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Pd-Catalyzed N-Arylation of Amides: Catalyst Development and Scope

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Pd-Catalyzed N-Arylation of Amides: Catalyst Development and Scope

A Capstone Project Submitted in Partial Fulfillment of the Requirements of the Renée Crown University Honors Program at Syracuse University

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Abstract

Recent development toward more efficient palladium catalyzed amidation reactions has been driven by mechanistic studies and the development of more efficient ancillary phosphine ligands. This review discusses these developments with regard to substrate scope and the nature of the corresponding catalyst systems. Emphasis will be placed on applications of palladium catalyzed amidation reactions and the synthetic utility of these methods.

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Acknowledgements

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Chapter 1

Introduction

Palladium-catalyzed cross-coupling has rapidly evolved as an efficient and valuable method for C-N bond formation. The Buchwald-Hartwig amination reaction has been employed for C-N bond formation using a wide variety of substituted amines with aryl halides and psuedohalide moieties.[1] The seemingly simple extension on this method, to C-N amidation reactions, has only recently been implemented. This was due in large part to the introduction of better catalyst systems using more reactive ancillary phosphine ligands. An increased mechanistic understanding of the coupling reaction aided the development of these new catalyst systems, which, in turn, broadened the scope of these reactions. As such, these conditions can now be adapted to a variety of amides and aryl halide substrates.

A facile synthetic method for C-N bond formation between substituted aryl and vinyl substrates and amides is attractive due to the ubiquitous nature of amides in biological systems. This pervasiveness of amide linkages is emphasized by the peptide bonds that join amino acid building blocks to form proteins. Additionally, amide bonds are present in an extensive collection of pharmaceuticals. For instance, Atorvastatin[2], the top-selling drug in the United States, which is prescribed to lower blood cholesterol, contains an amide bond (Figure 1). Similarly, Lisinopril[3] (angiotensin converting enzyme inhibitor), Valsartan[4] (an angiotensin II receptor

antagonist), and Diltiazem[5] (a calcium channel blocker used to treat hypertension and angina) all contain key amide linkages.

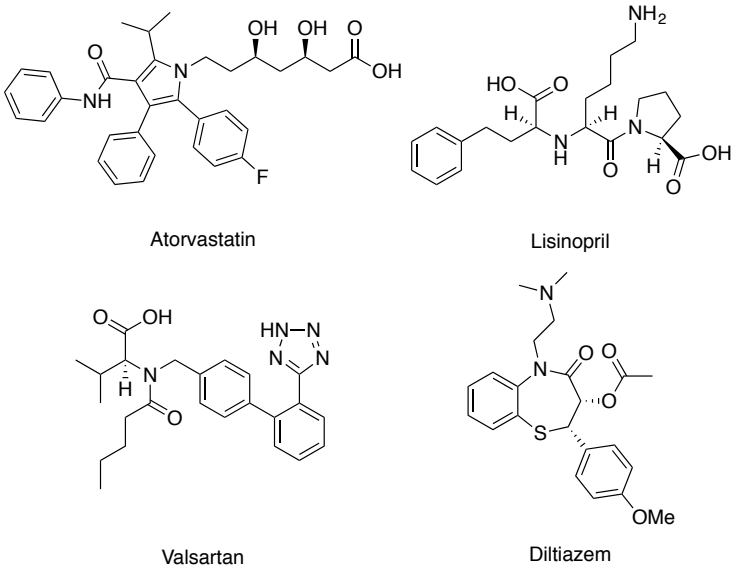


Figure 1. Structure of four important pharmaceuticals featuring a key amide bond.

