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Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide

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Abstract

Dialkylbiaryl phosphines are a valuable class of ligand for Pd-catalyzed amination reactions and have been applied in a range of contexts. This review attempts to aid the reader in the selection of the best choice of reaction conditions and ligand of this class for the most commonly encountered and practically important substrate combinations.

1. Introduction

Palladium-catalyzed amination of aryl, vinyl and heteroaryl halides and pseudohalides has rapidly emerged as a valuable tool in the synthesis of pharmaceuticals, natural products and novel materials.^{1–4} The development of Pd-catalyzed C–N coupling has significantly contributed to the streamlining of the synthesis of small molecule pharmaceutical agents, allowing more efficient syntheses and facilitating a modular approach to analogue synthesis.^{5–7} The significance of this methodology in this regard stems from the prevalence of aromatic amines in biologically active molecules,⁸ important classes include kinase inhibitors,^{9, 10} antibiotics^{11, 12} and CNS active agents.¹³

Breakthroughs in this area have typically been driven by the implementation of new classes of ligands. Notable examples include chelating diphenylphosphino ligands such as BINAP,^{14, 15} dppe¹⁶ and Xantphos,¹⁷ more electron-rich chelating phosphines such as Josiphos,¹⁸ N-heterocyclic carbenes¹⁹ and trialkylphosphines^{20, 21} that have served to continually increase the substrate scope and to render the reactions more efficient.^{22, 23} Despite the plethora of systems currently available for Pd-catalyzed C–N coupling, only a relatively limited group has seen extensive practical application. This reflects on a combination of the ease of use of a catalyst system, its robustness, availability of ligands and substrate scope. Catalysts based on dialkylbiaryl phosphines compare favorably with other systems in this regard and have been extensively applied in the synthesis of biologically active molecules.⁴ These ligands were first described by Buchwald for Pd-catalyzed cross-coupling in 1998.²⁴ Since then further work^{25–37} has led to the development of a versatile family of structurally related ligands (Section 2.1) that have been shown to generate highly active catalysts for a range of reactions, notably Pd-catalyzed amination⁴ and etherification of aryl halides,^{38, 39} arylation of enolates,⁴⁰ and Suzuki-Miyaura cross-coupling.^{41, 42} A key advantage of these ligands over some others is that the reactions can typically be performed without a dry-box in standard laboratory glassware.

Progress in this field has been brisk and reactions with these ligand systems can now be applied to a diverse array of substrates. The optimal ligand and other reaction parameters (such as Pd source, base, solvent and temperature) can vary for different substrate combinations. Part of the reason for this disparity stems from the wide variation in the electronic and steric properties of the nitrogen-based nucleophiles when compared to other cross-coupling processes such as the Suzuki-Miyaura reaction. The amine and amides can differ in nucleophilicity and pK_a which means that the rate determining step of the catalytic cycle can vary with substrate,⁴³ contributing to the difficulty in selecting the best conditions. It is the goal of this review to provide a practical guide to the use of these catalysts that will enable the practitioner to more easily select the most efficacious conditions for a given substrate combination. As a result, mechanistic details will only be discussed where they directly impinge on the choice of reaction conditions. A generalized catalytic cycle is illustrated in order to aid later discussion (Scheme 1).

There are a number of other thorough reviews on Pd-catalyzed C–N bond formation that the reader is guided to for descriptions of the advancement of the field and applications,^{22, 23, 44–57} for mechanistic aspects^{58–62} or applications on process development scale.^{2, 63, 64} There are also reviews specifically focussed on applications of dialkylbiaryl phosphine ligands in Pd-catalyzed amination and Suzuki cross-coupling reactions.^{4, 41}

2. Key Variables

The key reaction parameters of ligand, Pd source, base and solvent are discussed in detail below (Scheme 2). The selection is typically determined by both the structure of the amine and electrophile (see Section 3).

It is worth noting that there is often an interaction between these variables, for example, the best base for a reaction may change depending on the solvent employed. Therefore the optimization of reaction conditions can often be most efficiently achieved by a statistical DOE (Design of Experiment) approach.^{65, 66} Some of the considerations in the optimization of Pd-catalyzed amination reactions with dialkylbiaryl phosphine ligands may also apply to other ligand systems, however, the reader should be aware that many observations will not be directly transferable.

2.1 Ligand

One of the most important determinants of the success of a given amination reaction with dialkylbiaryl phosphine-based catalysts is the structure of the ligand. These ligands can typically be made in a one step procedure via addition of an aryl lithium or Grignard reagent to an appropriate aryne followed by quenching with a chlorophosphine.^{67, 68} As a result of the modularity afforded by this synthetic route numerous derivatives have been described and this has allowed fine-tuning of ligand structure for each application (Figure 1).

These ligands are air stable,⁶⁹ easily handled crystalline solids and a number are now commercially available. The original studies made use of DavePhos (**L8**) and JohnPhos (**L9**) for amination reactions^{24, 70} and these ligands have found ongoing application in the synthesis of natural products^{5, 71–74} and pharmaceuticals,^{75–79} including examples in process development.^{80, 81} Subsequently, several structural variants have been reported.^{82–88} A major breakthrough came with the discovery of XPhos (**L3**)⁸³ and RuPhos (**L2**),⁸⁴ which supply improved reactivity in a diversity of amination reactions. More recently, the ligand BrettPhos (**L1**)⁸⁵ was disclosed which confers the most active dialkylbiaryl-based phosphine system for the selective arylation of 1° amines. To date, the two most generally useful of these ligands for amination are **L1**^{85, 89} for the arylation of 1° amines and **L2** for 2° amines (Figure 2).^{89, 90}

A number of other ligands of this class are also commercially available and are valuable in Pd-catalyzed amination, their particular applications are discussed below (Figure 3). It should be noted that several closely related ligands were later developed by others and these can also provide active catalysts for Pd-catalyzed amination.^{26, 28, 31, 33, 34, 91}

The recent realization of the high reactivity of monoligated Pd(0) complexes towards oxidative addition has been decisive in the utilization of aryl chlorides in cross-coupling reactions.⁹² This might lead the reader to the conclusion that the ideal ratio of metal to ligand in these reactions is 1:1. For simple substrates this may be true, but an extra equivalent of ligand relative to Pd is often needed in order to stabilize the catalyst in difficult cases in which long reaction times are required or when a high TON at the metal center is desired.^{90, 93} This tactic is effective when using dialkylbiaryl phosphine ligands because in the presence of an extra equivalent of ligand the L_1Pd complex can still be the dominant species in solution.⁹⁴ It is also worth mentioning that an extra equivalent of ligand could be necessary for catalyst activation. This will be discussed in more detail in the following section.

2.2 Catalyst Activation

The efficiency with which the catalytically active, monoligated Pd(0) complex is formed before entry into the catalytic cycle is a key factor in the selection of reaction conditions for Pd-catalyzed amination reactions. If a Pd(II) salt such as $Pd(OAc)_2$ is used, reduction of Pd(II) to Pd(0) must occur before the cross-coupling reaction can take place. This can be brought about by the amine component in an amination reaction if the amine possesses hydrogen atoms α to the nitrogen atom as this enables the Pd(II) amine complex to undergo β -hydride elimination.⁹⁵ The efficiency of this process varies between amines and it may take a significant amount of time for all of the $Pd(OAc)_2$ to be reduced and enter into the catalytic cycle.^{96, 97} Furthermore, for the arylation of nucleophiles lacking a β -hydrogen such as 1° amides, 1° anilines or ammonia, another reductant must be present. $Pd(OAc)_2$, however, remains attractive on an industrial scale, although its source and morphology can have a strong impact on reactivity.⁹⁸ In some instances, reduction of Pd(II) to Pd(0) has been expedited by the addition of a tertiary amine (typically NEt_3).^{32, 99} Inclusion of phenylboronic acid as a reducing agent for Pd in the reaction mixture has been beneficial in some contexts.^{83, 100} This method is not always effective, however, perhaps because when the boronic acid is present stoichiometrically with respect to Pd the concentration of the boronic acid in the reaction medium is low which may have a deleterious effect on the efficacy and rate of the reduction step.

The phosphine ligand may also affect the reduction of Pd(II), however this process is likely slow with bulky, electron-rich dialkylbiaryl phosphines.¹⁰¹ In order to address this issue and to provide a convenient means of ensuring efficient reduction of Pd(II) a protocol has been developed whereby water mediates reduction of $Pd(OAc)_2$ by the phosphine.¹⁰² This procedure rapidly produces a highly active Pd catalyst that gives superior results to $Pd_2(dba)_3$, $Pd(OAc)_2/PhB(OH)_2$ or $[(allyl)PdCl]_2$ for the arylation of both amides¹⁰³ and anilines under the conditions examined. Using this method a number of demanding transformations can be efficiently accomplished, including the arylation of anilines with aryl chlorides at low catalyst loadings and the arylation of electron-deficient anilines in the presence of the weak base K_2CO_3 (Scheme 3).

An active catalyst can also be produced by $[(allyl)PdCl]_2$, here the catalytically active Pd(0) is generated by the attack of a nucleophile upon the allyl group.¹⁹ Unfortunately this complex is only applicable in a limited range of amination reactions with dialkylbiaryl phosphines.^{33, 88, 104}

The need for a reduction step to form Pd(0) can be avoided by the use of a stable Pd(0) complex as the Pd source. In conjunction with dialkylbiaryl phosphines the air-stable complexes Pd₂(dba)₃ or Pd(dba)₂ are suitable in a variety of situations.^{82–84, 87, 105–109} Coordination of dba to the metal can, however, attenuate the activity of the Pd catalyst.^{110, 111} Preheating Pd₂(dba)₃, ligand and base in solvent prior to the introduction of substrates can have beneficial effects on reproducibility,^{81, 112, 113} perhaps highlighting the importance of efficient formation of the L₁Pd complex.

As a result of the issues faced by these various Pd sources, efforts were made to devise a stable precatalyst^{19, 114, 115} containing the dialkylbiaryl phosphine ligand that would give direct access to a Pd complex within the catalytic cycle. Such a complex would also potentially be advantageous in providing a single component source of both Pd and ligand. Earlier efforts attempted to address this goal still required an exogenous reductant be present.^{83, 99} The intramolecularly coordinated amine complexes **1–5** have proven to be an ideal Pd source that can form the catalytically active L₁Pd complex under the reaction conditions simply by mixing with the reagents (i.e., no need to add a reducing agent) and are air and moisture stable.⁹³ These precatalysts can be made with a variety of biaryl phosphine ligands in 3 high yielding steps. Precatalysts with the ligands BrettPhos **1**, XPhos **2**, SPhos **3**, RuPhos **4** and *t*BuXPhos **5** are commercially available (Scheme 4).

Under the reaction conditions the amine nitrogen is deprotonated and the resulting Pd amide undergoes rapid reductive elimination to generate L₁Pd and indoline (this small amount of indoline is readily removed during workup and purification at the end of the reaction) (Scheme 5).

The active catalyst is fully generated in around 3 minutes at room temperature in the presence of a strong base such as NaOt-Bu. Activation can also be achieved with a weak base such as K₂CO₃ at 80 °C. These air-stable precatalysts provide extremely active catalysts in a variety of amination reactions, notably allowing the arylation of anilines with aryl chlorides to be performed with both low catalyst loadings and short reaction times (Scheme 6).^{89, 90, 116, 117}

The efficiency of these precatalysts is evidenced by the mild conditions under which these reactions can be performed. Indeed the oxidative addition of Pd(0) to an aryl chloride occurs at –40 °C with these precatalysts, illustrating the virtue of not having inhibitory additives such as dba present in the reaction mixture.⁹³

In summary, Pd(OAc)₂ and Pd₂(dba)₃ have been the most commonly utilized sources of Pd in amination reactions, however, the precatalysts **1–5** present a number of advantages (Scheme 7), ensuring that the active catalyst is formed. Many of these benefits are particularly felt in the case of difficult substrates or when low catalyst loadings or short reaction times are needed.

2.3 Solvent

Pd-catalyzed amination reactions with dialkylbiaryl phosphine ligands can be performed in a wide variety of solvents. Toluene and 1,4-dioxane are most commonly employed, although 1,4-dioxane has an unfavorable toxicity profile and can typically be replaced with Bu₂O.⁸⁵ Other ethereal solvents including THF,^{106, 118} 2-MeTHF⁸¹ and DME²⁴ can also be used. Toluene is particularly advantageous in the coupling of aryl iodides due its weak ability to solubilize the inorganic iodide salts formed during the course of the reaction (Section 3.1).⁹⁰ *t*-BuOH is an appropriate solvent in a numerous instances and when a higher reaction temperature is needed *t*-AmOH may be substituted.⁹⁸ These solvents have the beneficial property of aiding in the solubilization of inorganic bases, such as K₃PO₄, K₂CO₃ or KOH⁸³

leading to rate enhancement of the desired cross-coupling reactions. Furthermore, mixing *t*-BuOH with less polar solvents such as toluene can have a significant accelerating effect on amination reactions.⁸³ These solvents can also be effective in the dissolution of polar substrates. Similarly, polar, aprotic solvents such as DMSO, DMF and DMA have been successfully used in some examples,^{75, 119–122} both alone and in mixtures with other solvents.

In some instances Pd-catalyzed amination reactions are faster in DMF or DMA than in less polar solvents with K_3PO_4 as base,¹²³ however other studies have indicated lower yields¹²⁴ and increases in side reactions such as aryl halide reduction.¹²⁵ These polar solvents have also been found to be advantageous for amination reactions with these ligands in conjunction with microwave heating.^{126, 127}

Water can be an attractive reaction medium for performing cross-coupling reactions^{128, 129} due to its lack of toxicity or flammability. In certain cases Pd-catalyzed amination can be brought about in water with unmodified ligands such as **L3**.^{32, 83} If water immiscible, non-polar substrates are used the active metal catalyst presumably dissolves in micelles of the substrate. Hydrophilic derivatives of dialkylbiaryl phosphines with improved water solubility¹³⁰ have also been prepared,^{131–133} however, they have not yet been applied in Pd-catalyzed amination reactions. Biphasic reactions with water and a non-polar solvent such as toluene can result in enhanced functional group tolerance of bases such as KOH compared to monophasic systems.^{134–136}

Another solvent worthy of particular mention is α,α,α -trifluorotoluene.¹³⁷ Studies of Pd-catalyzed amination with dialkylbiaryl phosphine ligands in this medium or mixtures have shown it to possess certain advantages over toluene including reduced foaming in biphasic reactions¹³⁵ and better heating under microwave irradiation.^{138, 139} (For more specific recommendations of the choice of solvent, see Figures 6 – 8)

2.4 Base

The choice of base has a large bearing on the functional groups that may be present in amination substrates and thus has been the subject of considerable interest, including detailed mechanistic studies with some ligand systems.¹⁴⁰ Unfortunately, it is not possible to select the base purely on the grounds of the pK_a of the free N nucleophile as the pK_a is changed significantly by binding to Pd, which typically occurs before deprotonation (Scheme 1). Furthermore, inorganic bases such as Cs_2CO_3 can act heterogeneously in non-polar solvents where they can behave as much stronger bases than might be predicted from their solution phase pK_a value.¹⁴¹

Early studies of the Pd-catalyzed coupling of amines with aryl halides utilized NaOt-Bu as base in toluene.¹⁴² This remains the most versatile base for Pd-catalyzed amination reactions with dialkylbiaryl phosphine ligands, often giving the highest reaction rates and enabling the lowest catalyst loadings. Unfortunately, because NaOt-Bu is a relatively strong base ($pK_a = 17.0$) it can participate in undesirable side reactions with various electrophilic functional groups and some aromatic heterocycles and cause epimerization at acidic centers. KOt-Bu has also seen some application⁷⁷ but suffers from similar limitations and is generally less satisfactory. These observations have prompted the search for alternative bases. NaOMe is somewhat less basic ($pK_a = 15.5$) and can give better functional group tolerance than NaOt-Bu.^{99, 143} It should be noted that studies with other ligand systems for Pd-catalyzed amination have revealed NaOPh to be a useful base for the arylation of heteroaryl amines, perhaps as a result of its good solubility in dioxane.¹⁴⁴

LHMDS is another valuable strong base in Pd-catalyzed amination¹⁴⁵ with dialkylbiaryl phosphine ligands. In particular, LHMDS allows amination of aryl halides to be performed in the presence of protic functional groups such as phenols, aliphatic alcohols and amides (Scheme 8).^{86, 89, 106}

This base is especially convenient because of the commercial availability of solutions in both toluene and THF, removing the necessity of storage and handling of the hygroscopic solid base. LHMDS also allows the amination of haloheterocycles possessing a free NH group.^{84, 86, 89}

