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Biaryl Monophosphine Ligands in Palladium-Catalyzed C–N Coupling: An Updated User's Guide

Bryan T. Ingoglia[1], **Corin C. Wagen**[1], **Stephen L. Buchwald**[*]

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, United States

Abstract

Over the past three decades, Pd-catalyzed cross-coupling reactions have become a mainstay of organic synthesis. In particular, catalysts derived from biaryl monophosphines have shown wide utility in forming C–N bonds under mild reaction conditions. This work summarizes a variety of C–N cross-coupling reactions using biaryl monophosphines as supporting ligands, with the goal of directing synthetic chemists towards the ligands and conditions best suited for a particular coupling.

PRELUDE:

When I learned that I had received the 2018 Tetrahedron Prize for Creativity in Organic Chemistry, jointly with Professor John F. Hartwig of UC Berkeley, I felt a sense of great accomplishment. Accomplishment not specifically for me, but by my research group (and that of John's) in developing new chemistry that was both intrinsically interesting and of practical utility. The latter aspect is the reason that we have chosen to write this review to help practitioners in the field utilize palladium-catalyzed C–N coupling reactions more broadly, efficiently, and predictively in their own research efforts. We note that while we have limited this review to reactions using biaryl phosphine ligands, that many other good alternatives exist.

1. Introduction and General Principles

Transition metal catalysis enables mild and general access to molecular structures that would otherwise be challenging to prepare. In particular, palladium catalysts have become dependable tools in the rapid and modular construction of substituted aromatic compounds. The efficacy of such catalysts stems largely from the ability to tune their reactivity through modification of the ancillary ligand(s). To this end, biaryl monophosphines have emerged as a class of privileged ligands for a number of mechanistically related transformations. While we have focused this review on one class of ligands developed at MIT, many other groups have made important contributions, most notably, of course, the Hartwig laboratory.[1,2] Outstanding examples have also emerged from the laboratories of Beller,[3] Guram,[4] Nolan,[5] Organ,[6] Singer,[7] Stradiotto,[8] and many others.[9,10]

[*]: Corresponding Author: sbuchwal@mit.edu.

[1]:B.T.I. and C.C.W. contributed equally to this work.

Herein, we aim to summarize Pd-catalyzed carbon–nitrogen cross-coupling reactions that are enabled by biaryl monophosphine ligands (Figure 1). The purpose of this paper is to aid synthetic chemists in choosing the most appropriate ligand for a desired transformation. In addition to ligand selection, we discuss the impact of palladium source and reaction conditions (e.g., base, temperature, solvent) on the reaction outcome. We emphasize that this review is not designed to be comprehensive or to replace information in the primary chemical literature, but rather to serve as a complement to existing publications.

A generic mechanism for Pd-catalyzed C–N cross-coupling reactions is presented in Scheme 1. The catalytic cycle begins when a phosphine-ligated palladium(0) complex **(I)** undergoes oxidative addition to an aryl (pseudo)halide to give an aryl palladium(II) complex (**II**). The net substitution of the amine for the (pseudo)halide resembles a “transmetalation” event and is thought to comprise a two-step sequence: nucleophile (amine) binding, followed by deprotonation. In the first step, the Pd(II) center acts as a Lewis acid to bind the amine, forming amine-bound complex **III**, thereby acidifying the proton on the nitrogen atom. In the second step, base-mediated elimination of HX forms an amido complex (**IV**), which regenerates $L_nPd(0)$ upon reductive elimination with concomitant release of amine product. The rate-limiting step varies depending on the type of coupling reaction, and each of these elementary steps can be modulated by the ancillary ligand.

1.a. General Features of the Catalyst

Dialkyl biaryl monophosphine ligands were first reported in 1998, and they have since shown broad applicability to a diverse array of cross-coupling reactions.[11–15] The reactivity of catalysts supported by these ligands is influenced in complex ways by the ligand architecture, as summarized in Figure 2.

The large substituents on phosphorus lend stability to the ligands by slowing the rate of oxidation of the phosphorus atom. This feature makes these ligands of even greater practical use in synthetic chemistry, as they can be stored under ambient conditions.[16] The bulkiness of the ligands also facilitates the formation and enhances the relative stability of L_1Pd complexes.[17]

Biaryl monophosphines have been shown to be pseudobidentate ligands for Pd, which also promotes the formation of monoligated Pd complexes.[18] The lower aromatic ring can serve as a ligand for the Pd center through C1’ (Figure 3). An alternative binding mode is operative for ligands bearing 2-methoxy substituents on the top ring (e.g., Figure 3, BrettPhos, **L6**); however, this binding mode is not observed for ligands that have large groups (e.g., 1-adamantyl or *t*-Bu) on phosphorus,[19] or larger alkoxy groups at C2.[20] Substituents R^3 and R^4 enhances catalyst stability by suppressing cyclometalative pathways for deactivation.[21]The presence of R^3 also serves to favor the conformation in which the Pd sits over the bottom ring. This both facilitates the rate of reductive elimination and enhances the stability of catalytically important intermediates.

We will next discuss how specific structural features affect each elementary step (as summarized in Figure 2).

1.b. Oxidative Addition

In general, oxidative addition is fast for catalysts derived from dialkyl biaryl monophosphines even for less reactive electrophiles (e.g., aryl chlorides).[22] This is due to two main features: a) compared to $L_2Pd(0)$ complexes, the L_1Pd complexes formed with these ligands are more stable in the Pd(0) oxidation state, yet allow the aryl electrophile to approach more closely; and b) the alkyl groups on the phosphorus atom increase electron density on the Pd center (relative to triaryl phosphine-supported catalysts) and enhance the rate of oxidative addition. In terms of the aryl electrophile, the general order of reactivity is ArI > ArBr ~ ArOTf > ArCl ~ ArOMs. Using this hierarchy of reactivity exhibited by aryl (pseudo)halides, it is often possible to chemoselectively couple one electrophilic site, leaving another available for subsequent functionalization.

1.c. Transmetalation

Transmetalation refers to the process by which the nucleophilic coupling partner displaces the (pseudo)halide from the palladium center. Although this is the least well-understood step of the catalytic cycle, it is known to be generally sensitive to steric hindrance around the metal. Biaryl phosphines facilitate this step of the catalytic cycle by favoring low-coordinate L_1Pd complexes, which allows approach of the nucleophile to the metal center.[23]

The identity of the electrophile can have a significant impact on transmetalation. For example, when aryl triflates are employed as substrates, the triflate ion is dissociated from the metal center, rendering the complex formally cationic and opening a coordination site for the nucleophile; accordingly, transmetalation is usually faster in reactions employing aryl triflate electrophiles than analogous reactions employing aryl halide electrophiles.[19,24]

In many cases the rate of transmetalation is fastest for aryl chlorides (within the halide series), due to the increased polarity of the Pd–Cl bond, and smaller size of Cl relative to Br and I.[25] Indeed, aryl iodides can be challenging substrates, as the NaI formed during the reaction has been shown to have an inhibitory effect, although this issue can be circumvented by using a solvent that does not solubilize NaI (e.g., toluene).[26] In general, however, contrary to conventional wisdom from the early days of Pd coupling chemistry, the use of aryl iodide substrates should be avoided if possible.

1.d. Reductive Elimination

Reductive elimination is the last step of the catalytic cycle, which delivers the product and regenerates $L_nPd(0)$. The identity of the nucleophile plays a significant role in this elementary step: reductive elimination is more challenging for less nucleophilic coupling partners, such as diarylamines. There are three main ways that the structure of the ligand affects the rate of reductive elimination.

First, reductive elimination can be facilitated by withdrawing electron density from the metal center through the use of electron-poor phosphines (e.g., **L15**). The second strategy is to employ ligands bearing large alkyl substituents on the phosphorus atom (e.g., 1-adamantyl, *tert*-butyl), which force the aryl and amino ligands together, thereby shifting the ground state geometry closer to that of the reductive elimination transition state. Finally, it has been

established that reductive elimination is faster from three-coordinate Pd(II) complexes than four-coordinate complexes.[27,28] Accordingly, the hemilabile character of the bottom ring of biaryl monophosphine ligands allows L–Pd(Ar)NR_2 complexes to adopt the preferred T-shaped geometry for reductive elimination. Thus, in general, reductive elimination is a rapid process in most C–N cross-coupling reactions. However, it can be rate-limiting in reactions that form triarylamines.[29] Furthermore, the role of reductive elimination in coupling reactions of *N*-heterocycles or amides has not been studied in detail.

2. Precatalyst Selection

It is clear that selection of an appropriate ligand can determine the success or failure of a cross-coupling reaction, but the palladium source can have a dramatic impact as well. The most commonly employed sources of Pd are complexes such as $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(MeCN)_2$, $[PdCl(allyl)]_2$ and Pd_2dba_3. These metal sources are advantageous because they are bench-stable and commercially available. However, the metal must associate with the ligand, and with the exception of Pd_2dba_3, it must be reduced from Pd(II) to Pd(0) under the reaction conditions prior to entering the catalytic cycle.

The efficiency of the Pd(II) reduction step is dependent on the ligand used, the type of Pd source, and the reductant employed. The optimal reducing agent varies depending on the reaction conditions. Amines,[30–33] tertiary phosphines,[34] boronic acids,[35] and organometallic reagents (e.g., organozincs) have all been used.[36] With amines, β-hydride elimination from a Pd(II) amido complex is a major pathway; accordingly, nucleophiles that do not possess β-hydrogens, such as amides and anilines, are poor reductants. Tertiary phosphines, including bulky biaryl monophosphines, have been shown to reduce $Pd(OAc)_2$ in the presence of water to produce L–Pd(0) as well as an equivalent of phosphine oxide.[37] Organometallic reagents and boronic acids are used as sacrificial nucleophiles and successive transmetalation of two equivalents of the nucleophile onto Pd(II) followed by reductive elimination generates L–Pd(0), with concomitant formation of a C–C homocoupling product.

Some Pd(0) sources may also be used as precatalysts, such as Pd_2dba_3 and $Pd(PPh_3)_4$. However, in situ catalyst formation must still occur with both Pd(0) sources, which requires the displacement of already bound ligands such as dba or PPh_3. Generally, Pd(0) sources are air-sensitive and must be stored under inert atmosphere. Pd_2dba_3 is an exception to this, as the metal center is stabilized through π-backbonding with the dba ligand. However, the strength of this interaction may actually hamper catalyst reactivity.[38,39] Furthermore, commercial sources of Pd_2dba_3 are often contaminated with unreactive Pd(0) nanoparticles, which results in the formation of a less active catalyst.[40]

Over the past two decades, several types of pre-ligated Pd precatalysts have been developed to eliminate the need for in situ catalyst formation. These include π-allyl-,[41] indenyl-,[42] and palladacycle precatalysts[43–45] for phosphine ligands (Figure 4), as well as pyridine-based complexes for NHC ligands.[46] Of the palladacycle precatalysts, complexes **G3–G5** (where **G** denotes the generation of precatalyst) are most commonly used,[15] as they accommodate a wide range of bulky phosphine ligands, are bench-stable, and provide a reliable means of rapidly generating L–Pd(0). Upon exposure to base, the nitrogen atom is deprotonated,

forming an intermediate amido complex. This complex undergoes a subsequent intramolecular C–N reductive elimination to form the corresponding carbazole and L–Pd(0) (Figure 4b). The parent carbazole byproduct (generated from **G3**-type palladacycles) can on occasion be deleterious at room temperature[41] and in certain couplings (e.g., C–F cross-coupling).[47] Palladacycles **G4** and **G5** circumvent this issue by generating *N*-substituted carbazoles, but ligands bearing large adamantyl or *tert*-butyl groups on phosphorus (e.g., **L7**, **L8**, **L18**) do not readily form these types of precatalysts.[48] These potential issues can be avoided by using the corresponding oxidative addition complexes (**G6**) or π-allyl complexes, which are easily formed with a wide range of ligands and work well in a variety of cross-coupling reactions.[49]

Complexes with formula [(1,5-cyclooctadiene)(L–Pd)$_2$] have also been developed. These precatalysts are a pre-ligated form of Pd(0) that rapidly react with aryl (pseudo)halides. However, they are often air-sensitive, exhibit poor solubility in organic solvents, and not all biaryl monophosphine ligands form precatalysts of this type.[50]

3. C–N Cross-Coupling Reactions

Nitrogen-based nucleophiles display wide variability in basicity, nucleophilicity, and steric hindrance, and thus, a diverse set of catalysts is required to facilitate optimum cross-coupling for all types of nucleophiles. Although the choice of ligand generally has the most pronounced effect on reaction outcome, the selection of base, reaction solvent, and temperature can also be critical. Our discussion of the effect of these four variables will be organized based on the subclass of nucleophile.

3.a. Secondary Amines

Both aliphatic and aromatic secondary amines are most often coupled with aryl halides using RuPhos (**L11**)-supported catalysts. Cyclic amines (pyrrolidines, piperidines) are better substrates than acyclic amines, due to their decreased steric hindrance.[51] The most common conditions use NaO*t*-Bu in THF (Figures 5, 6), but base-sensitive substrates can be more effectively coupled using Cs_2CO_3 in *t*-BuOH (Figures 5, 6).[52] Protic substrates can be coupled using excess LiHMDS in THF, as the protic functional group is protected in situ by deprotonation (Figures 7, 8).[52,53] While RuPhos (**L11**) is typically the preferred ligand for secondary amine couplings, SPhos (**L10**) and XPhos (**L1**) have also been reported to be useful (Figures 8, 9).[15,53–55]

3.a.i. Hindered Secondary Amines—The coupling of secondary amines displaying α-branching is especially challenging, likely due to the difficulty of amine binding as a result of steric hindrance around the nitrogen atom. The difficulty of this binding can result in competitive C–O coupling with NaO*t*-Bu when it is used as the base. To address this problem, **L16** and **L17** were designed; these compounds bear electron-deficient aryl groups on phosphorus which produces a more Lewis-acidic catalyst and facilitates amine binding. The use of **L16** Pd G4 and **L17** Pd G4 allowed for (hetero)aryl bromides and chlorides to be coupled with these hindered amines in good yields (Figure 10).[56]

3.a.ii. Diarylamines—Diaryl amines are relatively challenging substrates for C–N coupling due to, at least in part, their low nucleophilicity and the difficulty of reductive elimination to form triaryl amines. Indeed, mechanistic studies indicate that reductive elimination is the rate-determining step for the arylation of diarylamines with RuPhos (**L11**)-supported catalysts.[29] Nevertheless, under optimized conditions, diarylamines can be coupled with (hetero)aryl chlorides using a RuPhos (**L11**)-supported catalyst (Figure 11).[52] Similar conditions are effective for coupling weakly nucleophilic iminostilbenes and iminodibenzyls (**44**).[57] For the latter reactions, the **G4** precatalyst is superior to the **G3** precatalyst, likely because **G3** precatalysts generate carbazole, which may compete with iminostilbenes and iminodibenzyls in binding to Pd.

3.b. Primary amines

A major challenge of primary amine couplings is preventing further arylation of the product (a secondary amine). For primary alkyl and aryl amines, BrettPhos (**L6**)-supported catalysts are generally effective and give excellent selectivity for monoarylated product. The use of NaO*t*-Bu in ethereal solvents (e.g., dioxane, *n*-Bu_2O) is common. Weaker bases, such as Cs_2CO_3 and K_3PO_4, are also frequently employed in combination with a variety of solvents (e.g., *t*-BuOH, PhMe, dioxane).

