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Development of Preformed Pd Catalysts for Cross-Coupling Reactions, Beyond the 2010 Nobel Prize

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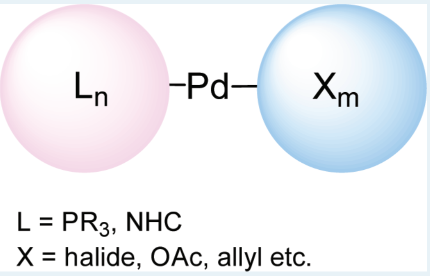
ABSTRACT: Strategies for the development of Pd catalysts based on utilization of L_2Pd and LPd species, beyond the contributions of the 2010 Nobel Laureates Richard Heck, Ei-ichi Negishi, and Akira Suzuki, along with their contemporaries, are reviewed. These well-defined, preformed Pd catalysts improve the selectivity and activity of selected cross-coupling reactions by reducing the metal loading and the ligand-to-metal ratios. This review describes predominantly the development of Pd precatalysts over the last 10 years and highlights the benefits often observed when using well-defined preformed catalysts relative to those generated in situ.



KEYWORDS: *cross-coupling, palladium, precatalysts*

1. INTRODUCTION

The 2010 Nobel Prize in Chemistry for Pd-catalyzed cross-coupling was one of the most highly anticipated awards within the synthetic organic and organometallic chemistry community.[1] The ongoing progress in cross-coupling[2−7] has not only had a significant impact on academic research, but it has also influenced the industrial arena for a variety of real world synthetic applications, such as the synthesis of natural products,[8,9] active pharmaceutical ingredients (API),[10] agrochemicals,[11] and materials for electronic applications.[12] The impact of these monumental discoveries was well recognized by synthetic practitioners, such as Nicolaou, who in a 2005 review stated, "*A new paradigm for carbon−carbon bond formation has emerged that has enhanced considerably the prowess of synthetic organic chemists to assemble complex molecular frameworks and has changed the way we think about synthesis.*"[13,14] A historic perspective on the development of this area by acknowledging the individual seminal contributions of Heck, Negishi, and Suzuki, along with the contributions of other pioneers who have made a significant impact of this area, was recently reviewed by our group in collaboration with Snieckus.[15] Therein, our intent was mainly to tell a story behind the evolution of cross-couplings involving successive "waves," leading over time to Pd as the metal of choice. Although the importance of ligand properties was highlighted as a "third wave" in that review, we could not elaborate on the role of the coordination number on Pd and its influence in selectivity and activity due to space limitations. However, we did touch upon the new trends, such as decarboxylative coupling, direct arylation (also known as C−H activation), etc. Therefore, herein, we focus mainly on the strategy behind the recent developments of L_2Pd- and LPd-based precatalysts and their significant reactivity and selectivity. In addition, new applications in cross-coupling chemistry are discussed, with particular emphasis on their relevance to the chemical and pharmaceutical industries. The new trend of using appropriate, well-defined precatalysts vs catalysts generated in situ is reviewed here by using representative results from our lab, along with those from other prominent groups. We have tried our best not to duplicate the theme behind our contemporary review article in *Angewandte Chemie*,[15] although there might be some unintentional overlaps here and there. Only after attempting the review, we realized that the topic is very vast and that we could not cite all the references, which was not intentional, but we tried our best to cover those pertaining to the precatalysts mentioned in the review.

The generally accepted catalytic cycle for cross-coupling reactions is shown in Scheme 1. The first step is the oxidative addition of an organic halide, or pseudohalide, to the assumed catalytically active species, $L_nPd(0)$, where L_n is the number (n) of ligands (L) coordinated to Pd. At this point, in Negishi-, Suzuki-Miyaura, and related coupling reactions, transmetalation with an organometallic reagent occurs, followed by reductive elimination to provide the desired product. In the Heck coupling, the oxidative addition is followed by migratory insertion of an olefin, followed by a β-hydride elimination/base-assisted H−X elimination sequence to give the final coupling product. The substituents on the olefin as well as the nature of the ligand influence the formation of linear vs branched or mixed products. In addition, cis and trans isomerized products can also be formed.

Since the original discoveries of these reactions, there have been significant developments in the area in terms of better understanding the reaction mechanism in which the role of the ligand is identified to be important. The electronic and steric nature of the ligand (L), and the coordination number of Pd

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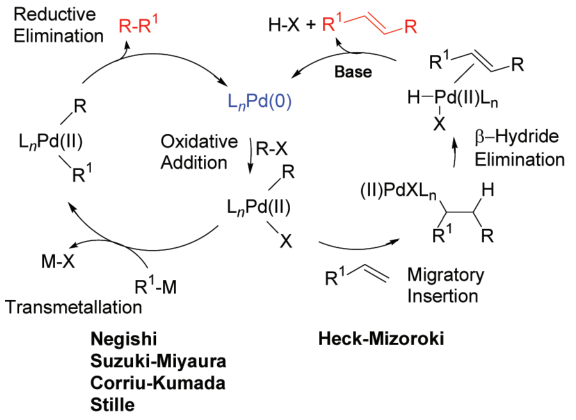
Scheme 1. General Mechanism of Cross-Coupling Reactions



significantly influence the two most important steps: namely, oxidative addition and reductive elimination (Scheme 1).[16]

Until the mid-1990s, PPh_3 was the most widely used ligand for palladium-catalyzed coupling reactions, in which the substrates were mostly aryl iodides and aryl bromides. The low reactivity of more challenging substrates, such as unactivated aryl chlorides, is often attributed to the relatively high bond dissociation energy of the C−Cl bond.[17] It was hypothesized that the ligand may be modified or substituted for another one so as to facilitate the oxidative addition of aryl halide (or related substrates) onto Pd(0), a critical rate-determining step in the palladium-catalyzed coupling reactions. Fu's pioneering report in 1998 on the use of sterically hindered, electron-rich trialkylphosphine ligands such as $P(t\text{-Bu})_3$ and PCy_3 demonstrated the possibility of using less reactive organic chlorides as coupling partners in palladium-catalyzed cross-coupling reactions,[18,19] although Osborn commented about the importance of the basicity (pK_a) and steric bulkiness (cone angle) as early as in 1989 for carbonylation reactions of aryl halides.[20] Koie has also described the application of $Pd/P(t\text{-Bu})_3$ in a C−N bond-forming reaction of an unactivated aryl chloride.[21] The utilization of such ligand systems, when combined with palladium, can facilitate C−C bond formation of more challenging substrates; for example, aryl chlorides, under milder reaction conditions.[19]

Figure 1 illustrates the results of some of the most notable efforts toward the development of highly active ligands for use in cross-coupling reactions during the past decade.[22] Among the front runners within the field of ligand development are Buchwald and co-workers, who developed a family of biaryl dialkylphosphine ligands that has expanded the scope of C−N and C−C couplings of aryl chlorides.[23−27] Hartwig and co-workers discovered pentaphenylferrocenyl di-*tert*-butylphosphine ligand (Q-Phos) as a powerful ligand in Pd catalyzed cross-coupling reactions[28] such as α-arylations of ketones,[29] esters, amides,[30] and even aldehydes,[31] in addition to C−N/O bond forming reactions.[32] Beller's group developed phosphines containing a bulky adamantyl group that are active for various C−C/N bond-forming reactions and carbonylation reactions,[33,34] while Nolan et al. have reported catalysts based on hindered *N*-heterocyclic carbene ligands, which can catalyze a wide variety of cross-coupling reactions.[35,36] Herrmann has also reported some noteworthy results using NHC ligands.[37] Generally, great progress has been made on the use of aryl chlorides in most types of cross coupling reactions, such as Buchwald−Hartwig amination,[21,38] Heck coupling,[39,40] α-arylation of ketones,[29] C−O bond formation,[41,42] and Stille reactions.[43]

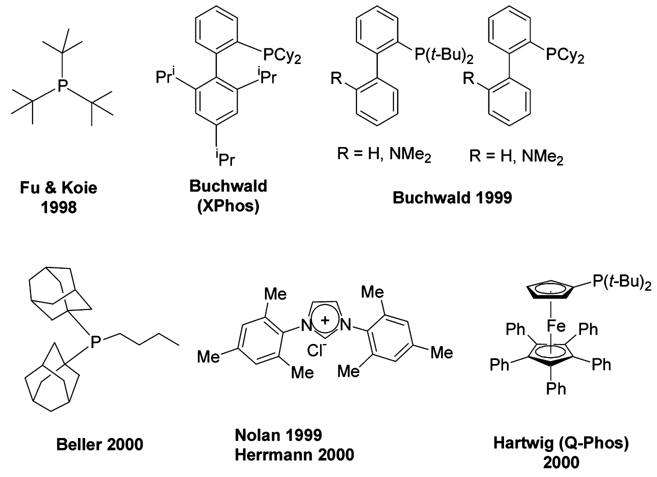
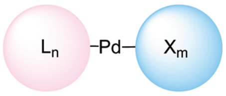


Figure 1. Electron-rich, bulky ligands used in palladium-catalyzed coupling reactions.

Despite those significant developments, most of the catalyst systems described above are formed in situ by mixing a palladium precursor, such as $Pd(dba)_2$ or $Pd(OAc)_2$, with a ligand; however, the dba ligand has been reported to significantly retard the activity of the catalyst when $Pd(dba)_x$ is used ($x = 1.5−2$).[44,45] Although $Pd(OAc)_2$ and $Pd(dba)_x$ are readily available Pd precursors, their purities vary significantly, depending on their preparation and supplier. In addition, from a practical point of view, many of the highly active electron-rich monophosphine ligands are air-sensitive and in some cases even pyrophoric (e.g., $P(t\text{-Bu})_3$), which results in further complications, particularly during the scale-up of a cross-coupling reaction. In addition, depending on the way a Pd precursor is mixed with a ligand, different catalytic species may be formed, which can adversely affect the activity and selectivity of the specific coupling reaction. This problem was not anticipated in the beginning of the cross-coupling era, but was identified and highlighted only in the last 5−10 years.

2. THE DEVELOPMENT OF PREFORMED CATALYSTS

For the above reasons, during the past decade, there has been a significant effort in developing "well-defined" preformed complexes. In addition to the pivotal role of the ligands, the nature of the Pd complex (**1**) can also impact in a significant way the activity and selectivity of a cross-coupling reaction. The size of the ligand can influence the coordination number of Pd, depending on how the complex is engineered.



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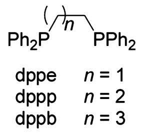
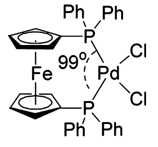
The Pd complex **1** is the pictorial representation of the catalyst. The steric and electronic properties of ligand L; the number, *n*, of L; the oxidation state of Pd (2+, 1+, 0); and even the nature of the spectator ion X (halide, allyl, etc.) can be varied readily and independently to engineer a catalyst for a suitable coupling reaction. This permits the fine-tuning of the catalytic species to have the desired properties to enhance the different steps in a catalytic cycle. The Holy Grail in cross-coupling methodology is the development of a "universal catalyst" that can achieve equally high conversions, regardless of the nature of coupling partners. This would be an extremely difficult feat to achieve, as there are still questions regarding many of the steps or pathways in the various catalytic cycles, despite ongoing active research in this area. Nonetheless, incremental steps have been taken to develop more robust and reproducible catalytic systems for specific reactions. In this review, our focus is to highlight the development and use of preformed Pd catalysts with the aim of improving the activity and selectivity of a particular reaction in comparison to the catalysts used in situ.