Hydroxide bases such as KOH or NaOH⁹⁸ are attractive on scale from an economic standpoint and these can be used in conjunction with dialkylbiaryl phosphines in Pd-catalyzed amination reactions, although they generally give slower reactions than alkoxides.^{83, 99} If powdered, hydroxide bases can be employed in toluene,⁹⁸ although aqueous phase reactions of water immiscible substrates have also been demonstrated without the need for a phase transfer catalyst.^{83, 146} It has been noted that the absence of a phase transfer catalyst can result in improved functional group tolerance.¹³⁶ Ba(OH)₂ can also mediate amination under very mild, biphasic conditions, rendering it applicable to substrates which are prone to base-mediated epimerization.¹³⁵

Weak inorganic bases such as Cs₂CO₃, K₃PO₄ or K₂CO₃ in place of alkoxides can bring significant benefits in the functional group tolerance of Pd-catalyzed amination reactions.¹⁴⁷ These bases provide more general conditions for substrates containing electrophilic functional groups such as ketones, esters and nitro aromatics.¹⁴⁷ Weak bases also facilitate the exploitation of aryl sulfonates as electrophiles, allowing these substrates to be cross-coupled without the requirement for slow addition of the electrophile.¹⁴⁸ They have also been instrumental in allowing the arylation of amides (Section 3.3). In non-polar solvents such as toluene, in which these inorganic bases have very low solubility, the deprotonation of the Pd-bound amine is thought to occur at the solid-liquid boundary.¹⁴⁹ In this situation, the particle size and shape of the inorganic base can be important in determining the rate and ultimate success of a cross-coupling reaction.^{150, 151} This topic has seen the most detailed discussion by Maes in the use of Cs₂CO₃ in Pd-catalyzed amination with BINAP as ligand,¹⁴⁹ although the findings are almost certainly applicable to biaryl phosphine ligands. Cs₂CO₃ from different suppliers exhibited varying reactivity and SEM imaging of the base showed a correlation between the particle properties and the activity of the base. In point of fact, pregrinding the Cs₂CO₃ or K₃PO₄ before application in amination reactions has sometimes been recommended.^{112, 113, 149} Such particle size effects have also been invoked in a recent study at Merck to explain the difference in outcome between reactions carried out with a magnetic stir bar and with an overhead stirrer.⁸¹ Reactions performed with the overhead stirrer took up to five times longer to reach completion, presumably because the magnetic stirrer facilitated the reaction by grinding the base *in situ*. Studies at Pfizer have revealed that the rate of agitation can severely impact the rate of these amination reactions as the high density of Cs₂CO₃ can lead it to sink to the bottom of the reaction vessel.¹⁰⁰ Scientists at LEO Pharma have found that inclusion of Celite in a reaction with Cs₂CO₃ as base in a Pd-catalyzed amination with **L3** as ligand had a significant beneficial effect on the yield, it was hypothesized that this effect results from the Celite preventing clumping of the Cs₂CO₃.¹⁵² Aggregation effects may also be responsible for the large excess of base that some authors have shown to be necessary in certain amination reactions.¹⁵³

On the other hand, in some reactions with weak inorganic bases it is the solubilized base that is important in bringing about the reaction¹⁵⁴ as evidenced by the rate accelerations that have been observed with more polar solvents such as DMA,¹²³ the presence of water^{155, 156} or additives such as 18-crown-6¹⁵⁷ when used in conjunction with these weaker inorganic

bases. Furthermore, it frequently turns out that Cs_2CO_3 is a more efficient base for amination reactions than K_2CO_3 , which may relate to its greater solubility in organic solvents.¹⁵⁸

Typically, alkali metal bases are moderately hygroscopic but they can usually be weighed into the reaction mixture in air without special precautions. If a substrate is moisture sensitive, however, (for example a hydrolyzable electrophile such as an aryl triflate) rigorous drying of the base¹⁵⁹ and/or the addition of molecular sieves^{87, 88} may be desirable. On the other hand, in some situations a beneficial effect of added water has been noted^{155, 156} perhaps as a result of improved solubilization of the base or by aiding in catalyst activation.¹⁰²

A potential alternative solution to improving the functional group tolerance is provided by soluble organic bases, such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene). These bases are, however, relatively expensive and have so far only proven effective in the amination of aryl nonaflates with anilines under microwave irradiation.¹⁶⁰

The advantages and disadvantages of the most commonly used bases are summarized in Figure 4.

3. Substrate

The structures of both the nucleophile and electrophile weigh substantially on the choice of reaction conditions. Aryl chlorides, bromides, iodides and sulfonates have distinct properties with respect to ease of oxidative addition. Furthermore, the halide or pseudohalide anion produced during the course of the reaction can also be significant.^{161–163} The presence of electron-donating or withdrawing substituents on the aromatic ring or of heteroatoms within the ring also impinges on the rate of all steps of the catalytic cycle. The presence of substituents *ortho* to the aryl halide can be critical in determining the rate of reaction; such substitution can facilitate some steps of the catalytic cycle (for example, reductive elimination), while potentially retarding others (for example, oxidative addition).

Similarly, N nucleophiles (e.g., aliphatic amines, anilines, amides, NH heterocycles) can possess widely differing nucleophilicity and $\text{p}K_{\text{a}}$ values as well as variable steric properties. These can also affect the rates of various steps on the catalytic cycle such as amine binding,⁴³ deprotonation and reductive elimination, therefore necessitating different ligands or reaction conditions. Hence the origin of the variation in optimal reaction conditions for different substrate combinations.

3.1 Electrophile

Initial studies on Pd-catalyzed aminations were carried out predominantly with aryl bromides as electrophiles. Aryl chlorides, however, are typically more attractive substrates due to their lower cost and wider availability.^{164, 165} The discovery of dialkylbiaryl phosphine ligands, among others, allowed these substrates to be engaged in amination reactions under milder conditions than had previously been reported.^{20, 166–168} The implementation of **L8** as ligand permitted deactivated aryl chlorides to be used²⁴ (this may now be effected with a variety of ligands).^{21–23, 26} With more modern ligand systems oxidative addition of $\text{L}_1\text{Pd}(0)$ is facile at or below room temperature (Scheme 9).⁹³ The amination of aryl chlorides is now a routine procedure and in some cases aryl chlorides gives more efficient reactions than aryl bromides.¹⁰⁹

Catalysts systems based on **L1** and **L2** allow the amination of electron-poor, -rich and -neutral aryl bromides and chlorides both with and without *ortho* substitution, to be achieved with high efficiency and low catalyst loadings for a broad range of 1° and 2° amines. For unfunctionalized substrates this is best brought about by using NaOt-Bu in combination with an ethereal solvent or toluene. For substrates bearing protic functional groups the combination of LHMDS and THF or dioxane is most useful. Weak bases can also give good results, a typical starting point for optimization is K₂CO₃/*t*-BuOH.

Intriguingly, aryl iodides, which are typically the easiest class of electrophile for C–C cross-coupling reactions, are relatively challenging substrates in Pd-catalyzed amination reactions.^{18, 169} Mechanistic studies have suggested that this results from the formation of unreactive Pd dimers bridged by iodide anions.¹⁷⁰ **L1**, however, which produces monomeric oxidative addition complexes in solution, allows aryl and heteroaryl iodides to be efficiently aminated with 1° amines (and **L2** may be used for 2° amines) (Scheme 10).⁹⁰ The choice of solvent has a strong influence on these reactions, non-polar solvents such as toluene give the best results due to the low solubility of the iodide salts formed during the course of the reaction, although *t*-BuOH can also be used successfully when dealing with polar substrates. At 100 °C a range of solvents can be used, although this can reduce the efficiency of the reactions. By using **1**, it is possible to accomplish the arylation of anilines with as little as 0.1 mol% Pd with Cs₂CO₃ as base, the lowest catalyst loadings that have yet been attained with a weak base.

A range of aromatic sulfonates is suitable as electrophiles for the Pd-catalyzed amination. The applicability of these substrates expands the range of available synthetic building blocks for cross-coupling as these compounds are readily accessible from phenols. Aryl triflates are the most reactive towards oxidative addition of this class.¹⁷¹ Unfortunately, they are also the most readily hydrolyzed by adventitious water, which can necessitate the addition of powdered molecular sieves to the reactions in order to improve yields.⁸⁸ Strong bases such as NaOt-Bu can also mediate triflate hydrolysis, particularly of electron-deficient substrates.¹⁷² This problem can be partly resolved by slow introduction of the aryl triflate to the reaction mixture¹⁷³ or by using LiOt-Bu which causes slower hydrolysis of the sulfonate.¹⁷⁴ The most convenient solution is provided by employing milder inorganic bases such as Cs₂CO₃.¹⁴⁸

Alternatively, aryl nonaflates¹⁷⁵ as electrophiles give similar reactivity in Pd-catalyzed amination with ligands including **L3** and **L4**,^{88, 107, 160} but undergo hydrolysis more slowly.¹⁷⁶ For these substrates implementation of soluble organic bases such as DBU, or for more difficult examples MTBD, is beneficial in conjunction with microwave heating (Scheme 11).¹⁶⁰

Aryl tosylates and benzenesulfonates are much more demanding substrates for Pd-catalyzed amination¹⁷⁷ due to their lower propensity to undergo oxidative addition.¹⁶³ They are, however, attractive from an economic standpoint due to their lower cost than aryl triflates. Dialkylbiaryl phosphine ligands can be successfully used for this transformation with a range of nitrogen nucleophiles, although the exact nature of the ligand has a strong influence on the outcome of the reaction, with **L3** providing much higher yields and conversion than less bulky ligands such as **L8**.⁸³ The most useful results are obtained with *t*-BuOH as the solvent in conjunction with a weak base such as Cs₂CO₃ or K₂CO₃. **L3** also allows the amidation of aryl tosylates to be realized.

Aryl mesylates present a more exacting class of substrates due to the even greater difficulty of oxidative addition, however, both **L1**⁸⁵ and Kwong's indole-based dialkylbiaryl phosphine ligands³² have been found capable of aminating these compounds. The weak base

K_2CO_3 is critical to the favorable outcome of these reactions (Scheme 12), stronger bases give lower yields due to competing cleavage of the sulfonate to the corresponding phenol.

By using **L6** it is also possible to affect the amidation of aryl mesylates (Scheme 13).¹⁰⁴ The combination of Cs_2CO_3 in *t*-BuOH is important in ensuring a successful outcome. The reaction is suitable for aryl mesylates with a range of steric and electronic properties, however, heteroaryl mesylates bearing a nucleophilic nitrogen atom provide lower yields, perhaps because these substrates act as nucleophilic catalysts for the undesired desulfonylation of the mesylates.

It should be noted that vinyl bromides, chlorides and triflates also constitute effective substrates under similar reaction conditions to the corresponding aryl halides,^{121, 159, 178–181} a feature that has been exploited in several innovative procedures to access heterocycles^{182–187} as well as in natural product synthesis.¹⁸⁸

Heteroaryl halides are a particularly important class of electrophile for C–N cross-coupling reactions because of the appearance of heteroaryl amines in a range of valuable pharmaceutical agents, notably kinase inhibitors.^{9, 10} Unfortunately these substrates are especially troublesome in metal-catalyzed C–N cross-coupling reactions; indeed even heteroaryl halides which are serviceable for Pd-catalyzed carbon-carbon bond forming reactions can be recalcitrant in amination reactions.¹⁸⁹ Such electrophiles can be envisaged to produce a number of difficulties. First, they display a wide spectrum of electronic properties relative to aryl halides and can thus present a more stringent test of the metal to undergo the steps of the catalytic cycle such as oxidative addition^{190, 191} or reductive elimination. Furthermore, if the heterocycles contain heteroatoms capable of coordination, for example pyridines, displacement of the phosphine ligand can occur, resulting in catalyst deactivation.¹⁹² Finally, these problems are compounded by the low solubility of these polar substrates in the solvents typically recommended for Pd-catalyzed amination such as toluene and dioxane. In these situations other solvents such as *t*-BuOH and DMF can be advantageous.^{89, 90}

The combination of the utility and challenge of these coupling partners has spurred research in this area. The coupling of halopyridines, -quinolines and -pyrimidines has received particular attention and some highly efficient catalyst systems are now available.^{18, 193} Early studies in this area with dialkylbiaryl phosphine ligands showed **L9** to constitute an effective catalyst system for the coupling of simple 1° and 2° amines with chloropyridines.⁸² These conditions were soon adopted by others in various synthetic applications.^{5, 75, 194–197} Following later developments in ligand design, synthetic work demonstrated that both **L7**^{198, 199} and **L3** can be very useful ligands in this context. More recent studies have shown that the most advantageous catalyst systems for the Pd-catalyzed amination of halogenated 6-membered ring heterocycles are comprised of **L1** for 1° amines and **L2** for 2° amines (Scheme 14).⁹⁰

5-Membered ring heteroaryl halides are recalcitrant substrates for Pd-catalyzed amination and low yields have often been encountered.²⁰⁰ Mechanistic studies have been directed towards understanding this effect with other ligand systems such as dppf²⁰¹ and $\text{P}(t\text{-Bu})_3$,²⁰² however, these results do not seem to be directly transferable to biaryl phosphines. Early efforts to engage these electrophiles in amination with dialkylbiaryl phosphine ligands showed that the successful outcome of the reactions is dependent on the correct choice of ligand. For the amination of halogenated thiophenes, furans, benzoxazoles and benzothiazoles with simple nucleophiles, **L3**, **L7** and **L2** were the ligands of choice.⁸⁴ Once again, **L1** and **L2** are the best ligands at the present time for these substrates (Scheme 15), however, it must be noted that these ligands do not represent a general solution for this class

of substrate.⁸⁹ Furthermore, catalyst loadings are typically higher and reactions times longer than for simple aryl halides.

3.2 Nucleophile: Anilines

The coupling of simple 1° anilines has typically been one of the easier classes of amination reactions due to the absence of β -hydrogen atoms capable of undergoing undesirable elimination of Pd-H. Furthermore the importance of diarylamines as a structural unit of numerous pharmaceutical agents^{9, 10} has prompted interest in this reaction. The coupling of anilines has also attracted study because of the attenuated nucleophilicity of anilines relative to aliphatic amines, which limits the applicability of S_NAr reactions in the construction of diarylamines. A number of examples of the coupling of anilines using dialkylbiaryl phosphines in the synthesis of pharmaceuticals have appeared.^{6, 120, 122, 197, 203} Catalysts based on **L1** are the most active for the arylation of these substrates and provide excellent selectivity for mono-diarylated products (ie. for formation of diarylamine rather than triarylamine). A precatalyst that can activate under the reaction conditions is markedly advantageous for this class of substrate as a result of the inability of anilines to mediate reduction of Pd(II). By using the combination of precatalyst **1** and **L1** it is possible to bring about the arylation of 1° anilines with aryl chlorides with both low catalyst loadings (0.01 mol% Pd) and short reaction times (1 h), a considerable improvement over other currently available catalyst systems (Scheme 16). Note in this case, the use of NaOt-Bu in conjunction with Bu₂O, a solvent that presents advantages over other ethereal solvents such as dioxane when used on scale.

Indeed, with **L1** it is possible to achieve the selective N-arylation of aminophenols (Scheme 17), providing complementary selectivity to that observed with Cu-based catalysts.¹¹⁷

The coupling of anilines in the presence of primary amides can be problematic. Use of catalyst based on **L3** effectively overcomes this issue and allows for the selective arylation of anilines in the presence of primary amides (Scheme 18).⁸³ Further, analogous to the results presented in Scheme 19, this provides complementary selectivity to what is observed when using a Cu-based catalyst.

The coupling of heteroaryl amines can be notably demanding, perhaps as a result of their low nucleophilicity and potential difficulty in undergoing reductive elimination. In this context the ligand **L4** is especially efficacious, allowing the arylation of a range of pyridyl- and pyrazoyl amines (Scheme 19).⁸⁶

L1 is also an effective ligand for this class of nucleophile under a variety of conditions, serving to further broaden the substrate scope (Scheme 20).⁸⁹

For the coupling of N-alkyl anilines, **L2** is generally the ligand of choice, the base/solvent combinations of NaOt-Bu/THF or Cs₂CO₃/*t*-BuOH providing a broad substrate scope (Scheme 21).⁸⁹

Cyclic amines such as indoline and N,N-diarylanilines are typically better coupling partners than N-alkyl anilines. An exception is N-methyl aniline which appears to be a privileged substrate for Pd-catalyzed amination. This amine readily undergoes arylation with a wide variety of ligand systems, often at lower catalyst loadings than are possible with other nucleophiles.

