

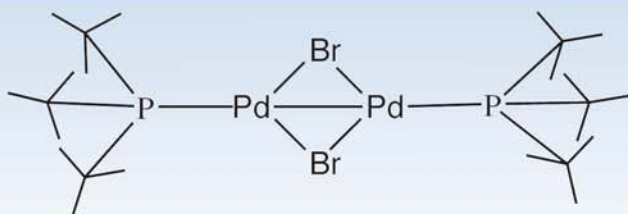


# Johnson Matthey Catalysts

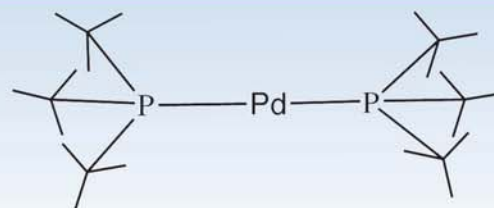
## Palladium Catalysts

for  $\alpha$ -Arylation Reactions

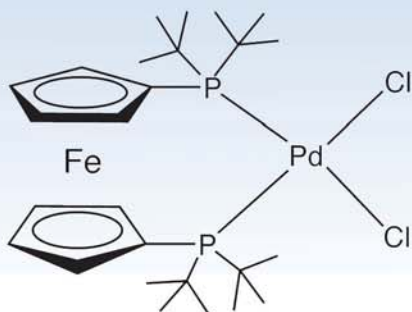
***Pd-113***



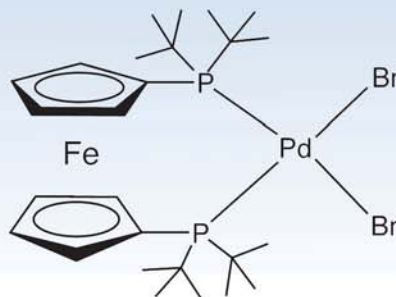
***Pd-116***



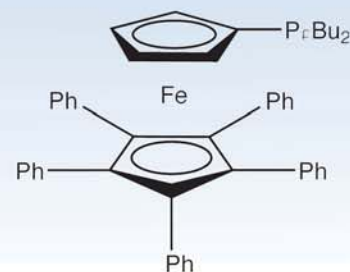
***Pd-118***



***Pd-128***



***Q-Phos***



Johnson's Matthey's catalysts have been identified as superior systems for the  $\alpha$ -arylation of ketones, esters, amides and aldehydes with substrates such as aryl and heteroaryl chlorides. These reactions can be carried out with very low catalyst loadings, under relatively milder conditions.

This new generation of catalysts are highly active and commercially available.

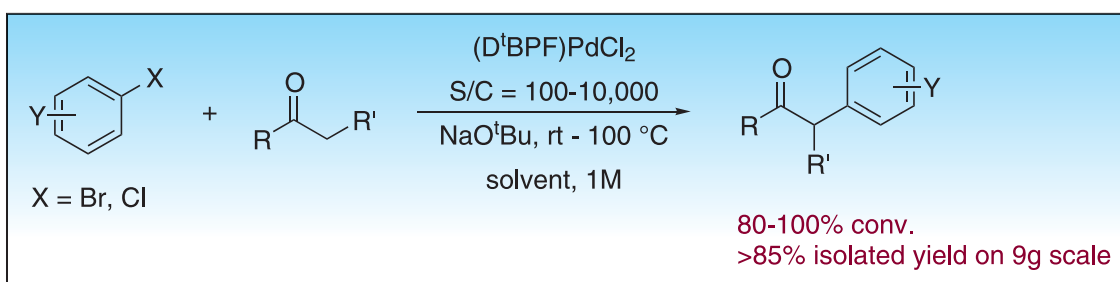
## Ketones

Johnson Matthey has identified  $D^tBPPdCl_2$  (Pd-118) and  $D^tBPPdBr_2$  (Pd-128) as two highly active air-stable catalysts for  $\alpha$ -arylation of ketones using aryl bromides and chlorides with very low catalyst loadings. The pre-formed and isolated catalysts were observed to be far superior to the respective *in situ* systems, both in terms of activity and reproducibility.