2.1. First Generation of Preformed Pd Catalysts. As early as in 1979, Kumada observed that the appropriate choice of ligand can have a profound influence on the outcome of a cross-coupling reaction.[46,47] The use of $PdCl_2(dppf)$ expanded the substrate scope of Kumada reactions to include the previously problematic alkyl Grignard reagents (Table 1).

Table 1. Kumada Coupling of Secondary Alkyl Magnesium Chlorides with Aryl Bromides Showing the Importance of a Bidentate Ligand with Larger Bite Angle

entry	catalyst	time (h)	bite angle (°)	*sec*-BuPh (%)	*n*-BuPh (%)
1	$(PPh_3)_2PdCl_2$	24	n/a	5	6
2	$dppePdCl_2$	48	85.8	0	0
3	$dpppPdCl_2$	24	90.6	43	19
4	$dppbPdCl_2$	8	94.5	51	25
5	$dppfPdCl_2$	1	99.1	95	2





$dppfPdCl_2$

This study highlights the dramatic positive effect of a bidentate ferrocenyl phosphine ligand[48] with a relatively large bite angle in catalysis (entry 5). The larger P–Pd–P angle (bite angle) is correlated in the above case to accelerate the reductive elimination of the coupled product after the transmetalation step, rather than allowing the alkyl moiety to sit on the Pd long enough to facilitate *β*-hydride elimination, which leads to destructive pathways such as the isomerization of *s*-butyl- to *n*-butyl-based product via the recoordination of the eliminated olefin to Pd.[46]

There are also a number of early examples in which the preformed Pd(II) catalyst $PdCl_2(PPh_3)_2$[49] or the Pd(0) complex $Pd(PPh_3)_4$[50,51] has been used as catalyst of choice. Although they do alleviate the problems associated with potentially deleterious Pd species formed in situ, they contain the less active PPh_3 ligand; therefore, it is necessary to limit the substrate scope to aryl iodides and activated aryl bromides. This does not mean that these catalysts are obsolete. On the contrary, all three aforementioned catalysts are still very commonly used in large-scale processes,[52−56] mainly because of their relatively lower cost in comparison with the lately developed more advanced catalysts. Many factors can affect the choice of a catalyst; however, in a somewhat simplified argument, the lower cost of these less active catalysts needs to be weighed against the required use of a more expensive coupling partner (Br or I vs Cl). A chemist who decides which catalyst to be used in a reaction should think of the overall cost of the process, rather than the upfront price of the catalyst.

2.2. Second-Generation Preformed Pd Catalysts. When the development of processes employing electron-rich alkyl phosphines as ligands was pioneered by Fu and Koie, a natural succession was for research groups around the world to prepare preformed palladium complexes incorporating this new type of ligand. Possibly, one driving force behind this was that the use of these air-sensitive, often pyrophoric, ligands in industrial processes would be highly problematic. If one could find a way of getting around this problem by employing a preformed Pd catalyst, in which the Pd–PR_3 bond was already in place, the use of the less reactive but more widely available organic chloride substrates could be made possible, even at a larger scale. The earliest examples of cross-coupling reactions involving organic chlorides employed the trialkylphosphine ligands, such as $P(t\text{-}Bu)_3$ or PCy_3 followed by, to some extent, JohnPhos (Buchwald's early generation) and NHCs (Figure 1). These were also the ligands to be first incorporated in the second generation preformed palladium catalysts.

Beller and Herrmann reported in 1995 the synthesis of a preformed thermally robust palladacycle dimer catalyst **2** and demonstrated its application in coupling chloroarene substrates in Heck, Suzuki, and even in amination reactions (Figure 2).[57−59] This palladacycle was synthesized by combining $Pd(OAc)_2$ with $P(o\text{-}tol)_3$, which slowly decomposes in air when stored as the free ligand. Five years later, in 2000, Beller demonstrated the preparation and isolation of the first Pd(0) monophosphine complexes **4**–**5** and their performance in the Suzuki coupling of aryl chlorides. These precatalysts contained electron-rich, air-sensitive phosphine ligands such as PCy_3 and 2-biphenyl-PCy_2. Notably, it was observed that the use of well-defined preformed catalyst **4** resulted in superior results in comparison with the use of in situ-formed catalysts $Pd_2(dba)_3$ or $Pd(OAc)_2/PCy_3$ (Table 2).

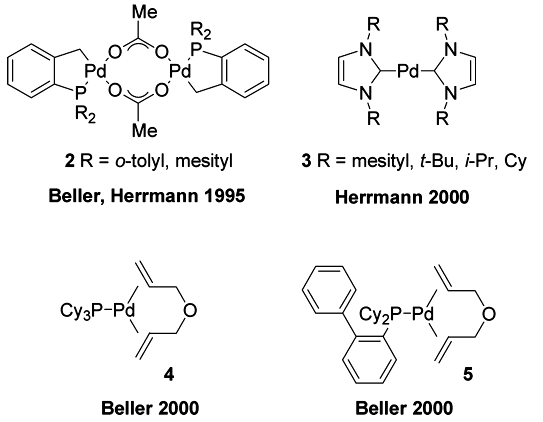
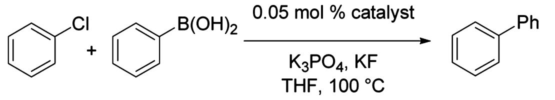


Figure 2. Early examples of preformed Pd catalysts.

Concurrently, Herrmann reported the first synthesis of a preformed Pd(0) dicarbene complex **3** (Figure 2).[37] He observed, however, a 25% decrease in the product yield in a Suzuki coupling when employing the preformed catalyst as opposed to the in situ formed one. Nevertheless, this seminal work by Herrmann and Beller constitutes the beginning of the development of a second generation of preformed Pd catalysts.

Table 2. Beller's Preformed Catalyst 4 in Suzuki Reactions



entry	catalyst	yield (%)[a]
1	$Pd_2(dba)_3/PCy_3$ (1:1)	8
2	$Pd(OAc)_2/PCy_3$ (1:1)	11
3	$Pd(OAc)_2/PCy_3$ (1:2)	28
4	**4**	79

[a] Determined by GC with hexadecane as internal standard.

3. PREFORMED CATALYSTS CONTAINING TERTIARY PHOSPHINE LIGANDS

As described in the introduction, until the mid-1990s, the less active triarylphosphine PPh_3 and, to some extent, P(*o*-tol)$_3$ were the ligands of choice for use in cross-coupling reactions. This restricted the substrate scope to the use of aryl iodides and activated aryl bromides. Fu, among others, pioneered the use of highly active trialkylphosphines in the more challenging cross-coupling reactions of organic chlorides. At the expense of the higher activity came the air-sensitive, often pyrophoric, properties of the required ligands, which greatly complicated the practical aspects of carrying out the reactions in a safe manner, particularly on large scale. This section will focus on the efforts and advances made to prepare stable preformed catalysts containing these highly active tertiary phosphine ligands. Examples will be highlighted to demonstrate that quite often the activities of the precatalysts are superior to that of the in situ generated catalysts from a Pd precursor and the free ligand.

The preformed catalysts containing tertiary phosphine ligands can be categorized in two groups, depending on the nature of the proposed catalytically active Pd(0) species: $L_2Pd(0)$ and LPd(0). The $L_2Pd(0)$ catalysts can be prepared and isolated, but are moderately air-sensitive, as in the case of the well-known $Pd(PPh_3)_4$, and do not require activation in situ to form the catalytically active Pd(0) species. They can also be generated in situ in the reaction mixture from $L_2Pd(II)X_2$ precatalysts. The LPd(0) catalysts have not been isolated, but are generated in situ from the preformed Pd catalysts, such as Pd(I) dimers, $(LPdX)_2$; Pd(II) dimers, $(LPd(II)X_2)_2$; and palladacycles.

3.1. L_2Pd(0) Catalysts. Having established that $Pd_2(dba)_3$/P(*t*-Bu)$_3$ was a viable catalytic system for the Negishi coupling of 4-chloroanisole, Fu continued to investigate use of the preformed Pd(0) catalyst Pd[P(*t*-Bu)$_3$]$_2$ to understand the substrate scope for a wide range of aryl and heteroaryl chlorides with aryl and alkyl zinc reagents (Scheme 2).[60]

Hartwig also investigated preformed Pd[P(*t*-Bu)$_3$]$_2$ in amination reactions and observed a significant increase in activity when the precatalyst was used in comparison with the in situ generation of the catalyst from $Pd(dba)_2$ and P(*t*-Bu)$_3$ (Table 3).[61]

Notably, in this case, a 1:2 metal-to-ligand ratio provided results superior to a 1:1 Pd-to-ligand ratio. Generally, this is not a universally true observation, as Hartwig has demonstrated that at room temperature, a 1:0.8 Pd-to-ligand ratio has provided significantly higher activity than that of a 1:2 ratio.[38] Fu also observed a similar trend in Suzuki couplings at room temperature. Use of a 1:1 ratio of P(*t*-Bu)$_3$ to Pd furnishes a very active catalyst, whereas a 2:1 ratio leads to a very slow reaction.[19] For bulky monodentate phosphines, it is somewhat presumed that the active Pd(0) species in the oxidative addition step is an LPd species. At room temperature, there may not be sufficient energy for one of the ligands in an L_2Pd catalyst to dissociate, thereby making this precatalyst less active in cross-coupling reactions at ambient temperatures. Despite this anomaly, on the basis of our experience in this area, we recommend the use of preformed LPd-based catalysts vs in situ-generated catalyst, from a reproducibility stand point, especially during scale-up and manufacture. However, we do understand that by properly engineering the process, skilled workers can reach more optimal results in catalysis using in situ-generated catalysts.

Scheme 2. Negishi Coupling Using Aryl Chlorides

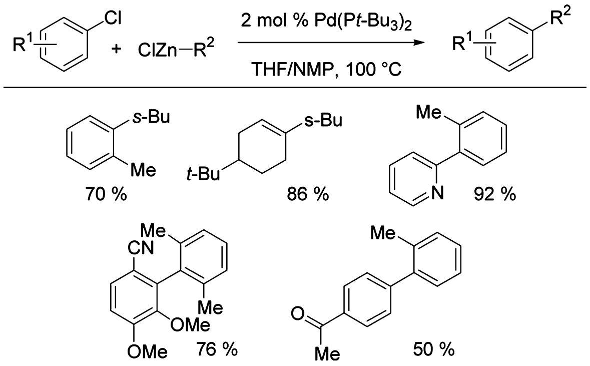
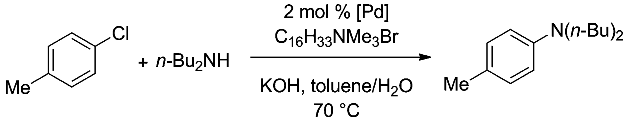


Table 3. Amination Using Pd[P(*t*-Bu)$_3$]$_2$ vs in Situ



entry	catalyst	yield (%)[a]
1	$Pd(dba)_2$/P(*t*-Bu)$_3$ 1:1	<30
2	Pd[P(*t*-Bu)$_3$]$_2$	100

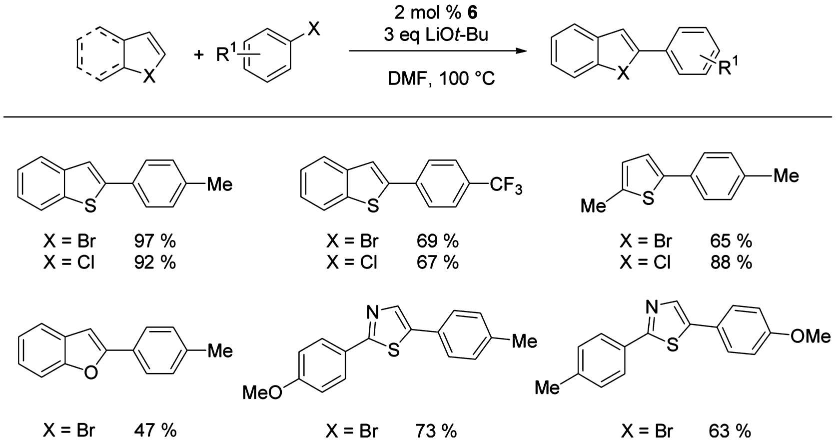
[a] Yield determined by GC.

