald-type ligands)
- Extensive mechanistic studies

| Common *in situ* pre-catalysts | |
|---|---|
| $Pd(dba)_2$ | $Pd_2(dba)_3$ |
| $Pd(OAc)_2$ | $[PdCl(allyl)]_2$ |

**Pros:**

✓ Lower cost per kilogram

✓ Freedom to change ligand

**Cons:**

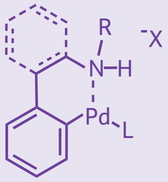
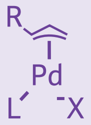
- ✗ Frequently require:
  - ✗ Higher catalyst loadings
  - ✗ Longer optimisations and more forcing conditions
  - ✗ More complex downstream purification
- ✗ Formation of catalyst dependant on conditions
- ✗ Possible internal modification of catalyst

## Preformed pre-catalysts

- Formed before exposure to reagents

**Advances in this area:**

- Development of Buchwald Palladacycles
- Development of π-allyl pre-catalysts

| Common preformed pre-catalysts | |
|---|---|
|  |  |
| R = H, Me X = Cl, OMs | |

**Pros:**

✓ Decreased catalyst loadings

✓ Faster process optimisation

✓ Milder conditions

✓ Simpler downstream purification

**Cons:**

✗ Longer preparations and lead times

✗ Higher manufacturing costs

*In situ* systems offer a lower cost per kilogram of pre-catalyst but frequently require higher catalyst loadings and a highly optimised, intricately controlled process with more forcing conditions. Due to the conditions required for *in situ* pre-catalysts use, they often lead to complex downstream purification processes to remove residual palladium and by-products formed as a result of poor selectivity and catalyst generation.

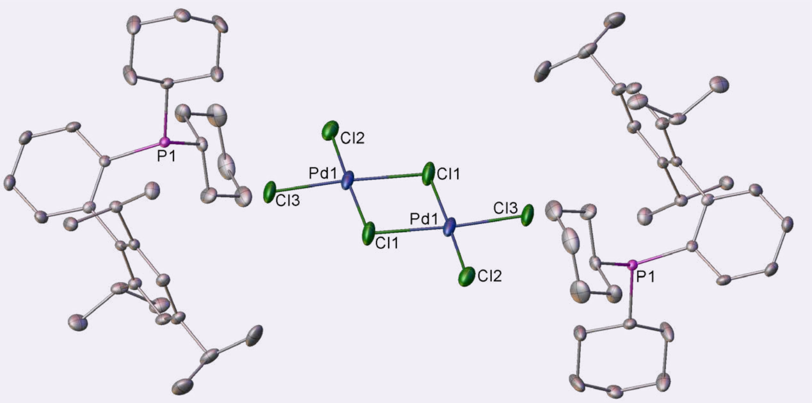
Preformed pre-catalysts offer decreased catalyst loading, time to process optimisation and milder reaction conditions with simpler downstream purification of products. The highly tuned nature of preformed pre-catalysts has come, until recently, at the cost of a more time and labour-consuming synthesis that leads to longer lead times and higher upfront costs per kilogram. While these costs can appear somewhat prohibitive in the early stages of development, the decreased time to an optimised process outweighs the downstream costs associated with *in situ* systems, especially for chemistry involving advanced and unique ligands.

In response to the limitations associated with both *in situ* and preformed pre-catalysts, JM has developed the DyadPalladate™ pre-catalysts to support advancements in the use of cross-coupling reactions.

# What are DyadPalladate™ pre-catalysts?

DyadPalladate™ pre-catalysts are a series of bisphosphonium palladate complexes featuring tertiary phosphonium ligands that are effective catalysts for Suzuki-Miyaura cross-coupling reactions and Buchwald-Hartwig aminations of (hetero)aryl halides. They are the newest pre-catalysts developed by JM that have been shown to be a cost-effective and sustainable alternative to traditional advanced cross-coupling pre-catalysts while maintaining comparable performance to advanced pre-catalysts and similar lead times to *in situ* pre-catalysts. Our portfolio currently contains a range of DyadPalladate™ pre-catalysts featuring seven Buchwald-type ligands for various cross-coupling reactions (Table 1).