3.b.i. Primary Aliphatic Amines—Primary aliphatic amines can be coupled in the presence of unprotected secondary amines. Even methylamine, the smallest primary amine substrate, can be selectively monoarylated by a variety of aryl chlorides (Figure 12).[19] As in the case of secondary amines, the use of LiHMDS allows for protic functional groups to be tolerated (Figure 13).[52]

Primary amines can also be coupled to (hetero)aryl bromides, chlorides, and triflates using a weaker base, DBU, and AlPhos (**L18**)-supported catalysts in MTBE (Figure 14). This method tolerates unprotected protic functional groups and allows highly base-sensitive substrates to be coupled, including primary alkyl halides (**64**).[58]

When the primary amine is sterically encumbered (e.g., 1-adamantylamine, tritylamine), BrettPhos-based catalysts are not efficacious. Instead, *t*-BuPhCPhos (**L12**) and CyPhCPhos (**L13**) are superior ancillary ligands. Specifically, *t*-BuPhCPhos (**L12**) is an effective ligand for unhindered aryl bromides and chlorides, whereas CyPhCPhos (**L13**) promotes couplings of *ortho*-substituted aryl bromides and chlorides (Figure 15).[59]

3.b.ii. Primary Anilines—In general, aryl amines derived from six-membered-ring (hetero)arenes couple to aryl (pseudo)halides smoothly with low catalyst loadings (Figures 16–18).[19,51,60] The use of *t*-BuBrettPhos (**L7**) as a supporting ligand and LiHMDS as the base allows unprotected five-membered heteroaryl halides to be suitable electrophiles in this type of process (Figure 19).[61]

Five-membered-ring heteroaryl amines are challenging substrates.[62] In general, AlPhos (**L18**)-supported catalysts display the most general scope (Figure 20).[58] However, other less expensive ligands are effective in certain cases. For example, *t*-BuBrettPhos (**L7**) can be used with 2-aminobenzimidazoles (Figure 21) or 2-aminothiazoles (Figure 22), but gives

low yields for some amines (e.g., 2-aminooxazoles).[20,61–64] EPhos (**L9**)-supported catalysts give good yields for aminoazoles, which is attributed to suppression of off-cycle *O*-bound complexes (Figure 23).[20]

3.c. Ammonia and Hydrazine

Monoarylation of ammonia is challenging because the products, primary (hetero)aryl amines, are competent nucleophiles which can competitively undergo a second arylation to form diarylamines. Many methods have circumvented this problem by using an ammonia surrogate like benzophenone imine or LiHMDS, producing a protected product that is transformed into the desired primary (hetero)aryl amine after the coupling reaction is complete.[51]

However, recent advances in ligand design from our group[65] and others[8,66] have enabled the direct monoarylation of ammonia. In the case of dialkyl biaryl monophosphines, ligands with larger alkyl groups on phosphorus, like AdBrettPhos (**L8**) and Me_3(OMe)XPhos (**L3**), are effective at suppressing diarylation (Figure 24). In particular, Me_3(OMe)XPhos (**L3**) is superior for six-membered (hetero)arenes, whereas AdBrettPhos (**L8**) is best for five-membered heteroarene couplings. A third ligand, Me_3(OMe)PhXPhos (**L5**), works well for *ortho*-substituted substrates. A typical reaction employs NaO*t*-Bu as the base and dioxane as the solvent. Commercially available solutions of ammonia in dioxane were found to be suitable for this reaction.[65]

Hydrazine presents similar challenges, as the product arylhydrazine can undergo a subsequent arylation at either nitrogen atom. Furthermore, hydrazine is a potential explosive, particularly in the presence of transition metals.[67] Although benzophenone hydrazone can in some cases be employed as a stable hydrazine surrogate, access to unprotected arylhydrazines permits facile synthesis of a wider variety of heterocycles and hydrazones.[68]

As in the case of ammonia, the use of large alkyl groups on phosphorus is needed to suppress diarylation. In order to perform this reaction more safely, the cross-coupling was conducted using continuous flow technology. The combination of *t*-BuBrettPhos (**L7**) Pd G1 and NaO*t*-Bu in THF selectively and rapidly couples hydrazine (as a solution in THF) with aryl chlorides. The resulting arylhydrazines were directly used in a condensation reaction to form the corresponding hydrazone, pyrazole, or indole (Figure 25).[67]

3.d. Amides, Ureas, Carbamates, and Sulfonamides

The coupling of amides, ureas, carbamates and sulfonamides can generally be achieved with phosphine ligands bearing larger groups (i.e., 1-adamantyl or *t*-Bu) on phosphorus. The combination of weak inorganic bases (e.g., Cs_2CO_3, K_3PO_4) in *t*-BuOH is most commonly employed.

3.d.i. Primary Amides—*t*-BuBrettPhos (**L7**)- and Me_4*t*-BuXPhos (**L14**)-supported catalysts can couple primary amides with aryl (pseudo)halides (Figures 26, 27).[69–71] Amides are inherently weak nucleophiles, and consequently aryl chlorides, triflates, and mesylates are superior to bromides and iodides for this reaction, since the Pd(II) complexes formed by oxidative addition are more electrophilic.[69] Catalysts based on **L7** and **L14** also prevent the

formation of κ^2-amidate complexes, which are known to cause catalyst decomposition.[69–71] In cases where both catalysts give product, the use of *t*-BuBrettPhos (**L7**) is recommended, since reactions tend to be substantially faster than with Me_4*t*-BuXPhos (**L14**).[71]

t-BuBrettPhos (**L7**)- and Me_4*t*-BuXPhos (**L14**)-supported catalysts are unable to couple primary amides to five-membered heteroaryl bromides. However, this transformation can be realized by using an AdBrettPhos (**L8**)-supported catalyst system (Figure 28). The increase in reactivity is attributed to the bulkier alkyl groups on phosphorus, which promote the challenging reductive elimination of small electron-rich heterocycles.[72] As is the case for primary anilines, AlPhos (**L18**)-supported catalysts (with DBU in MTBE) are effective for the amidation of a range of aryl electrophiles, including five-membered-ring heterocycles (Figure 29).[58]

The Pd-catalyzed amidation reaction can be applied to a one-pot synthesis of substituted *N*-aryl benzimidazoles. Anilines and primary amides are coupled to 1,2-dihaloarenes using *t*-BuBrettPhos (**L7**)-derived catalysts, Cs_2CO_3, and *t*-BuOH. The *bis*-coupled product condenses intramolecularly to give benzimidazoles in good yield (Figure 30). When different halides are used (e.g., 1-bromo-2-chlorobenzene), the weakest carbon–halogen bond undergoes coupling first, and since the more nucleophilic aniline couples before the less nucleophilic primary amide, the final product is formed with complete regiocontrol.[73]

3.d.ii. Secondary Amides—Cyclic secondary amides (i.e., lactams) and *N*-methyl amides can be coupled to aryl chlorides and triflates with catalysts derived from AlPhos (**L18**) or Me_4*t*-BuXPhos (**L14**) (Figure 31). As with cyclic secondary amines, the cyclic nature of lactams is thought to "tie back" the *N*-alkyl substituent, allowing for a more facile transmetalation.[58,69]

Me_4*t*-BuXPhos (**L14**), *t*-BuBrettPhos (**L7**), and AlPhos (**L18**) are unable to couple most acyclic secondary amides (namely, amides larger than *N*-methyl amides). Instead, a JackiePhos (**L15**)-supported catalyst can be employed, along with K_2CO_3 or Cs_2CO_3 and 3 Å molecular sieves in toluene (Figure 32). The electron-deficient phosphine is thought to promote binding of nitrogen and thereby accelerate transmetalation. Under these conditions, aryl nonaflates, triflates, and chlorides can be coupled; however, the use of aryl bromides and iodides appear to inhibit transmetalation and thus, these electrophiles are unsuitable reaction partners.[74]

3.d.iii. Ureas, Carbamates, and Sulfonamides—Ureas, carbamates, and sulfonamides react similarly to amides. Primary ureas and carbamates can be coupled when AlPhos (**L18**)[58] or *t*-BuBrettPhos (**L7**)[75] are used as supporting ligands (Figures 33, 34). Primary sulfonamides are suitable nucleophiles when *t*-BuBrettPhos (**L7**) is employed (Figure 35),[76] although *t*-BuXPhos (**L2**) has also shown promise as an ancillary ligand.[77]

Secondary acyclic ureas, carbamates, and sulfonamides can be coupled to aryl triflates, chlorides, and nonaflates using a JackiePhos (**L15**)-supported catalyst (Figure 36).[74] As in the case of secondary amides, the effectiveness of **L15** can be attributed to the electron-

withdrawing aryl groups on phosphorus, which enhance the Lewis acidity of palladium and thereby promote the binding of these weak nucleophiles.

3.e. Imidazoles and Triazoles

Using catalysts derived from Me_4*t*-BuXPhos (**L14**) or Me_3(OMe)*t*-BuXPhos (**L4**), substituted imidazoles and benzimidazoles can be regioselectively arylated at the less hindered position with aryl bromides, chlorides, and triflates (Figure 37). Imidazoles are potent catalyst poisons, and therefore, pre-complexation of ligand and palladium (by preheating ligand and Pd_2dba_3, or by using a precatalyst) is necessary for high and reproducible yields.[78,79] These conditions are suitable for the *N*2-arylation of 1,2,3-triazoles, although benzotriazoles give a nearly 1:1 mixture of *N*1 and *N*2 isomers (Figure 38).[80]

4. Conclusion

Palladium catalysis is a versatile tool for constructing carbon–nitrogen bonds under mild conditions. The palladium source, supporting ligand, base, temperature, and solvent all have an effect on the reaction outcome. Furthermore, these variables often strongly influence each other: for instance, the choice of ligand may affect the optimal base for a particular process. A summary of each of the effects of these variables in the context of C–N coupling reactions is presented below.

Palladium source:

The use of precatalysts is recommended when possible in order to reliably and rapidly generate L–Pd(0). With precatalysts, many nitrogen nucleophiles can be coupled under mild conditions with low catalyst loadings.[51] In cases where a precatalyst is not available, it is recommended to use a known procedure to ensure that Pd(0) is formed, such as the water-mediated reduction of $Pd(OAc)_2$.[37]

Base:

The most widely used base for C–N coupling is NaO*t*-Bu, which typically allows for fast reactions and low catalyst loadings. Occasionally, other strong bases are used, such as LiHMDS. This can be advantageous when protic functional groups (e.g., carboxylic acids, amides, alcohols, indoles, etc.) are present, as initial deprotonation “protects” the functional group, allowing for subsequent C–N coupling.[81–83]

However, the use of a strong base can cause undesired side reactions or, in combination with amines, the decomposition of certain substrates.[84] In these cases, weak inorganic bases (e.g., Cs_2CO_3, K_3PO_4, K_2CO_3) allow for broader functional group tolerance. Cs_2CO_3 gives the fastest reaction rate of the weak inorganic bases, likely owing to the greater solubility of cesium salts in organic solvents compared to smaller alkali metals, but it is also more expensive and hygroscopic. These bases are typically mostly insoluble in the reaction mixture, and catalyst turnover can therefore be dependent on particle size. On large scales, this can lead to reproducibility challenges. Furthermore, reactions using weak bases are generally slower and require higher catalyst loadings.[51]

Catalysts supported by AlPhos (**L18**) are able to couple a broad range of primary amines and amides to a wide variety of (hetero)aryl electrophiles using DBU as the base. This reaction exhibits excellent functional group tolerance due to the low basicity of DBU.[58]

Temperature:

Most C–N coupling reactions with moderately complex substrates proceed at or above 60 °C. Although in many cases the on-cycle elementary steps are likely fast at room temperature, higher temperatures allow the palladium catalyst to be active in the presence of coordinating functional groups (e.g., pyridines, nitriles). Typical reaction temperatures used for the coupling of aliphatic or aromatic amines are around 80 °C, but there are instances where the temperature can be decreased if necessary. For instance, if the starting materials are thermally unstable, lower temperatures in combination with higher catalyst loadings will often give a better result. In contrast, challenging couplings involving a weak inorganic base or hindered nucleophiles require high temperatures (>100 °C) for catalytic turnover.

Solvent:

Palladium-catalyzed C–N coupling has been reported in a variety of solvents, including alcohol solvents (e.g., *t*-BuOH, *t*-AmOH), ethereal solvents (e.g., THF, 1,4-dioxane, 2-MeTHF, *tert*-butyl methyl ether), and aromatic solvents (e.g., toluene).[15,51] However, there are some notable exceptions. Chlorinated solvents (e.g., chloroform) have been reported to react with certain Pd(0) sources to form off-cycle oxidative addition complexes, and they are therefore undesirable.[50] Strongly coordinating solvents, like acetonitrile or pyridine, inhibit amine coordination by competitively binding palladium. Finally, the solubility of the reactants can be low in nonpolar solvents (e.g. pentane, hexane), hindering reaction progress. The importance of the latter consideration cannot be overstated. *It is essential that the substrates be soluble in the reaction mixture. Insolubility is one of the most common reasons that reactions fail to give good yields of products.*

Ligand:

Ligand choice tends to have the most pronounced effect on reaction outcome since changing the ancillary ligand modifies the catalyst structure. The appropriate ligand for a given reaction is determined largely by the class of nucleophile. For the coupling of primary amines, BrettPhos (**L6**) is most often employed, although AlPhos (**L18**) works well for challenging electrophiles (e.g., five-membered heterocycles).[51,58] RuPhos (**L11**)-based catalysts efficiently couple a variety of secondary amine nucleophiles.[51] For less nucleophilic compounds, such as amides, larger ligands like *t*-BuBrettPhos (**L7**), AdBrettPhos (**L8**) or AlPhos (**L18**) are used.[51,58,61] Ultimately, the choice of ligand will also depend on the intended application: while the AlPhos (**L18**)-supported catalyst displays excellent functional group tolerance in many C–N coupling reactions, it is employed in higher loading, and the ligand is more expensive than BrettPhos (**L6**), *t*-BuBrettPhos (**L7**), or AdBrettPhos (**L8**).[58]

To summarize this work and to aid in selecting an appropriate ligand for a given reaction, we have developed a flowchart organized based on nucleophile (Figure 39). The ligands listed in each box are listed in order of (i) most effective ligand for the transformation and (ii)

commercial availability. Listed beneath each box are the corresponding references. We hope the community finds this organizational flowchart useful, although we note that this updated user's guide cannot replace the vast wealth of chemical literature on Pd-catalyzed C–N cross-coupling. A concise summary of the material addressed in this manuscript, in addition to the flowchart in Figure 39, can be found in the supplementary information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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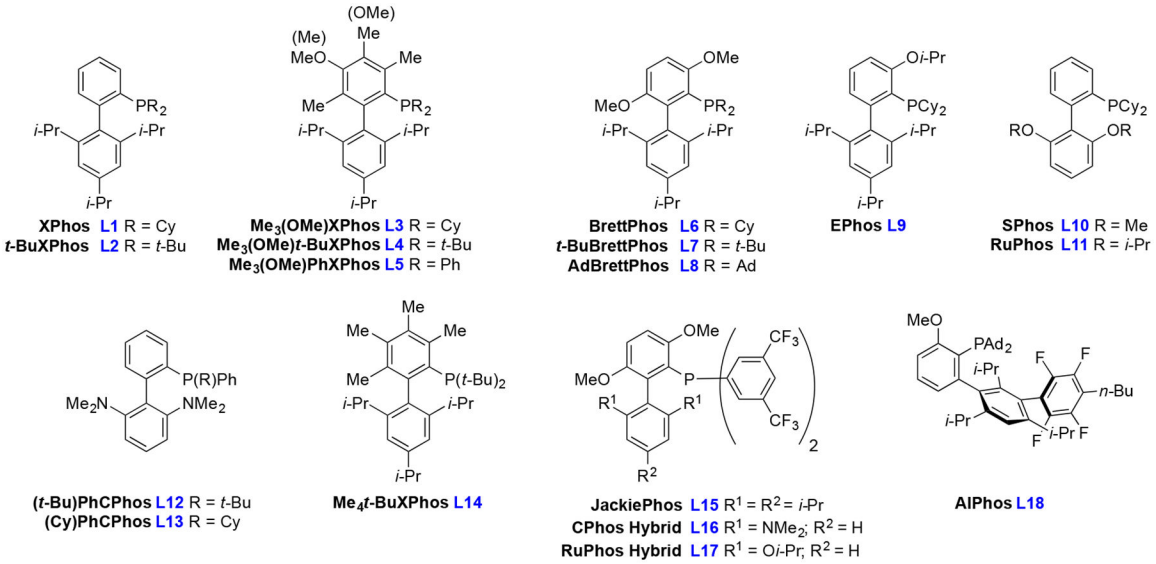


Figure 1.
Examples of biaryl monophosphine ligands.

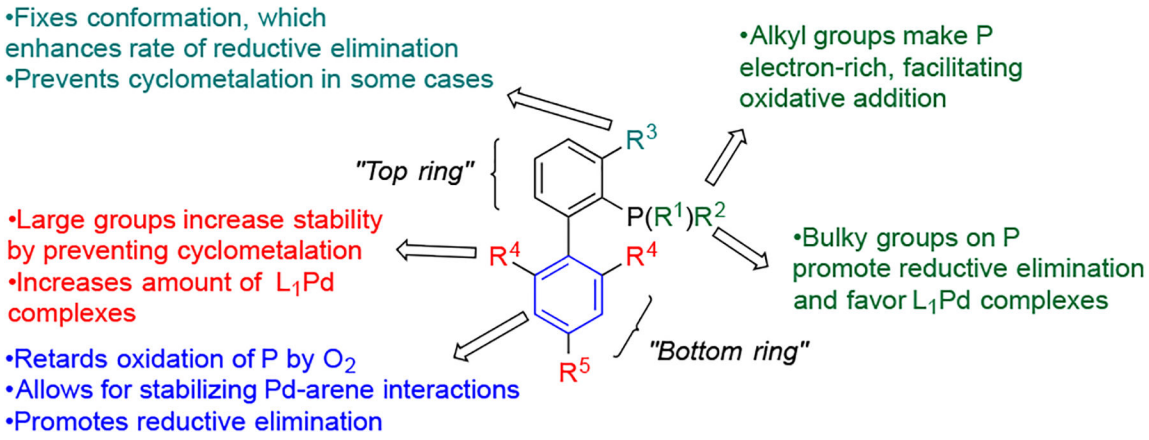


Figure 2.
Features of dialkyl biaryl monophosphines.