Typically, $L_2Pd(0)$ catalysts generally display higher activities in cross-coupling reactions at elevated temperatures. This is due to the thermodynamic stability of the $L_2Pd(0)$ (14 electron) species vs the kinetic stability of LPd(0) (12 electron) species. The interesting results obtained by Fu in Negishi couplings and by Hartwig in amination reactions using Pd[P(*t*-Bu)$_3$)]$_2$ as catalyst prompted researchers to further investigate the potential of these catalysts in other coupling reactions.

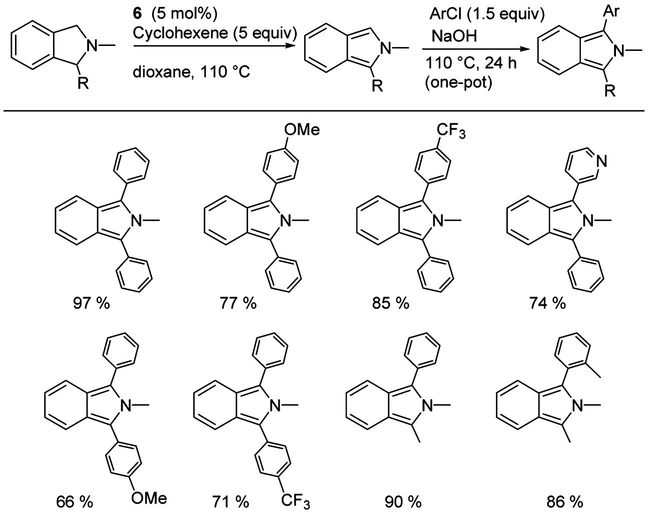
The transition-metal-catalyzed C−H arylation has recently attracted a lot of attention because of its operational simplicity.[62−71] In this field as well, use of Pd[P(*t*-Bu)$_3$]$_2$ has met with success. Mori and co-workers recently reported the direct arylation of heteroarenes with aryl bromides and aryl chlorides using $L_2Pd(0)$ catalyst (**6**).[72] Scheme 3 shows the coupling of various electron-withdrawing or -donating aryl bromides and chlorides with benzothiophene to afford the coupling products in good to excellent yields. In addition, the reaction with other thiophene derivatives proceeded similarly to afford the corresponding C−H arylation products, even with unactivated and activated aryl chlorides.

Suginome and coauthors reported a one-pot conversion of isoindolines to 1-arylisoindoles, which can be accomplished via a sequential dehydrogenation/C−H arylation reaction catalyzed by Pd[P(*t*-Bu)$_3$]$_2$ **6** (Scheme 4).[73] For example, C1-

Scheme 3. Pd-Catalyzed C−H Arylation of Heteroarenes with Aryl Halides



Scheme 4. Palladium-Catalyzed One-Pot Dehydrogenation/C−H Arylation of 1-Substituted Isoindolines



substituted 2-methylisoindoles underwent C−H arylation smoothly with various aryl chlorides. Noticeably, the authors compared the performance of preformed catalyst **6** with in situ-generated catalyst system from $Pd(dba)_2/2P(t\text{-}Bu)_3$, and found **6** to be significantly more active (98% vs 69%). This, again, highlights the superiority of the preformed catalyst vs the in situ-generated one. Dehydrogenation of 1-aryl-2-methylisoindolines and 1,2-dimethylisoindoline took place cleanly to give the corresponding isoindoles, which underwent subsequent C−H phenylation to afford the final products in good to excellent yields. Electron-rich as well as electron-deficient aryl chlorides reacted in high yields, and 3-chloropyridine successfully took part in the C−H arylation, giving good yield of the biaryl. Likewise, C−H phenylation of 4-methoxyphenyl-substituted and 4-trifluoromethylphenyl-substituted isoindole gave the corresponding 1,3-diarylisoindoles, respectively, in good yields.

$Pd[P(t\text{-}Bu)_3]_2$ was for a long time the only commercially available $L_2Pd(0)$ catalyst. The commercially available $Pd(PPh_3)_4$ is believed to dissociate to $Pd(PPh_3)_2$ during catalysis, however, often significantly less active than that of a trialkylphosphine containing catalyst. The main reason for the lack of commercial availability of many examples of $L_2Pd(0)$ complexes was the tedious procedures that were used to prepare these compounds. One known method employs a highly volatile and unstable precursor $Pd(\eta^3\text{-}C_3H_5)(\eta^5\text{-}C_5H_5)$,[74] whereas another involves a synthesis using $Pd(dba)_x$ with the ligand, followed by recrystallization of the crude product with a large amount of solvent under cryogenic conditions.[60,75] Although $Pd(\eta^3\text{-}1\text{-}PhC_3H_4)(\eta^5\text{-}C_5H_5)$ has been recently reported[76] as a new precursor to generate $L_2Pd(0)$ in situ, its utility to synthesize the preformed catalysts has not been

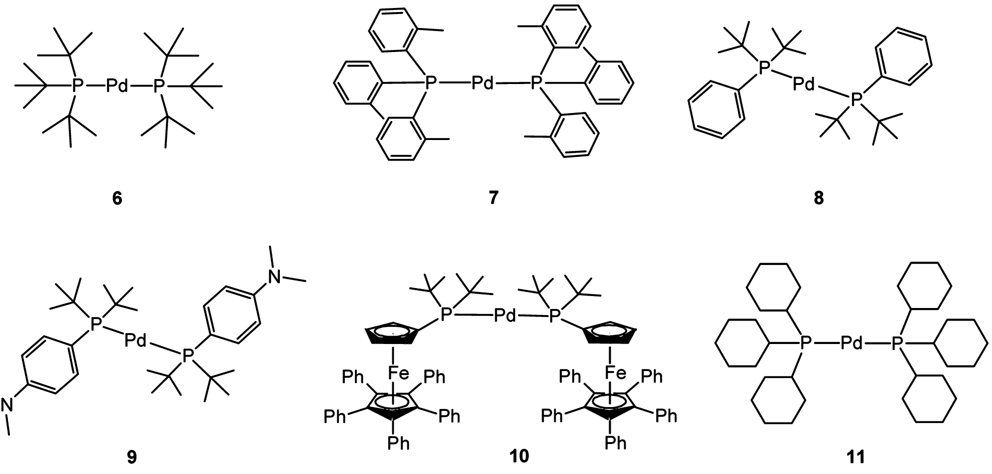
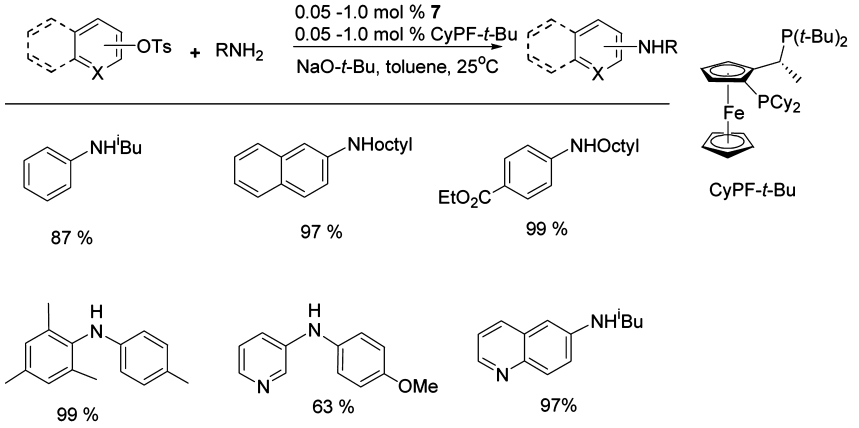


Figure 3. Commercially available preformed $L_2Pd(0)$ catalysts.

Scheme 5. Coupling of Tosylates with Primary Alkylamines and Arylamines Catalyzed by 7 and CyPF-*t*-Bu



demonstrated. In addition, the reported synthesis of the precursor requires extremely cryogenic conditions. More recently, Colacot and co-workers reported a general and novel route to make a series of $L_2Pd(0)$ catalysts (Figure 3).[77−79] The method provides the synthesis of $L_2Pd(0)$ compounds in nearly quantitative yield on scale, specifically for sterically bulky, electron rich phosphines such as $P(t\text{-Bu})_3$, PCy_3, $P(o\text{-tol})_3$, $P(t\text{-Bu})_2Ph$, $P(t\text{-Bu})_2(4\text{-}Me_2NC_6H_4)$, and $P(C_5H_4FeC_5Ph_5)(t\text{-Bu})_2$ (QPhos), although this approach is not limited to these ligands alone.

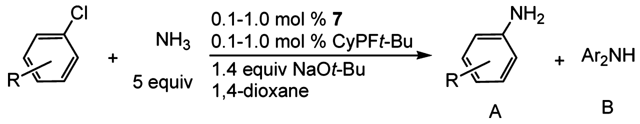
The one-pot process uses readily available, inexpensive air-stable precursor $(COD)PdBr_2$ with a stoichiometric amount of phosphine ligand in the presence of a Brønsted base (e.g., alkali hydroxides) in a protic solvent.

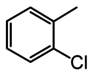
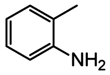
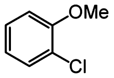
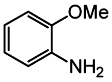
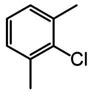
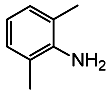
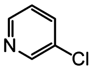
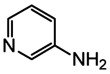
The new $L_2Pd(0)$ catalysts that we recently developed have shown promising results not only from our lab, but also from academia for the development of new processes and methods. Those results are briefly summarized below.

Consistent with the previous work on the selective monoarylation of primary amines,[3] Hartwig and co-workers developed routes for the challenging processes of amination of unreactive aryl tosylates as well as selective monoarylation of ammonia. They found $Pd(Po\text{-tol}_3)_2$ **7** to be the best Pd precursor for the aryl tosylate aminations.[80] When combined with Josiphos ligand CyPF-*t*-Bu (Scheme 5), it was possible to couple primary amine with tosylates at room temperature to form the corresponding secondary arylamines in high yields with complete selectivity for the monoamination product. Scheme 5 shows that primary alkylamine or arylamine can react with aryl and heteroaryl to form secondary amine products with excellent yield. The reaction can tolerate various sensitive functional groups in addition to coupling sterically hindered substrates smoothly.

Hartwig used the same catalyst system (**7** with CyPF-*t*-Bu) for coupling aryl chlorides and heteroaryl chlorides ranging from electron-deficient to electron-rich with ammonia in high yields and high selectivities (Table 4).[81] For example, reactions of 2-chlorotoluene and 2-chloroanisole with ammonia afford good yields of coupled products with only 0.1% catalyst loading. The conditions for reactions of aryl chlorides proved to be suitable for the reactions of heteroaryl chlorides. The reaction of 3-chloropyridine with ammonia occurred in 64% isolated yield. None of the other Pd(0) catalysts worked effectively.

