

Commercial Development of Palladium(0) Catalysts for Highly Selective Cross-Coupling Reactions

New preformed $L_2Pd(0)$ (L = tertiary phosphine) catalysts now available

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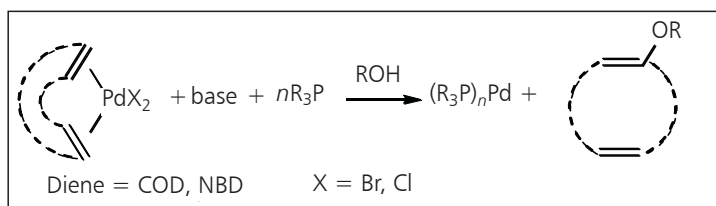
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Palladium-catalysed cross-coupling has huge importance for the synthesis of many organic molecules at both laboratory and industrial scale. A range of commercially available preformed $(R_3P)_2Pd(0)$ catalysts have now been developed and are available from Johnson Matthey. Some unique and highly selective applications of these palladium catalysts for various cross-coupling reactions, including novel reactions such as carbohalogenation reactions, Negishi coupling of aryl chlorides and copper-free Sonogashira coupling, are highlighted in this review.

Introduction

Palladium-catalysed cross-coupling has become one of the most powerful synthetic methods in organic and organometallic chemistry. It has found numerous applications (1–6) in the laboratory, in addition to the commercial production of pharmaceuticals, agrochemicals and electronic materials. The importance of the method was recognised by the awarding of the 2010 Nobel Prize in Chemistry to the original pioneers: Professors Heck, Negishi and Suzuki (7). For a historical perspective of Pd catalysed cross-coupling contextual to the Nobel Prize see the recent review (8).

It is now commonly accepted that $L_nPd(0)$ (n = number of ligands) is the active catalytic species to facilitate a cross-coupling transformation. However, until recently there were not many commercially available examples of preformed $(R_3P)_2Pd(0)$ catalysts. Recently, we reported our development of a novel, general and practical synthetic route to a variety of preformed $L_2Pd(0)$ catalysts (see **Scheme 1**). This process produced catalysts in excellent yield, specifically using the bulky, electron-rich tertiary phosphine ligands tBu_3P , Cy_3P , $(o\text{-tol})_3P$, $tBu_2(Ph)P$, $tBu_2(p\text{-Me}_2N\text{-C}_6\text{H}_4)P$, $(C_5H_4FeC_5Ph_5)(tBu)_2P$ (Q-Phos) and $tBu_2(Np)P$ (see **Table 1**). These $L_2Pd(0)$



Scheme 1. The development of a general and practical route to various preformed $(R_3P)_2Pd(0)$ catalysts

Table I
Examples of $L_2Pd(0)$ Catalysts Developed with Some of Their General Applications

Ligand (L)	Product ID ^a	³¹ P-NMR δ , ppm ^b	General applications
^t Bu ₃ P	Pd-116	86.5	Negishi, Suzuki, Heck, Stille – aryl chlorides and bromides
Cy ₃ P	Pd-137	39.2	Suzuki coupling – aryl triflate in the presence of the halide
(<i>o</i> -tolyl) ₃ P	Pd-141	-7.3	Monoarylation of amines/NH ₃ – aryl chlorides, bromides and tosylates
^t Bu ₂ (Ph)P	Pd-148	67.6	Suzuki coupling – aryl bromides and chlorides
^t Bu ₂ (<i>p</i> -Me ₂ N-C ₆ H ₄)P	Pd-149	64.5	Suzuki, Heck, Cu-free Sonogashira – aryl chlorides and bromides
Q-Phos	Pd-150	59.0	Carbohalogenation, Suzuki – aryl chlorides, bromides and iodides
^t Bu ₂ (Np)P	Pd-151	45.5	α -Arylation, Suzuki, Negishi – aryl chlorides and bromides

^aAll Product IDs are trademarks of Johnson Matthey Plc

^bNMR conditions are given in Reference (9)

catalysts are now commercially available at scales ranging from gram to multi-kilogram quantities (9, 10). An example of the crystal structure of one of the complexes is given in **Figure 1** (11).