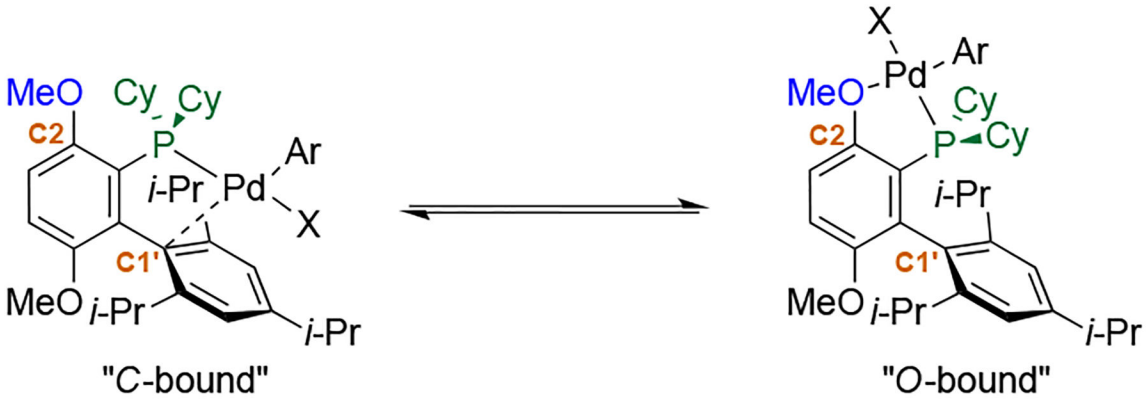


Figure 3.
Binding modes of BrettPhos (**L6**).

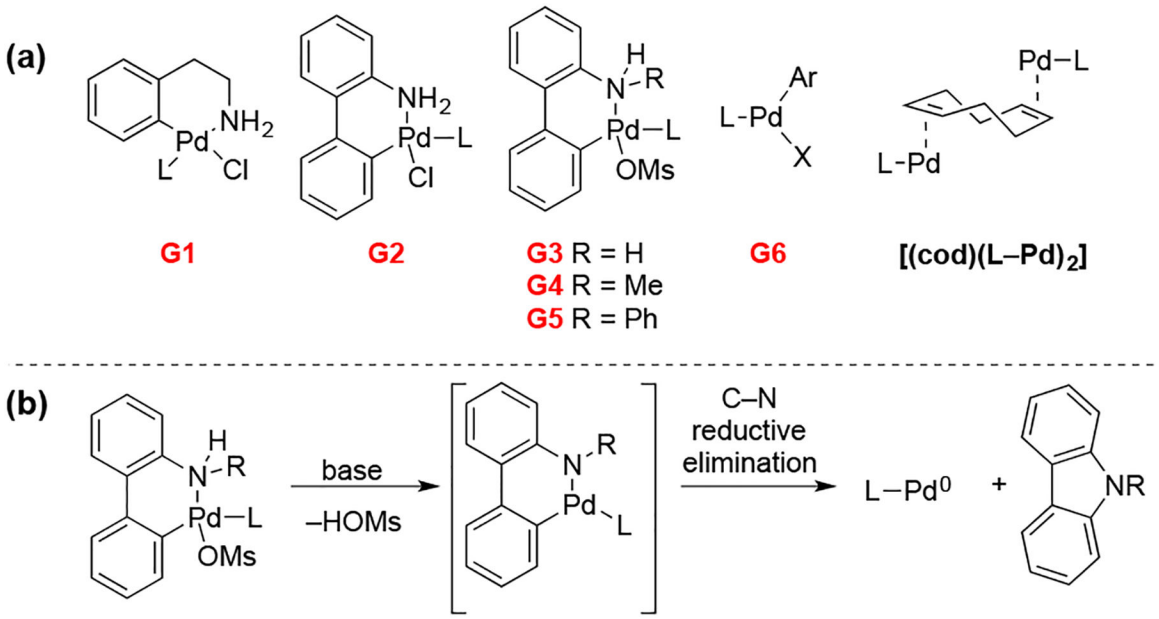


Figure 4.

(a) Pre-ligated palladium precatalysts.[45,48–50] (b) Base-mediated activation of palladacycle precatalysts.

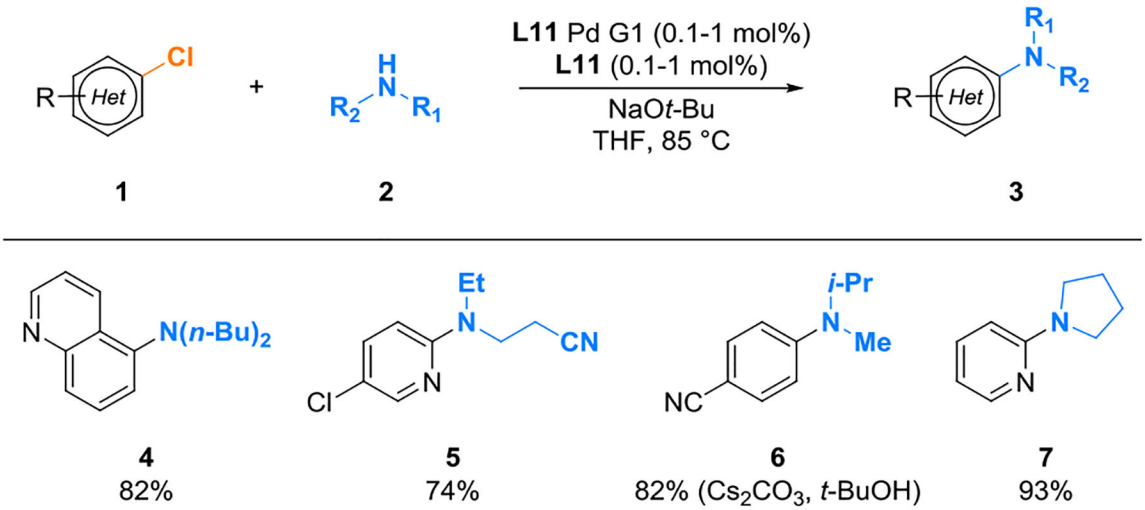


Figure 5.

RuPhos-supported catalysts can couple cyclic and acyclic secondary amines to aryl chlorides.[52]

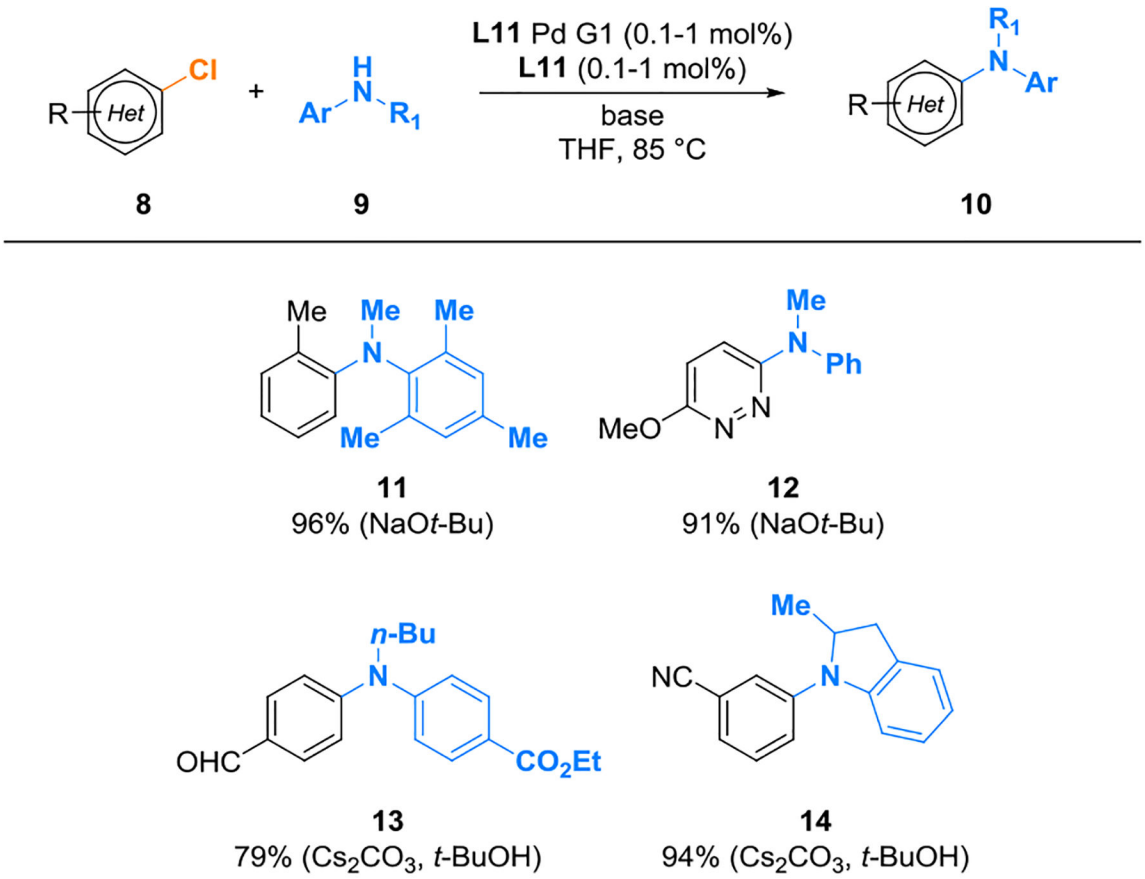


Figure 6.
Coupling of aryl alkyl amines with RuPhos-supported catalysts.[52]

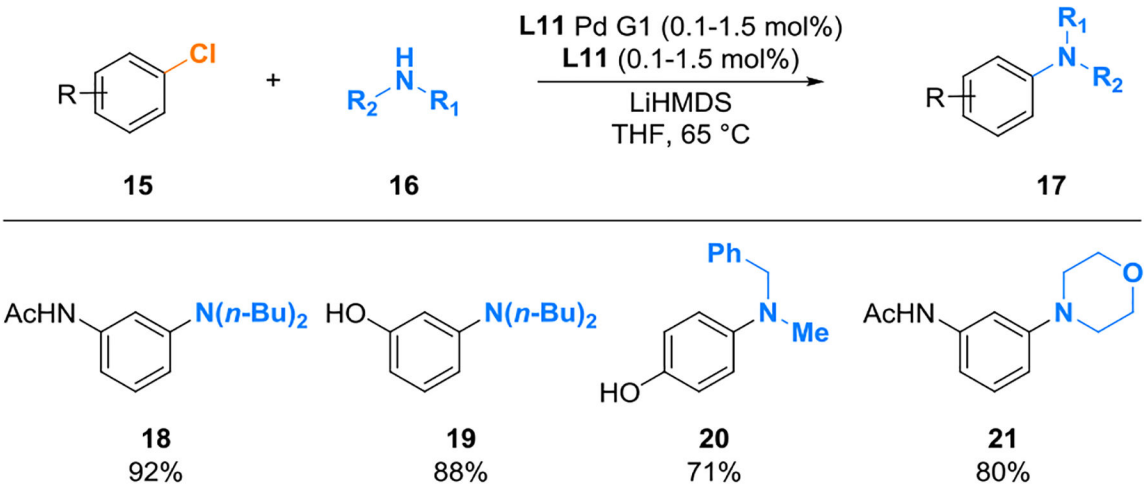


Figure 7.
LiHMDS allows protic functional groups to be tolerated in the coupling of secondary aliphatic amines.[52]

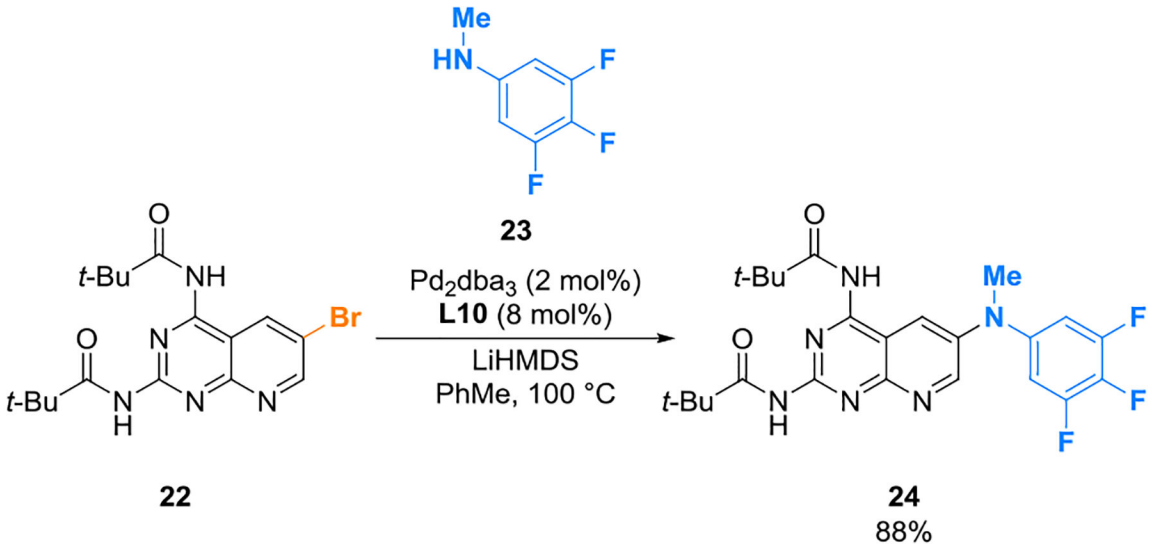


Figure 8.
LiHMDS enables the coupling of a complex aryl bromide.[53]

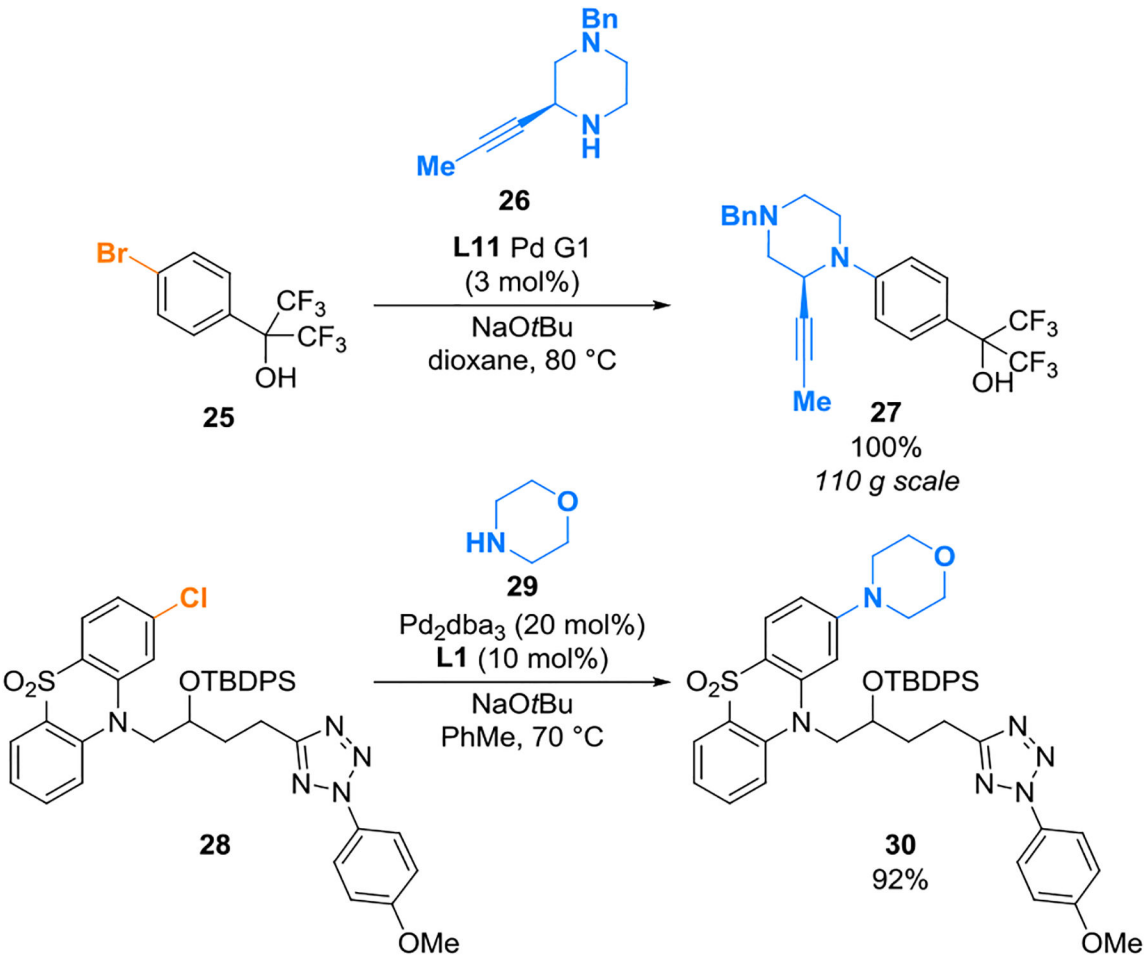


Figure 9.
C–N coupling of secondary aliphatic amines with complex electrophiles.[54,55]