Table 4. Coupling of Aryl Chlorides with Ammonia[a]

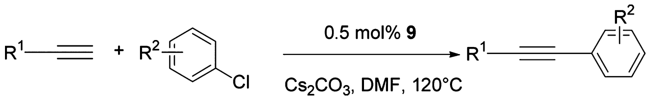


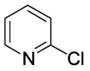
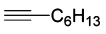
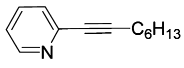
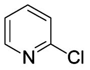
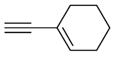
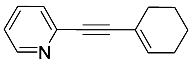
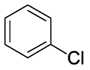
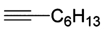
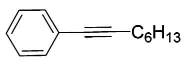
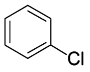
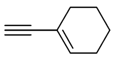
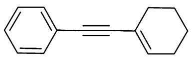
entry	aryl halide	[Pd] loading (mol %)	product	yield (%)	A:B
1		0.1		64	17:1
2		0.1		84	>50:1
3		1.0		89	>50:1
4		1.0		64	>50:1

[a] *T* 100 °C, 24 h.

Our lab also reported preliminary results of a copper-free Sonogashira coupling of aryl and heteroaryl chlorides with alkynes successfully using **9** as the catalyst (Table 5).[77,78]

Table 5. Sonogashira Reactions of Aryl and Heteroaryl Chlorides Using 9

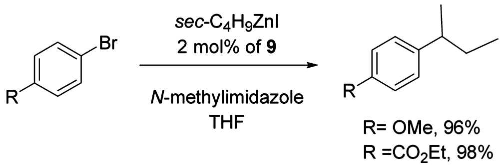


entry	aryl chloride	acetylene	product	yield (%)
1				94
2				90
3				91
4				85

Noteworthy was that none of the remaining catalysts in the $L_2Pd(0)$ series (**6**−**11**) was capable of carrying out this transformation under identical reaction conditions. This highlights the importance of ligands for successfully carrying out a specific catalytic reaction.

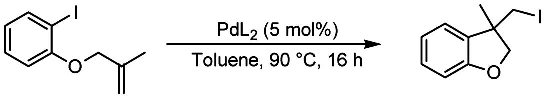
More recently, Lipshutz reported that catalyst **9** is very good in stereo- and chemoselective cross-couplings of alkenyl and aryl bromides with secondary alkyl zinc iodides with the aid of *N*-methylimidazole as the key additive (Scheme 6).[82]

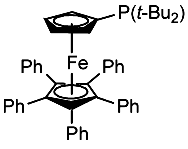
Scheme 6. Cross-Coupling of Aryl Bromide with *sec*-C_4H_9ZnI



In addition to this, the introduction of novel Pd precatalysts could result in the discovery of new chemical reactivity that was previously not possible using other more established catalysts. One such example is the intramolecular carboiodination recently reported by Lautens.[83] From a range of $L_2Pd(0)$ catalysts, $Pd(Q\text{-}Phos)_2$ was identified as the most effective catalyst for this transformation (Table 6). Running the reaction at 100 °C with 2.5 mol % of **10** gave full conversion of the starting material within 4 h, with 95% isolated yield (Table 7, entry 1). With these optimized conditions, a number of intramolecular cyclizations were explored. Both five- and six-membered rings could be formed to produce various oxygen- and nitrogen-containing heterocycles as well as a carbocycle in high yields (Table 7, entries 1−5). For the formation of five-membered rings in high yields, milder conditions are required in comparison with the formation of six-membered rings. The analogous reaction with an aryl bromide or chloride did not give the corresponding carbohalogenation product, suggesting that sp^3 C−Cl and C−Br reductive elimination may be more difficult than that of C−I reductive elimination. Thus far, the reaction does not work if β-hydrogens are present in the cyclized alkyl Pd(II) halide intermediate. Instead, olefin isomerization or Heck-type products are formed.

Table 6. Carboiodination Using $L_2Pd(0)$ Catalysts

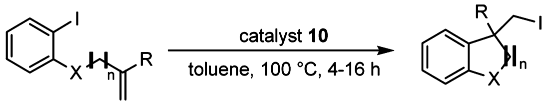


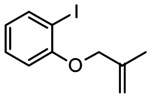
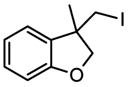
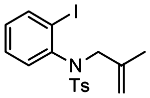
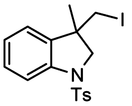
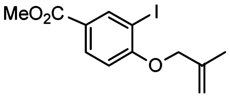
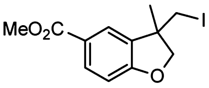
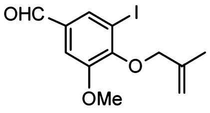
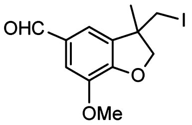
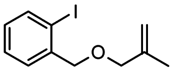
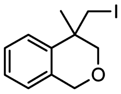


Q-Phos

entry	ligand	yield (%)
1	Q-Phos	82
2	$P(t\text{-}Bu)_3$	61
3	$PPh\,t\text{-}Bu_2$	76
4	PCy_3	0
5	$P\,o\text{-}tol_3$	0

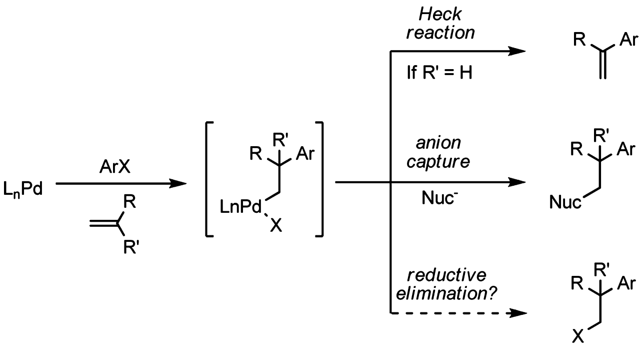
Table 7. Scope of Palladium-Catalyzed Intramolecular Carboiodination



entry	substrate	product	yield (%)
1			95
2			93
3			92
4			96
5			86

The authors proposed a mechanism for this transformation in which the Pd oxidative addition intermediate goes through direct reductive elimination to form the product, instead of β-H elimination to form the Heck type product, as shown in Scheme 7.

Scheme 7. Proposed Mechanism for Intramolecular Carboiodination

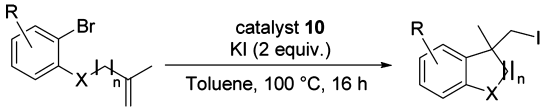


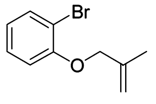
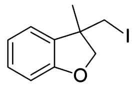
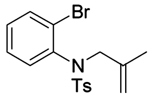
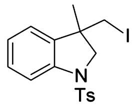
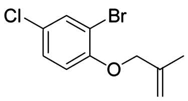
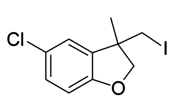
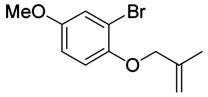
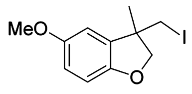
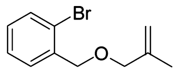
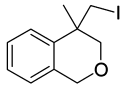
More recently, the same authors reported the use of the same catalyst for halogen-exchange carboiodination, which now allowed for the use of aryl bromides as starting material, as shown in Table 8.[84]

In addition, polyunsaturated aryl iodide substrates are amenable for domino carbohalogenation reactions yielding complex bicyclic alkyl iodides containing multiple stereogenic centers in high yields with good diastereoselectivities (Scheme 8).[84]

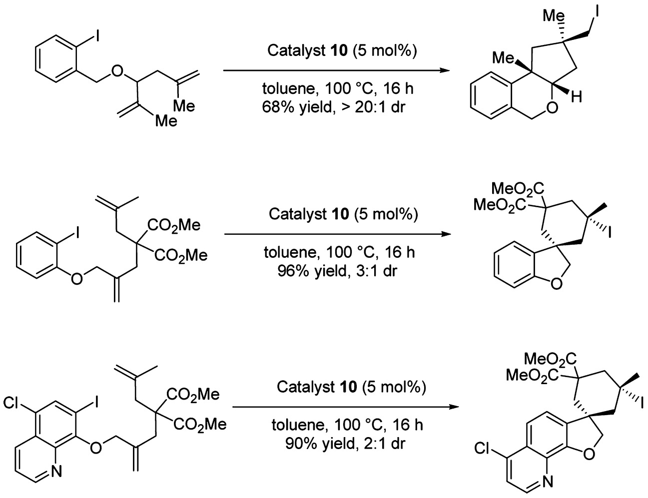
3.2. L_2PdCl_2 Catalysts. Although the $L_2Pd(0)$ catalysts are highly active, these compounds are typically air- and moisture-sensitive. However, if one knows how to handle the well-known tetrakis (triphenylphosphine)palladium, $Pd(PPh_3)_4$, these $L_2Pd(0)$ catalysts can be stored and handled using similar

Table 8. Palladium-Catalyzed Halogen-Exchange Process



entry	substrate	product	yield (%)
1			89
2			91
3			90
4			92
5			71

Scheme 8. Complex Molecule Synthesis via Carbohalogenation



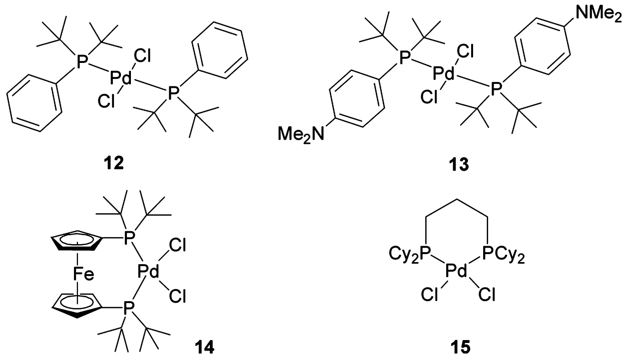
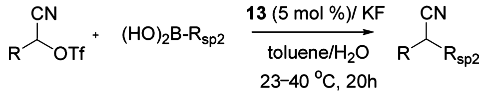
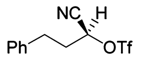
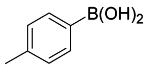
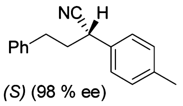
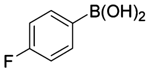
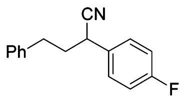
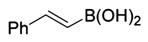
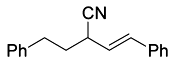
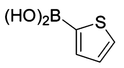
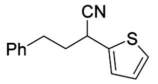
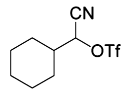
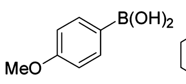
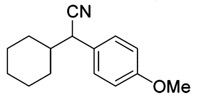


Figure 4. Commercially available preformed L_2PdCl_2 catalysts.

Table 9. Stereospecific Suzuki Cross-Coupling of Alkyl α-Cyanohydrin Triflates



entry	cyanohydrin	boronic acid	product	yield (%)
1	 **(*S*)-a** (99 % ee)		 (*S*) (98 % ee)	91
2	**(±)-a**			76
3	**(±)-a**			94
4	**(±)-a**			56
5				31

protocols. On the other hand, the class of L_2PdX_2 precatalysts is reasonably stable toward air, moisture, and temperature. Ligand L_2 of L_2PdX_2 can be monodentate (**12**, **13**) or bidentate, (**14**, **15**), as depicted in Figure 4. This family of catalysts is one of the most active, frequently employed catalysts in industrial processes, both on a small and large scale.[85] Their applications will be highlighted with selected examples from the literature, demonstrating the potential of these catalysts not only to improve the efficiency of the previously known reactions, but also enabling the discovery of new technologies.