The synthesis of triarylamines has also been investigated. Using a catalyst based on **L2** diarylamines can be arylated to afford the corresponding triarylamines in excellent yields (Scheme 22).^{89,90}

Further, utilizing a catalyst based on **L9**, triaryl amines can be assembled in a one pot procedure from an aniline and two different aryl halides. This method provides a means for the rapid formation of the desired unsymmetrical product from readily available starting materials in one step (Scheme 23).²⁰⁴

3.3 Nucleophile: Aliphatic Amines

The arylation of primary aliphatic amines has been the subject of study with numerous classes of ligand and some highly efficient catalyst systems have been described.^{18, 205} Dialkylbiaryl phosphines are also very successful in this context; catalysts based on **L1** are the most efficacious. By exploiting this system simple aliphatic amines can be coupled with electron-neutral, -rich and -poor, as well as *ortho*-substituted, aryl chlorides with 0.05 mol% Pd (Scheme 24). The best results are given by a base/solvent combination of NaOt-Bu/Bu₂O.⁸⁵

Substrates bearing protic functional groups can also be efficiently employed when LHMDS is used as base in conjunction with **1** (Scheme 25).⁸⁹

Importantly, these catalysts are much less efficient for the arylation of secondary amines which means that excellent selectivity for monoarylation of a 1° amine can be achieved. Indeed 1° amines can be arylated in the presence of 2° amines with this catalyst system (Scheme 26).⁸⁵

The ability to selectively perform arylation in this way alleviates the need for protecting groups and can contribute to improving the efficiency of synthetic routes. The high selectivity exhibited by **L1**-based catalysts is exemplified by the ability to monoarylate methylamine, providing a convenient access to N-methyl anilines (Scheme 27). It should be noted that the selective arylation of anilines in the presence of aliphatic amines is also possible by using **L3** or **L7** as ligand.^{43, 83}

The cross-coupling of secondary aliphatic amines with aryl halides was one of the earliest reaction classes to be explored in Pd-catalyzed amination.¹⁴² N-Aryl cyclic amines, in particular N-aryl piperazines, are a frequent constituent of CNS-active pharmaceutical agents.¹³ **L2** is the best dialkylbiaryl phosphine for this transformation, permitting the arylation of a range of simple cyclic amines at low catalyst loadings with aryl and heteroaryl chlorides in a variety of substitution patterns (Scheme 28).⁸⁹

The lowest catalyst loadings are generally secured by using NaOt-Bu as base; Cs₂CO₃ or LHMDS can alternatively be used in conjunction with more highly functionalized substrates, although somewhat higher catalyst loadings are typically required (Scheme 29).

Acyclic secondary amines are often more challenging substrates, presumably as a result of the greater propensity of these substrates to undergo undesired β-hydride elimination.⁴⁸ **L2**, however, can also provide highly efficient catalysts for the arylation of this class of substrate (Scheme 30).⁸⁹ At present no suitable catalyst system has been reported for the coupling of hindered secondary amines, particularly with *ortho*-substituted aryl halides. This is presumably due to two factors: 1) a slower rate of transmetalation (amine binding/deprotonation) and 2) a competitive rate of β-H elimination relative to reductive elimination.

The arylation of dimethylamine can present a particular difficulty, perhaps due to the further enhanced potential of the intermediate Pd amido complex to undergo undesired β hydride elimination. This transformation can be realized, however, under mild conditions, either with **L4** in conjunction with LHMDS as base at room temperature or **L3** with K₃PO₄ at 110°C.¹¹⁶ Under these conditions dimethylamine can be arylated with a range of electron-

rich and electron-deficient aryl chlorides in the presence of a number of functional groups (Scheme 31).

3.4 Nucleophile: Amides

The Pd-catalyzed arylation of amides provides a convenient complementary approach to the Cu-mediated Goldberg reaction.²⁰⁶ This process was initially demonstrated with the chelating ligand Xantphos^{207, 208} and it was thought that a chelating ligand was necessary in order to prevent the formation of unwanted κ^2 interactions of the amide with the Pd center.²⁰⁹ However, it was shown that **L3** is able to affect the arylation of lactams, carbamates, primary amides and N-methyl formamides, including for the first time the amidation of aryl sulfonates.^{83, 210} **L3** has also been established to be superior to chelating ligands for intramolecular amidation of aryl chlorides.¹¹³

Detailed studies with dialkylbiaryl phosphines have been directed towards the arylation of oxazolidinones,²¹¹ sulfonamides,²¹² and sulfamides.²¹³ Scientists at GlaxoSmithKline have determined that **L4** is the optimal ligand for the room temperature arylation of *t*-Bu-carbamate.²¹⁴ The use of this ligand is also fruitful in the vinylation of N-Boc hydrazine.¹²¹ Further studies revealed that ligand **L5** is more effective than **L3** for amidation, providing an effective catalyst system for a range of substrates including lactams, primary amides and sulfonamides and a single example of an N-methyl substituted amide.⁸⁷ Subsequently the scope of aryl amidation was expanded to include *ortho*-substituted aryl chlorides by the introduction of **L6** (Scheme 32).¹⁰³ Notably, the H₂O activation procedure proved to be the most effective way to generate an active catalyst (Section 2.1). In all cases amidation is best accomplished with weak bases such as K₂CO₃, K₃PO₄ or Cs₂CO₃.

Similar conditions are effective for the amidation of aryl mesylates (Scheme 13). So far **L6** is the only ligand that has been reported to be effective for this transformation.¹⁰⁴

The biaryl phosphine ligand **L10** allows the intermolecular arylation of acyclic secondary amides.⁸⁸ This had not previously been achieved with either Pd or Cu catalysis except for formamides and *N*-methyl and *N*-phenyl amides (Scheme 33), which explains the difficulty of the reaction and the design of the ligand. Note that the presence of molecular sieves is usually necessary in these reactions in order to prevent hydrolysis of the amide by adventitious water.

3.5 Nucleophile: NH Heterocycles

The Pd-catalyzed coupling of NH heterocycles with aryl halides is also an area of considerable interest. Studies with chelating ligands have suggested that reductive elimination can be challenging in these cases.²¹⁵ The first application of dialkylbiaryl phosphines in this context was for the N-arylation of indoles with aryl bromides and triflates and in one example an aryl chloride.¹⁰⁵ A range of indoles can be arylated efficiently with aryl bromides, chlorides, iodides and triflates, the preferred ligand depending both on the nature of the leaving group of the electrophile and the steric hindrance about the indole NH. For simple substrates **L8** can be used. By employing a variety of other ligands including **L11** and **L12** it was also possible for the first time to bring about the Pd-catalyzed N-arylation of both 2- and 7-substituted indoles, as well as the N-arylation of indoles with *ortho*-substituted aryl bromides (Scheme 34). Previously such reactions had been plagued by competing arylation at C3 as well as the formation bis-arylated products.²¹⁶

Subsequent studies by Beletskaya have shown that the use of di- or trivalent metal counterions in these reactions can result in selective arylation at the 2 or 3 position of indole (i.e., C–C rather than C–N bond formation).²¹⁷ Typically, NaOt-Bu was found to be the base of choice, however, K₃PO₄ can be used for substrates bearing electrophilic functional

groups. Unfortunately, some of the best ligands used in these studies are not trivial to access. Prior deprotonation of the heterocycle with BuLi can also be successful.¹⁷⁸ Later it was discovered that **L3** is an effective ligand for the N-arylation of indoles, even permitting the N-arylation of indoles with aryl benzenesulfonates.⁸³

The cross-coupling of more acidic heterocycles such as indazole and pyrazole has proven to be more problematic with Pd catalysis. By the use of **L4** or **L5**, however, it is possible to couple indazoles, pyrazoles, benzimidazole and in one case imidazole with a variety of aryl and heteroaryl halides (Scheme 35).⁸⁶

The formation of N1 or N2 arylated indazole was found to be dependent on the nature of base and the reaction temperature. For the arylation of indazole with 3-bromoanisole, arylation occurs selectively at N1 in the presence of NaOt-Bu in toluene at 80°C or with Cs₂CO₃ at 105°C in 1,4-dioxane. If, however, NaOt-Bu is used at 100°C mixtures of N1 and N2 arylated products are formed. A possible explanation for these observations is that kinetic binding of Pd occurs at N2 and so when deprotonation of the Pd-bound amine is rapid, arylation at N2 is observed. If, however, deprotonation of the Pd-bound amine is slow (e.g., NaOt-Bu in toluene at 80 °C) then migration of the metal to N1 can take place and arylation is seen at this position.

In order to bring about the arylation of imidazole or benzimidazole **L5** is the best dialkylbiaryl phosphine (Scheme 36).⁸⁶ This is, however, a challenging transformation and the reaction has not yet been extended to more complex nucleophiles of this type.

3.6 Nucleophile: Benzophenone imine and hydrazone

The Pd-catalyzed cross-coupling of benzophenone imine with aryl halides with subsequent hydrolysis of the resultant N-aryl imine permits the conversion of aryl halides to anilines,²¹⁸ a process that has been extensively applied in organic synthesis. A number of other ammonia equivalents have been used to accomplish this goal,^{219–223} however, benzophenone imine remains the most widely used as the reaction can be performed in the presence of a range of functional groups, with aryl bromides, chlorides and triflates as electrophile and with *ortho*-substituted electrophiles. Benzophenone imine is commercially available and the intermediate N-aryl imine can be converted to the desired aniline by hydrogenation, transamination with hydroxylamine, or by acid-catalyzed hydrolysis. The direct Pd-catalyzed coupling of free NH₃ with aryl halides is also possible,^{108, 224–226} however, the functional group tolerance remains limited unless a high pressure of NH₃ is used.²²⁷ Of the dialkylbiaryl phosphines, both **L9**⁸² and **L3**^{83, 228} have been used successfully for the arylation of benzophenone imine with aryl chlorides and sulfonates. The mildest conditions reported to date are afforded by exploiting **L4** (Scheme 37).¹⁵⁷

The use of the weak base K₃PO₄ at 30°C provides excellent functional group tolerance, however, the reaction is limited to aryl bromides and extended reaction times are required. By using NaOt-Bu in toluene at 65°C reactions could be completed in 0.5 h. It is important to note that it is strongly advised that commercial benzophenone imine be distilled before use as nucleophile in any Pd-catalyzed amination reaction.²²⁹

The arylation of LiHMDS using a catalyst based on **L13** has also been reported as an efficient and more atom economical method for the conversion of aryl chlorides or bromides to the corresponding anilines in high yields (Scheme 38).²²¹ However, because LiHMDS is hindered, *ortho*-substituted aryl halides are poor substrates. Further, the high basicity of LiHMDS limits the functional group tolerance of this method. On this basis benzophenone imine still remains the ammonia equivalent of choice for discovery chemists.

The Pd-catalyzed arylation of benzophenone hydrazone is also of interest as the resulting N-aryl hydrazones are intermediates in the Fischer indole synthesis and as such can undergo thermal or acid-catalyzed sigmatropic rearrangement to yield indoles.²³⁰ The mildness of the conditions permits access to indoles which are challenging to make under more conventional conditions. Alternatively, reaction of the intermediate hydrazones with 1,3-diketones permits access to functionalized pyrazoles.¹⁹⁶ As a result of the practical utility of these processes, the Pd-catalyzed arylation of benzophenone hydrazone with aryl bromides and chlorides using dialkylbiaryl phosphines has undergone thorough optimization by scientists at Rhodia (Scheme 39).⁹⁸

These studies revealed that **L3**, **L8** and **L14** can all constitute highly efficient catalyst systems for this reaction,⁸³ allowing the reaction to be performed in 3 – 4 h with 0.1 mol% Pd. When using protic solvents such as *t*-AmOH, finely ground NaOH is the best base, however, in toluene NaOt-Bu is more effective. Pd(OAc)₂ is a useful Pd source here despite the absence of a nucleophile capable of reducing Pd(II) to Pd(0) for entry into the catalytic cycle. In these experiments adventitious H₂O-mediated reduction of Pd(II) by the phosphine must have occurred.

4 Guidelines for Optimization

Figures 6 – 8 provide a summary of typical reaction conditions for Pd-catalyzed cross-coupling reactions with various substrate classes. The exact choice of conditions will depend to a large extent on both the structure of the substrate as well as the goals of optimization, for example, maximization of yield, minimization of catalyst loading, minimization of reaction time or generality for a variety of substrates if analogues of a particular compound are to be synthesized. When attempting to improve a set of reaction conditions, analysis of the by-products of reaction can be informative. For example, observation of significant amounts of reduced aryl halide ($\text{ArX} \rightarrow \text{ArH}$) can indicate that reductive elimination is slow relative to β -hydride elimination and that a ligand which is better at promoting reductive elimination should be used (e.g., by switching from a dicyclohexylphosphino to di-*t*-butylphosphino ligand⁸⁶). Sometimes formation of this by-product can also be suppressed by running reactions at a lower temperature, perhaps implying that in some instances the formation of this by-product is related to catalyst decomposition. Indeed the nature of the reductant in these reactions is not always obvious, even reactions with nucleophiles possessing no β -hydrogen atoms, such as anilines, can produce significant quantities of the reduced arene. Conversely, low conversion of starting aryl halide can be improved by raising the reaction temperature or increasing the catalyst loading. An important cause of low conversion is also inefficient formation of L_1Pd , hence switching from Pd(OAc)₂ or Pd₂(dba)₃ to precatalysts **1–5** can also be highly beneficial.⁹³ Alternatively, if mass balance is poor this can reveal that the base is interacting adversely with a functional group in one of the substrates, suggesting the use of a weaker base, for example, Cs₂CO₃ in place of NaOt-Bu. Another common by-product is the phenol corresponding to the aryl halide or pseudo-halide ($\text{ArX} \rightarrow \text{ArOH}$). This results from either desulfonylation of an aryl sulfonate substrate or from competing coupling of water with the aryl halide.²³¹ In either case this product can be minimized by thorough drying of the reagents¹⁵⁹ and the addition of activated molecular sieves to the reaction mixture.⁸⁸ The phenol thus formed can also undergo Pd-catalyzed C-O bond formation with another molecule of aryl electrophile to generate the symmetrical diaryl ether ($\text{ArX} \rightarrow \text{ArOAr}$).³⁸ Pd-Catalyzed amination reactions can also produce symmetrical biaryls ($\text{ArX} \rightarrow \text{ArAr}$). Various mechanistic hypotheses have been advanced to explain the formation of these by-products,^{232–237} however, they tend to occur most commonly in amination reactions when transmetalation is difficult. Hence switching to ligands that are less sterically encumbered or more electron-deficient at phosphorus can be helpful. Furthermore, this reaction can be more prevalent in dipolar,

aprotic solvents such as DMF, DMA and DMSO,^{233, 234} hence moving to an ethereal solvent or *t*-BuOH can bring improvements in the outcome of the reaction while maintaining substrate solubility (Figure 5).

5 Conclusions

The Pd-catalyzed arylation of nitrogen nucleophiles using dialkylbiaryl phosphine ligands has undergone considerable development since the discovery of this ligand class. Much of this progress has been driven by innovations in ligand design, but also by attention to the optimization of reaction conditions. As a result, useful catalyst systems of this type are available for many classes of electrophile and nitrogen nucleophile. The reactions can now often be employed with complex substrates and low catalyst loading.

In general, catalysts based on the ligand **L1** are the most powerful for 1° amines, and those based on **L2** for 2° amines. For certain classes of nucleophile such as amides and NH heterocycles, other dialkylbiaryl phosphine ligands are typically more appropriate. Individual substrate combinations may, however, necessitate a different ligand system as a result of structural peculiarities of the nucleophile and electrophile. It is also crucial to realize that the base/solvent combination is not a hard and fast selection for a given type of substrate. The reaction conditions summarized in Figures 6 – 8 are given as starting points for optimization.

It is important to reemphasize the significance of efficient formation of catalytically active, yet kinetically stable (towards decomposition), L₁Pd species under the reaction conditions, which depends on the correct choice of Pd source for the reaction. In this regard precatalysts **1–5** that activate very effectively *in situ* are often the most desirable.

It is hoped that this review has supplied some insight into the selection of reaction conditions for a given amination process and the rationale for further optimization. The reader should be aware, however, that some substrates such as certain heteroaryl halides and hindered amines are at present refractory to Pd-catalyzed cross-coupling and remain enticing challenges for the on-going further development of ever more efficient and general catalyst systems.