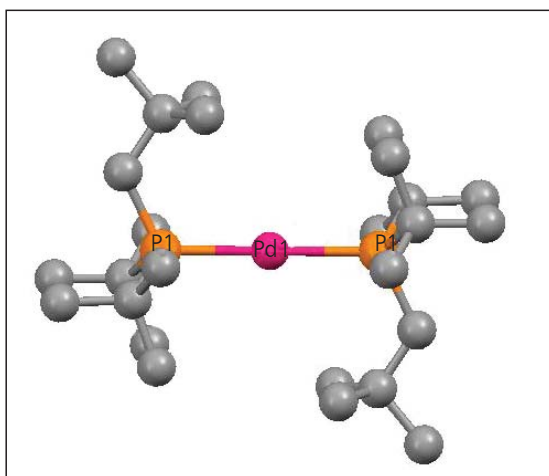


Fig. 1. X-Ray structure of $Pd(^tBu_2(Np)P)_2$, showing a linear P–Pd–P orientation

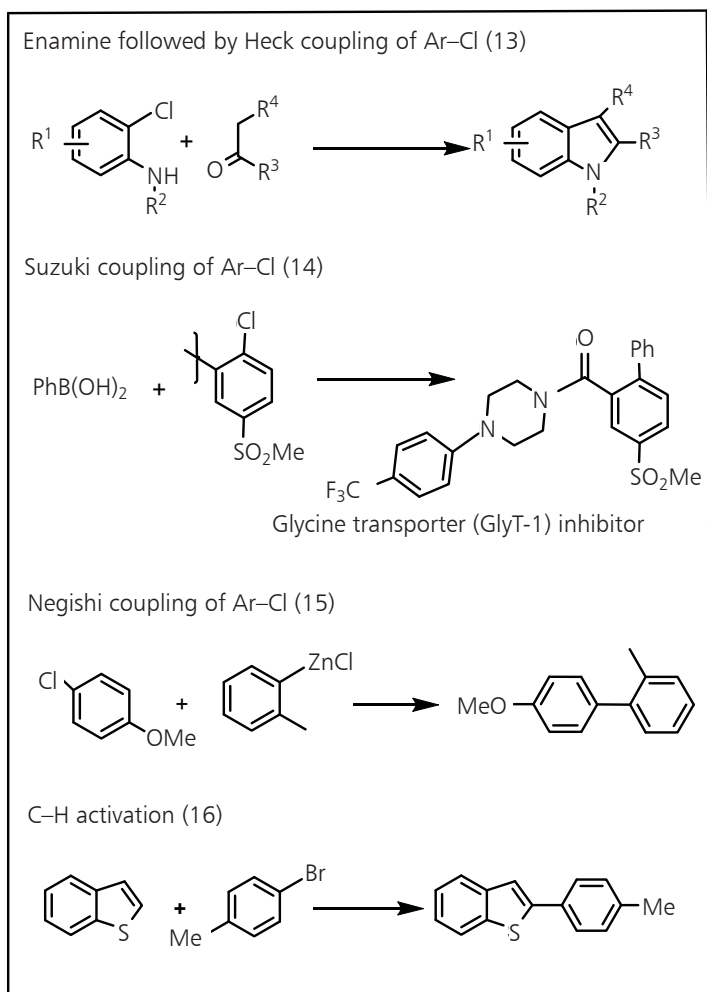
Although these $L_2Pd(0)$ complexes with the exception of $Pd(^tBu_3P)_2$ have only recently been made available commercially (**Table I**), several have shown some unique and interesting applications as summarised below. A detailed review on the applications of these catalysts as well as the newly developed LPd based catalysts is underway (12).

Selected Applications of $Pd(^tBu_3P)_2$

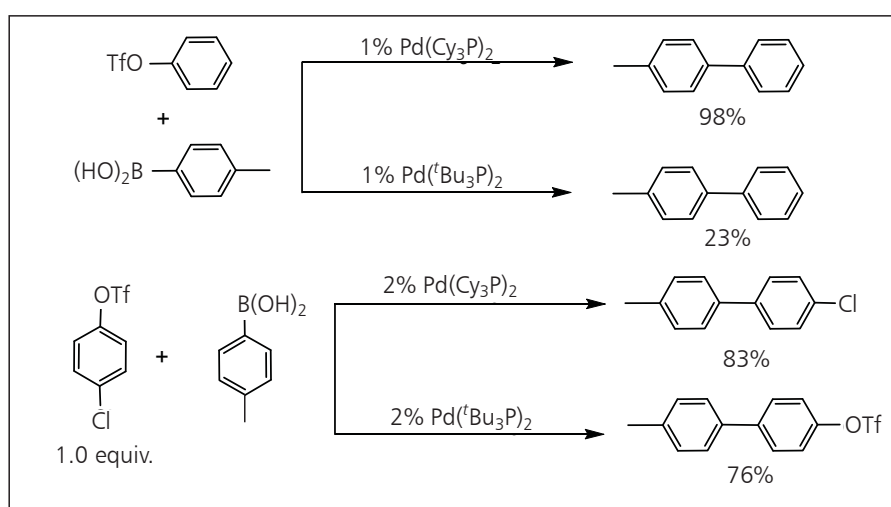
Of the various catalysts listed in **Table I**, $Pd(^tBu_3P)_2$, the potential of which was originally identified by Fu (2, 6) in the early 2000s, is one of the best new generation catalysts. $Pd(^tBu_3P)_2$ has been shown to be superior in many applications when compared to the classical $Pd(Ph_3P)_4$. Selected examples of aryl chloride couplings using $Pd(^tBu_3P)_2$ are shown in **Scheme II** (13–16).