**Pd-192, [HXPhos]$_2$[Pd$_2$Cl$_6$]**



$^{31}$P NMR Ō: 18.0ppm
$^{1}J_{HP}$= 490 Hz

Pd-P bond distances: 6 - 8 Å

**Key features:**

- Cost-effective
- Sustainable alternative to *in situ* systems
- Maintains performance
- Highly scalable process

Figure 1. Structure of Pd-192

In terms of the structure, the dipalladate(II) dianion has a diamond core structure with terminal Pd–Cl bond lengths in the range of 2.32 – 2.34 Å and bridging Pd–Cl bond lengths in the range of 2.27 – 2.28 Å. The dipalladate(II) unit is planar and has a metal-metal separation of 3.4 Å. Data has also confirmed the separation of the dianion from the phosphonium counterions (see Figure 1).

| Catalogue ID | Description | CAS# |
|---|---|---|
| Pd-192 | [HXPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-04-5 |
| Pd-193 | [HRuPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-00-1 |
| Pd-194 | [HSPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-02-3 |
| Pd-195 | [HBrettPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-08-9 |
| Pd-196 | [H*t*BuXPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-05-6 |
| Pd-197 | [H*t*BuBrettPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-09-0 |
| Pd-201 | [HPCy$_3$]$_2$ [Pd$_2$Cl$_6$] | 2548904-13-6 |
| Pd-202 | [HP(*t*Bu)$_3$]$_2$ [Pd$_2$Cl$_6$] | 2548904-14-7 |
| Pd-203 | [HP(*n*Bu)(Ad)$_2$]$_2$[Pd$_2$Cl$_6$] | 2548904-17-0 |
| Pd-205 | [HJohnPhos]$_2$ [Pd$_2$Cl$_6$] | 2548904-06-7 |

Table 1. Available DyadPalladate™ pre-catalysts

# A better alternative to traditional cross-coupling catalysts

DyadPalladate™ pre-catalysts hold similar advantages to other preformed pre-catalysts, but their synthesis is more concise, requiring fewer steps (see Figure 2) from a simple, abundant palladium source. As such, they benefit from very short manufacturing times. DyadPalladate™ pre-catalysts can be produced in kilogram quantities in just a few hours, compared to the more complex process to synthesise π-allyls and Buchwald palladacycles, which can take many days. Further advantages of DyadPalladate™ pre-catalysts include their reduction of waste due to highly concentrated manufacturing conditions and higher yields, thus reducing their environmental impact and making them a greener alternative to traditional cross-coupling (see Figure 2). These factors all result in lower overall costs, less palladium loss during manufacturing and an overall more environmentally agreeable process.