The expansion of palladium-catalyzed amine coupling to amide substrates was desirable due to the relatively limited number of catalytic amide bond formation methods. Traditionally, amide bond formation requires relatively harsh conditions and displays low functional group tolerance. In 1906, Goldberg published the first aryl amidation conditions with a copper catalyst.[6] This method required harsh conditions, with temperatures above 200°C, and only gave moderate yields of the desired products. At times, stoichiometric copper was required to effect these transformations. From both a cost-efficiency and environmental standpoint, stoichiometric cooper reduces the attractiveness of this method for industry and pharmaceutical applications. In addition, the high temperature and long

reactions times prove to limit the utility of this method. Schotten-Bauman conditions allow for the preparation of amides from acyl halides and amines in the presence of base. While this is a straightforward and useful method to prepare amides, it is limited to simple substrates that are resistant to hydrolysis.[7] Additionally, amides are often synthesized from amines and carboxylic acids, but these reactions require stoichiometric coupling reagents.[8] Metal catalyzed coupling reactions offer an attractive alternative to C-N bond formation due to the potential for high functional group tolerance, mild conditions, and minimization of side products.

Palladium has traditionally been employed as the metal of choice for cross coupling reactions due to its highly reactive nature, inherent selectivity, and broad substrate scope. Several transformations that were originally effected by nickel or copper have been improved through a switch to palladium. For instance, the stereoselectivity of the Nigishi reaction, used to form conjugated dienes from aryl halides and organoaluminum reagents, was significantly improved when the nickel catalysts were replaced with a palladium.[9] While the discovery of palladium as a catalyst has dramatically improved the scope of many reactions, it has certainly not replaced nickel and copper in all cross-coupling reactions. Many synthetically useful copper and nickel cross-coupling reactions have been developed, however, these reactions are outside the scope of this review.

The development of successful amidation conditions has proved more challenging than the analogous amination reactions due to the decreased

nucleophilicity of amides compared to amines. Further, this alternative coupling partner results in modified geometry of intermediates, highlighting the requirement for specificity in ligand development. Thus, a search for improved conditions for amidation led to intricate mechanistic studies that broadened the scope of both amination and amidation reactions.

Chapter 2

Mechanism

2.1 Bidentate Ligands

The general catalytic cycle for amidation reactions is displayed in Figure 2. While the change in nucleophile from an amine to an amide necessitates modification of the ligand, palladium source, and reaction conditions, the general mechanism that amidation and amination reactions proceed through are believed to be equivalent. First, the active palladium zero catalyst species is formed through reduction of palladium (II) salt, or through ligation of an ancillary ligand species to palladium zero. The palladium then oxidatively inserts into the aryl halide to form the Pd^{II} amido complex. From there, the reaction proceeds through a ligand exchange, which includes amide binding and deprotonation. The exchange of an amide for the halide occurs through either an associative of dissociative mechanism.[10] Finally, the aryl amide product is released as the complex undergoes reductive elimination, reforming the active catalyst to propagate the cycle.

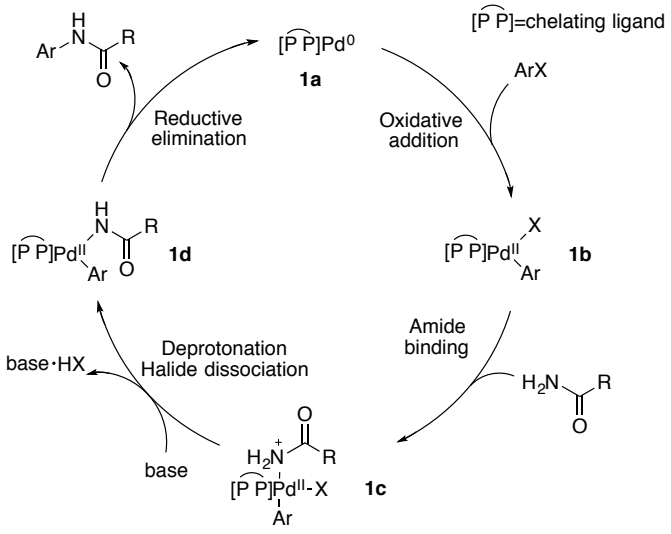


Figure 2. Proposed catalytic cycle for amidations employing bidentate ligands, illustrating an associative ligand exchange step.