Selectivities of $Pd(Cy_3P)_2$ and $Pd(^tBu_3P)_2$

Laboratory studies using preformed catalysts and literature reports of *in situ* systems (17) have shown that $Pd(Cy_3P)_2$ is a unique catalyst which



Scheme II. Selected reactions of $Pd(tBu_3P)_2$



Scheme III. Selectivity of $Pd(Cy_3P)_2$ vs. $Pd(tBu_3P)_2$ in Ar-Cl coupling (18)

can selectively carry out aryl triflate coupling in the presence of a chloride. Interestingly, Pd(^tBu₃P)₂ shows the reverse selectivity (**Scheme III**) (18).

Unique Selectivity of Pd(Q-Phos)₂

Among the many L₂Pd(0) catalysts selected from **Table I** or generated *in situ* using commercially available ligands, Pd(Q-Phos)₂ has recently been identified as a unique catalyst for effective carbiodination, a new type of carbon-carbon bond forming reaction reported by Lautens (**Scheme IV**) (19). In this case the Heck reaction is inhibited, and it is thought that the reductive elimination of the halide might be taking place after oxidative addition.

Recently the same group modified the reaction conditions to make the iodide in 95% yield (**Scheme V**) from the corresponding bromide by iodide exchange (20).

Pd(^tBu₂(*p*-Me₂N-C₆H₄)P)₂ for Sonogashira and Negishi Coupling

Preliminary studies indicate that Pd(^tBu₂(*p*-Me₂N-C₆H₄)P)₂ is a very good catalyst for the Sonogashira coupling of

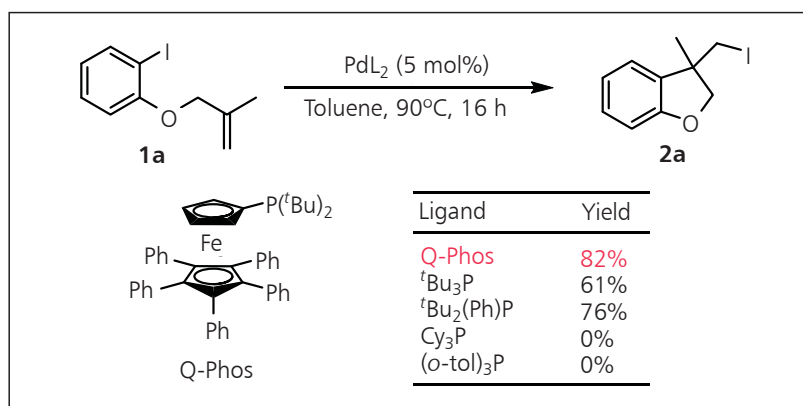
heteroaryl chlorides or activated aryl chlorides in the absence of copper (**Scheme VI**) (9). More detailed work will be published later (21).

Lipshutz recently identified Pd(^tBu₂(*p*-Me₂N-C₆H₄)P)₂ as a very useful catalyst for the aryl bromide Negishi coupling of alkyl zinc iodides very effectively with excellent regioselectivity (**Scheme VII**) (22,23).