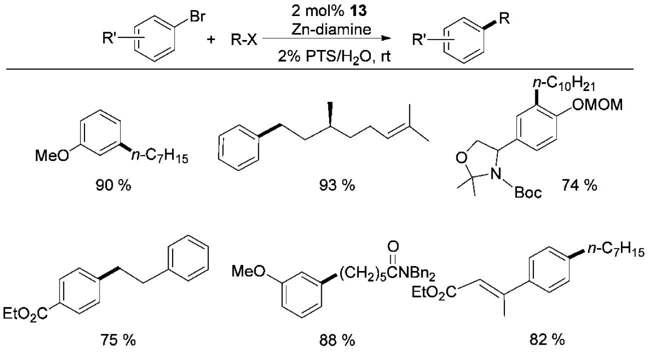
Guram has earlier shown that **13** is a very good catalyst for Suzuki coupling of aryl and heteroaryl halides containing NH_2 functionalities.[86] Falck later reported a Suzuki coupling[87] (Table 9) that stereospecifically couples a functionalized, sp^3-hybridized stereogenic carbon to aryl, heteroaryl, and vinyl boronic acids under mild conditions, using **13** as catalyst. The coupling proceeds with complete inversion of configuration. The resultant nitrile can be easily converted to a variety of alternative functional groups of value in organic synthesis.

As shown in Table 9, for (*S*)-α-cyanohydrin triflates, cross-coupling stereospecifically furnished the *S* enantiomer of the product in excellent yield (entry 1). The coupling was tolerant of electron-withdrawing substituent (entry 2). Likewise, a vinyl boronic acid was quite successful, smoothly generating the corresponding adduct in high yield (entry 3). Extension of the Suzuki technology to heteroaromatic boronic acids was still problematic (entry 4). The influence of steric crowding was more evident when present near the secondary cyanohydrin center and if a β-hydrogen was present (entry 5).

Lipshutz reported Negishi type couplings in aqueous micelles using catalyst **13** and a designer surfactant (Scheme 9).[88] This new methodology provides a remarkably straightforward means of effecting transition metal catalyzed Csp^2-Csp^3 bond constructions in the absence of a stoichiometrically preformed organozinc coupling partner. Scheme 9 illustrates a number of representative aryl bromides that have been alkylated. Both simple alkyl and several functionalized primary alkyl iodides and bromides led to good isolated yields, indicative of considerable generality. Also included are products bearing ester residue, an amide, and a highly adorned aromatic ring.

Grasa and Colacot investigated the utility of **14** in the α-arylation of ketones.[89] Following the successful application of

Scheme 9. Zinc-Mediated Couplings between Primary Alkyl Iodides and Aryl Bromides in Water at RT Using 13 As Catalyst



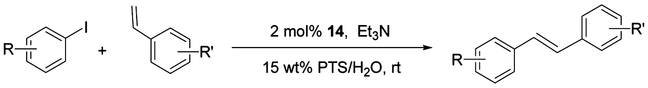
air-stable **14** in Suzuki reactions,[90] the same complex was used to catalyze the coupling between various aryl halides and acetophenone derivatives with isolated yields up to 93% (Table 10). Although sterically hindered aryl chlorides, such as 2-chloro-*m*-xylene and chloromesitylene proceeded smoothly at 60 °C in high conversions in the arylation of propiophenone (entry 3), the electron-rich 4-chloroanisole required higher temperature to reach full conversion. Inversely, the effect of the ketone substrate was also studied using difficult aryl chlorides, such as 2-chloro-*m*-xylene (entries 4–8).[91] Various acetophenone derivatives reacted efficiently with sterically hindered 2-chloro-*m*-xylene to give the products in good to excellent isolated yields.

After Heck first introduced cross-coupling using aryl halides and alkenes, there has been significant development for utilization of this important transformation.[92−94] Recently, Lipshutz reported Heck reactions at room temperature in water as the only solvent, using **14** as catalyst and PTS as surfactant (Table 11).[95]

Both electron-rich (entries 1, 2, 4, and 5) and electron-poor (entry 3) aryl iodides smoothly afforded unsymmetrical (*E*)-stilbenes. Highly functionalized tetrahydroisoquinoline can be readily reacted with 4-methoxystyrene at 25 °C (entry 6). Work-up in some cases involved partitioning between 2:1 brine/H_2O and 3:1 hexanes/EtOAc, followed by extraction with 3:1 hexanes/EtOAc. This protocol leaves PTS in the aqueous phase, along with a substantial amount of the palladium catalyst.

Carbonylation reactions have been increasing in organic chemistry for the atom-efficient introduction of carbonyl centers in aldehydes, acids, esters, and amides.[96,97] Barnard reported the use of **15** as a catalyst,[98] for the conversion of

Table 11. Heck Couplings of Aryl Iodides with Styrenes Using 14 As Catalyst



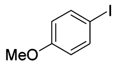
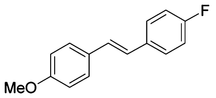
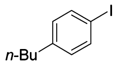
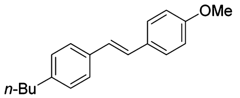
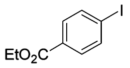
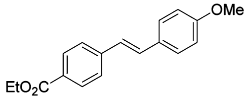
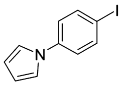
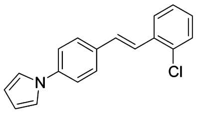
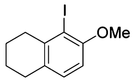
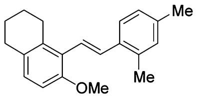
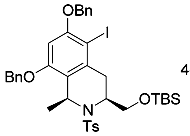
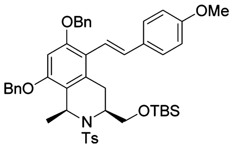
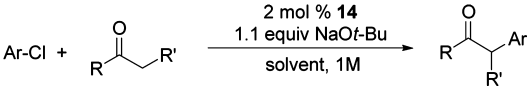
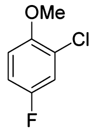
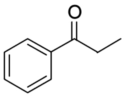
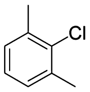
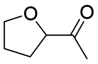
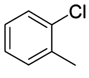
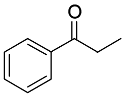
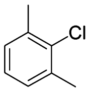
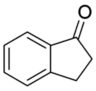
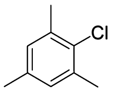
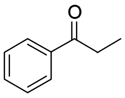
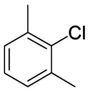
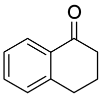
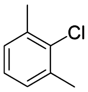
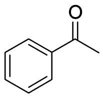
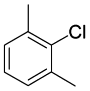
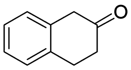
entry	aryl halide	R'	product	yield (%)
1		4-F		94 (9:1, E/Z)
2		4-OMe		96 (9:1, E/Z)
3		4-OMe		97 (93:7, E/Z)
4		2-Cl		95 (88:12, E/Z)
5		2,4-Me$_2$		94 (19:1, E/Z)
6		4-OMe		90 (9:1, E/Z)

Table 10. α-Arylation of Propiophenone with Aryl Chloride Catalyzed by 14

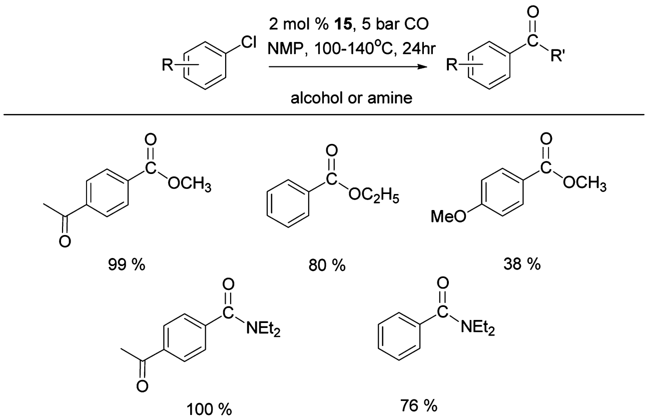


entry	Ar-Cl	ketone	conditions	conv. (%)[a]	entry	Ar-Cl	ketone	conditions	conv. (%)[a]
1			THF 60 °C	93 (61)	5			dioxane 100 °C	61
2			THF 60 °C	99 (93)	6			dioxane 100 °C	99
3			THF 60 °C	91 (90)	7			dioxane 100 °C	91
4			dioxane 100 °C	99 (92)	8			dioxane 100 °C	99

[a] Conversion was determined by GC. Isolated yields reported in parentheses.

relatively challenging aryl chloride substrates to esters and amides via alkoxy and aminocarbonylation. As can be seen from Scheme 10, a variety of aryl chlorides can be utilized.

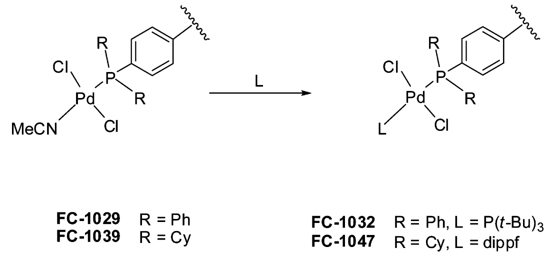
Scheme 10. Alkoxycarbonylation and Aminocarbonylation of Aryl Chloride



Although electron-neutral or electron-poor substrates are typically useful, electron-rich aryl chlorides are still problematic.

A problem faced, in particular by the pharmaceutical industry, is removal of residual Pd in the final coupling product. One solution may be to employ catalysts that are anchored to a solid support and which can be easily removed by simple filtration at the end of the reaction. A number of precursors to $L_2Pd(0)$ catalysts are commercially available as solid support precatalysts, named FibreCats (FC; Scheme 11).[99,100,119d] The ligand, L, can be any mono or bis phosphine ligand within a large range; for example, Q-Phos, dppf, BINAP. These tunable FibreCats with bulky electron rich ligands can do challenging arylchloride Suzuki coupling effectively.[100]

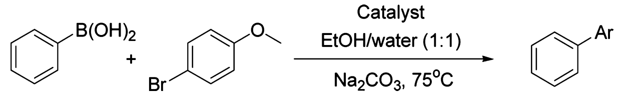
Scheme 11. Tunable Pd-Based FibreCats



Similar to classical nonsupported catalysts, use of preformed FibreCat catalysts may result in superior turnover numbers (TON) and turnover frequencies (TOF) (Table 12, entries 1–4) compared with the use of in situ catalysis (entry 5).[119d]

3.3. Precursors to LPd(0) Catalysts. For certain types of Pd-catalyzed cross-coupling reactions, the metal-to-ligand ratio is important. This is understandable because the 12-electron-based LPd(0) is kinetically more active than the 14-electron species. A few reports are available in the literature, where the catalyst system is more active when a 1:1 ratio of phosphine to palladium is used.[29,38,101] For this purpose, several classes of preformed $LPdX_n$ catalyst were reported and showed great activity in cross-coupling reactions.