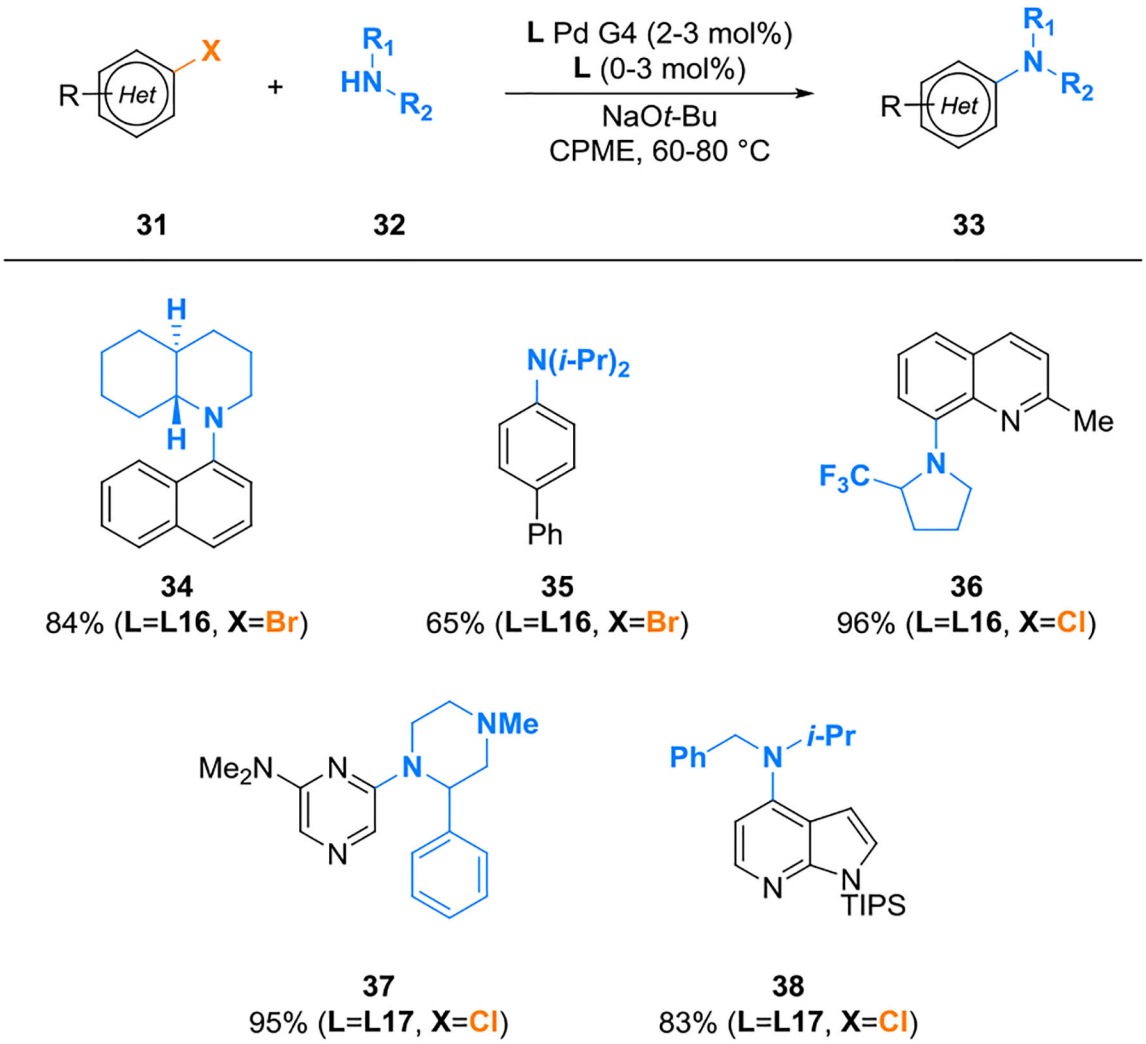


Figure 10.
Coupling of α-branched secondary amines.[56]

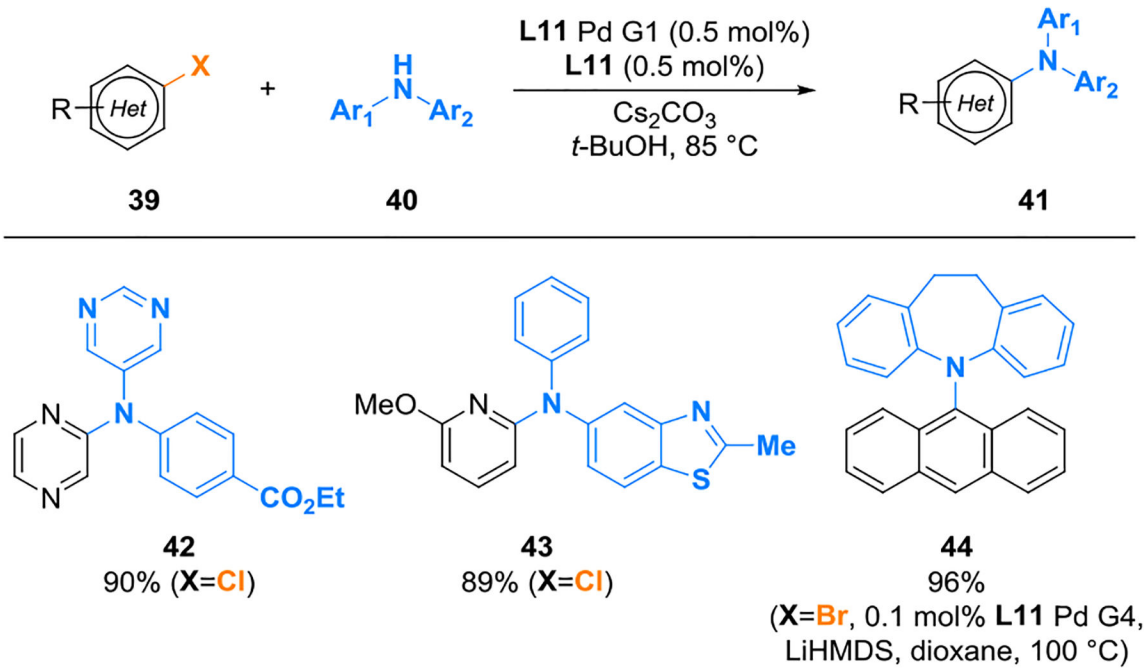


Figure 11.
RuPhos-supported catalysts allow the arylation of diarylamines.[52,57]

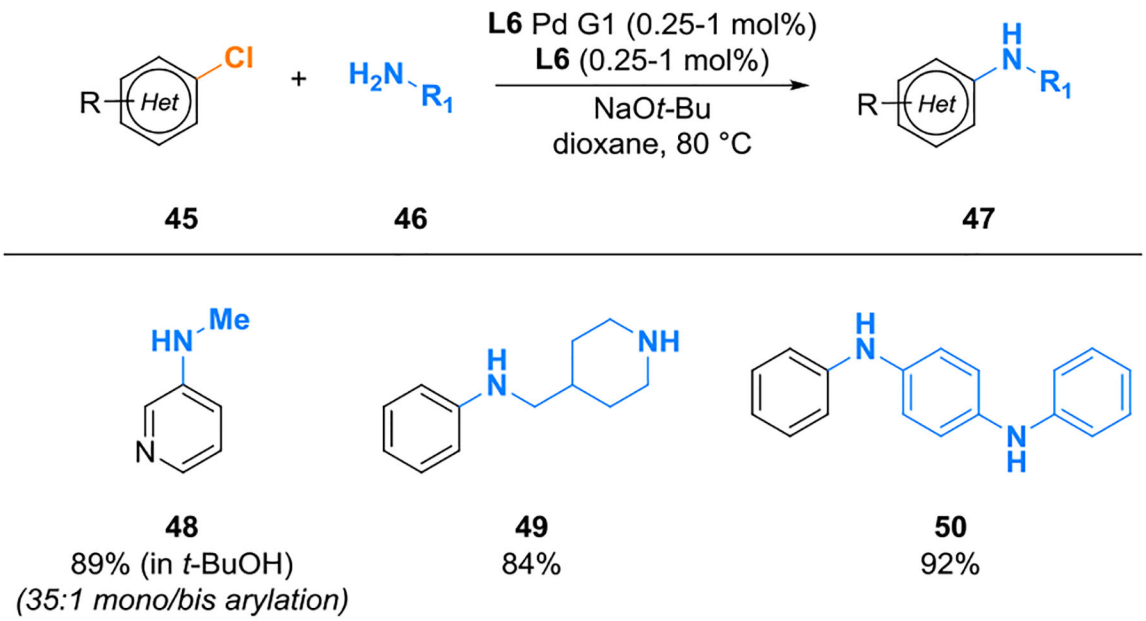


Figure 12.
BrettPhos enables selective coupling of primary amines in the presence of secondary amines.[19]

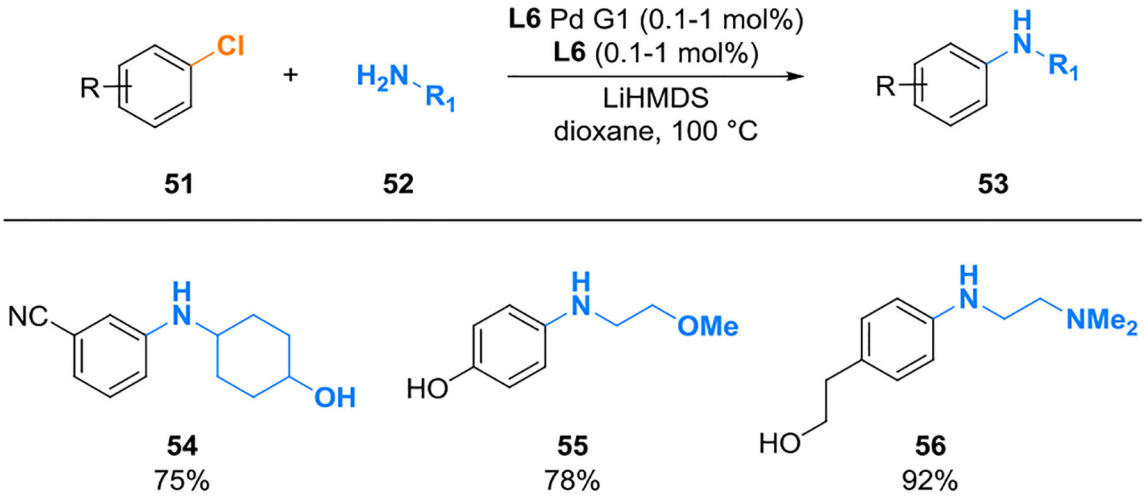


Figure 13.
LiHMDS enables C–N coupling of primary amines in the presence of alcohols.[52]

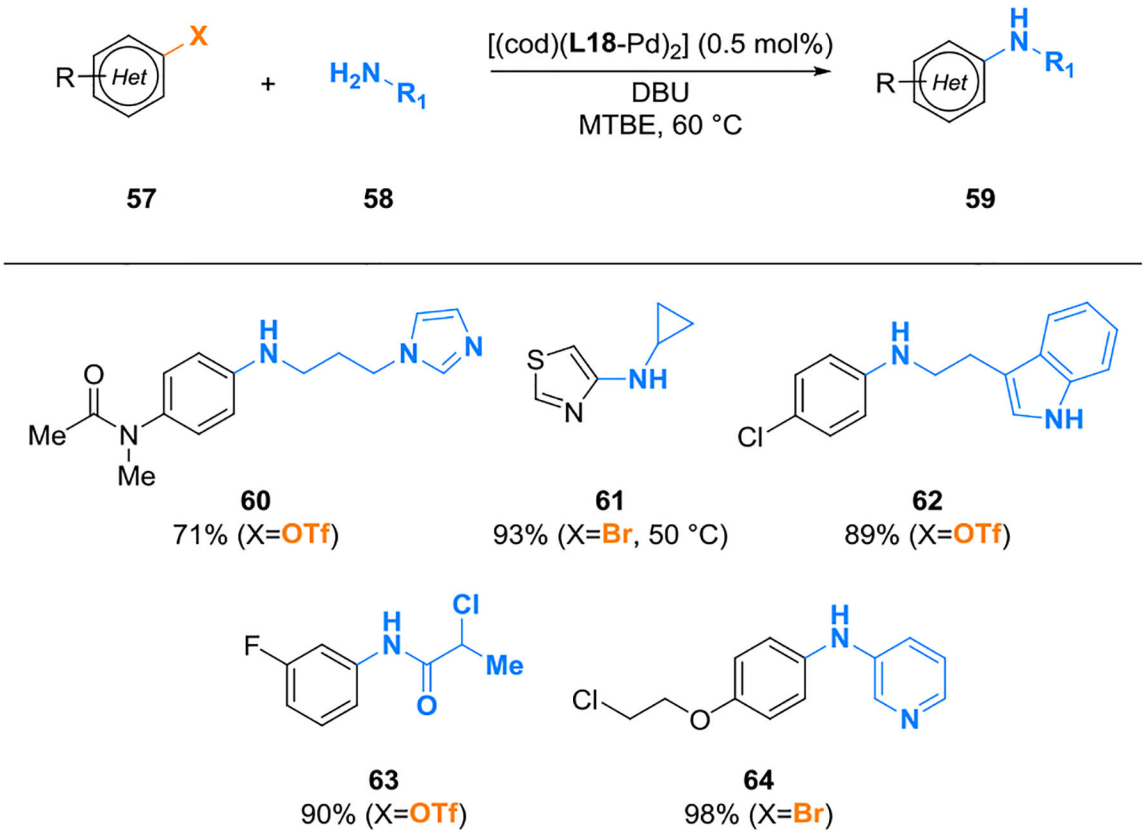


Figure 14.