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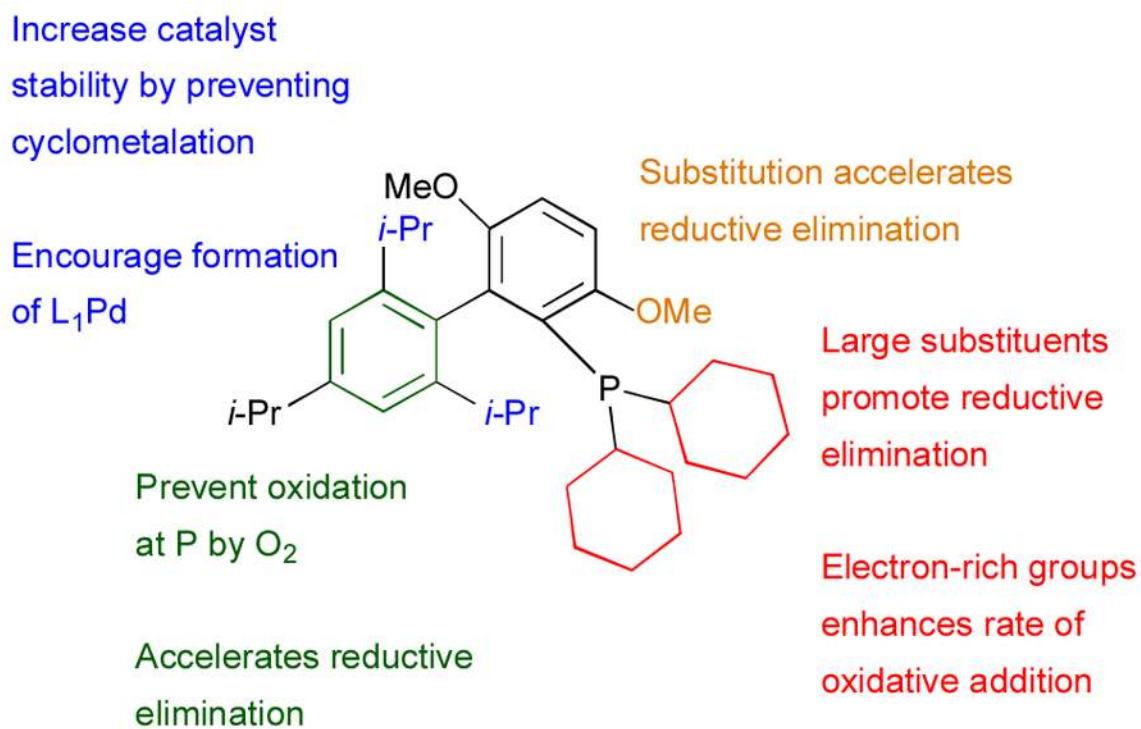
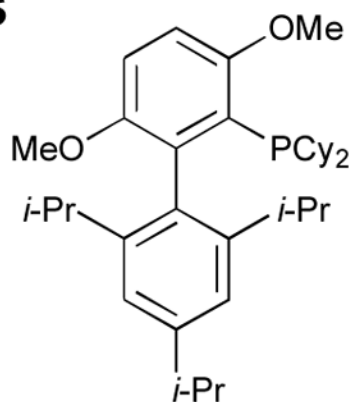
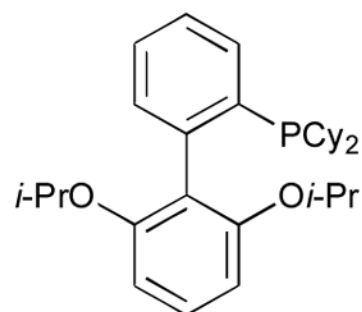


Figure 1.
Important structural features of dialkylbiaryl phosphine ligands.

Key Amination Ligands



L1



L2

Name	<i>BrettPhos</i>	<i>RuPhos</i>
Best nucleophiles	Primary alkyl amines Primary anilines	Secondary alkyl amines Secondary anilines

Figure 2.
Key dialkylbiaryl phosphine ligands for amination.

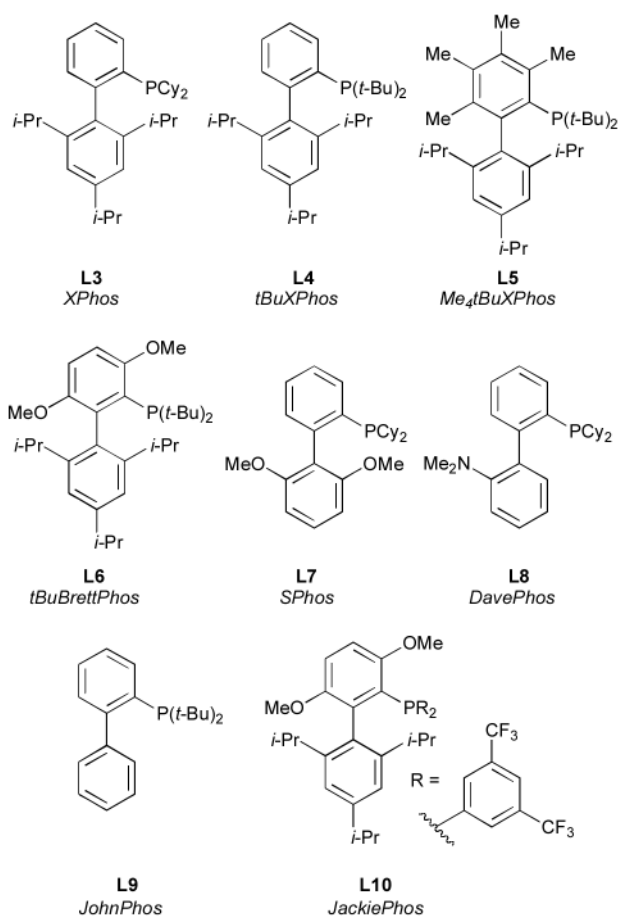


Figure 3.
Other important dialkylbiaryl phosphine ligands for amination.

Base	Advantages	Disadvantages
NaOt-Bu	Permits highest reaction rates and lowest catalyst loadings	Incompatible with many electrophilic functional groups
LHMDS	Allows utilization of substrates bearing protic functional groups Useful for low temperature amination	Solid base is air sensitive Incompatible with some functional groups at elevated temperature
Cs ₂ CO ₃	Provides excellent functional group tolerance and often highest reaction rate of weak bases	Expensive Can be hard to stir on large scale
K ₃ PO ₄ , K ₂ CO ₃	Excellent functional group tolerance Often most efficient for the arylation of amides Economically attractive	Can require relatively high catalyst loadings and long reaction times

Figure 4.
Comparison of bases typically used in Pd-catalyzed amination.

Problem	Possible causes	Solutions
Low conversion	Inefficient formation of active catalyst	Employ readily activatable precatalysts 1-5
	Low rate of reaction	Increase catalyst loading Perform reaction at a higher temperature
Poor mass balance/ low yield	Incompatibility of base with functional groups in substrate	Employ a weaker base with better functional group tolerance, for example, Cs ₂ CO ₃ or K ₃ PO ₄
Formation of: 	Catalyst decomposition	Perform reaction at a lower temperature
	Inefficient reductive elimination	Use a ligand that gives faster reductive elimination
	Presence of adventitious water in reaction	Dry reagents Add activated molecular sieves
	Presence of adventitious water in reaction	Dry reagents Add activated molecular sieves
	Inefficient transmetalation	Use a ligand that is less sterically hindered or more electron-deficient at P
	Unsuitable solvent for reaction	Attempt reaction in <i>t</i> -BuOH or ethereal solvent

Figure 5.
Simplistic troubleshooting guide for Pd-catalyzed amination.

Nucleophile	Ligand	Typical conditions	Pd source	References
Anilines				
	L1	NaOt-Bu, dioxane or K ₂ CO ₃ , <i>t</i> -BuOH 90 - 110 °C	1 or Pd ₂ (dba) ₃	[85,89,90,116]
	L1	LHMDS, dioxane or K ₂ CO ₃ , <i>t</i> -BuOH 100 - 110 °C	1 or Pd ₂ (dba) ₃	[89,90]
	L4	NaOt-Bu, toluene, 80 - 110 °C	Pd ₂ (dba) ₃	[86]
	L2	NaOt-Bu, THF or Cs ₂ CO ₃ , <i>t</i> -BuOH 65 - 110 °C	4 or Pd ₂ (dba) ₃	[89]
Aliphatic amines				
	L1	NaOt-Bu, dioxane or K ₂ CO ₃ , <i>t</i> -BuOH 90 - 110 °C	1 or Pd(OAc) ₂	[85,89]
	L2	NaOt-Bu, THF or Cs ₂ CO ₃ , <i>t</i> -BuOH 65 - 110 °C	4 or Pd(OAc) ₂	[89,90,116]
Amides				
	L6	Pd(OAc) ₂ , K ₃ PO ₄ , <i>t</i> -BuOH, 110 °C	H ₂ O activation Pd(OAc) ₂	[103,104]
	L10	K ₂ CO ₃ or Cs ₂ CO ₃ , 3 Å MS, toluene 110 °C - 130 °C	[Pd(allyl)Cl] ₂	[88]
NH Heterocycles				
	L8 or others	NaOt-Bu, toluene, 80 - 100 °C	Pd ₂ (dba) ₃	[86,105]
	L4	NaOt-Bu, toluene, 60 - 105 °C	Pd ₂ (dba) ₃	[86]
Benzophenone imine and hydrazone				
	L4	K ₃ PO ₄ , DME, 30 °C or NaOt-Bu, toluene, 65 °C	Pd ₂ (dba) ₃	[83,158]
	L13	NaOH, <i>t</i> -AmOH, 103 °C	Pd(OAc) ₂	[98]

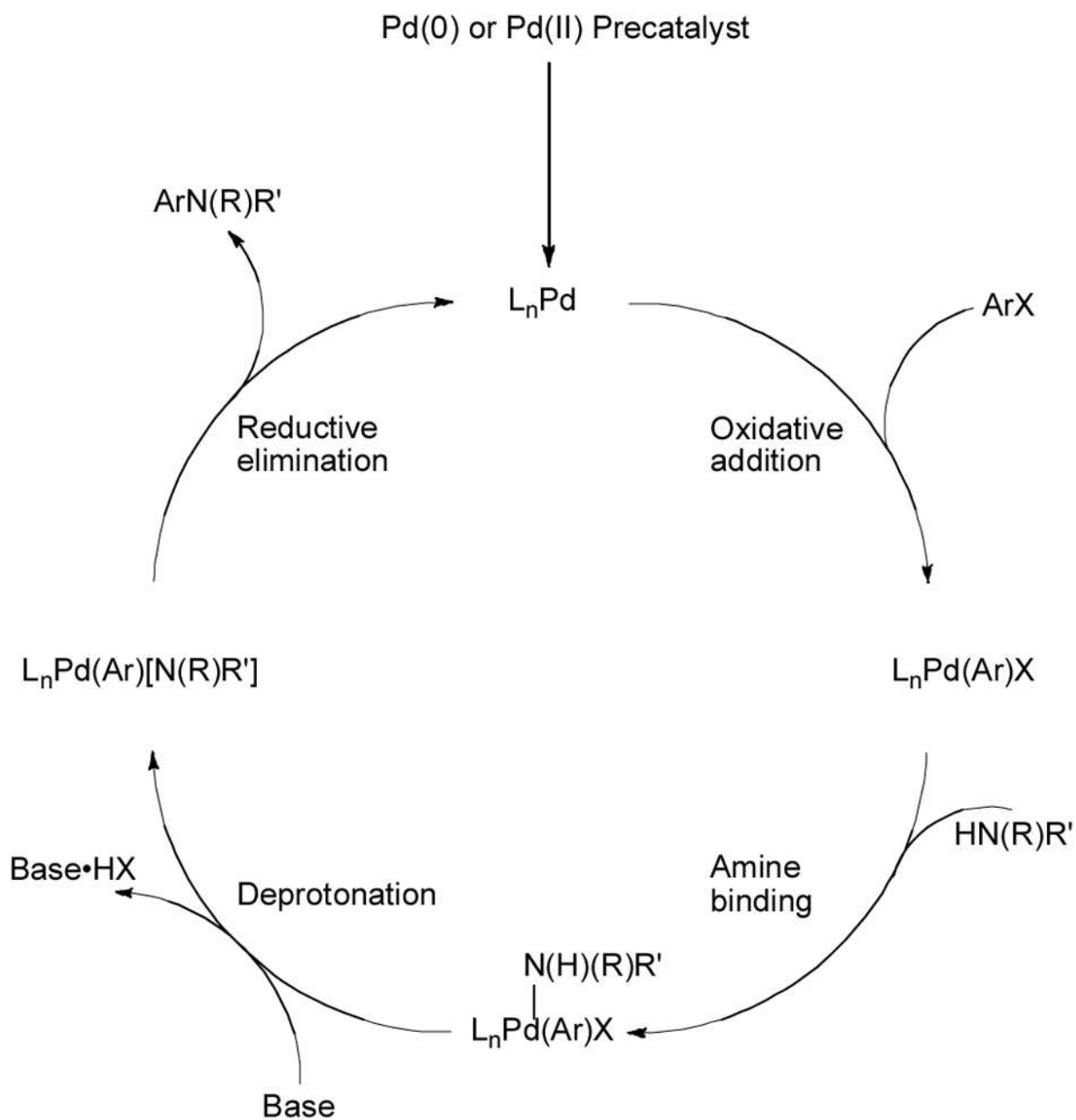
Figure 6.
Summary of reaction conditions used for different classes of nucleophile.

Electrophile	Nucleophile	Ligand	Typical conditions	Pd source	References
Aryl bromides and chlorides					
	$R-NH_2$	L1	NaOt-Bu, dioxane or K_2CO_3 , t-BuOH 90 - 110 °C	1 or $Pd(OAc)_2$	[85,89]
	$R-NH-R'$	L2	NaOt-Bu, THF or Cs_2CO_3 , t-BuOH 65 - 110 °C	4 or $Pd(OAc)_2$	[89,90,116]
	$R-C(=O)NH_2$	L6	$Pd(OAc)_2$, K_3PO_4 t-BuOH, 110 °C	H ₂ O activation $Pd(OAc)_2$	[103]
	$R-NH_2$	L1	NaOt-Bu, dioxane or K_2CO_3 , t-BuOH 90 - 110 °C	1 or $Pd(OAc)_2$	[85,89]
	$R-NH-R'$	L2	NaOt-Bu, THF or Cs_2CO_3 , t-BuOH 65 - 110 °C	4 or $Pd(OAc)_2$	[89,90,116]
	$R-C(=O)NH_2$	L6	$Pd(OAc)_2$, K_3PO_4 t-BuOH, 110 °C	H ₂ O activation $Pd(OAc)_2$	[103]
Aryl iodides					
	$R-NH_2$	L1	NaOt-Bu or Cs_2CO_3 , toluene 80 - 110 °C	1 or $Pd(OAc)_2$	[90]
	$R-NH-R'$	L2	NaOt-Bu or Cs_2CO_3 , toluene 80 - 110 °C	4 or $Pd(OAc)_2$	[90]
	$R-NH_2$	L1	K_2CO_3 , t-BuOH 110 °C	1 or $Pd(OAc)_2$	[90]
Aryl sulfonates					
	$R-NH_2$	L3	K_2CO_3 , t-BuOH Cs_2CO_3 toluene/t-BuOH, 5:1 80 - 110 °C	$Pd(OAc)_2$ or $Pd_2(dba)_3$	[83]
	$R-NH-R'$	L3	Cs_2CO_3 toluene/t-BuOH, 5:1 80 - 110 °C	$Pd(OAc)_2$ or $Pd_2(dba)_3$	[83]
	$R-C(=O)NH_2$	L3	K_2CO_3 , t-BuOH 110 °C	$Pd(OAc)_2$ PhB(OH) ₂ activation	[83]
	$R-NH_2$	L1	K_2CO_3 , t-BuOH 110 °C	1 or $Pd(OAc)_2$	[85]
	$R-C(=O)NH_2$	L6	Cs_2CO_3 , t-BuOH 110 °C	$Pd(OAc)_2$ H ₂ O activation	[104]

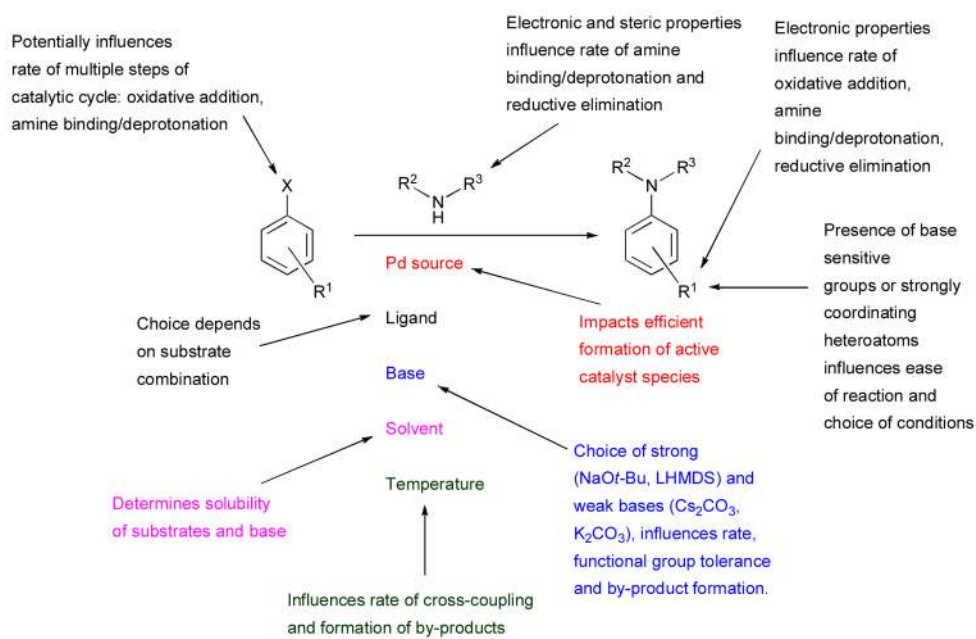
Figure 7. Summary of reaction conditions used for different classes of electrophile.