Table 12. The Performance of FibreCats Compared with in Situ-Formed Catalyst



entry	catalyst	loading (mol %)	time (h)	yield[a]	TON	TOF (h^{-1})
1	FC-1032	0.25	2	88 (72)	352	176
2	FC-1039	0.25	2	100 (94)	400	200
3	FC-1029	0.25	2	100 (94)	400	200
4	Pd-Smopex-111[b]	0.25	2	92 (78)	368	184
5	$Pd(OAc)_2/2Ph_3P$	0.50	4	100 (94)	200	50

[a] Isolated yield in parentheses. [b] Solid supported $Pd(OAc)_2$

The first class of precursors to LPd(0) catalysts that were effectively used in cross coupling was the palladacycles. The groups of Herrmann and Beller independently reported palladacycles (Figure 2) as a class of precatalysts in cross-coupling,[102] which sparked a great deal of interest among other research groups to investigate the potential of this area. Palladacycles can be broadly divided into two categories: (i) those in which the palladacycle is formed via a carbopalladation of the ligand itself and (ii) those in which the palladacycle is formed from Pd and a hemilabile ligand that subsequently dissociates during the catalytic cycle. Examples of the first category include the Beller–Herrmann precatalyst (prepared from P(*o*-tol)$_3$ and $Pd(OAc)_2$) (Figure 2), Buchwald precatalyst **16**[103] (formed from JohnPhos and $Pd(OAc)_2$), and Vilar's Pd(I) dimer **17**[104,105] (Figure 5). Activation of these precatalysts to form the catalytically active species LPd(0) may occur via reduction by the action of an amine and a base.[106] Examples of precatalysts falling into the second category are Solvias palladacycle **18**[107,108] and Buchwald's recently developed catalyst **19**.[109] These complexes all contain a monodentate ligand that is proposed to stay coordinated to the Pd center throughout the catalytic sequence. Buchwald proposes an activation mechanism of this type of palladacycles whereby the precatalyst (e.g., **19**) is deprotonated to generate the catalytically active LPd(0) species and *N*-methylindoline.[109]

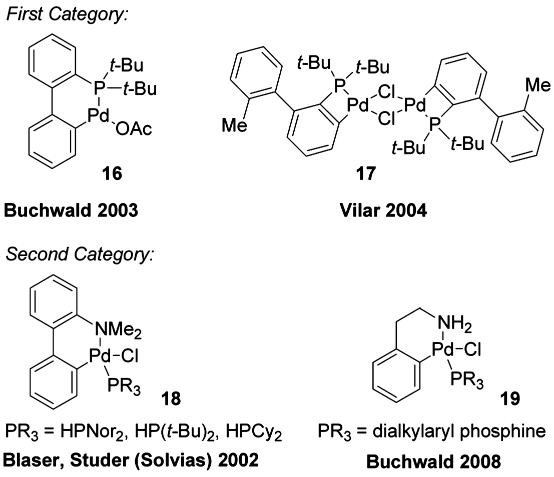
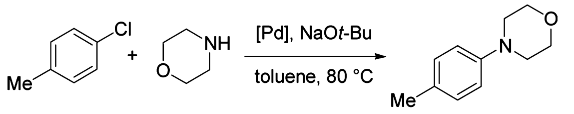


Figure 5. Selected examples of palladacycles as precatalysts.

In this review, our aim is not to provide a complete history of the development of palladacycles and their use in catalysis. However, if the reader is interested, a number of excellent reviews are available on the subject.[110−112] We have chosen to exemplify the most striking advances by focusing on a few examples of palladacycles developed in more recent years, which we believe constitute the precatalysts with most promising potential for use in large-scale industrial processes. This is based both on our appreciation of the ease of preparation of the complex and its performance in cross-coupling chemistry. In this regard, in 2003, Buchwald reported the preparation of palladacycle **16** and demonstrated its superior application in amination reactions in comparison with the in situ systems (Table 13).[103] First, the preformed catalyst is air-stable; thus, reactions can be set up in air while performing small scale lab reactions, although we do not recommend practicing cross-coupling catalysis in air because the Pd(0) species can get destroyed with time and temperature; hence, more loading of the catalyst is required, in addition to the safety concerns, reproducibility and selectivity. Second, in the in situ chemistry, a Pd-to-ligand ratio of 1:2 was typically required for an efficient reaction.[113] This can contribute to a significantly higher cost process when carried out on large scale. Third, using the preformed palladacycle catalyst could result in a considerably shorter reaction time while maintaining the high yield of product.

Table 13. Palladacycle 16 As Precatalyst in a Standard Amination Reaction

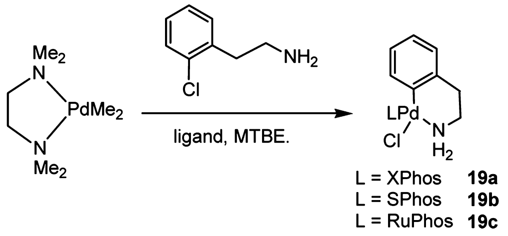


entry	[Pd]	time (h)	yield (%)
1	0.5 mol % $Pd(OAc)_2$/JohnPhos (1:2)	4	93
2	0.5 mol % **16**	2	97

Following this initial proof of principle, it would take another 5 years for the Buchwald group to develop and disclose the next generation of palladacycles. Although palladacycle **16** belongs to the first generation (Figure 5), the most recent precatalysts can be categorized into the second generation. It should be noted that palladacycles in the second category can be modified easily by the use of different ligands, such as various tertiary phosphines and NHCs.

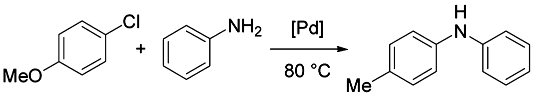
The next generation palladacycles developed by Buchwald can be readily prepared from aliphatic amine *o*-chlorophenethylamine (Scheme 12).[109] The precatalysts, when reacted with a base such as NaO*t*-Bu or K_2CO_3, are proposed to generate the catalytically active LPd(0) species and have shown excellent activities in Suzuki coupling and amination reactions.

Scheme 12. Palladacycle Prepared from Pd-Based Aliphatic Amine Complex



As was the case with the previously reported precatalyst, the use of palladacycle **19a** resulted in significantly superior activity in amination reactions relative to that observed using the in situ formed catalyst from $Pd_2(dba)_3$ and XPhos (Table 14).

Table 14. Preformed vs in Situ Catalysis Using XPhos



entry	[Pd]	time (min)	conv (%)
1	0.05 mol % $Pd_2(dba)_3$/XPhos	35	25[a]
2	0.1 mol % **19a**	35	100

[a] No further conversion was observed.

This family of precatalysts has been further expanded and improved by variations of the dialkylarylphosphine ligand. A remarkable generality has been demonstrated using two of these catalysts in amination reactions (Figure 6).[114]

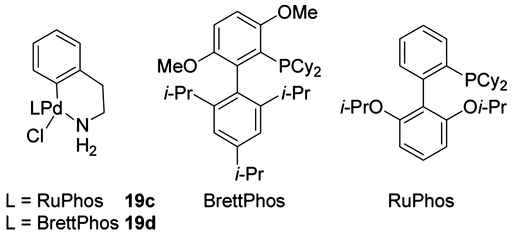
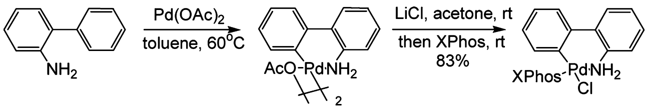


Figure 6. Catalysts for amination reactions.

Buchwald also reported third-generation palladacycle **20**, which could be prepared by a one-pot reaction starting from 2-aminobiphenyl and $Pd(OAc)_2$ (Scheme 13). This precatalyst was applied in Suzuki coupling reactions carried out at room temperature.[115] This allows the coupling of a wide range of (hetero)aryl halides and triflates with excellent functional group tolerance. The fast catalysis under extremely mild reaction conditions makes the coupling of unstable polyfluorophenyl and five-membered 2-heterocyclic boronic acids possible with a wide range of aryl (pseudo) halides. The rate increase is associated with the fast generation of the catalytically active species from an easy-to-prepare precatalyst **20**. As shown in Scheme 14, substrates with large noncoordinating ortho substituents are well tolerated. Heteroaromatic compounds readily underwent the coupling to form the desired products in excellent yields. Trisubstituted polyfluorophenylboronic acids could be employed to give products with high yield.

Scheme 13. Palladacycle Prepared from 2-Aminobiphenyl

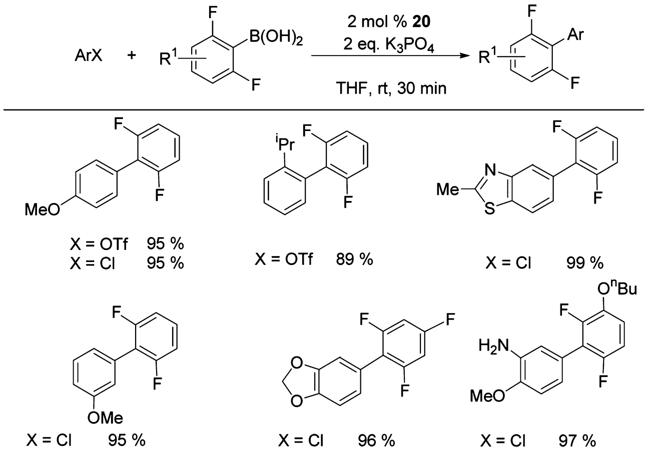


20

Another noteworthy example of palladacycles was reported by Bedford and co-workers in 2003. They disclosed a family of second category palladacycle precatalysts containing the highly active PCy_3 ligand (Figure 7).[116]

As expected, the use of precatalyst **21a** in the Suzuki coupling of 4-chloroanisole with phenylboronic acid provided superior results in comparison with the in situ system composed of $Pd(OAc)_2$ and PCy_3 under identical reaction conditions (Table 15).

Scheme 14. Coupling of Polyfluoroboronic Acids to Aryl Chlorides, Bromides, And Triflates



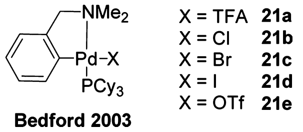
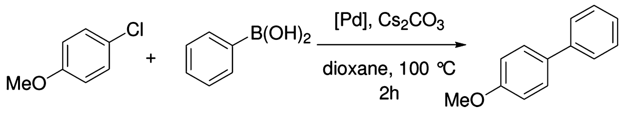


Figure 7. PCy_3-containing precatalysts.

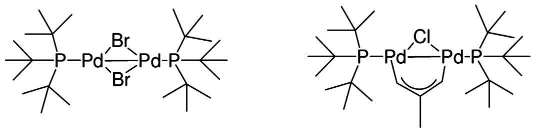
Table 15. Palladacycle 21a in Suzuki Coupling



entry	[Pd]	conv (%)[a]
1	0.01 mol % $Pd(OAc)_2/PCy_3$ (1:1)	2.5
2	0.01 mol % **21a**	71

[a]Determined by GC.

Another precursor to LPd(0) catalysts is the dimeric $[Pd(\mu\text{-}Br)(t\text{-}Bu_3P)]_2$ **22**, whose potential was identified originally by Hartwig as an active catalyst for amination reactions (Figure 8).[117,118] The originally reported route to make this complex gives modest to moderate yield, perhaps due to decomposition of the catalyst during workup.[119] However, after process modifications and developments, dimer **22** is now commercially available in bulk quantities.[119]

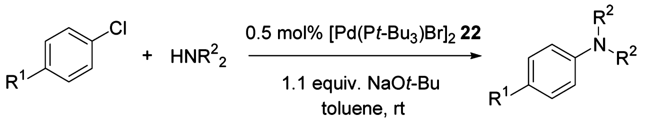


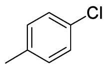
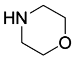
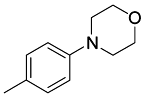
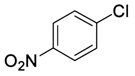
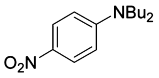
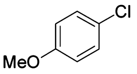
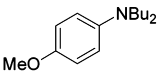
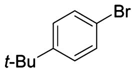
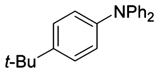
22 **23**

Figure 8. Pd(I) dimers as precatalysts.