Coupling primary amines and base-sensitive substrates using DBU and an AlPhos-supported catalyst.[58]

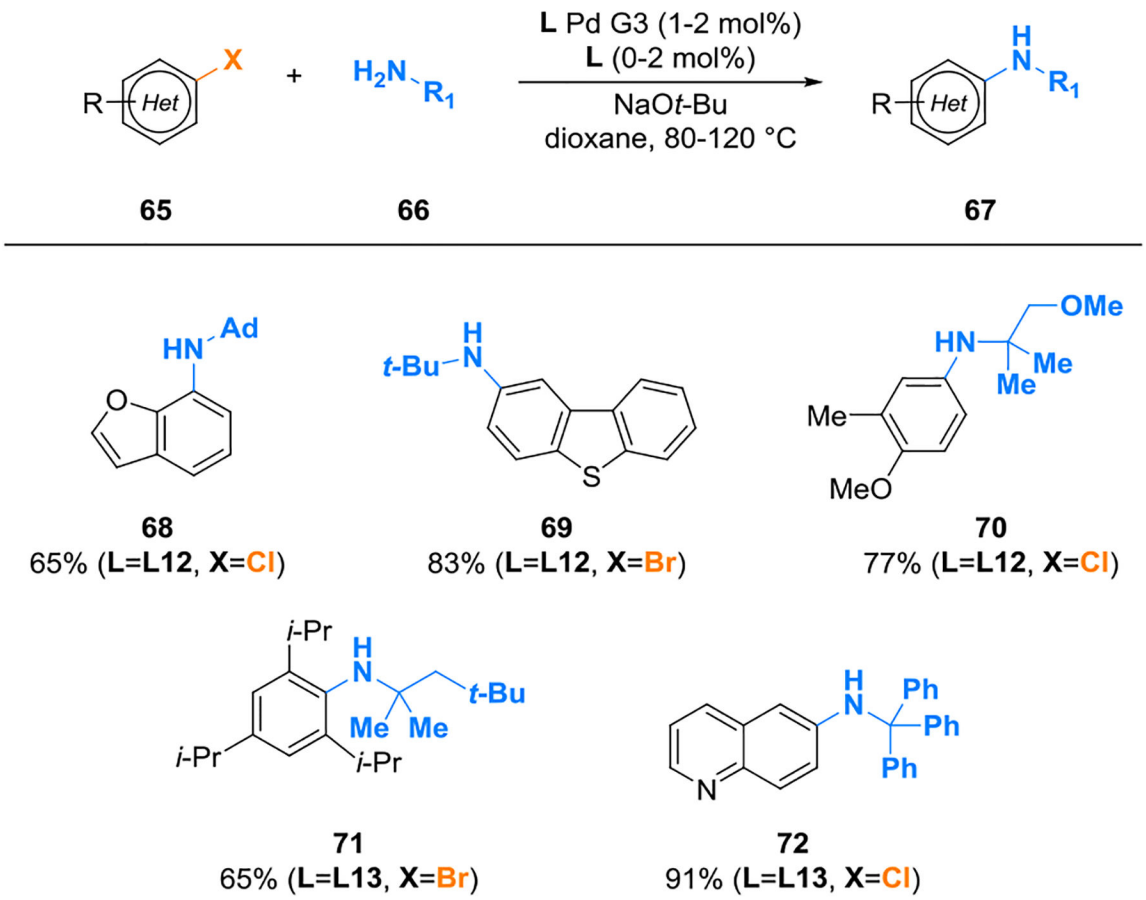


Figure 15.

t-BuPhCPhos and CyPhCPhos enable coupling of highly hindered primary aliphatic amines.[59]

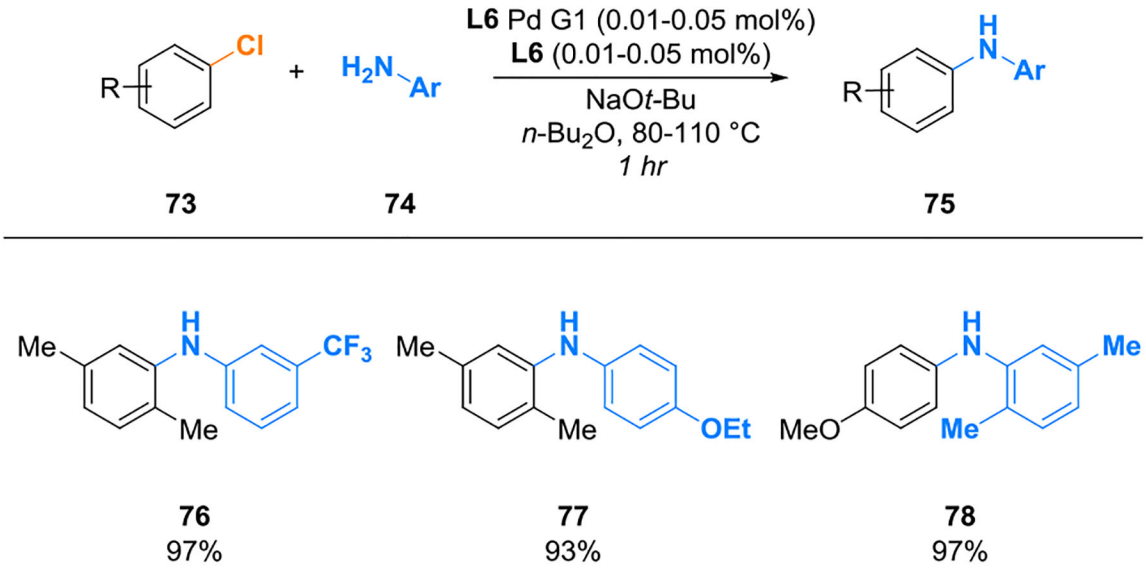


Figure 16.

BrettPhos-supported catalysts couple primary anilines to aryl chlorides with low catalyst loadings.[19]

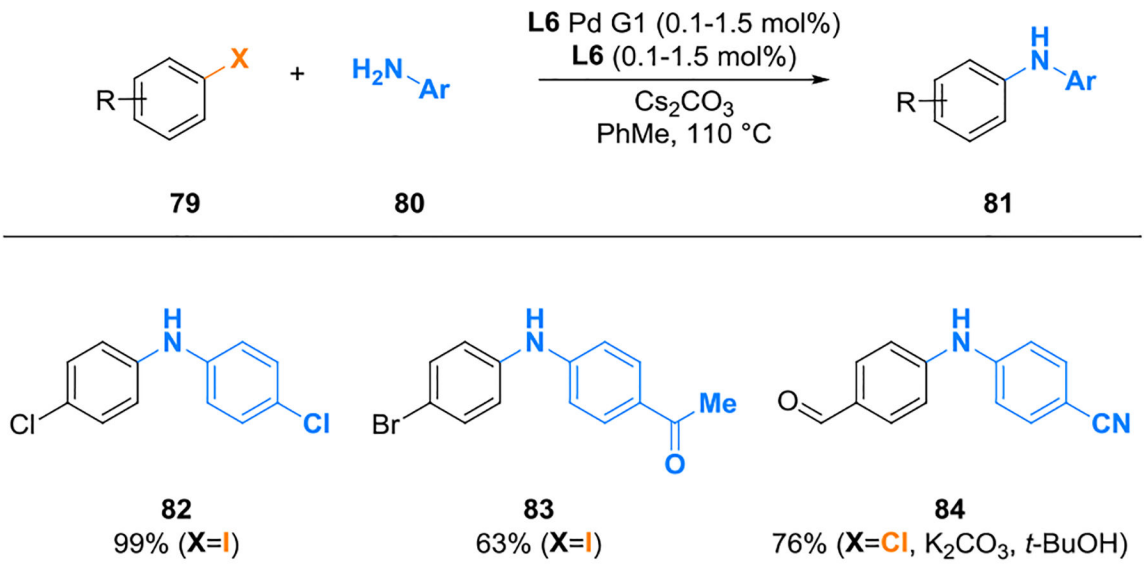


Figure 17.
BrettPhos-supported catalysts couple functionalized aryl halides and aryl amines using Cs_2CO_3.[51]

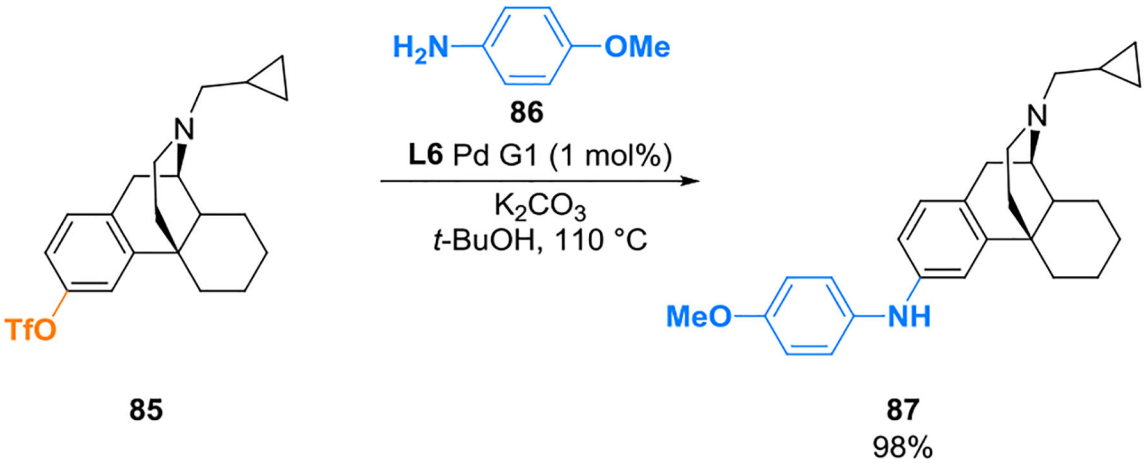


Figure 18.
A BrettPhos-derived precatalyst enables the efficient amination of an aryl triflate.[60]

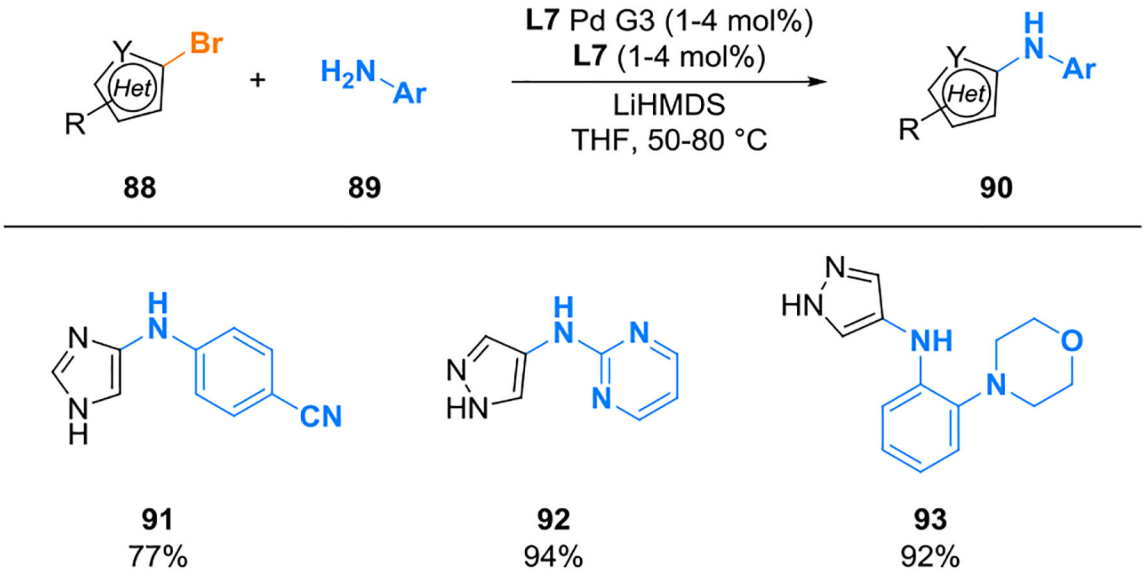


Figure 19.

With LiHMDS, *t*-BuBrettPhos-supported catalysts couple primary amines to unprotected five-membered imidazole and pyrazole bromides.[61]

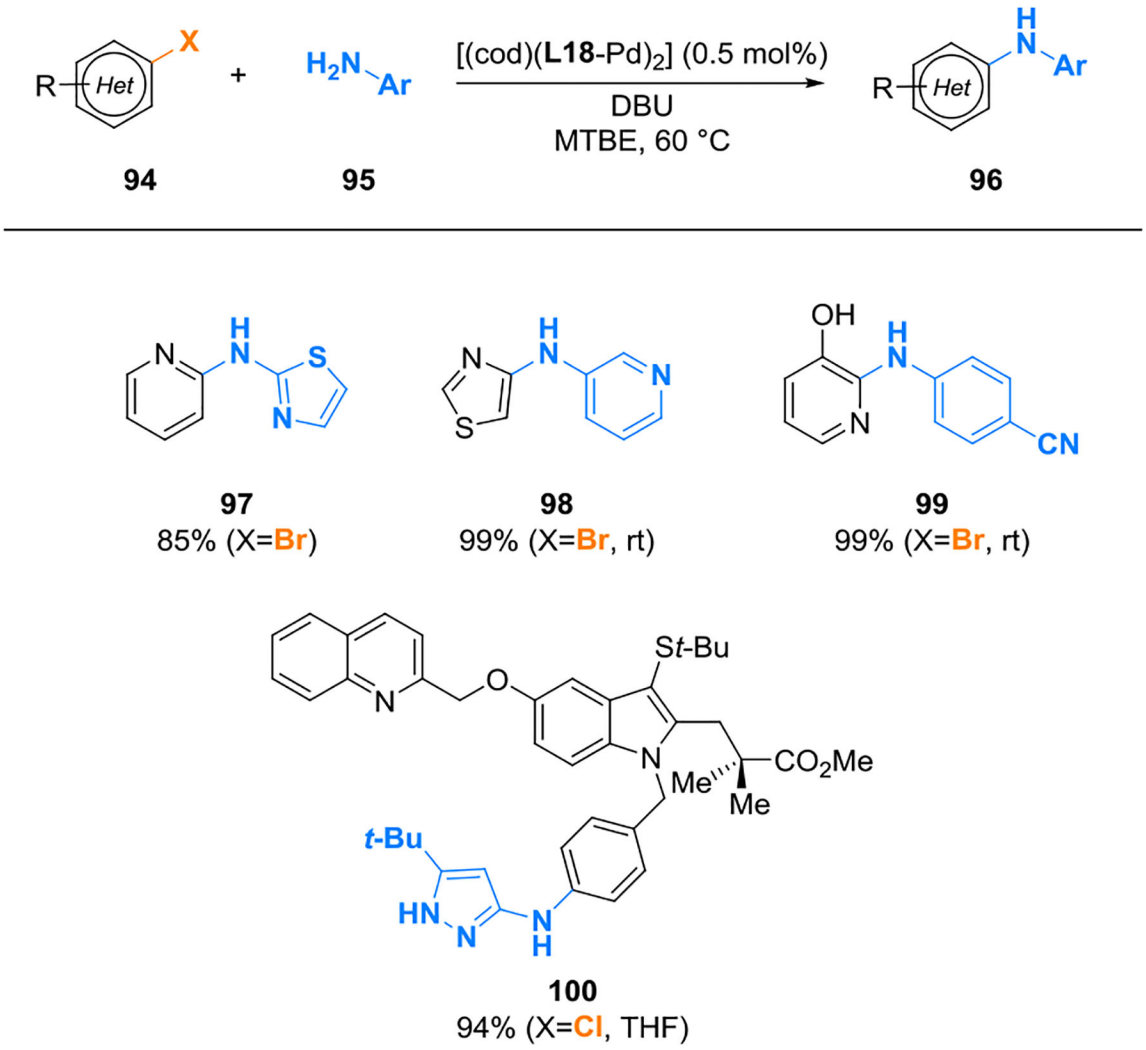


Figure 20.

AlPhos-supported catalysts can couple a diverse range of heteroaryl halides and amines.[58]

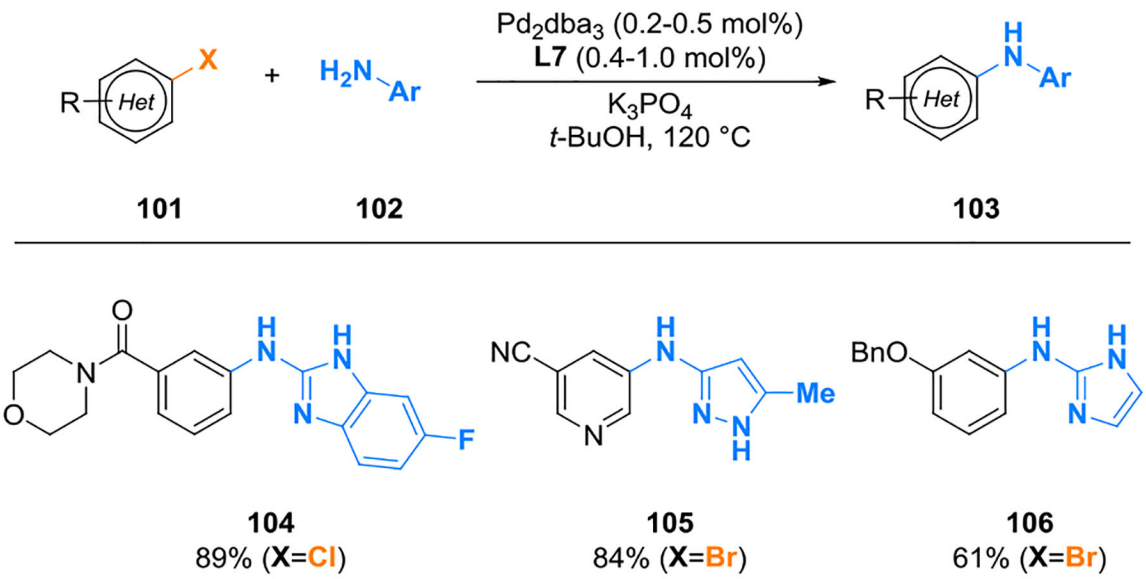


Figure 21.

t-BuBrettPhos-supported catalysts can couple 2-aminoimidazoles and benzimidazoles to aryl halides.[63]