Electrophile	Nucleophile	Ligand	Typical conditions	Pd source	References
	R-NH ₂	L1	K ₂ CO ₃ , <i>t</i> -BuOH 110 °C	1 or Pd(OAc) ₂	[89]
	R-NH-R'	L2	NaOt-Bu, THF or Cs ₂ CO ₃ , <i>t</i> -BuOH 85 °C	4 or Pd(OAc) ₂	[89]
	R-NH ₂	L1	LHMDS, THF 100 °C or K ₂ CO ₃ , <i>t</i> -BuOH 110 °C	1 or Pd(OAc) ₂	[89]
	R-NH-R'	L2	NaOt-Bu, THF 85 °C or Cs ₂ CO ₃ , <i>t</i> -BuOH 85 °C	4 or Pd(OAc) ₂	[89]
	R-NH ₂	L1	K ₂ CO ₃ , <i>t</i> -BuOH 110 °C	1 or Pd(OAc) ₂	[89]
	R-NH-R'	L3 or L7	NaOt-Bu, toluene 100 °C	Pd ₂ (dba) ₃	[84]
	R-NH ₂	L1	LHMDS, THF 65 °C	1 or Pd(OAc) ₂	[146]
	R-NH-R'	L2	LHMDS, THF 65 °C	4 or Pd(OAc) ₂	[146]
	R-NH ₂	L1	NaOt-Bu, toluene 65 - 100 °C	1 or Pd(OAc) ₂	[89]
	R-NH ₂ R-NH-R'	L2 or L7	NaOt-Bu, toluene 100 °C	Pd ₂ (dba) ₃	[84]

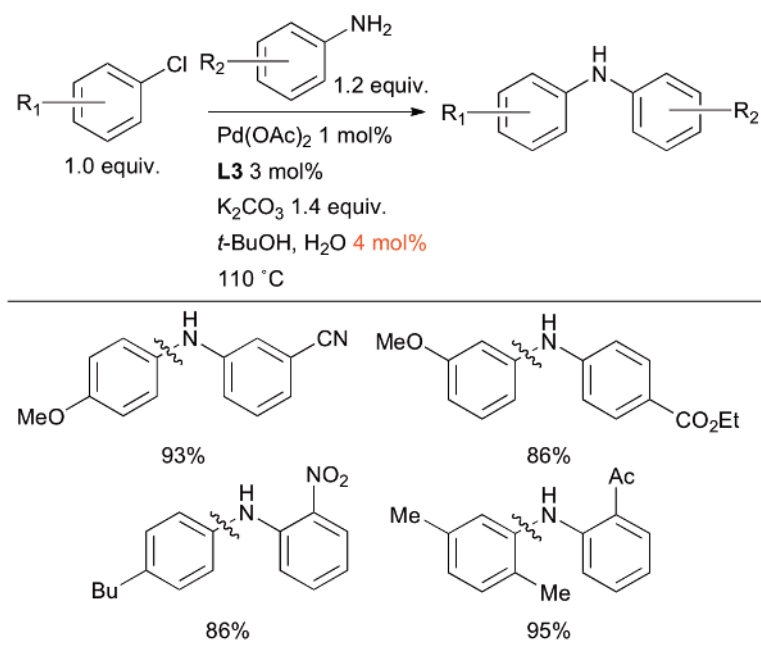
Figure 8.
Summary of reaction conditions used for different classes of heteroaryl electrophile.



Scheme 1.
Generalized catalytic cycle for Pd-catalyzed amination with dialkylbiaryl phosphines.

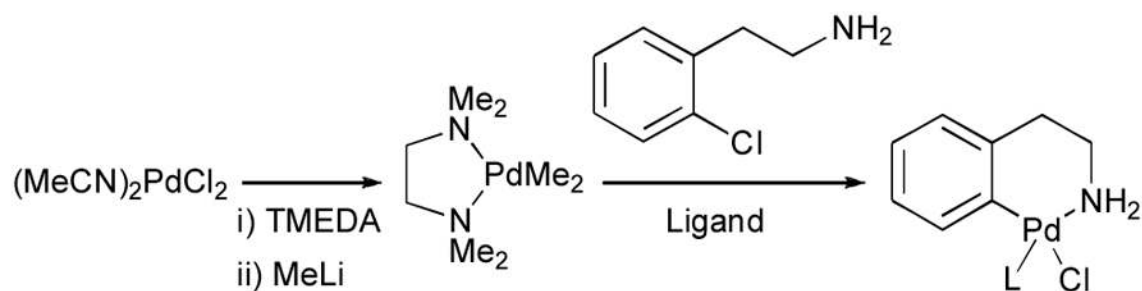


Scheme 2.
Factors influencing the outcome of a Pd-catalyzed amination reaction.



Scheme 3.

Water-mediated reduction of Pd(II) salts permits efficient amination of electron-deficient anilines.

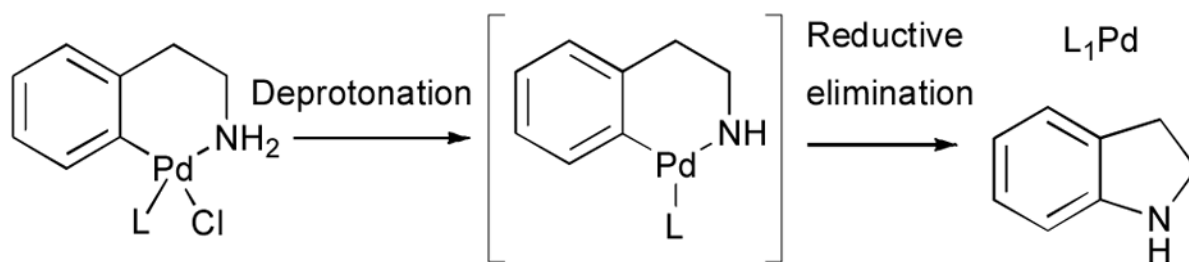


Commercially available for L =

- 1 BrettPhos
- 2 XPhos
- 3 SPhos
- 4 RuPhos
- 5 *t*BuXPhos

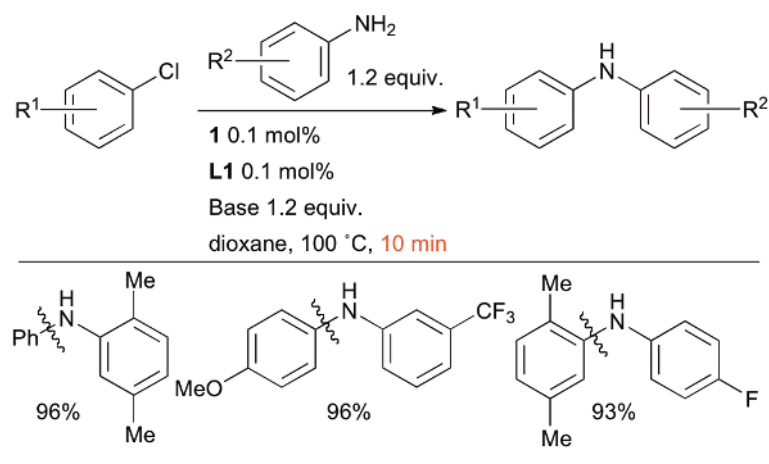
Scheme 4.

Synthesis of amine bound oxidative addition precatalyst.



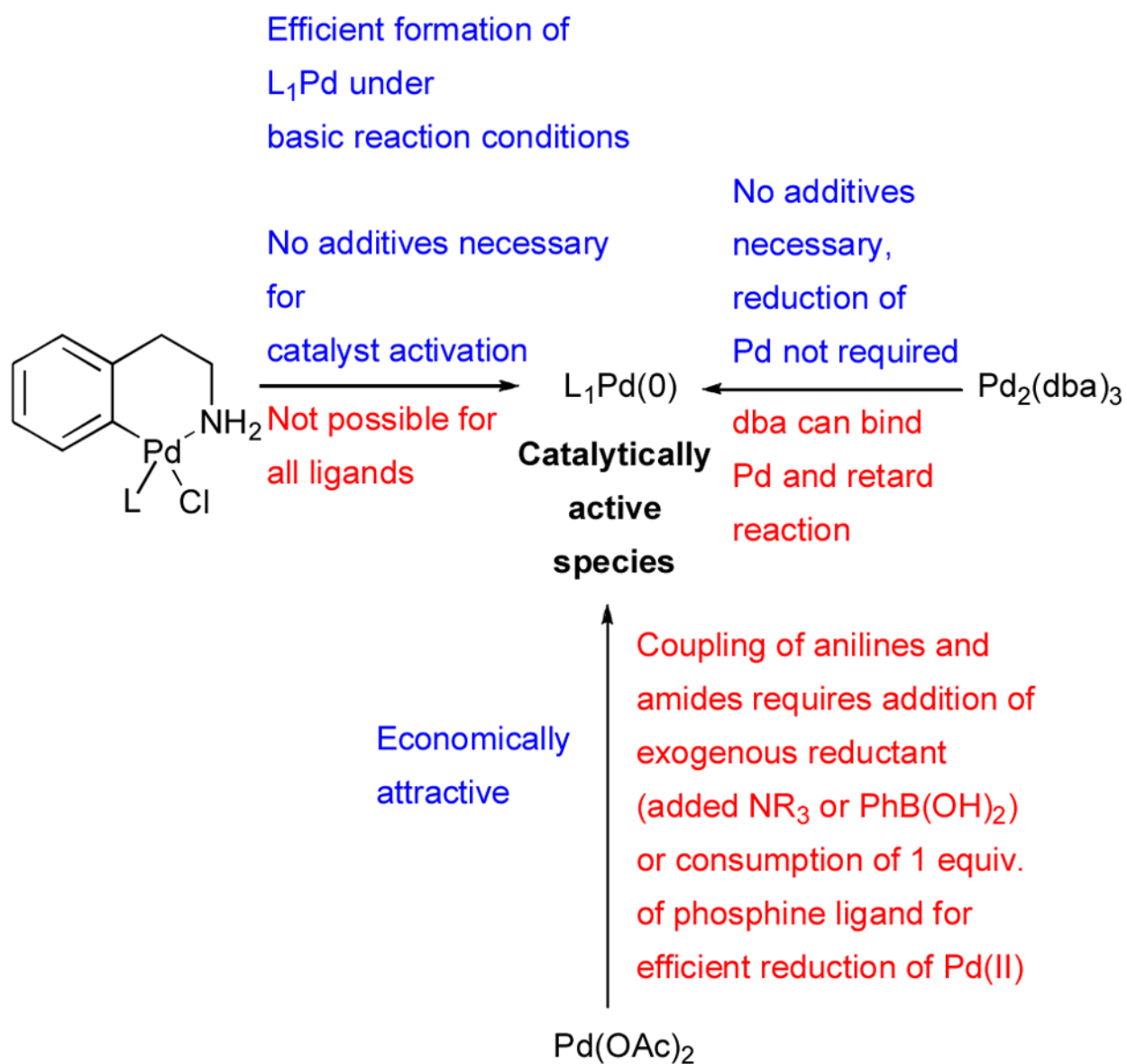
Scheme 5.

Activation of intramolecularly coordinated amine oxidative addition precatalyst.

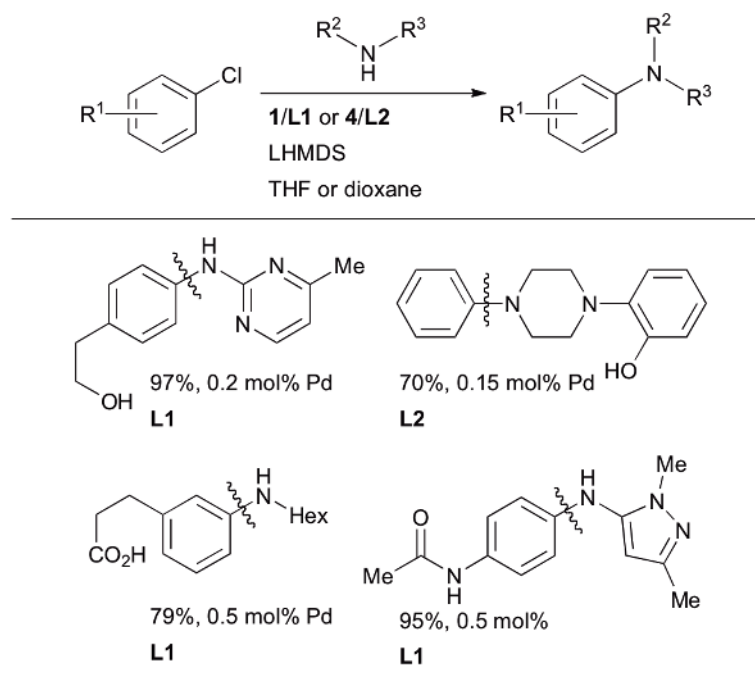


Scheme 6.

The application of precatalyst **1** allows arylation of anilines with low catalyst loading and short reaction times.

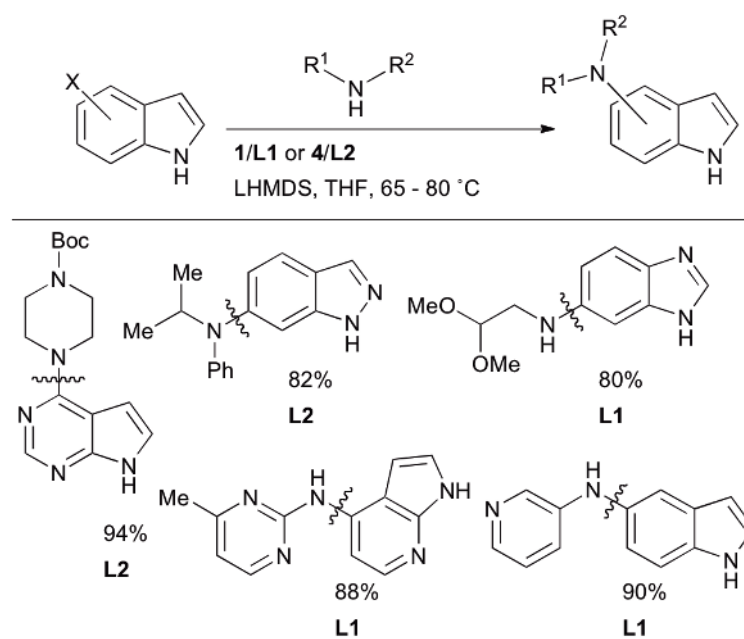


Scheme 7.
Considerations for choice of Pd source for amination reactions.

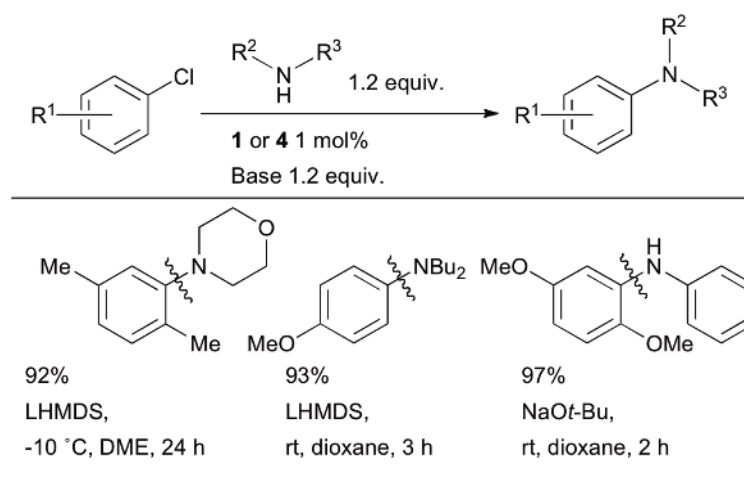


Scheme 8.