Catalyst **22** showed a remarkably high activity, even at room temperature.[117] As illustrated in Table 16, aryl chlorides with varied electronic properties reacted with dialkyl amines to give the coupled product within 15 min. Because of the shorter reaction time, the process can tolerate functional groups, such as nitro groups, that are typically unstable when the aminations are conducted with NaO*t*-Bu base. In addition, reactions of aryl bromides with diarylamines also occurred in high yield (entry 4).

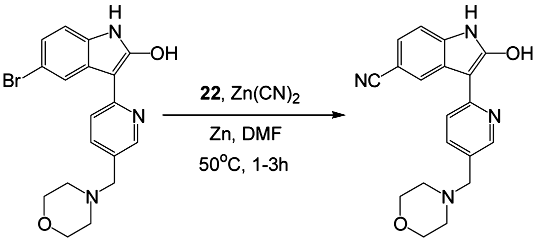
Table 16. Rapid Amination of Aryl Halides with 22 as Catalyst at Room Temperature



entry	aryl chloride	amine	time (min)	product	yield (%)
1			15		88
2		$HNBu_2$	15		97
3		$HNBu_2$	15		87
4		$HNPh_2$	60		96

Ryberg recently reported a robust and mild method for the cyanation of indole (Scheme 15).[120] Pd(I) dimer **22** (1.25 mol %) was identified as the catalyst of choice, and provided high yields of the product, even on a 5 kg scale.

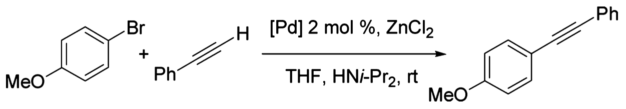
Scheme 15. Cyanation Reaction Using 22 As Catalyst



More recently, a report has become available on the use of the new Pd(I) dimer **23** (Figure 8) and its application in the Zn-promoted Sonogashira reaction of aryl bromides.[121] In model studies, it was found to be significantly more active than dimer **22** (96% vs 75% conversion) under identical reaction conditions and slightly more active than the in situ generated catalyst (85% conversion) (Table 17). This dimer, however, is not yet commercially available.

A new class of LPd(0) precursors was recently disclosed by Colacot and co-workers (Figure 9).[122] Initial results, obtained in collaboration with Shaughnessy, revealed Pd(allyl)-DTBNpPCl **24** as a highly active catalyst in amination and α-arylation reactions.[123] Aminations involving aryl bromides could in some cases be carried out at room temperature

Table 17. Sonogashira Reactions of Aryl Bromides



entry	[Pd]	conv (%)[a]
1	$Pd_2(dba)_3/P(t\text{-}Bu)_3{\cdot}HBF_4$ (1:1)	85
2	**23**	96
3	**22**	75

[a]Determined by GC.

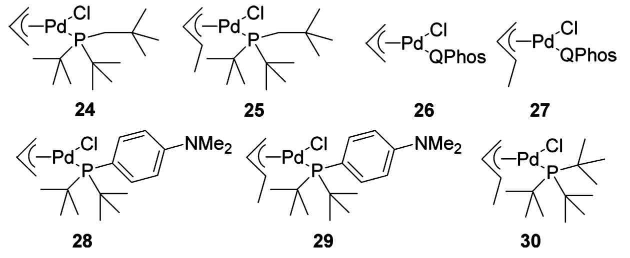
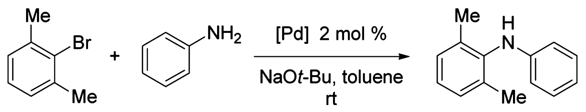


Figure 9. LPd (π-allyl)Cl catalysts. [QPhos = 1,2,3,4,5-pentaphenyl-1′-(di-*tert*-butylphosphino)ferrocene)].

under air, whereas aryl chlorides required elevated temperatures under an N_2 atmosphere. However, for safety and reproducibility, reactions on scale are best carried out under inert conditions.

It was observed that amination reactions catalyzed by preformed catalyst **24** provided results superior to those obtained using the in situ generated catalyst from $Pd_2(dba)_3$ and the free DTBNpP (di-*tert*-butyl neopentyl phosphine) ligand (Table 18). In addition, the preformed catalyst is air-stable when stored at lower temperatures, which avoids handling of the pyrophoric ligand.

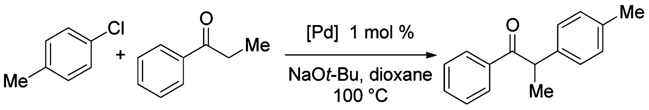
Table 18. Preformed vs in Situ Catalysis in Amination Reactions Using DTBNpP



entry	[Pd]	yield (%)
1	$Pd_2(dba)_3$/DTBNpP (1:1)	77
2	Pd(allyl)DTBNpPCl **24**	95

A number of catalysts containing the DTBNpP ligand were investigated in the α-arylation reaction of acetophenone with 4-chlorotoluene (Table 19). In this reaction, it was found that $L_2Pd(0)$ catalysts performed superior to LPd(0) catalysts. The use of $Pd(DTBNpP)_2$ and precatalyst $Pd(DTBNpP)_2Cl_2$ provided the desired product with quantitative conversion (entries 3 and 4), but in situ generated LPd(0) and Pd(allyl)DTBNpPCl (**24**) gave considerably lower conversions (entries 1 and 2).

Table 19. Preformed vs in Situ Catalysis in α-Arylation Reactions Using DTBNpP



entry	[Pd]	conv (%)[a]
1	$Pd_2(dba)_3$/DTBNpP (1:1)	42
2	Pd(allyl)DTBNpPCl **24**	79
3	$Pd(DTBNpP)_2$	99
4	$Pd(DTBNpP)_2Cl_2$	99

[a] Determined by GC.

Colacot and co-workers further investigated the role of the π-allyl moiety of the catalyst as well as the effect of the nature of the tertiary phosphine ligand on the outcome of catalytic transformations.[122] For this purpose, a number of additional π-allyl precatalysts were prepared and investigated in amination, Suzuki, and α-arylation reactions (Figure 9, **25**−**30**). For the amination of aryl bromides, carried out at ambient temperature, the general trend observed was that the Pd(crotyl) complexes showed higher activities than their corresponding Pd(allyl) precatalysts (Table 20, entries 1 vs 2, 3 vs 4, and 5 vs 6).

As has been a common theme throughout this review, it is also noted that the preformed Pd(crotyl)(QPhos)Cl **27** catalyst performed better than the in situ catalysis using Pd(dba)x (x = 1.5 or 2) in conjunction with the free Q-Phos ligand (Table 20, entry 4 vs Table 21, entries 1 and 2). In addition, the use of LPd(0) precursor Pd(crotyl)QPhosCl resulted in considerably faster reaction rates than the $L_2Pd(0)$ catalyst $Pd(QPhos)_2$ (Table 21, entry 3), demonstrating the importance of the nature of the catalytically active Pd species for the reaction outcome.

The same range of precatalysts was also investigated in a room temperature Suzuki coupling (Table 22). Again, the Pd(crotyl) complexes proved superior to the corresponding Pd(allyl) precatalysts (entries 1 vs 2, 3 vs 4, and 7), with the exception of the $P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)$-based catalysts, in which both precursors provided very low conversion to the desired biaryl product (entries 5 and 6).

For the α-arylation of 1-tetralone, a selected number of π-allyl catalysts was investigated (Table 23). Surprisingly, in this case, the reactivity of the Pd(allyl) vs the (Pd crotyl) complexes was observed to be reversed relative to that seen in the room temperature amination and Suzuki reactions. Pd(allyl)QPhosCl **26** and $Pd(allyl)P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)Cl$ **28** proved to be more active catalysts than their crotyl counterparts (Table 23, entries 1 vs 2, 4 vs 5). Notably, the desired product was obtained in 91% yield using only 0.05 mol % loading of $Pd(allyl)P(t\text{-}Bu)_2(p\text{-}NMe_2C_6H_4)Cl$ (entry 3).

4. PREFORMED CATALYSTS CONTAINING NHC LIGANDS

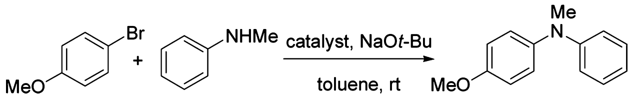
In addition to tertiary phosphines, another prominent class of ligands is the *N*-heterocyclic carbenes (NHCs). Consistent with tertiary phosphine-containing catalysts, palladium complexes bearing NHC ligands can be divided into two groups, $(NHC)_2Pd(0)$ and (NHC)Pd(0), according to the proposed catalytically active species generated from the precatalyst.

4.1. $(NHC)_2Pd(0)$ Catalysts. In contrast to tertiary phosphine ligands, there are only two examples of an isolated $(NHC)_2Pd(0)$ catalyst.[37,124−126] Herrmann demonstrated in the mid-1990s the use of this precatalyst in Heck reactions, and Caddick showed its use in the amination of a chloroarene and Suzuki reactions.

Reports of preformed Pd(0) complexes of NHC ligands and their applications to cross-coupling reactions are relatively rare.[127] To the best of our knowledge, these catalysts have not been utilized to the same extent as $(PR_3)_2Pd(0)$ catalysts, the latter being readily available even on large scale. This could be due to tedious methods of preparation and the extremely air-sensitive nature of the complexes.[128,129] $(NHC)_2Pd(0)$ complexes are generally not particularly active due to the strong NHC−Pd bond, which presumably results in slow ligand dissociation to form the true catalytically species. As an isolated example, Lee recently reported a $(NHC)_2Pd(0)$ catalyst stabilized by maleic anhydride (Figure 10).[130]

4.2. (NHC)Pd(0) Catalysts. All remaining reported NHC containing preformed catalysts are proposed to generate LPd(0) as the active catalyst.[35]

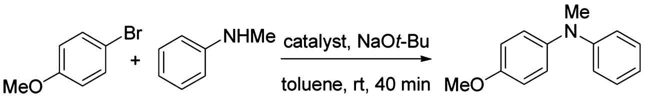
Table 20. Amination of 4-Bromoanisole Using Catalysts 24−30



entry	catalyst (mol %)	time (h)	conversion[a] (%)	entry	catalyst (mol %)	time (h)	conversion[a] (%)
1	**24** (1.0)	6	99	5	**28** (1.0)	22	18
2	**25** (1.0)	3	100	6	**29** (1.0)	22	95
3	**26** (1.0)	6	97	7	**30** (1.0)	3	100
4	**27** (1.0)	3	100[b]				

[a]Determined by GC. [b]Reaction is completed within 40 min.

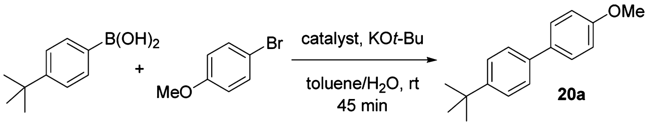
Table 21. Preformed vs in Situ Catalysis Using Q-Phos Ligand[a]



entry	catalyst	conversion (%)[b]
1	0.25 mol % $Pd_2(dba)_3$/0.5 mol % Q-Phos	35
2	0.5 mol % $Pd(dba)_2$/0.5 mol % Q-Phos	80
3	0.5 mol % $Pd(Q\text{-}Phos)_2$	9

[a]4-Bromoanisole (1.6 mmol), *N*-methylaniline (2.0 mmol), NaO*t*-Bu (2.4 mmol), toluene (2.0 mL). [b]GC conversion, average of at least two runs.