### References:

$\alpha$ -Arylation of Ketones Using Highly Active, Air-Stable  $(D^tBPF)PdX_2$  (X = Cl, Br) Catalysts. Grasa, G.; Colacot, T.J. *Org. Lett.*, **2007**, 9, 5489-5492.

A Highly Practical and General Route for  $\alpha$ -Arylations of Ketones Using Bis-phosphinoferrocene-Based Palladium Catalysts, Grasa, G. A.; Colacot, T. J. *Org. Proc. Res. Dev.*, **2008**, 12, 522-529.



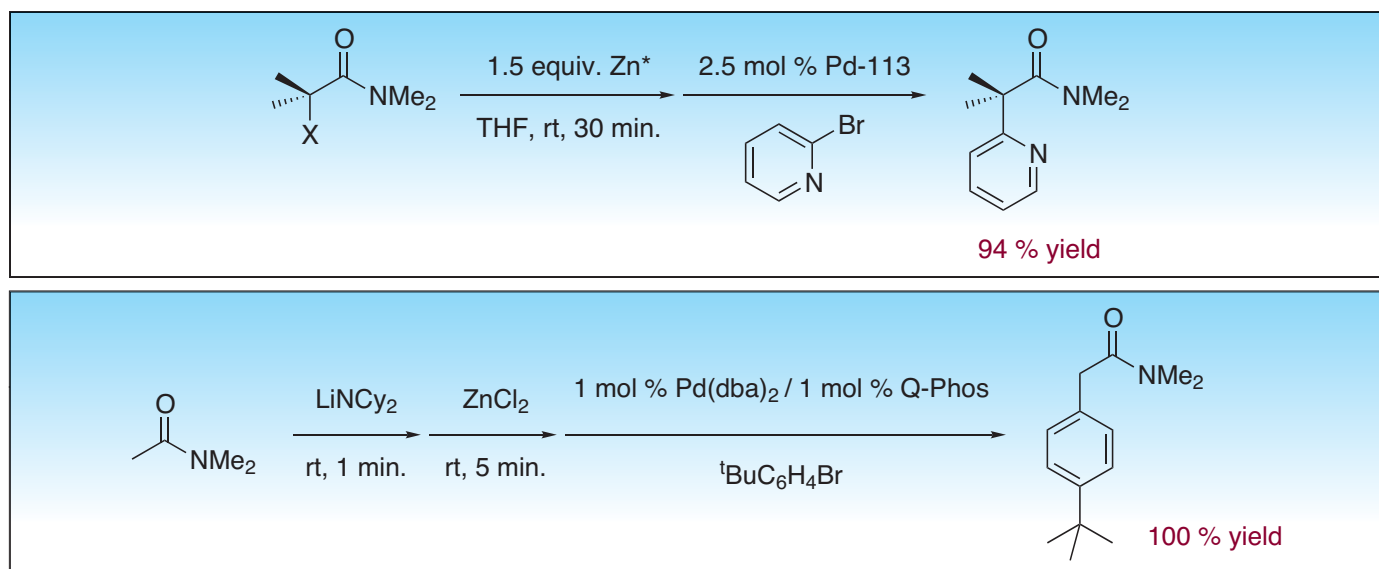
## Amides

The intermolecular  $\alpha$ -arylation of Zn enolates of amides was reported in excellent yield under mild conditions with catalysts bearing the hindered pentaphenylferrocenyldi-*tert*-butylphosphine, tradename Q-Phos with  $Pd(dba)_2$  or dimeric Pd(I) complex,  $\{Pd(t-Bu_3P)Br\}_2$  (Pd-113) under Reformatsky conditions. Depending on the substrate and conditions, the choice of the base becomes very critical. As an

example, Hartwig has successfully employed *sec*-BuLi in the arylation of several substrates.