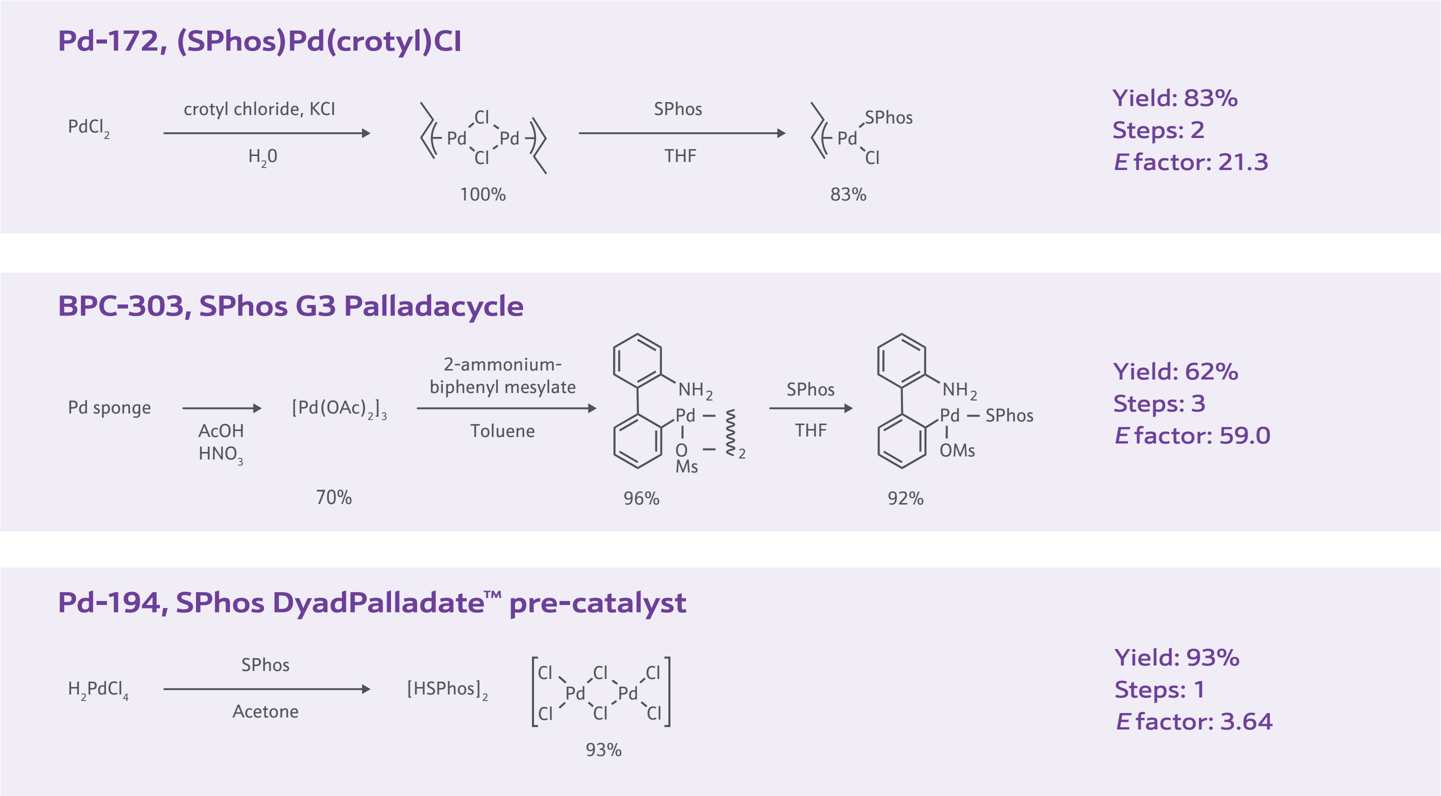
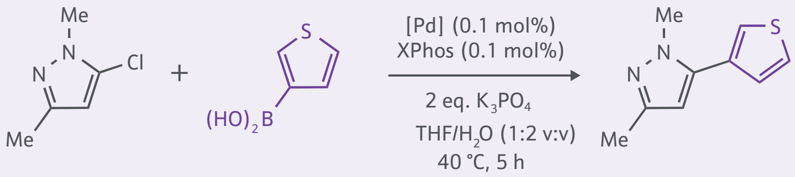


Figure 2. Comparison of synthetic routes and environmental impact, as judged by the *E* factors, for different preformed pre-catalysts: a π-allyll (Pd-172), a Buchwald palladacycle (BPC-303) and a DyadPalladate™ pre-catalyst (Pd-194)

# Model applications and reactions

DyadPalladate™ pre-catalysts have been tested with several challenging cross-coupling reactions, including Suzuki-Miyaura reactions (see Figure 3), Heck Reactions and Buchwald-Hartwig Aminations (see Figure 4). These have demonstrated that the DyadPalladate™ pre-catalysts have comparable reactivity to advanced pre-catalysts as they are able to generate a comparatively efficient active palladium species. Investigations are still underway to determine the exact mechanism to form the active catalyst from the pre-catalyst.

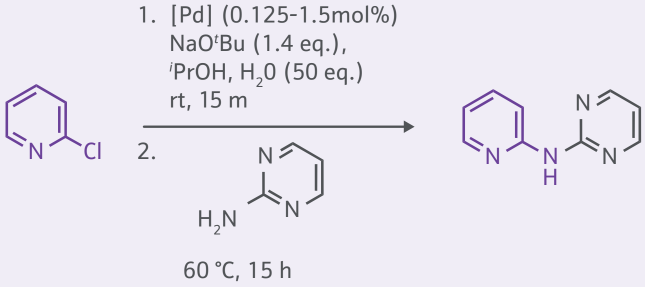
### Heteroaromatic synthesis - Suzuki-Miyaura



| Pre-catalyst | GC conversion [%] | GC yield [%] |
|---|---|---|
| $[HXPhos]_2[Pd_2Cl_6]$, Pd-192 | 91 | 84 |
| (XPhos)Pd(crotyl)Cl, Pd-170 | 94 | 93 |
| XPhos G4 | 96 | 96 |
| XPhos G3, BPC-301 | 90 | 90 |
| $Pd(OAc)_2$ + XPhos | 98 | 94 |
| $[Pd(crotyl)Cl]_2$ + XPhos | 88 | 86 |
| $H_2PdCl_4$ + XPhos (pre-mixed in THF) | 46 | 41 |