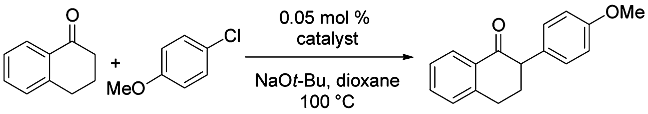
Table 22. Room Temperature Suzuki Coupling Reactions[a]



entry	catalyst (0.05 mol %)	conversion (%)[b]
1	Pd(allyl)P(*t*-Bu)$_2$NpCl **24**	13
2	Pd(crotyl)P(*t*-Bu)$_2$NpCl **25**	99
3	Pd(allyl)Q-PhosCl **26**	2
4	Pd(crotyl)Q-PhosCl **27**	100[c]
5	Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl **28**	3
6	Pd(crotyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl **29**	7
7	Pd(crotyl)P(*t*-Bu)$_3$Cl **30**	100

[a]4-Bromoanisole (1.6 mmol), 4-*tert*-butyl-benzene boronic acid (1.76 mmol), KO*t*-Bu (1.92 mmol), toluene (1.8 mL), water (0.2 mL). [b]GC conversion, average of at least two runs. [c]85% isolated yield.

Table 23. Low Catalyst Loading α-Arylation Reactions[a]



entry	catalyst	time (h)	conversion (%)[b]
1	Pd(allyl)Q-PhosCl **26**	3	80
2	Pd(crotyl)Q-PhosCl **27**	3	23
3	Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl **28**	22	100 (91)
4	Pd(allyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl **28**	3	96
5	Pd(crotyl)P(*t*-Bu)$_2$(*p*-NMe$_2$C$_6$H$_4$)Cl **29**	3	7

[a]4-Chloroanisole (2.0 mmol), 1-tetralone (2.0 mmol), NaO*t*-Bu (3.8 mmol), dioxane (2.0 mL). [b]GC/MS conversion. Average of two runs. Isolated yield in parentheses.

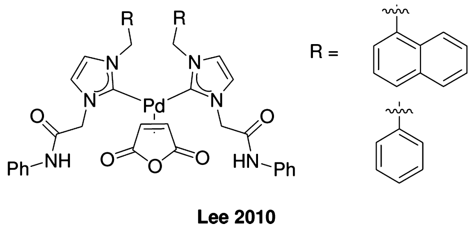


Figure 10. Maleic anhydride-stabilized preformed (NHC)Pd(0) catalysts.

Similar to their phosphine counterparts, a number of palladacycles containing NHCs have also been reported during the past eight years (Figure 11). Iyer demonstrated the activity of dimethylbenzylamine palladacycles **31a** and **31b** in Mizoroki−Heck coupling reactions, although the substrate scope was limited to aryl bromides or activated aryl chlorides.[131] The *N*-palladacycle **32** containing a triazolin-5-ylidene, reported by Herrmann, was capable of coupling aryl chlorides; however, palladium black was formed in the reaction mixture.[132,133] Finally, the dimethylbenzylamine palladacycles **33a−d** reported by Nolan initially in 2003 and subsequently in 2008 have shown to display higher activities in a number of cross-coupling reactions.[134,135] Ying's work within the field of NHC ligated palladacycles is also noteworthy.[136,137]

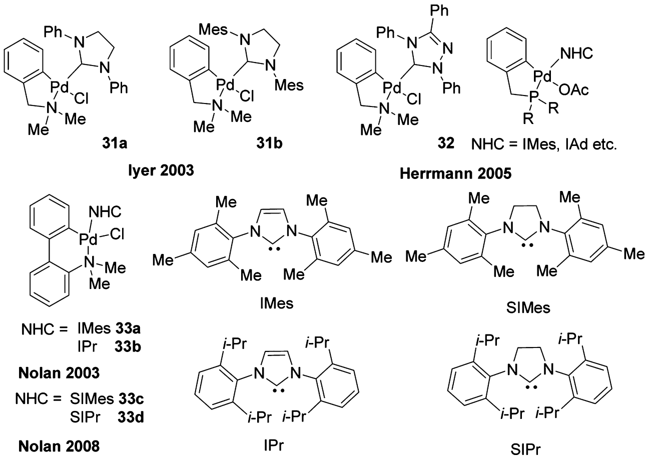


Figure 11. Selected NHC-containing palladacycles.

Most frequently, however, the (NHC)Pd(0) catalysts are generated from (NHC)Pd(II) dimer precatalysts. Nolan and co-workers have studied the amination reaction of aryl chlorides and reported the superior activity of Pd(II) dimer **35** (Figure 12) compared with the in situ generated catalyst (Table 24).[138−140]

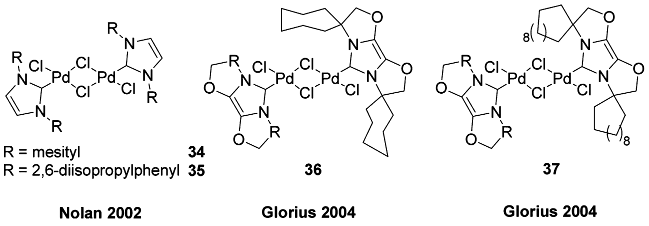
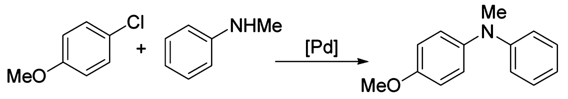


Figure 12. Preformed Pd(II) dimers containing NHC's.

Table 24. Preformed vs in Situ Catalysis Using IPr



entry	[Pd]	conditions	yield (%)
1	1 mol % $Pd_2(dba)_3$/IPrHCl (1:2)	KO*t*-Bu, dioxane, 100 °C	91
2	0.5 mol % **35**	KO*t*-Am,[a] DME, 80 °C	88

[a] Am = amylate.

Another noteworthy example of a Pd(II) dimer NHC catalyst was reported by Glorius in 2004 (Figure 12). This family of catalysts displayed high activity in Suzuki-Miyaura and Sonogashira reactions.[35]

A second class of precatalysts for the generation of (NHC)Pd(0) catalysts are palladium acetate[141] and acetylacetonato complexes[142] (Figure 13). Despite their reported impressive activities in Suzuki−Miyaura, *α*-arylation, and amination reactions, they have not yet reached widespread use in organic synthesis.

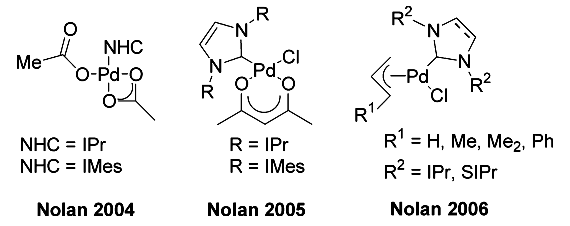


Figure 13. (NHC)Pd(0) catalysts.

Nolan reported a third class of (NHC)Pd(0) precursors, namely the (NHC)Pd(allyl)Cl catalysts (Figure 13). Interestingly, out of this series of catalysts, the cinnamyl derivative was found to have activity superior to the other precursors in Suzuki−Miyaura and Buchwald−Hartwig amination reactions.[143] Again, despite the extreme high activity displayed by this catalyst, to the best of our knowledge, it has not yet found widespread use within the synthetic organic chemistry community.

The fourth, and final, class of catalyst that is proposed to generate the (NHC)Pd(0) catalytically active species is the PEPPSI family of precatalysts (Figure 14). Organ reported catalysts **38** and **39** and demonstrated their excellent activity in Suzuki−Miyaura reactions and the synthesis of highly sterically hindered biaryl systems.[144]

Lee and co-workers have also developed a number of pyridine-containing NHC-based Pd catalysts.[145] They studied the activity of these complexes vs that of chelating bidentate ligands in Suzuku−Miyaura reactions and found catalysts **40**−**42** to be more efficient (Figure 14). This supports the hypothesis that LPd(0) catalysts are generally more active than $L_2Pd(0)$ species.

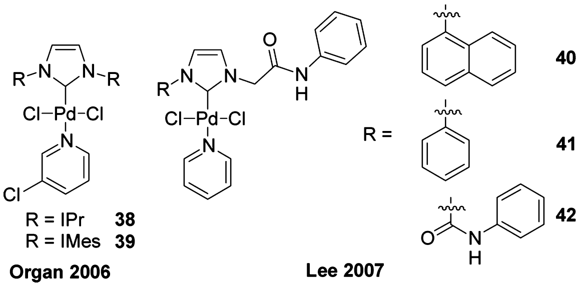


Figure 14. PEPPSI-type Pd(II) precatalysts.

The use of NHCs as ligands in cross-coupling reactions is still a field in its infancy, and results from the past 10 years represent the potential of their preformed Pd complexes as efficient catalysts.

5. CONCLUSION: CATALYTIC TRANSFORMATION BEYOND 2010 NOBEL PRIZE

When Heck, Suzuki, and Negishi, along with Stille, Kumada, and Sonogashira, first disclosed their seminal reports on cross-coupling reactions more than 30 years ago, nearly all reports of palladium-catalyzed coupling reactions described the use of aryl and vinyl bromides, iodides, and sulfonates as substrates; more challenging substrates, such as chlorides, were rarely employed. Furthermore, catalyst loadings were usually high, and reaction conditions, typically harsh. With the second generation (preformed) catalysts developed during the past decade, more and more challenging substrates can now be coupled under milder conditions in more environmentally friendly media, with exceptional activity and selectivity. The catalysts covered in this review demonstrate how new catalyst development can significantly expand the scope of these highly valued organic transformations.

In addition to the ligand characteristics, for several cross-coupling reactions, there is a significant difference between L_2Pd- and LPd-based precatalysts. For example, although $Pd(Q\text{-}Phos)_2$ was demonstrated to be a very good catalyst for carbohalogenation, it did not perform well in amination, as opposed to Pd(Q-Phos)crotylCl precatalyst under similar conditions. Similar observations have been noticed for tritertiary butylphosphine-based precatalysts, such as $Pd(t\text{-}Bu_3P)_2$ and $[Pd(t\text{-}Bu_3P)(\mu\text{-}Br)]_2$. Typically, if the reaction requires harsher conditions, L_2Pd-based catalysts are more suited because of the thermodynamic stability of 14-electron species vs the LPd-based 14 electron species. Among the L_2Pd-based precatalysts, L_2PdX_2 is preferred because of their air and moisture stabilities; however, for certain types of reactions and substrates, already activated $L_2Pd(0)$ catalyst is required. This comes to the conclusion that there is no universal cross-coupling catalyst available as of today. However, by applying logic, experience, and intuition, today we are closer to predicting a few catalysts for many cross-coupling transformations.

Preformed catalysts containing tertiary phosphine ligands are still at the forefront; they are the catalysts of choice, in particular, for larger scale industrial processes. Many of them are now commercially available in multikilogram quantities. Preformed catalysts containing NHC ligands have been demonstrated to have good activity in classical coupling reactions using the less reactive aryl chlorides; however, the discovery of novel chemical reactions using this type of catalyst and the frequent use on large scale are yet to come.

As we mentioned in the earlier review;[15] direct arylation; decarboxylative coupling; coupling involving sp^3 carbons; recyclable catalysts with no metal leaching; proper understanding of the structure−activity relationships of catalysts and substrates; and, of course, detailed understanding of the mechanisms involving the real rate determining steps are still challenging. However, because of the industrial and academic importance of cross-coupling reactions, more research will continue to go into this area as a means to solve many problems in synthesis.

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Notes

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