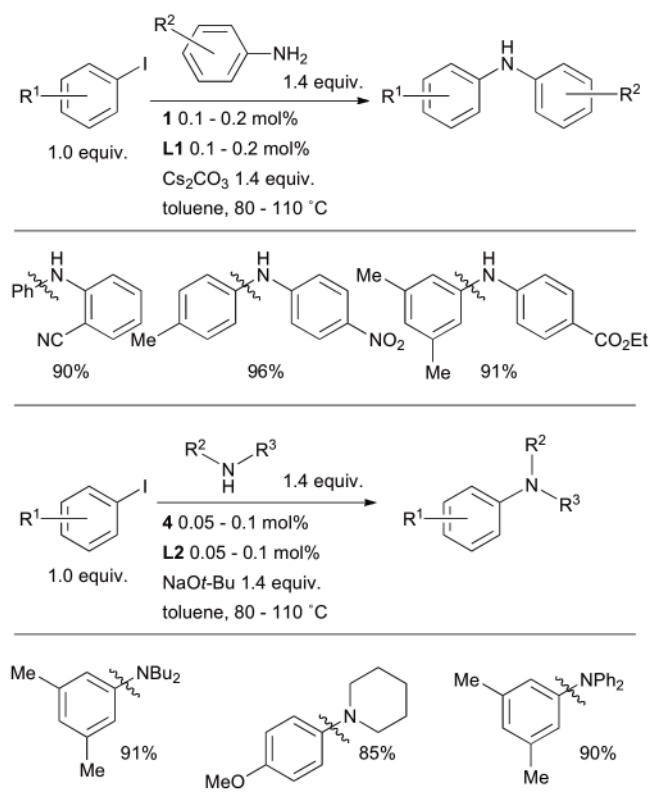
Use of LHMDS as base permits the cross-coupling of substrates bearing protic functional groups.



Scheme 9.
Amination of aryl chlorides at or below room temperature.

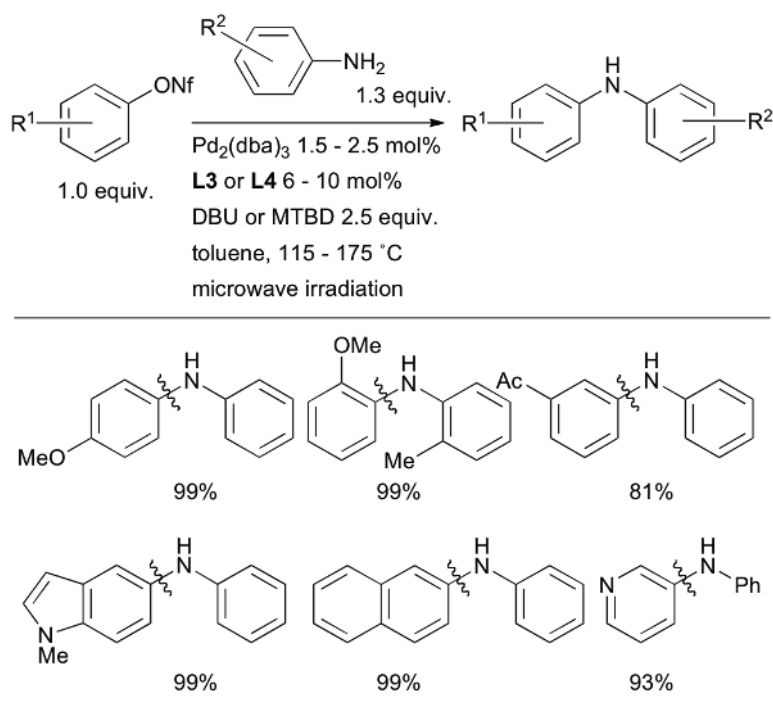


Scheme 10.
Efficient Pd-catalyzed amination of aryl iodides using **L1** and **L2** as ligands in toluene.



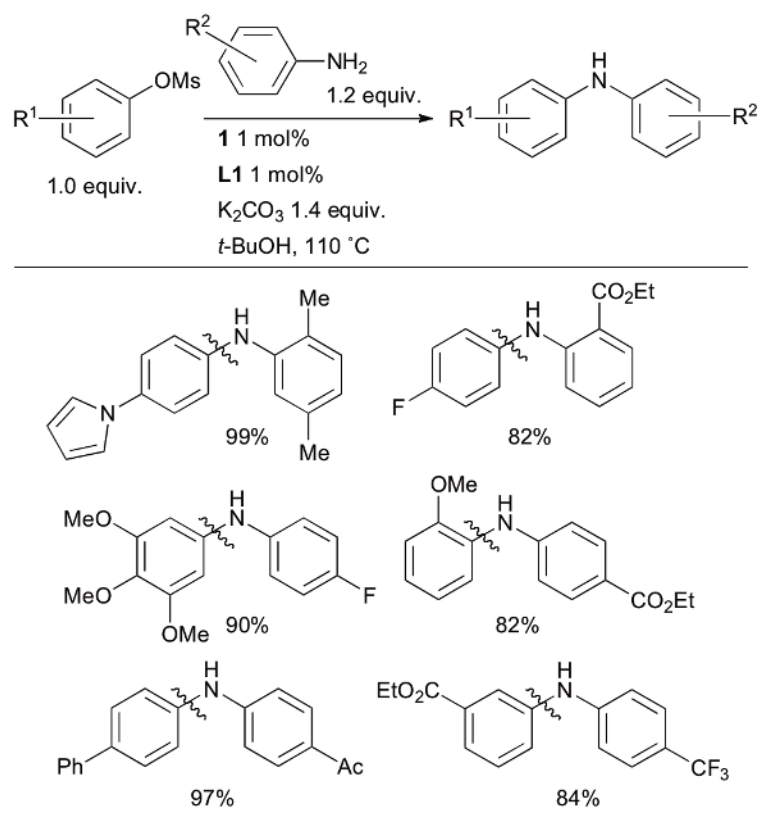
Scheme 11.

Pd-catalyzed coupling of anilines and aryl nonaflates under microwave irradiation.

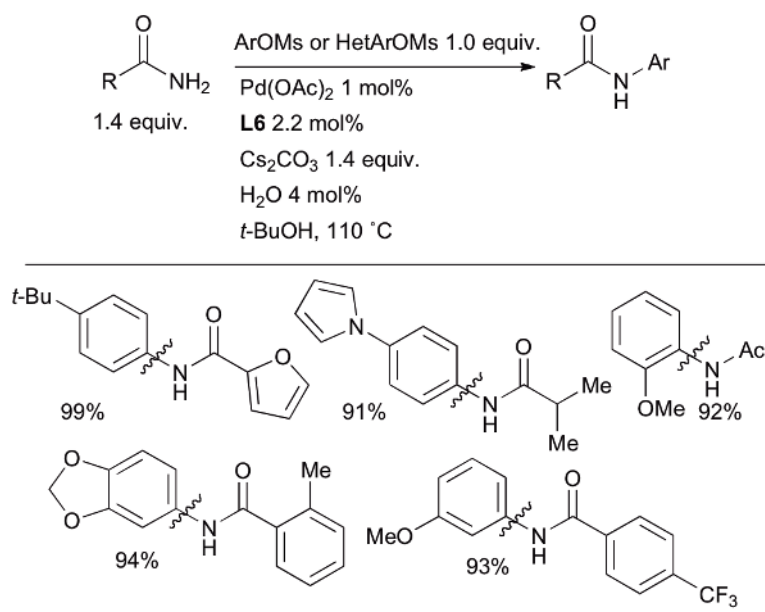


Scheme 12.

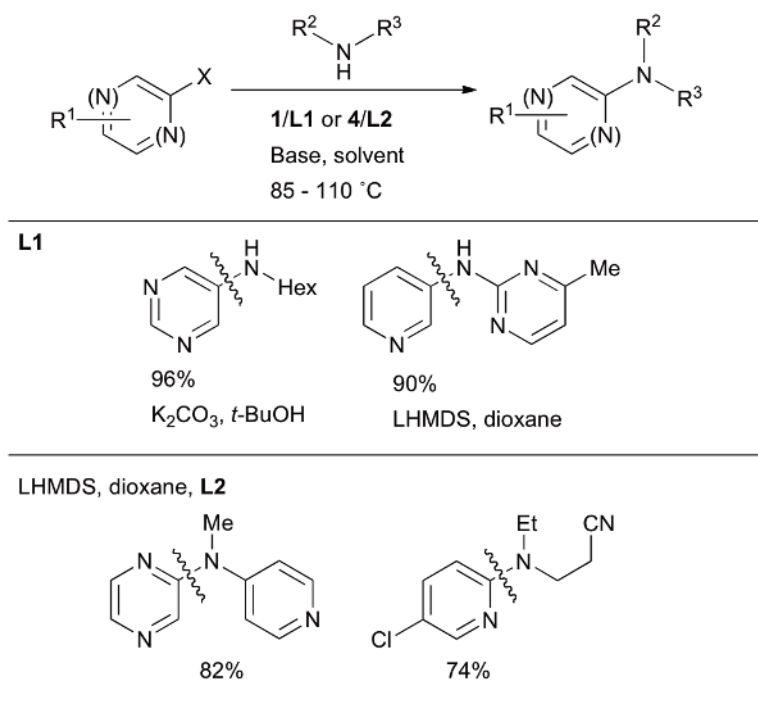
Pd-catalyzed coupling of anilines and aryl mesylates employing **L1** as ligand.



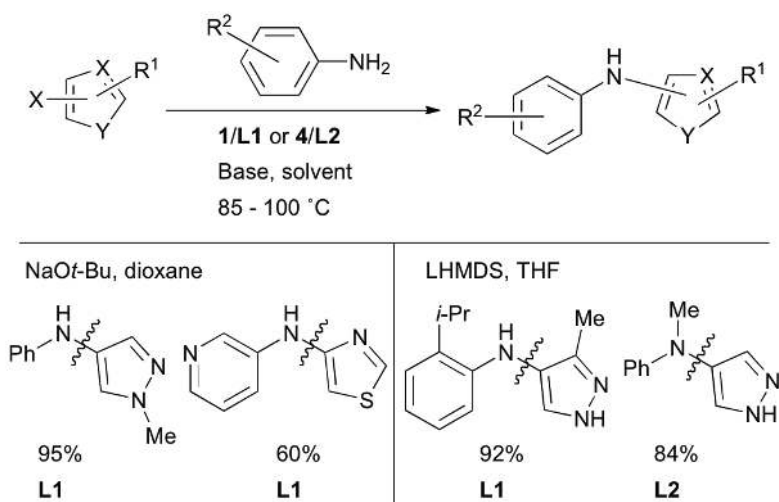
Scheme 13.
 Amidation of aryl mesylates employing **L6** as ligand.



Scheme 14.
 Pd-catalyzed amination of 6-membered ring heteroaryl halides using **L1** and **L2**.

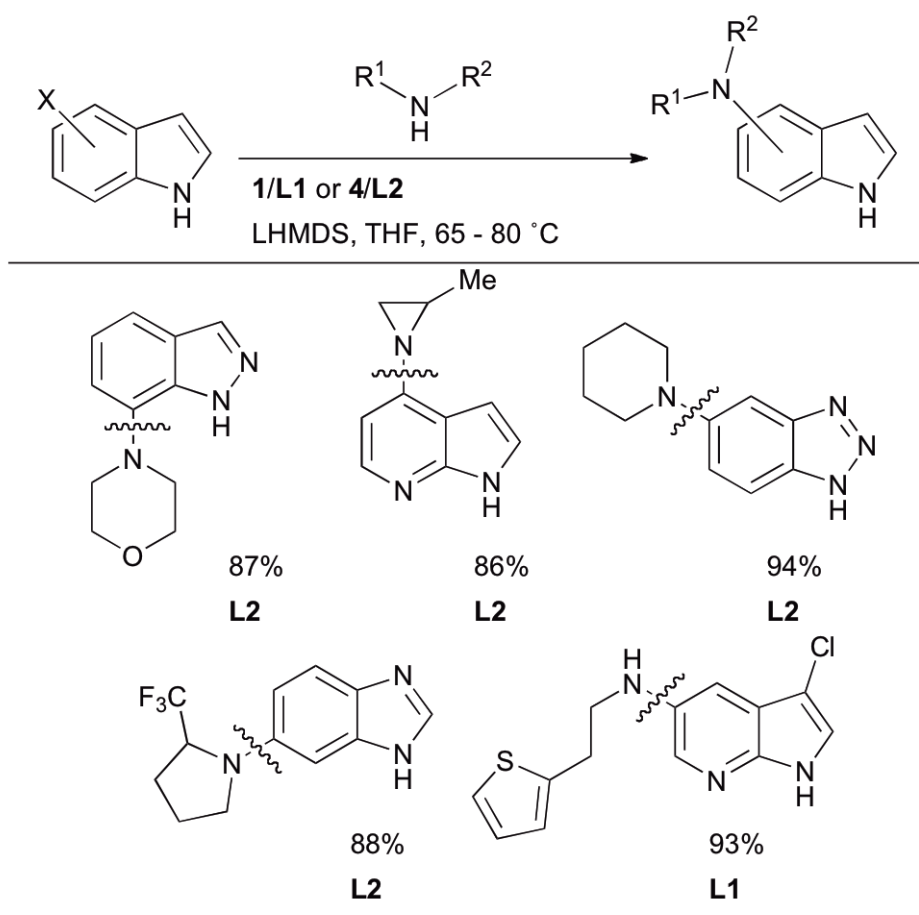


Scheme 15.
Amination of 5-membered ring heteroaryl halides using **L1** or **L2** as ligand.



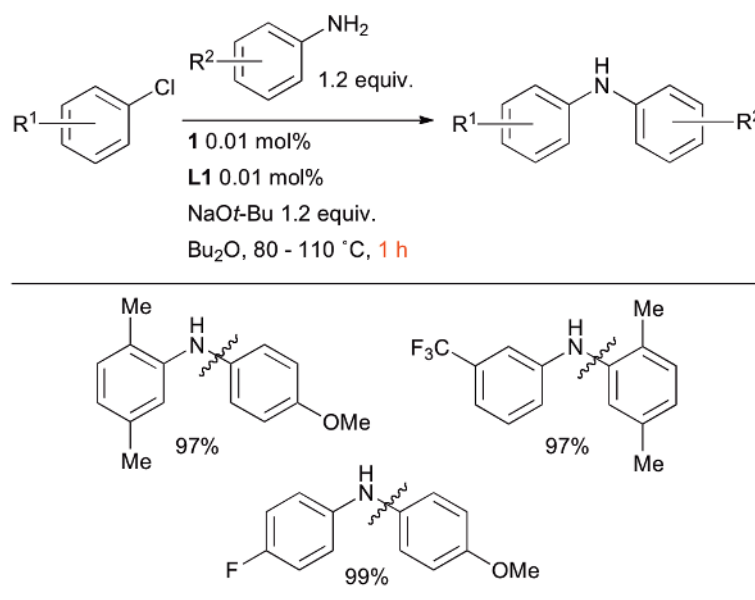
Scheme 16.

The selective arylation of 1° anilines can be conducted with high efficiency using **L1**.



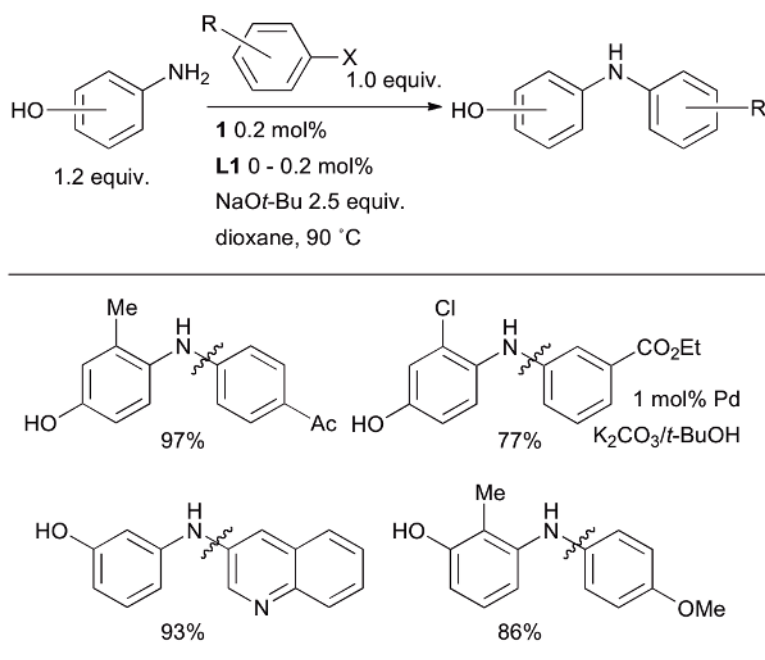
Scheme 17.

L1-based catalyst systems permit the selective N-arylation of aminophenols.



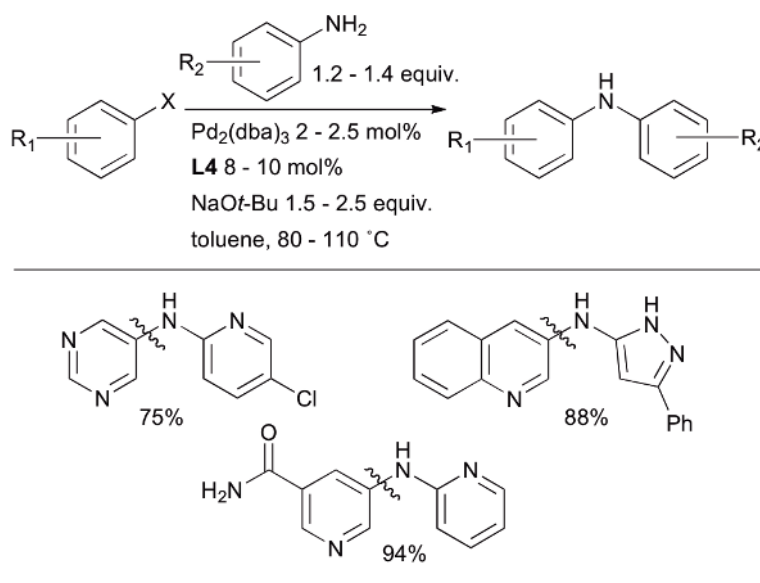
Scheme 18.