### References:

Palladium-Catalyzed Intermolecular  $\alpha$ -Arylation of Zinc Amide Enolates under Mild Conditions. Hama, T.; Culkin, D. A.; Hartwig, J. F., *J. Am. Chem. Soc.*, **2006**, 128, 4976-4985.



## Esters

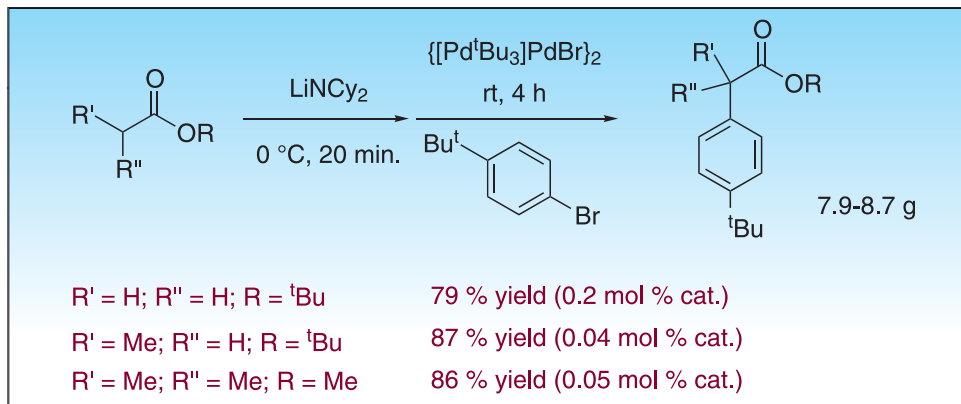
Recent work from Hartwig's lab established a general method suitable for a broad scope of substrates including aryl chlorides. The work carried out demonstrated that Pd-113 gives considerably better yield in comparison to the *in situ* system (Pd(dba)<sub>2</sub>-t-Bu<sub>3</sub>P). For the bromides, the less expensive base Cy<sub>2</sub>NLi can be used, while for aryl chlorides, NaHMDS is very effective. Although both Pd-113 and Q-Phos can be used for coupling a Reformatsky reagent with aryl chlorides, the catalyst system Q-Phos-Pd(dba)<sub>2</sub> seems to be more general.

### References:

Palladium-Catalyzed  $\alpha$ -Arylation of Esters with Chloroarenes, Hama, T.; Hartwig, J. F., *Org. Lett.* **2008**, 10, 1549-1552.

$\alpha$ -Arylation of Esters Catalyzed by the Pd(I) Dimer {[P(<sup>t</sup>-Bu)<sub>3</sub>]PdBr}<sub>2</sub>, Hama, T.; Hartwig, J. F., *Org. Lett.* **2008**, 10, 1545-1548.

Palladium-Catalyzed  $\alpha$ -Arylation of Esters and Amides under More Neutral Conditions, Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F., *J. Am. Chem. Soc.* **2003**, 125, 11176-11177



$THF.BrZn-CH_2-C(=O)OtBu + ArCl \xrightarrow[THF / 70^\circ C / 12h]{1 \text{ mol } \% Pd(dba)_2 / 1 \text{ mol } \% Q-phos}$			$Ar-CH_2-C(=O)OtBu$		
entry	ArCl	yield <sup>a</sup> (%)	entry	ArCl	yield <sup>a</sup> (%)
1		95	3		85
2		86	4		83

<sup>a</sup> Isolated yield (average of two runs) for reactions of 0.5 mmol of chloroarene in 2 mL of THF