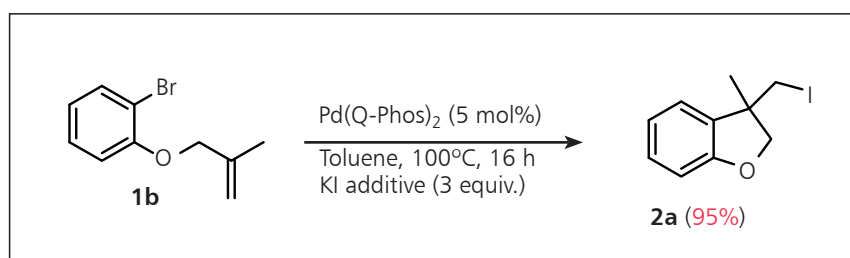
Pd(*o*-tolyl)₃P)₂ for Monoarylation of Ammonia and Primary Amines

Hartwig utilised Pd(*o*-tolyl)₃P)₂ as a unique amination catalyst, in the presence of the hindered Josiphos ligand CyPF^tBu, for the monoarylation of primary amines using challenging aryl tosylate substrates under very low Pd loadings (**Scheme VIII**) (24). Hartwig believes that the rigidity of the chelated ring might be one of the factors favouring this selectivity.

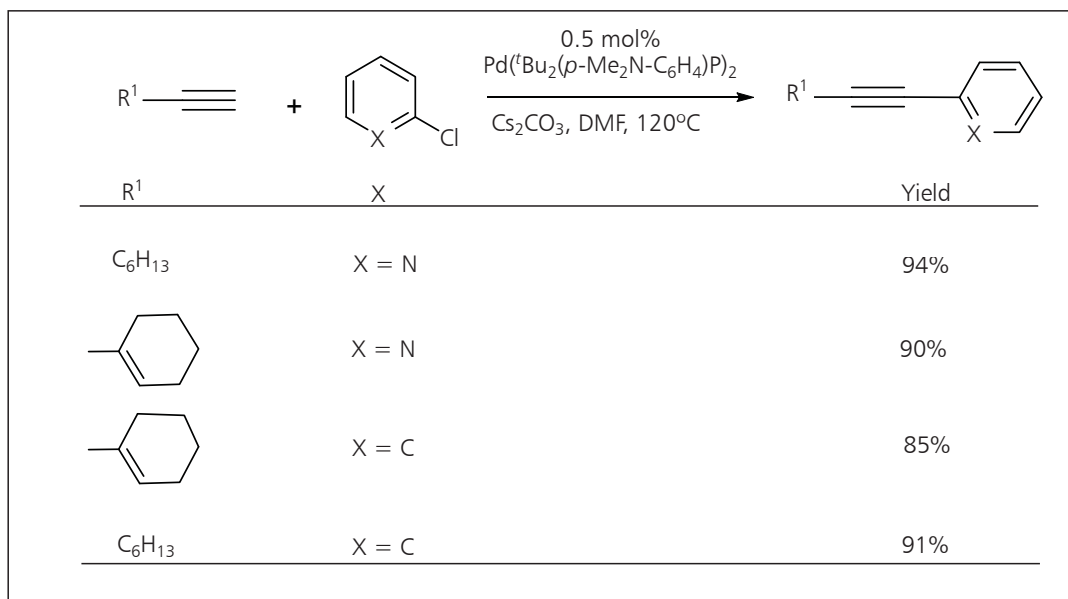
This chemistry has also been extended to monoarylation of ammonia with aryl and heteroaryl chloride substrates, with selectivities for primary aryl amines, **A**, up to 98% in good yield (**Scheme IX**) (25).



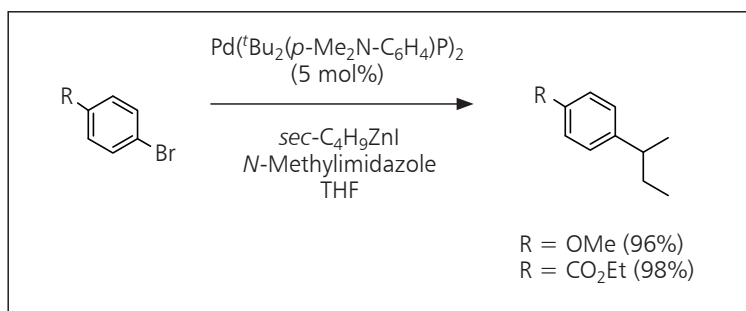
Scheme IV. Pd(Q-Phos)₂-catalysed carbiodination (19)