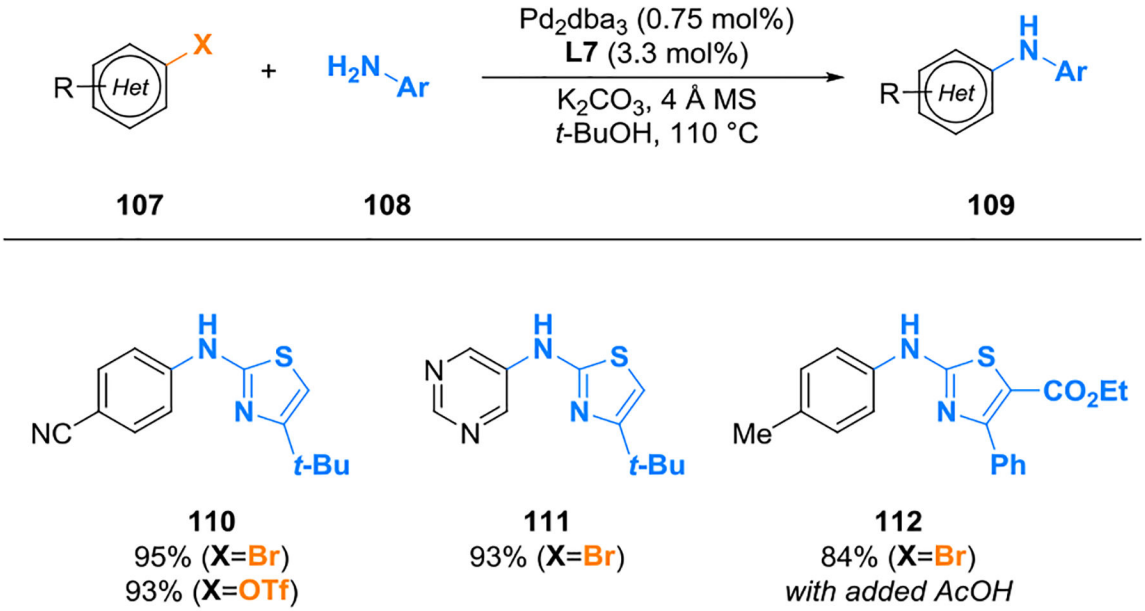


Figure 22.
t-BuBrettPhos-supported catalysts can arylate 2-aminothiazoles.[64]

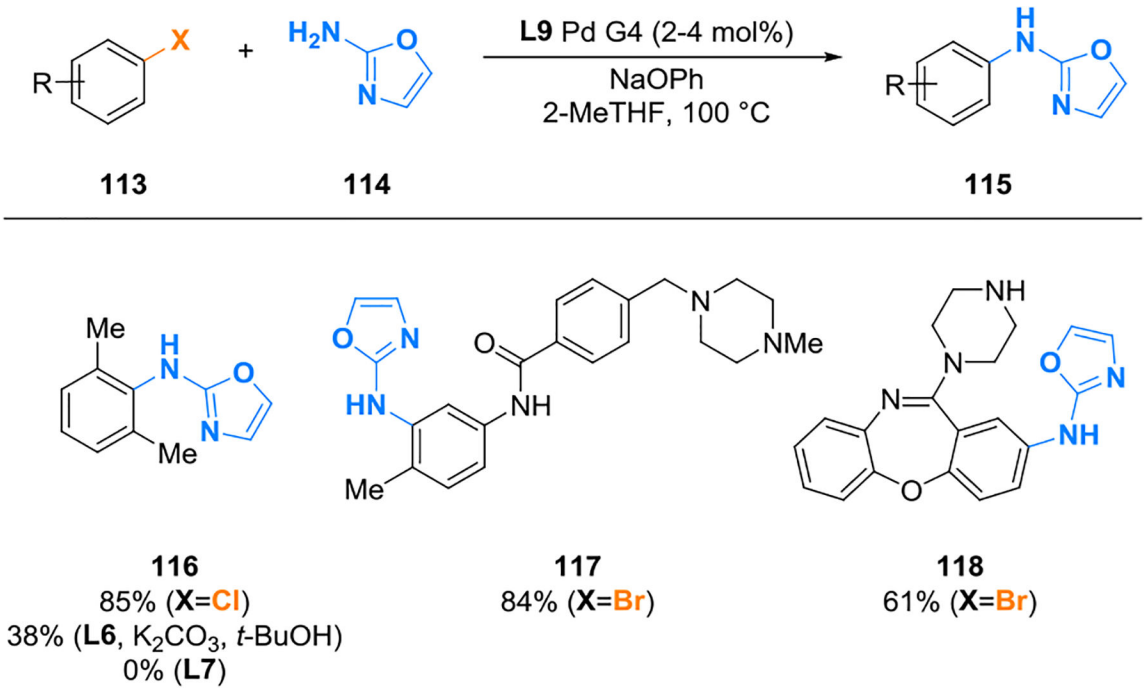


Figure 23.
EPhos enables arylation of 2-aminooxazole, a challenging nucleophile.[20]

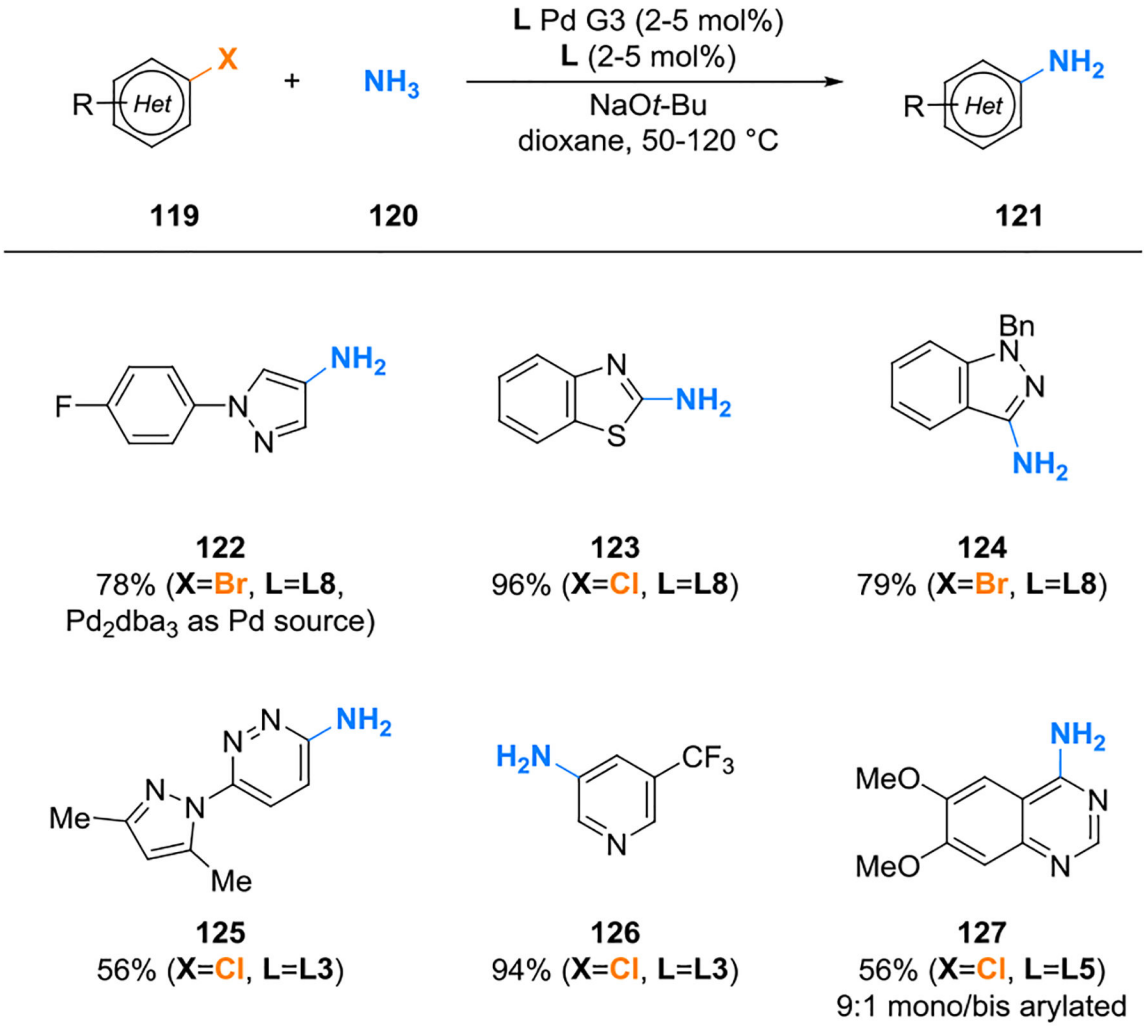


Figure 24.
Ammonia can be monoarylated by five- and six-membered arenes and heteroarenes.[65]

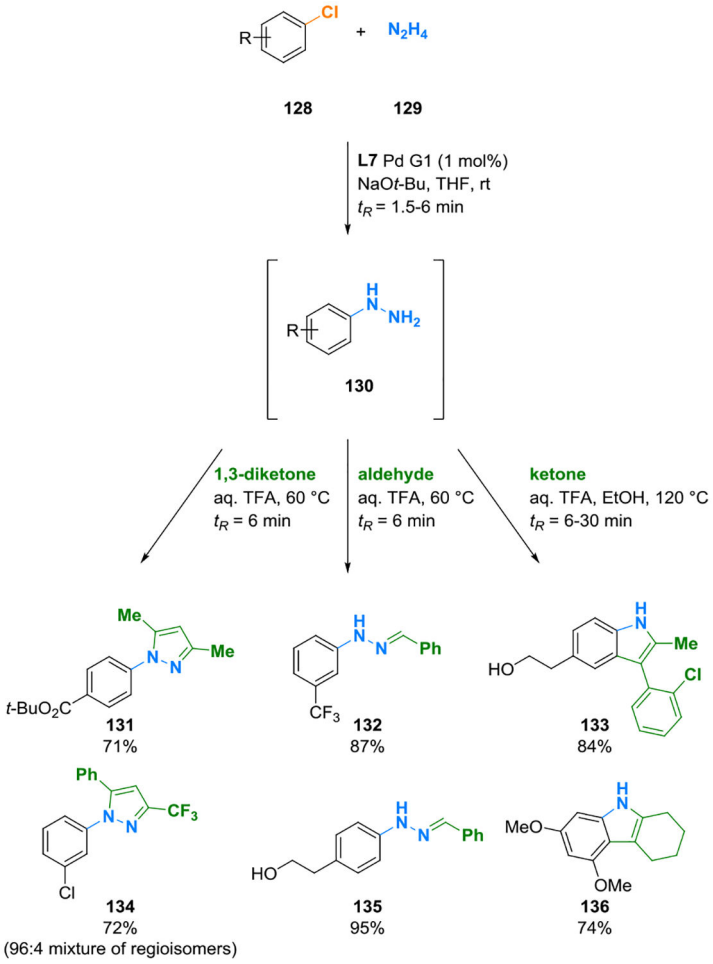


Figure 25.

Coupling of hydrazine to aryl chlorides, and subsequent formation of azoles and hydrazones under continuous flow conditions.[67]

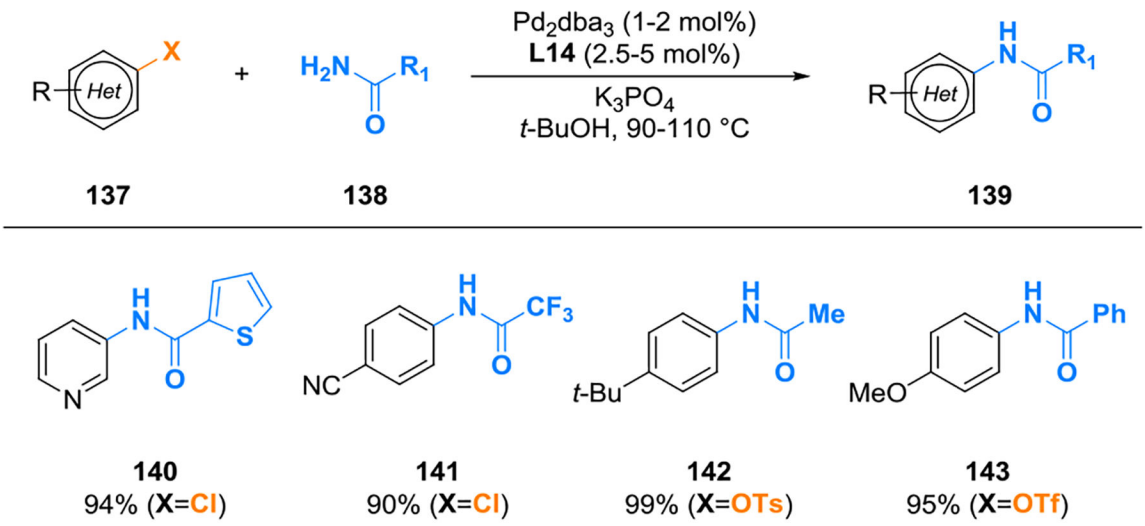


Figure 26:
Me_4*t*-BuXPhos-supported catalysts couple aryl (pseudo)halides with primary amides[69]

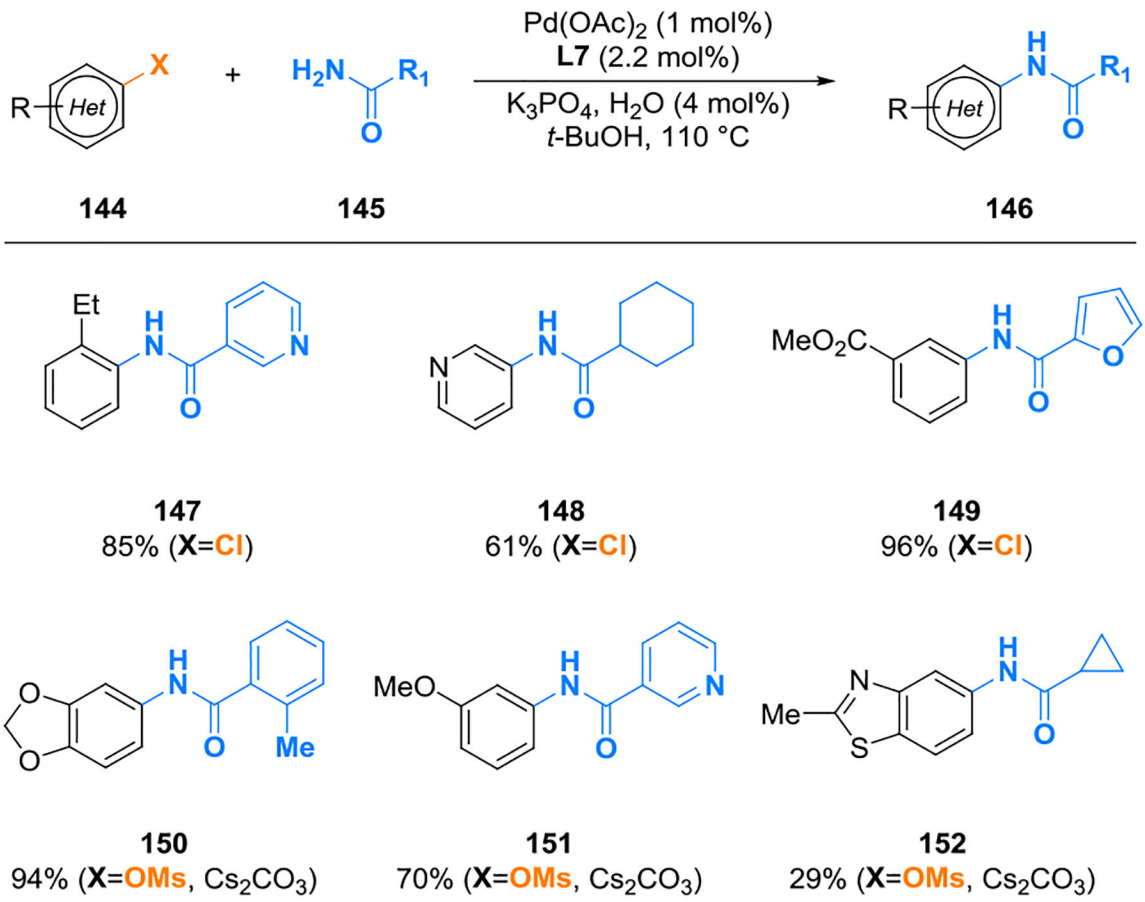


Figure 27.

t-BuBrettPhos-supported catalysts couple aryl chlorides and mesylates with primary amides.
70–71