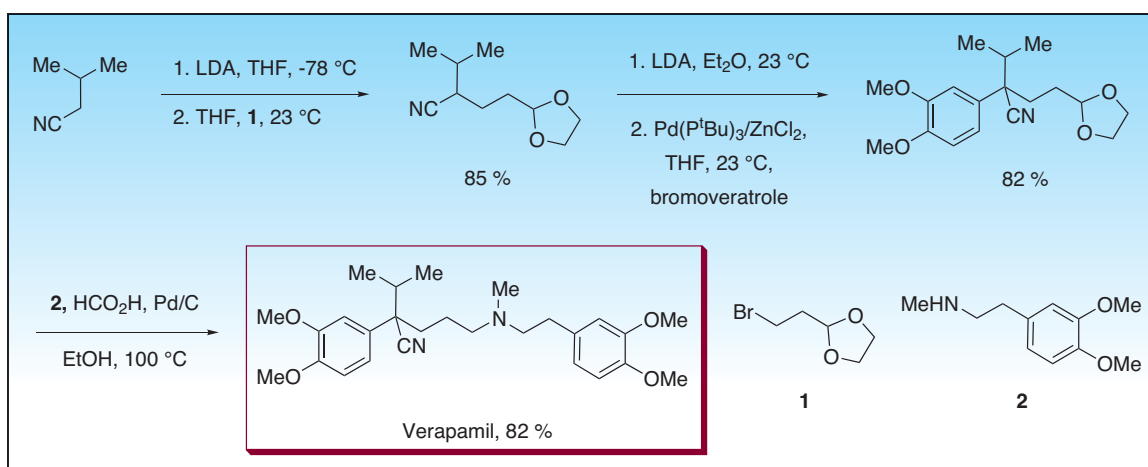
## Nitriles

The selective mono arylation of acetonitrile and primary nitriles has been accomplished using  $\alpha$ -silyl nitriles in the presence of  $\text{ZnF}_2$ . For secondary nitriles, zinc cyanoalkyl reagents were used. Palladium (0) complexes of  $t\text{-Bu}_3\text{P}$  (Pd-116) and XantPhos were identified as efficient catalytic system for such transformations. Using this methodology, an efficient synthesis of verapamil could be realized, affording the target molecule in a 57% over-

all yield, starting from readily available isobutyronitrile. Verapamil is a drug used in the treatment of heart disease.

### References:

Mild Palladium-Catalyzed Selective Monoarylation of Nitriles, Wu, L.; Hartwig, J. F., *J. Am. Chem. Soc.* **2005**, 127, 15824-15832.



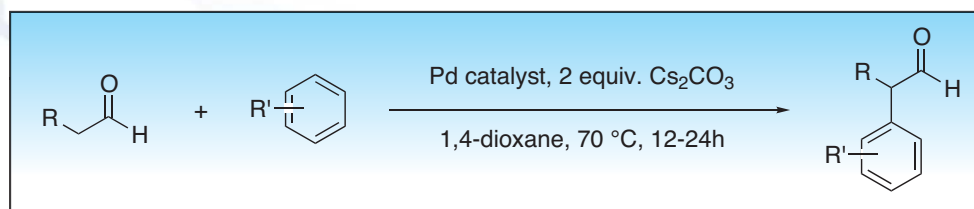
## Aldehydes

The  $\alpha$ -arylation of aldehydes is very challenging due to the competing aldol condensations under the basic cross-coupling reaction conditions. Recent work from Hartwig's lab identified  $[\text{Pd}(\text{allyl})\text{Cl}]_2$  in conjunction with Q-Phos and dppf as very efficient catalytic systems for both aryl- bromide and chloride substrates. Prior to Hartwig's report, only three very limited methodologies (Miyaura, Bertrand and Buchwald) were available. John-

son Matthey offers the fully formed Pd complexes of dppf and XantPhos as well as the Q-Phos ligand.

### References:

Palladium-catalyzed  $\alpha$ -arylation of aldehydes with bromo- and chloroarenes catalyzed by  $[\{\text{Pd}(\text{allyl})\text{Cl}\}_2]$  and dppf or Q-phos, Vo, G. D.; Hartwig, J. F., *Angew Chem., Int. Ed.* **2008**, 47, 2127-2130.



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