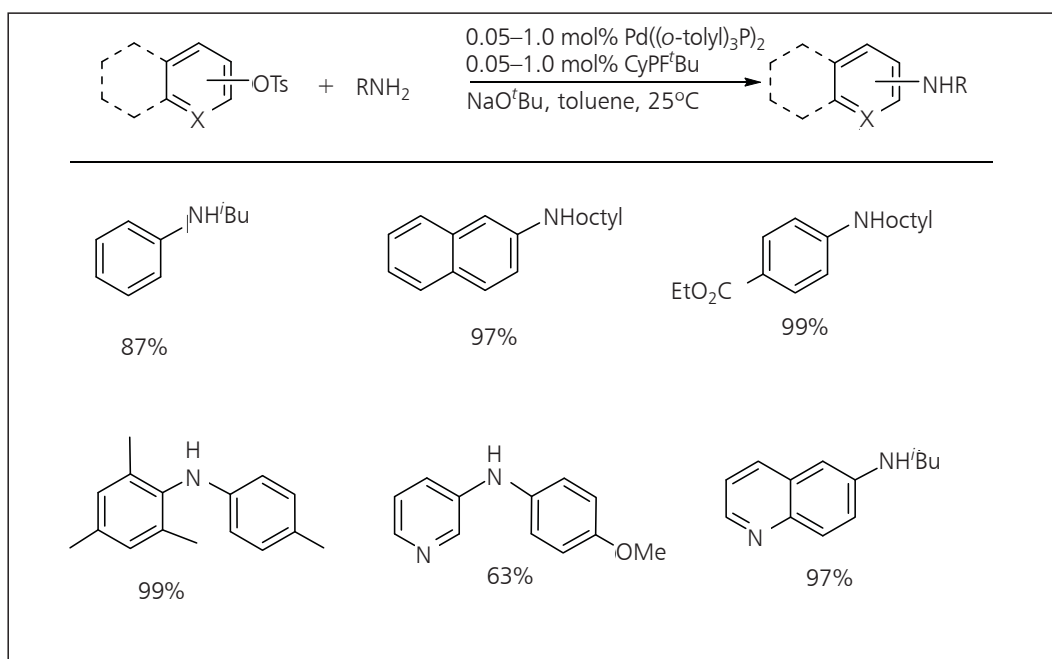
Scheme V. Carbobromination followed by iodide exchange (20)



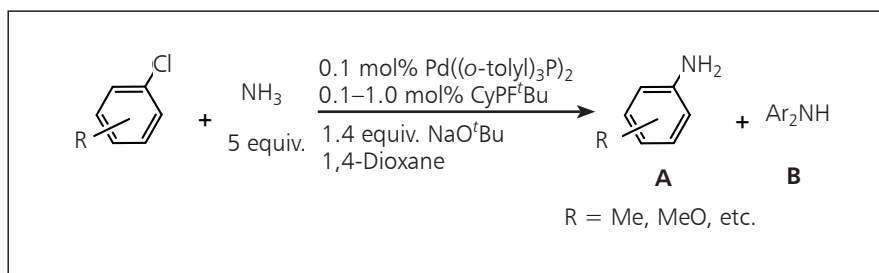
Scheme VI. Cu-free Sonogashira coupling of aryl and heteroaryl chlorides



Scheme VII. Pd(tBu₂(p-Me₂N-C₆H₄)P)₂-catalysed sp²-sp³ Negishi coupling at milder temperatures



Scheme VIII. Monoarylation of primary amine with aryl tosylate



Scheme IX.
Monoarylation of ammonia

Glossary

Term	Definition
ArOTf	aryl triflate
ArOTs	aryl tosylate
COD	1,5-cyclooctadiene
CyPF ^t Bu	(2 <i>S</i>)-1-[(1 <i>S</i>)-1-[bis(1,1-dimethylethyl)phosphino]ethyl]-2-(dicyclohexylphosphino)ferrocene (Josiphos SL-J009-2)
NBD	norbornadiene
Np	neopentyl
Q-Phos	1,2,3,4,5-pentaphenyl-1'-(di- <i>tert</i> -butylphosphino)ferrocene
RT	room temperature

Conclusion

A highly effective method for the synthesis of highly active precatalysts of general formula $L_2Pd(0)$ has been developed, which is pivotal for the availability of these catalysts in commercial quantities. These tertiary phosphine (L) based $L_2Pd(0)$ complexes show very promising applications with excellent selectivity in cross-coupling. The complexes discussed in this article are described in **Table 1**, with a summary of their specific applications.

The difference in selectivity for each catalyst for a particular reaction is quite fascinating. Many more new applications of these catalysts are yet to come.

For more applications of precatalysts developed beyond the 2010 Nobel Prize, see the recent review (12).

Acknowledgement

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