Figure 3. Heteroaromatic synthesis - Suzuki-Miyaura coupling

### Heteroaromatic synthesis - Amination



| Pre-catalyst | GC conversion (0.3 mol% Pd) [%] | GC conversion (0.125 mol% Pd) [%] | GC yield (0.125 mol% Pd) [%] |
|---|---|---|---|
| [(BrettPhos)Pd(crotyl)]OTf, Pd-173 | >99 | 73 | 67 |
| BrettPhos G4 | 89 | 58 | 48 |
| BrettPhos G3, BPC-304 | >99 | 55 | 51 |
| $[HBrettPhos]_2[Pd_2Cl_6]$, Pd-195 | >99 | 71 | 65 |
| $Pd_2(dba)_3$ + BrettPhos | - | - | - |
| $[Pd(allyl)Cl]_2$ + BrettPhos | - | - | - |
| $Pd(OAc)_2$ + BrettPhos | - | - | - |

Figure 4. Heteroaromatic synthesis - Buchwald-Hartwig Amination

# Summary

Historically, catalyst development has relied heavily on *in situ* formed catalyst systems, which come with associated costs. Preformed pre-catalysts, such as the Buchwald palladacycles and π-allyls, have helped overcome these costs with their ability to efficiently transition from the stable Pd(II) pre-catalyst to the $L_1Pd$ oxidative addition complex. However, advanced pre-catalyst application has been very limited by their more time and labour-consuming synthesis.

## DyadPalladate™ pre-catalysts have allowed us to overcome the limitations of preformed pre-catalysts by offering several advantages:

- Reduced process costs associated with catalyst contributions
- Simple, scalable, efficient and much more rapid synthesis
- Similar reactivity to other pre-catalysts, while still providing air and moisture stability, and often enhanced reactivity compared to *in situ* systems

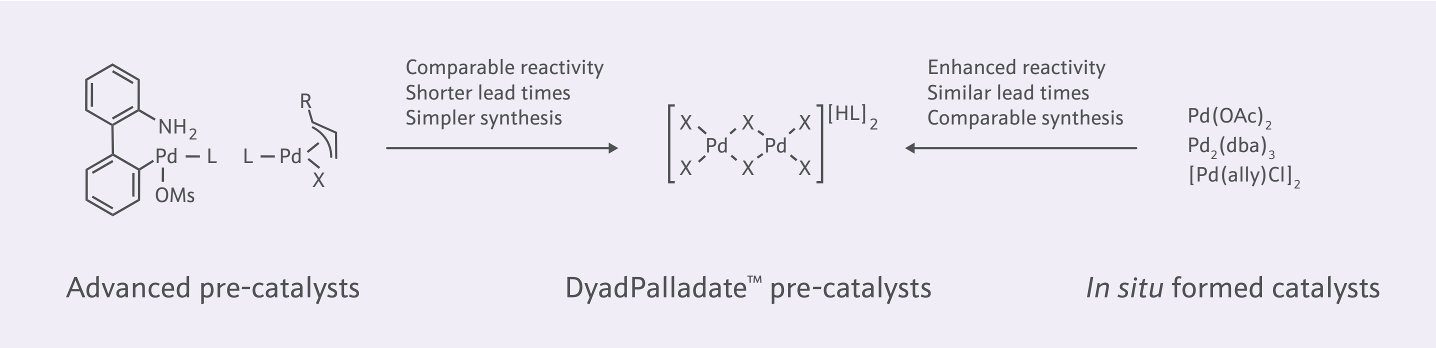


Figure 5. Summary of the advantages of DyadPalladate™ pre-catalysts compared to advanced pre-catalysts and *in situ* formed catalysts

At JM, we currently have a series of 10 different DyadPalladate™ pre-catalysts in our portfolio with further research underway to better understand and apply these novel and cost-effective pre-catalysts to other challenging reactions. They are available as individual products from 1 gram up to multi-kilogram quantities.

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To find out more about DyadPalladate™ pre-catalysts
visit matthey.com or email pharma@matthey.com