L3-based catalysts allow the selective arylation of an aniline in the presence of a primary amide.⁸³



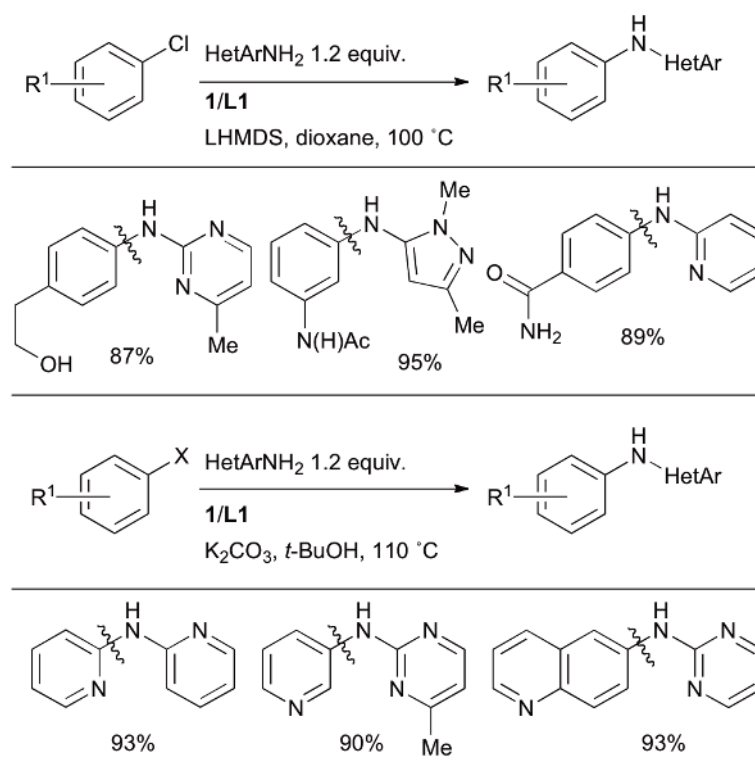
Scheme 19.

L4 can be a useful ligand for the arylation of electron-deficient heteroarylamines.



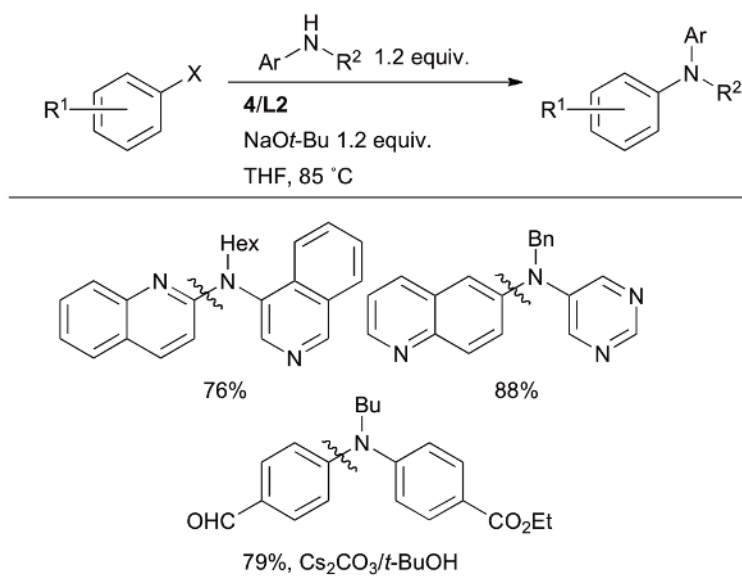
Scheme 20.

L1 provides an efficient catalyst system for the amination of 1° heteroarylamines under various reaction conditions.

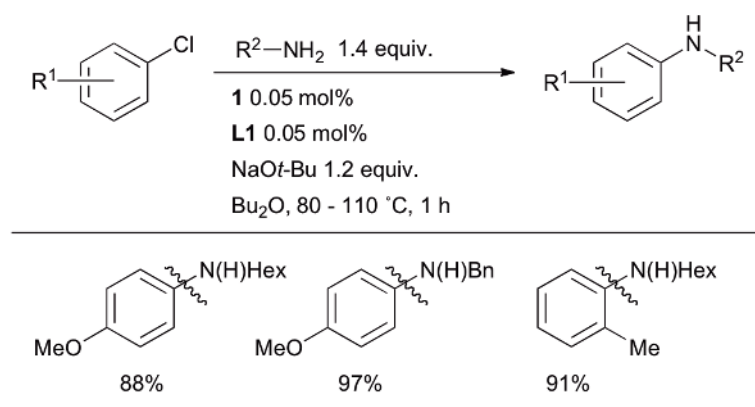


Scheme 21.

L2 is the best dialkylbiaryl phosphine for the arylation of 2° anilines.

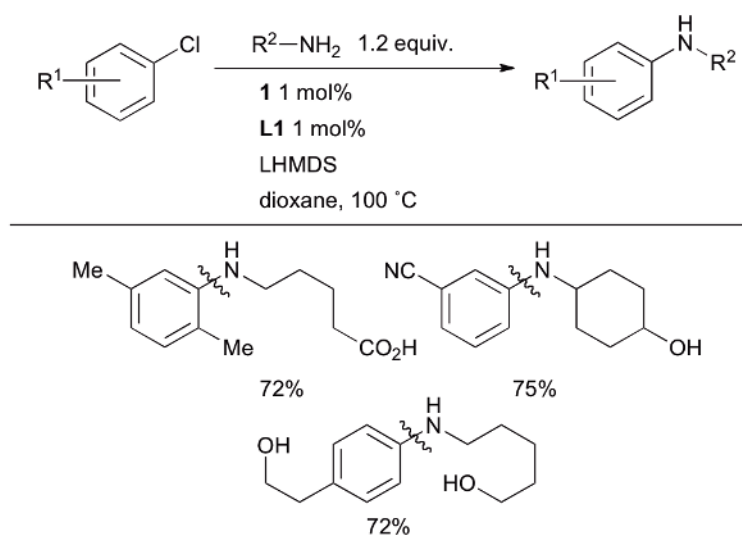


Scheme 22.
L2-based catalyst for the arylation of diarylamines.



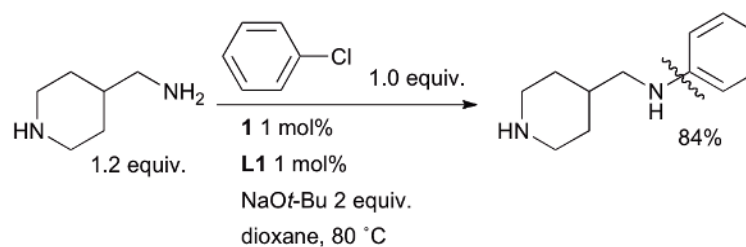
Scheme 23.

The use of an **L9**-based catalyst for the synthesis of triarylamines from anilines and aryl halides.



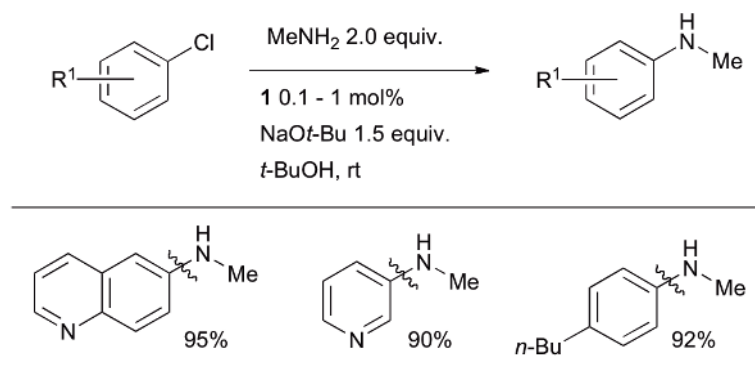
Scheme 24.

L1 permits the coupling of 1° aliphatic amines with low catalyst loadings and short reaction times.



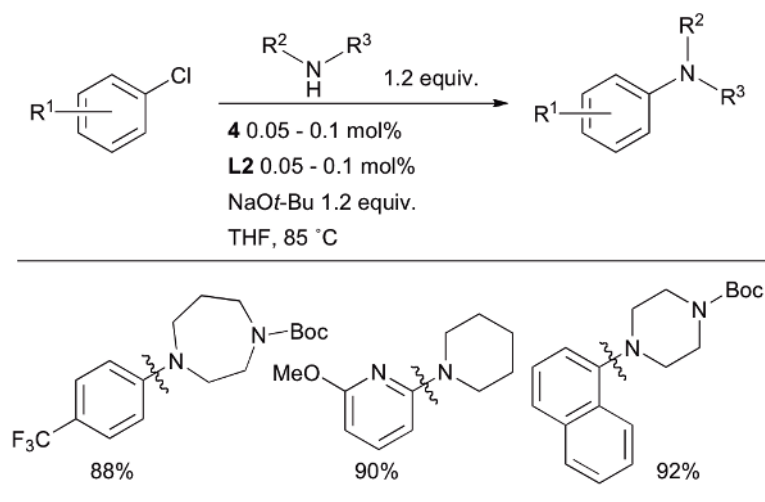
Scheme 25.

L1 is the best ligand for the reaction of 1° aliphatic amines.



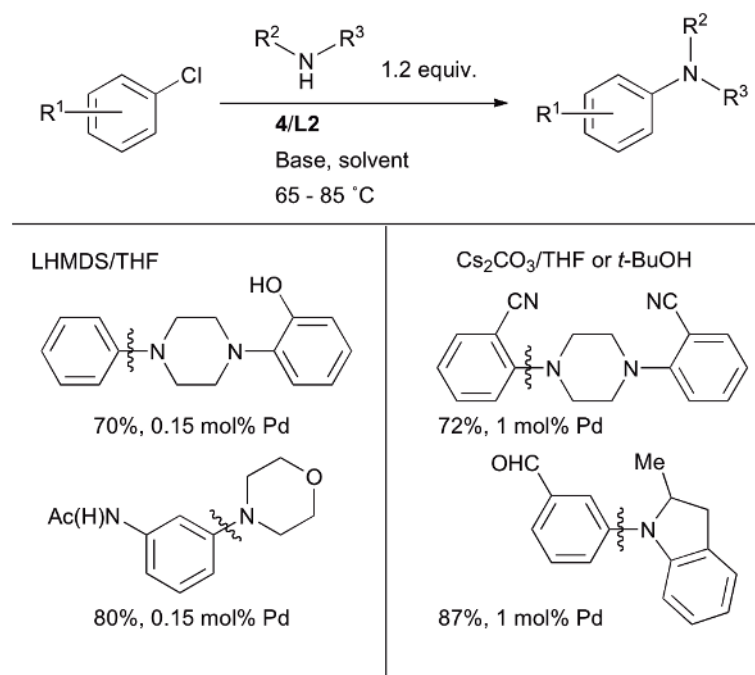
Scheme 26.

L1-based catalyst systems provide excellent selectivity for the arylation of 1° amines in the presence of 2° amines.



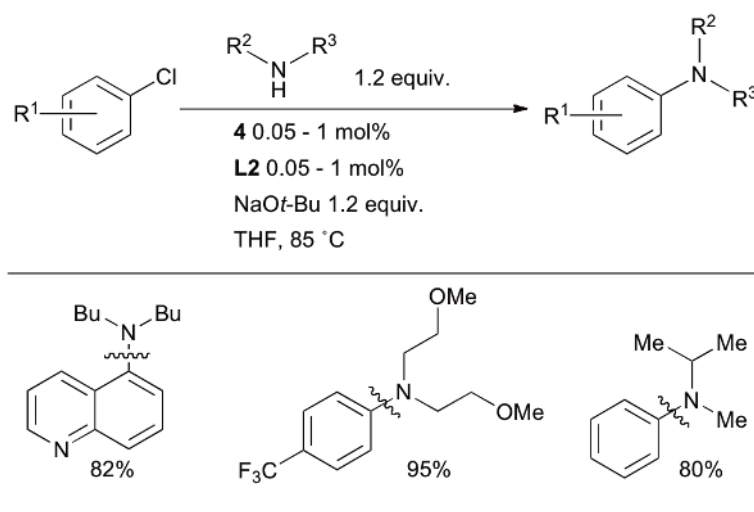
Scheme 27.

The efficient monoarylation of methylamine can be accomplished by the use of a **L1**-based catalyst system.



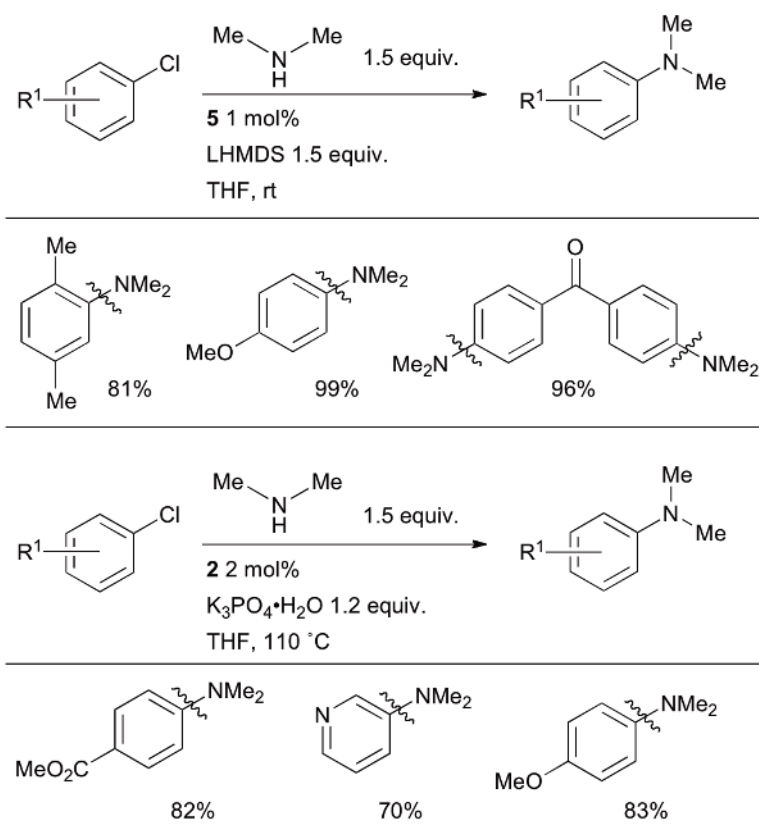
Scheme 28.

L2 can be used for the arylation of cyclic 2° aliphatic amines under a variety of conditions.



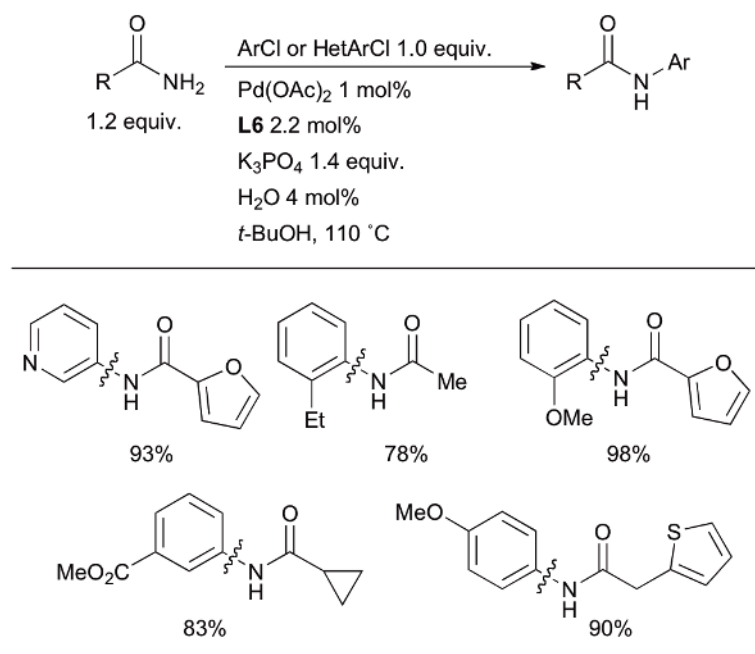
Scheme 29.

L2 can be used for the arylation of cyclic 2° aliphatic amines under a variety of conditions.