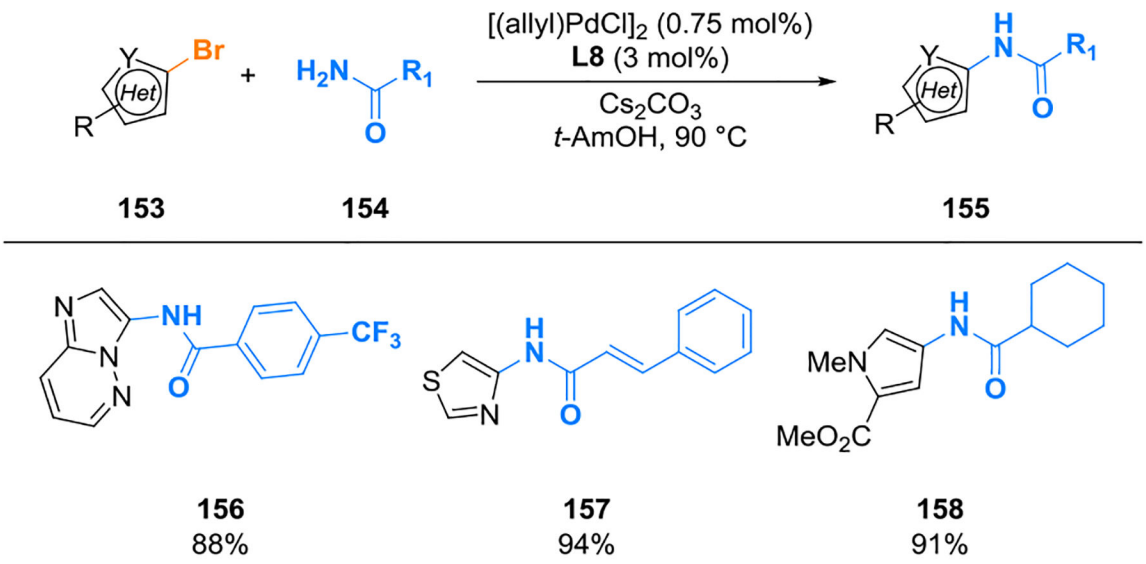
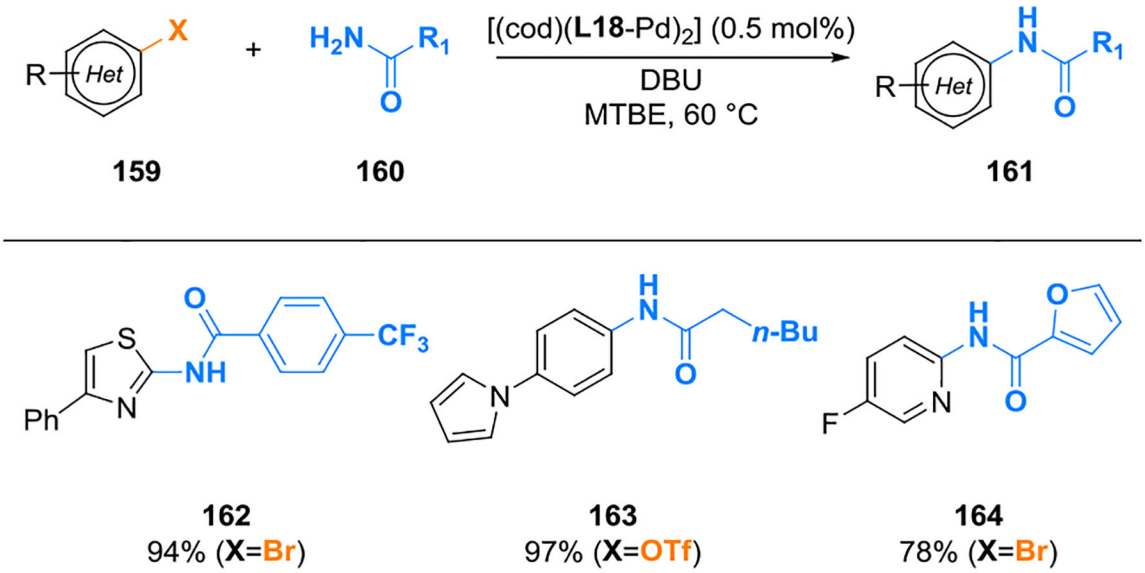


Figure 28.

AdBrettPhos-supported catalysts can couple primary amides to five-membered-ring heteroaryl bromides.[72]



162
94% (**X**=**Br**)

163
97% (**X**=**OTf**)

164
78% (**X**=**Br**)

Figure 29.
AlPhos enables coupling of primary amides with diverse heteroaryl (pseudo)halides.[58]

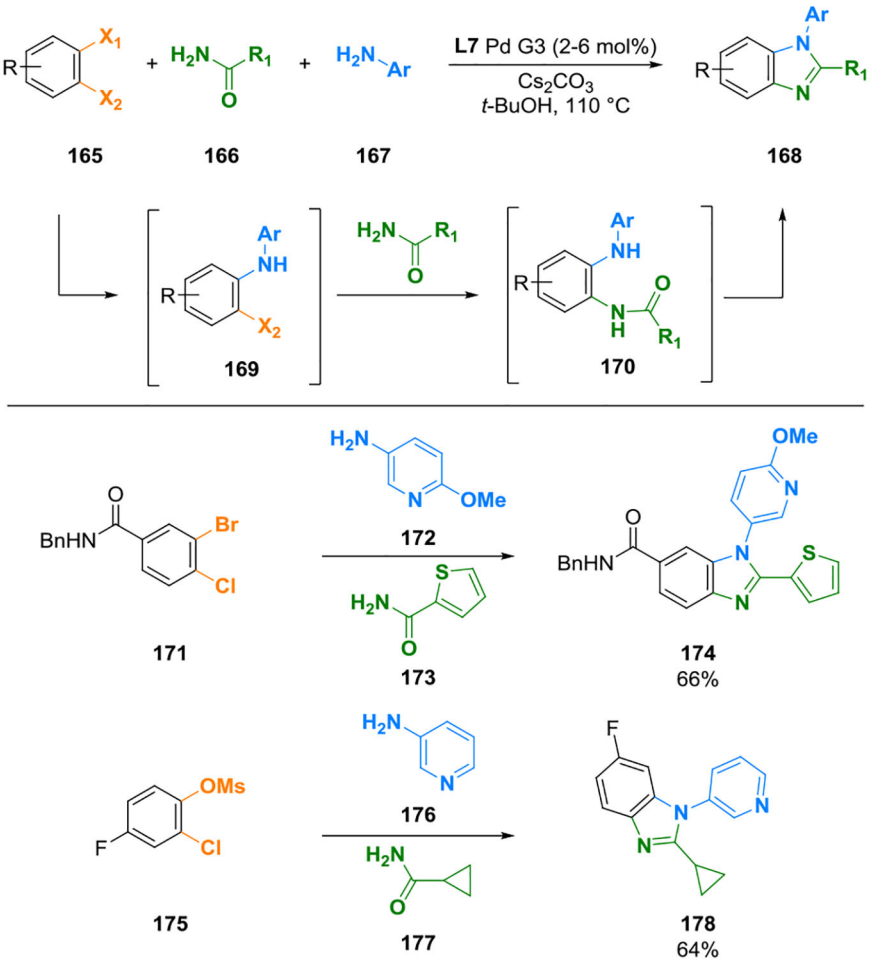


Figure 30.
t-BuBrettPhos enables the synthesis of *N*-aryl benzimidazoles.[73]

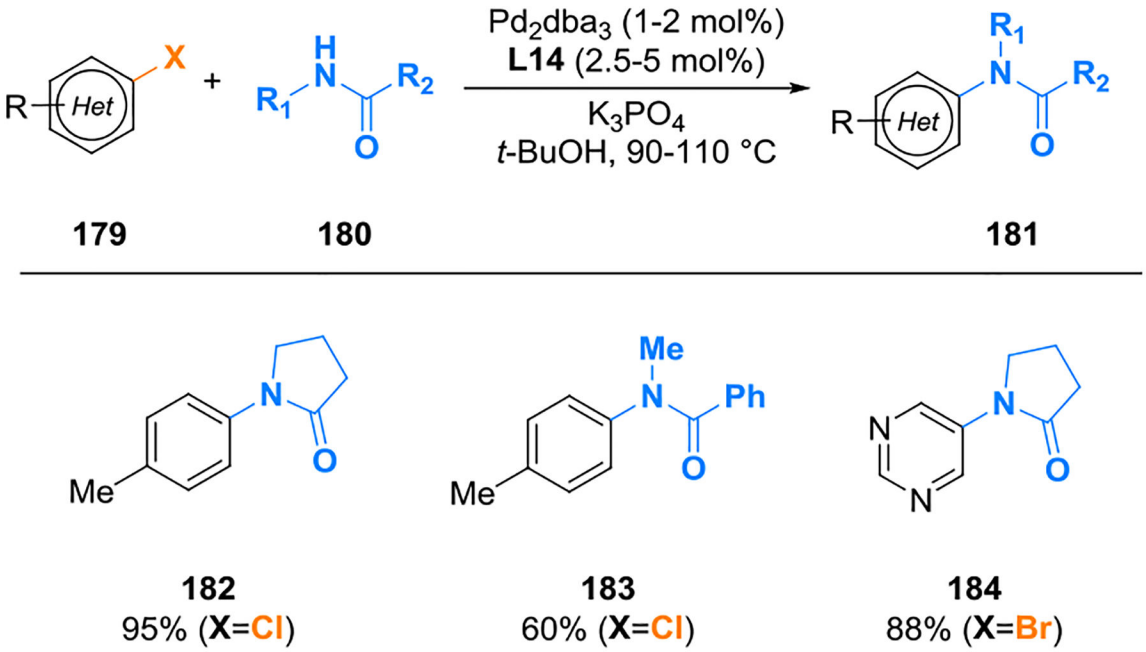


Figure 31.

Lactams and *N*-methyl amides can be coupled under the same conditions as primary amides.[69]

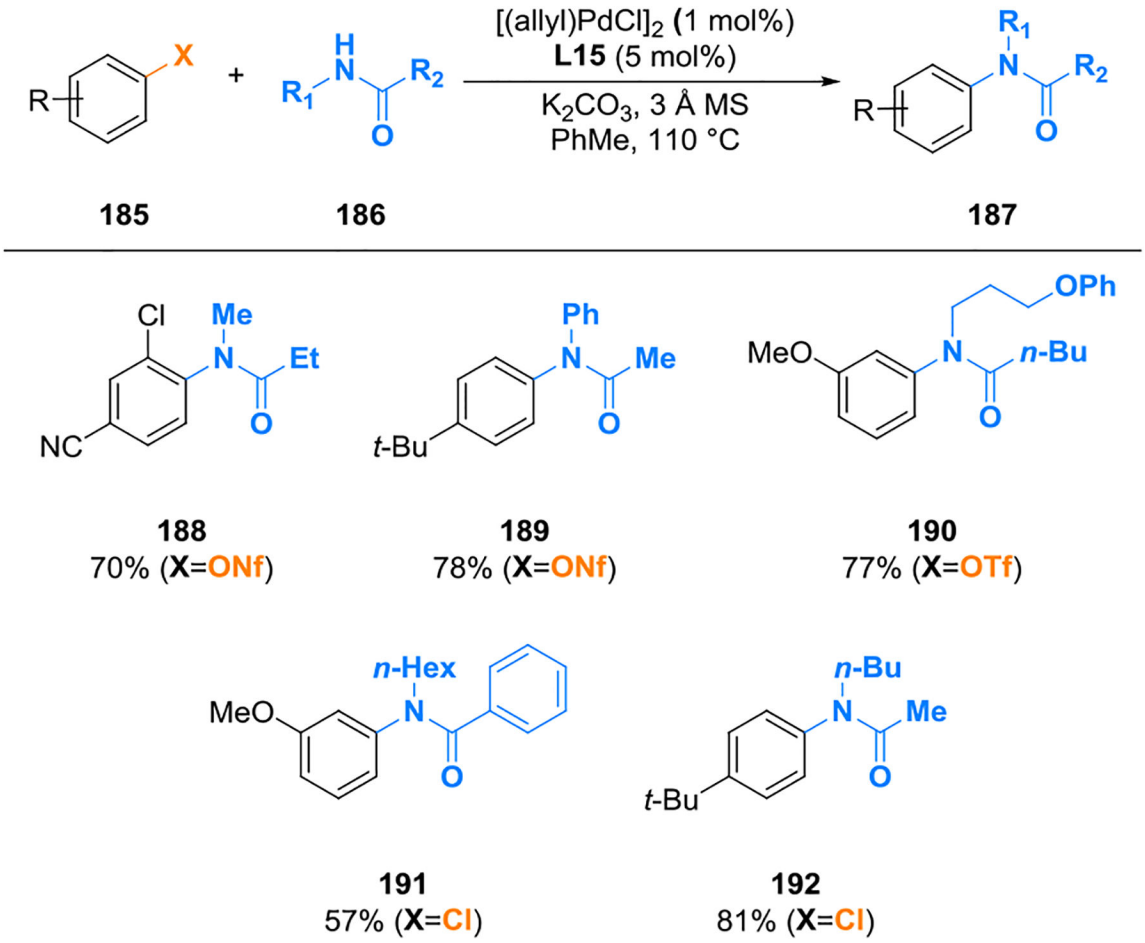


Figure 32.
JackiePhos-mediated coupling of secondary amides with aryl chlorides, triflates, and nonaflates.[74]

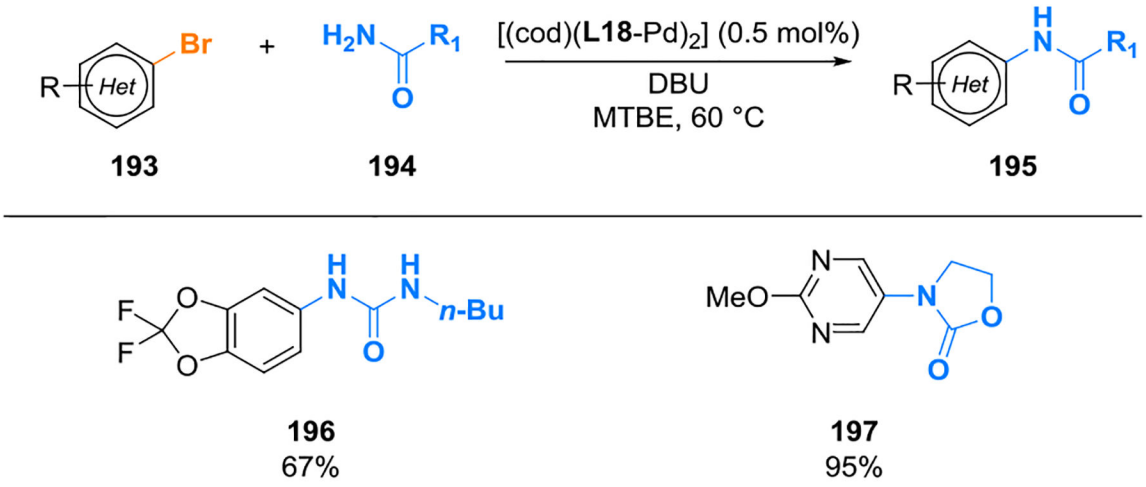


Figure 33.

AlPhos-supported catalysts can couple ureas and carbamates to aryl bromides.[58]

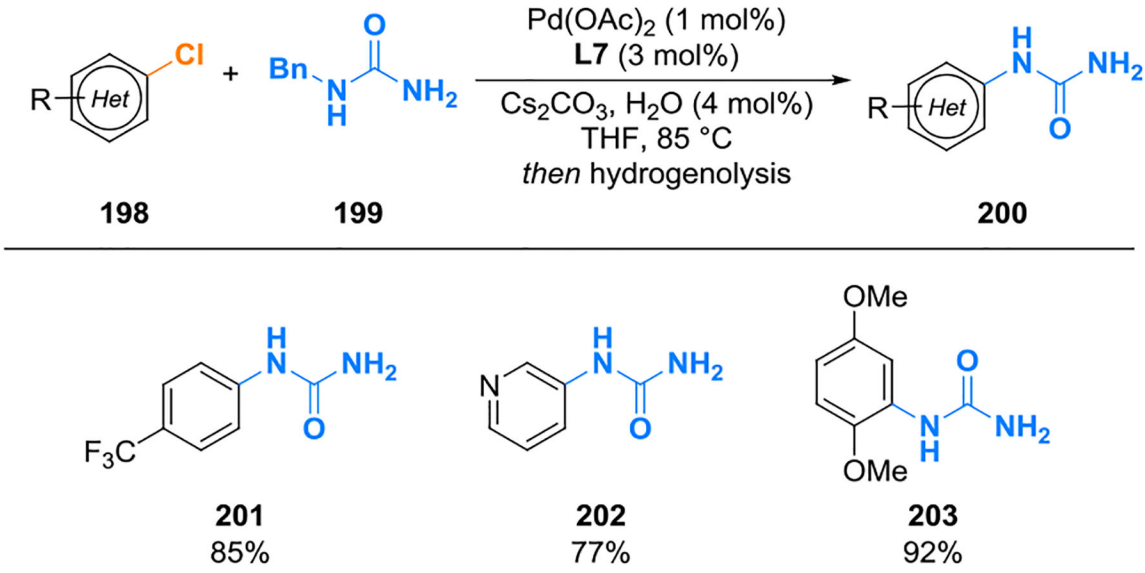


Figure 34.

t-BuBrettPhos enables coupling of benzyl-protected urea to aryl chlorides.[75]

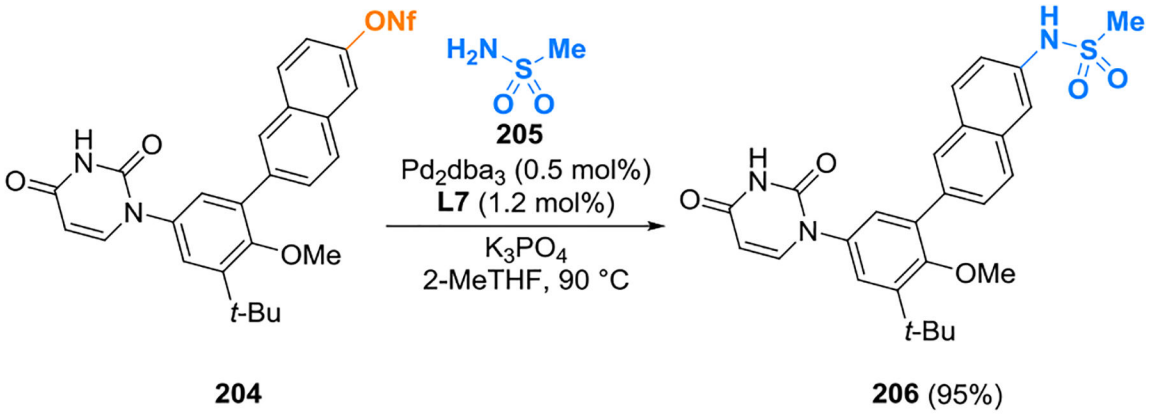


Figure 35.

t-BuBrettPhos-supported catalysts can couple an aryl nonaflate with a primary sulfonamide.[76]

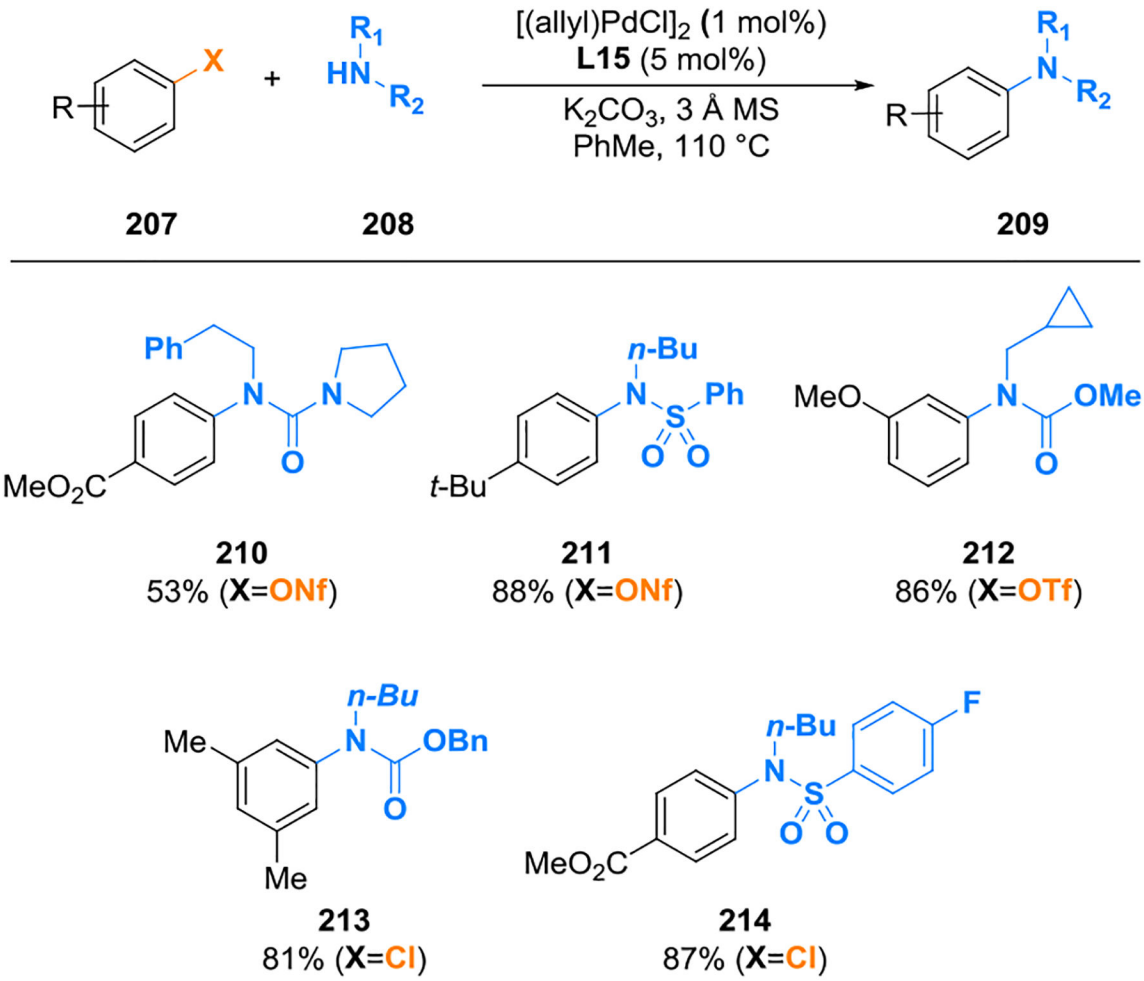


Figure 36.

JackiePhos couples secondary ureas, carbamates, and sulfonamides to aryl (pseudo)halides.[74]

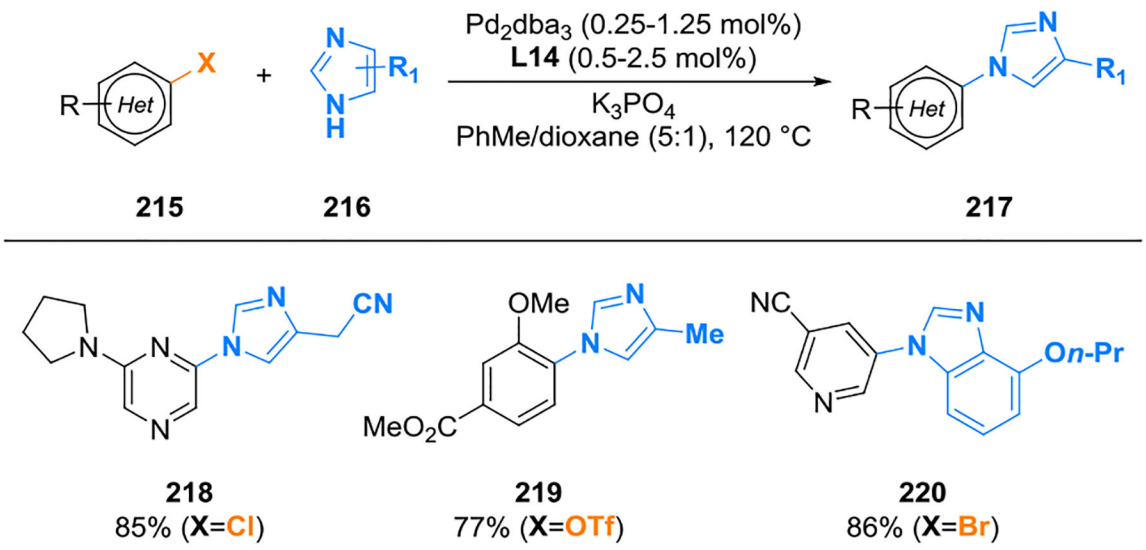


Figure 37.
Regioselective arylation of imidazoles and benzimidazoles.[78]

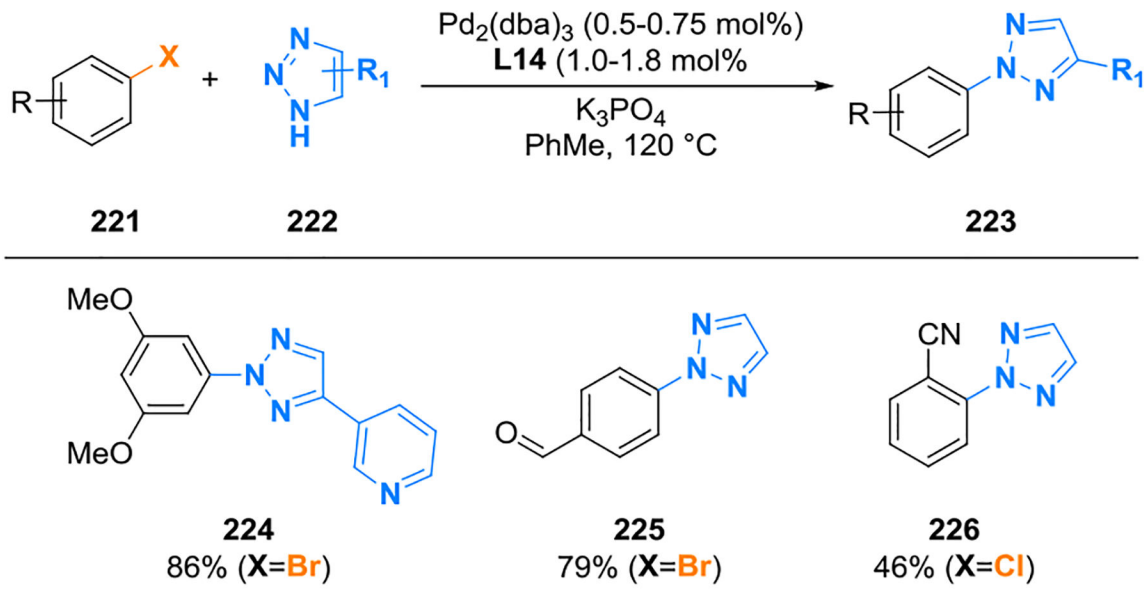


Figure 38.
Regioselective arylations of triazoles.[80]

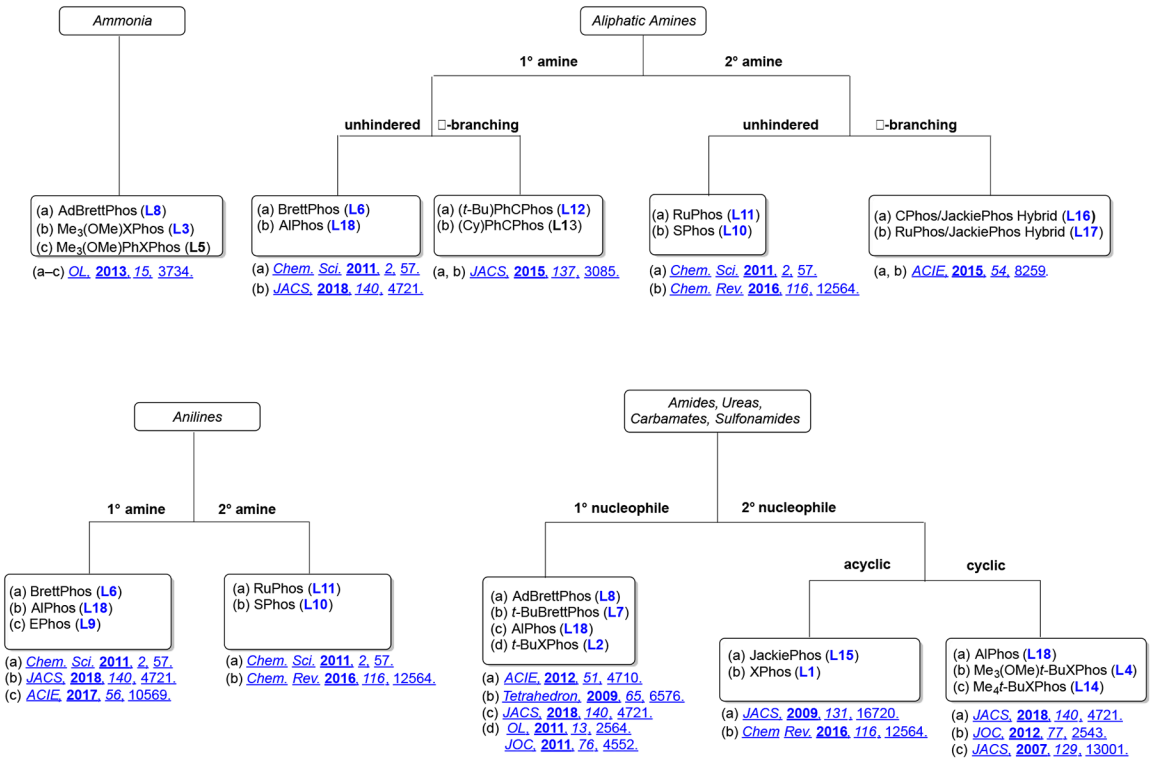
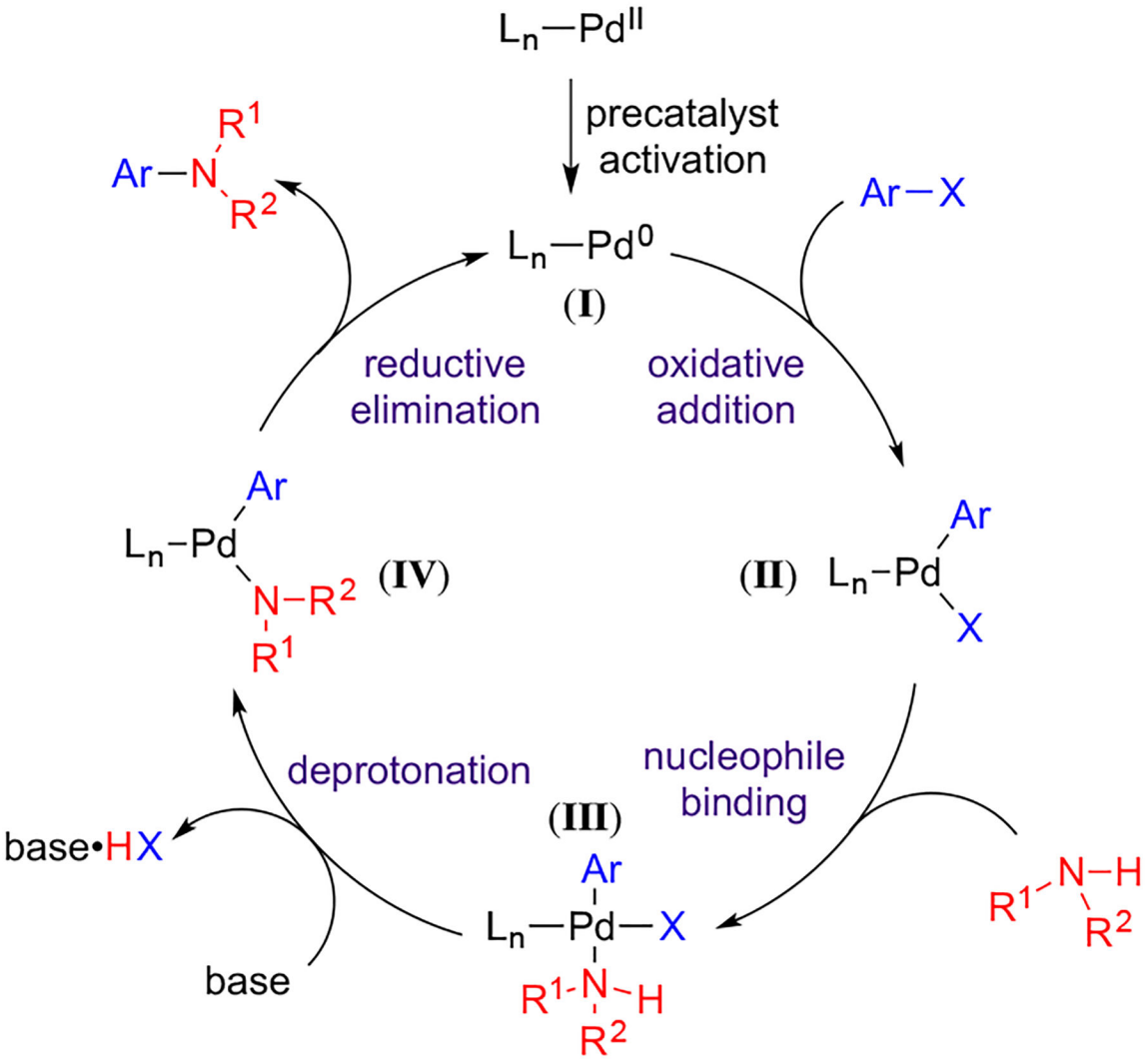


Figure 39.

Ligand selection flowchart based on nucleophile. Blue text indicates ligands that are commercially available.



Scheme 1.
General catalytic cycle for C–N cross-coupling reactions.