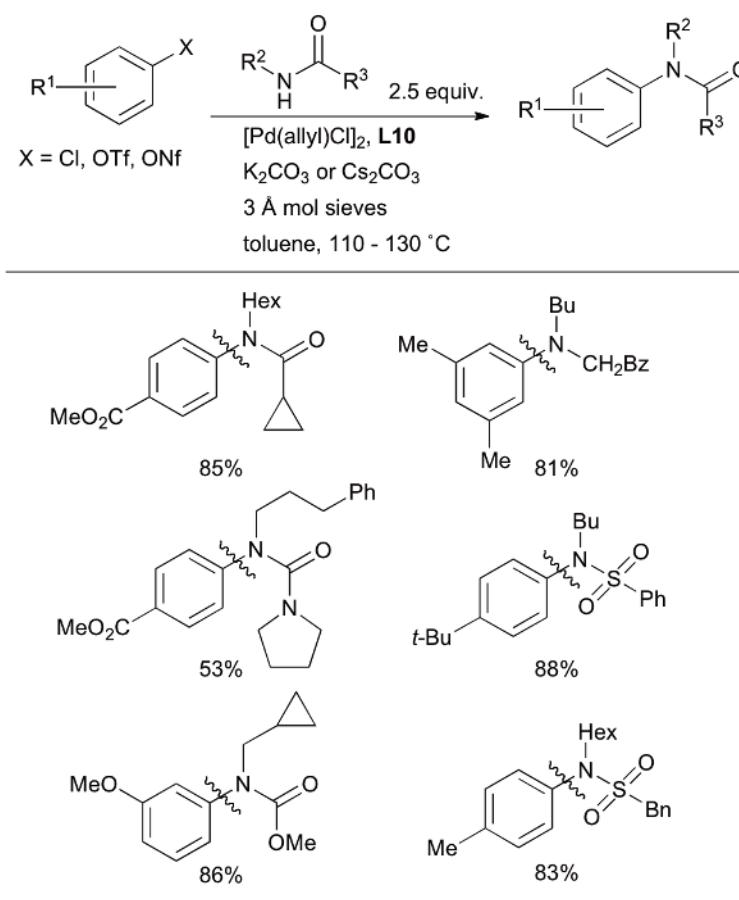
Scheme 30.

L2 is the most effective ligand for the cross-coupling of acyclic aliphatic amines.



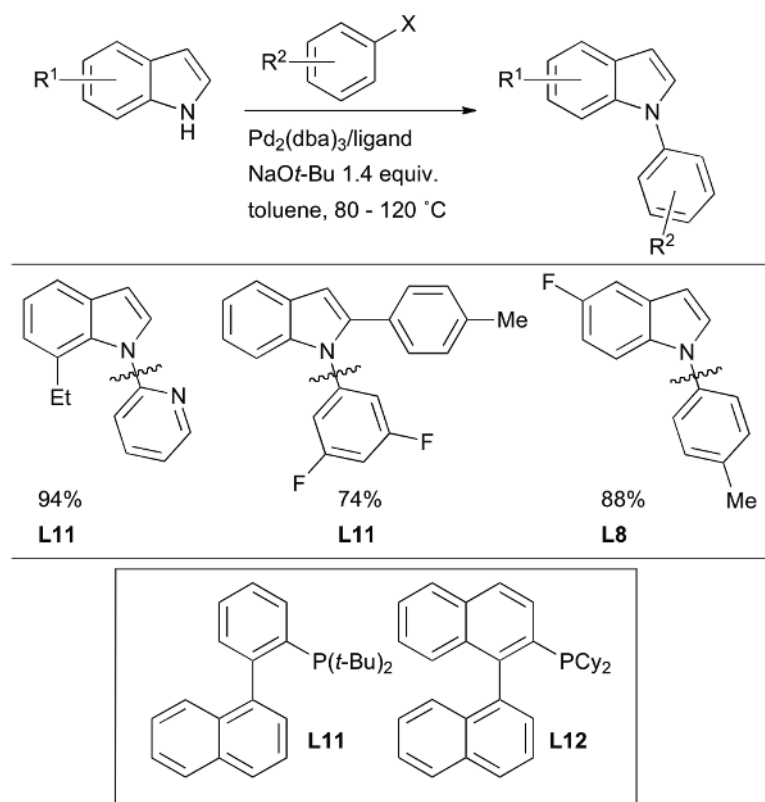
Scheme 31.

Catalysts based on **L3** or **L4** can affect the arylation of dimethylamine.

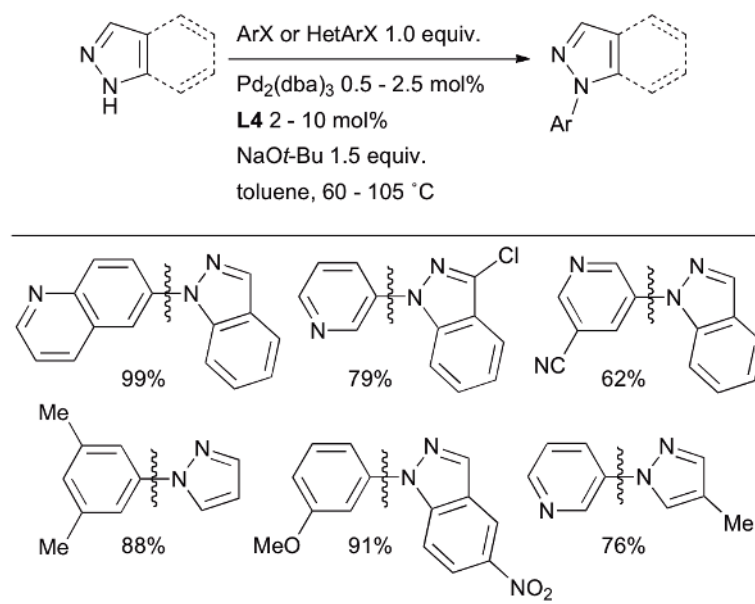


Scheme 32.

L6 is the best dialkylbiaryl phosphine for the arylation of 1° amides.

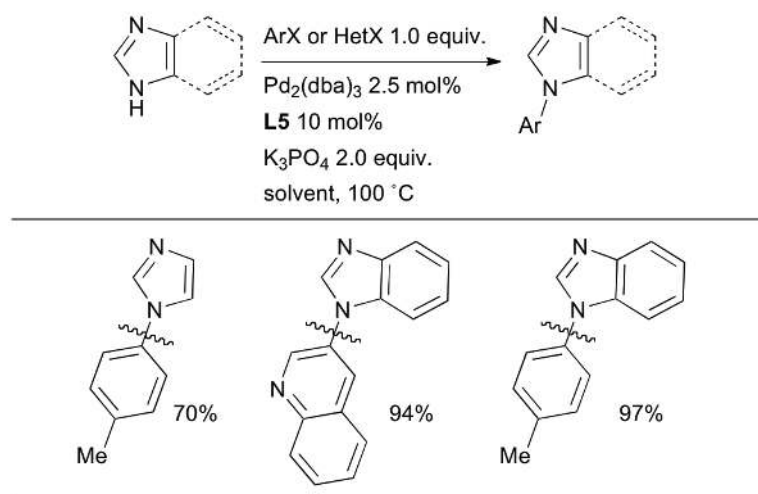
**Scheme 33.**

Arylation of 2° amides, ureas, carbamates and sulfonamides is possible by using **L10** as ligand.



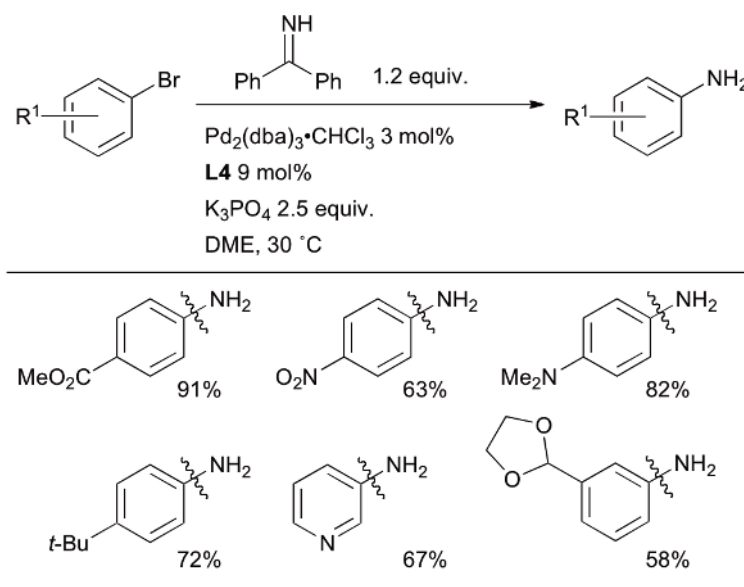
Scheme 34.

A variety of dialkylbiaryl phosphine ligands are suitable for the N-arylation of indoles.



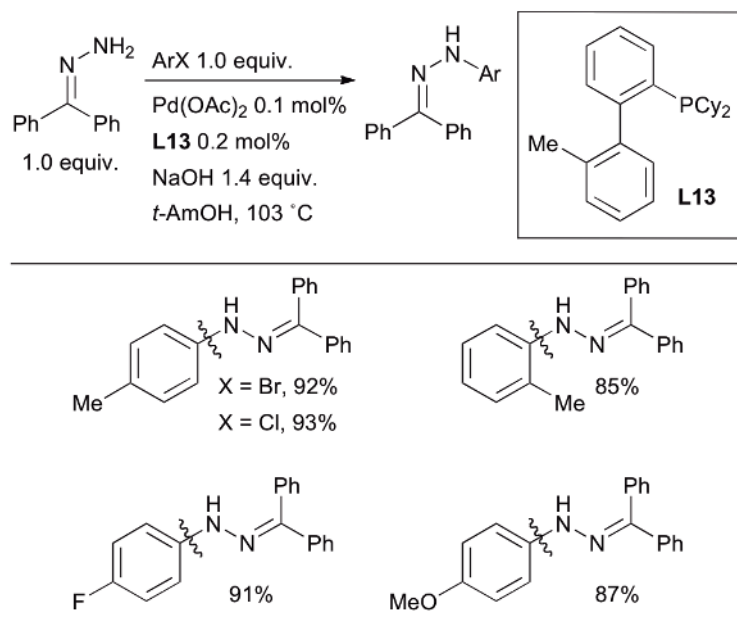
Scheme 35.

L4 is a useful ligand for the arylation of indazoles and pyrrazoles.



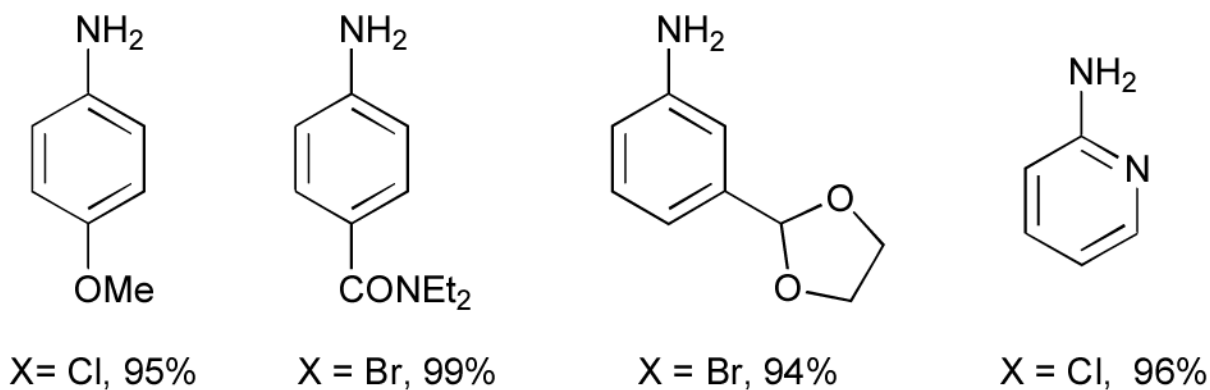
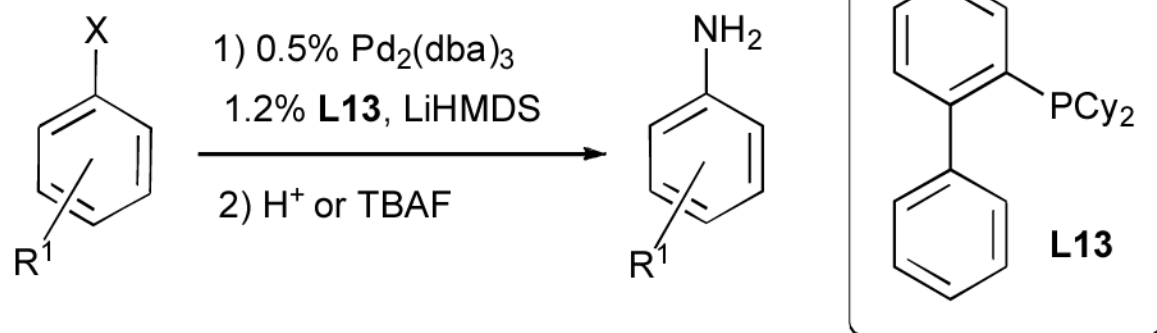
Scheme 36.

The arylation of imidazole and benzimidazole can be brought about in some cases by using **L5** as ligand.



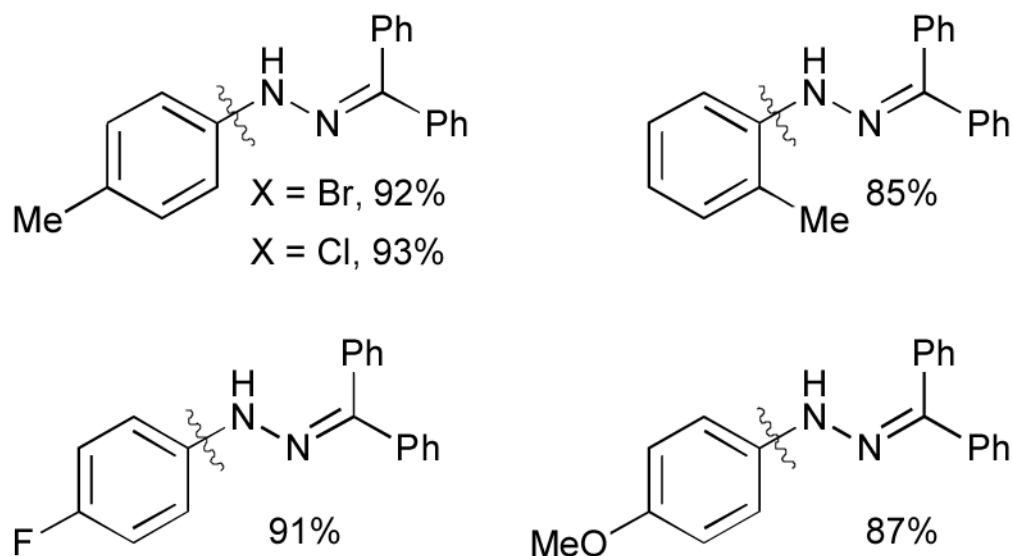
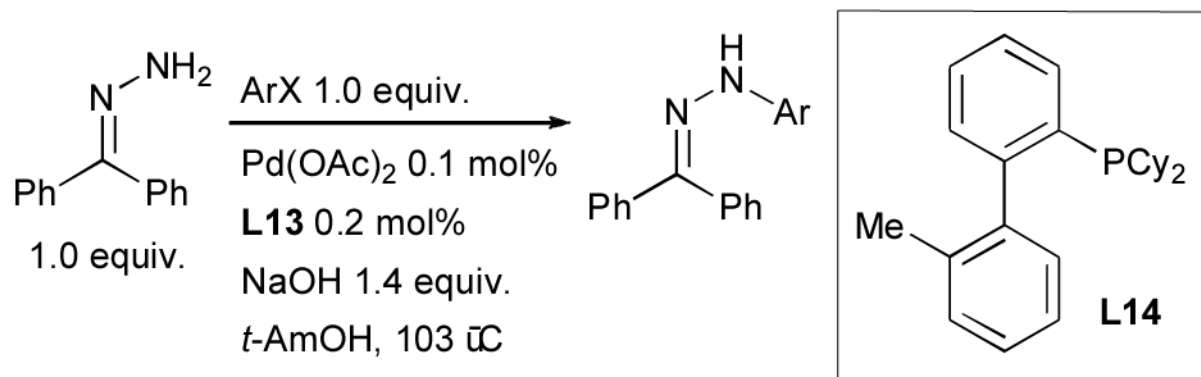
Scheme 37.

L4 is a useful ligand for the conversion of aryl bromides to anilines.¹⁵⁷



Scheme 38.

L13 is a useful ligand for the conversion of aryl halides to anilines using LiHMDS as the ammonia surrogate.²²¹



Scheme 39.

Benzophenone hydrazone can be effectively arylated with aryl chlorides and bromides.