When a bidentate ligand, such as **L11** (Figure 3), is used to effect these transformations, the active catalyst species **1a** is generated with the ligand occupying two coordination sites on the palladium. The coordinating moieties of most bidentate ligands are typically two phosphine groups, as is the case with **L11**. This catalyst species oxidatively inserts into the aryl halide, increasing the formal oxidation state of palladium from (0) to (II). In general, the rate of oxidative addition for varied halide substrates follows a trend: C-I>C-Br>>C-Cl>>>C-F. Electron-donating substituents on the aryl substrate favor this step. Since the rate of oxidative addition for substituted aryl halides/pseudohalides does not match the general trend in reaction rates for amidation, it is unlikely that oxidative addition is the slow step.[10] Oxidative addition is only rate-limiting in one special case where a very low aryl halide concentration is present.[11]

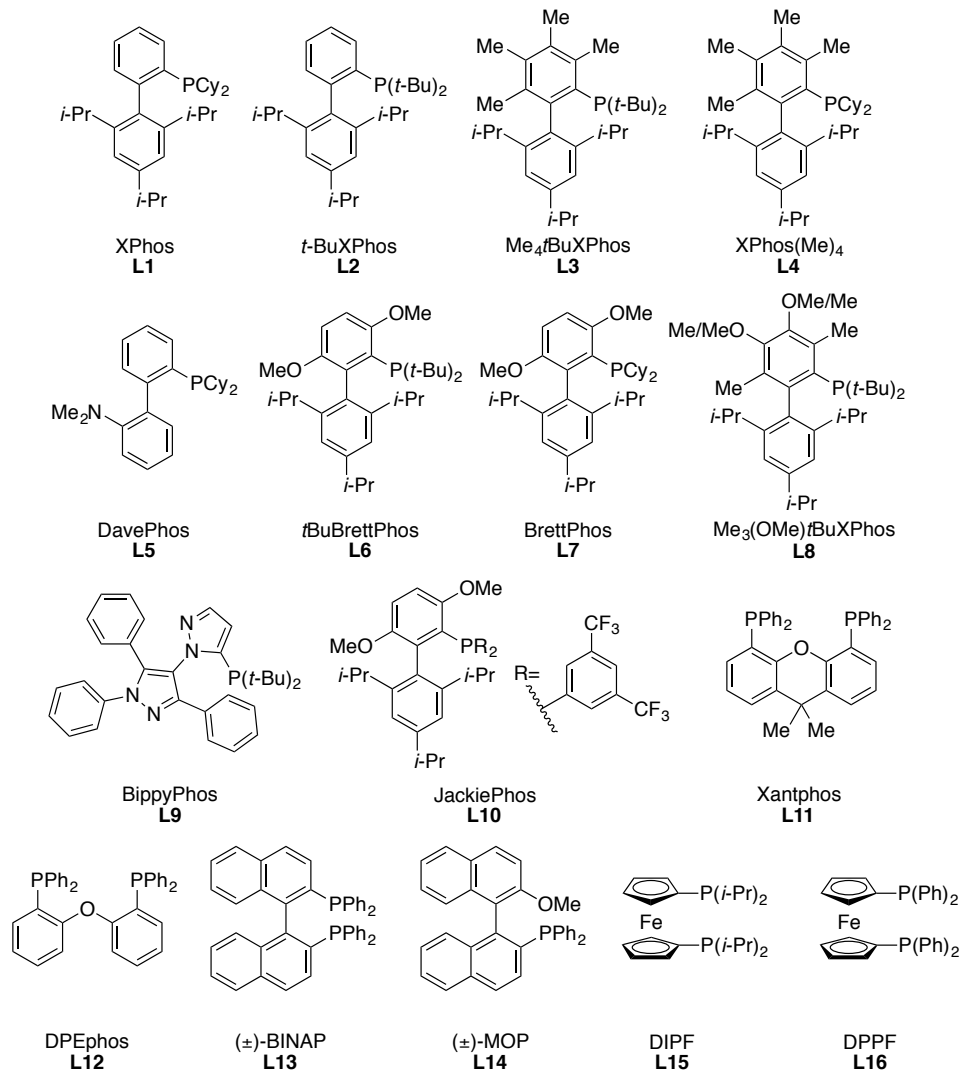


Figure 3. Important ligands for amidation.

In the case of associative ligand exchange (Figure 2), the amide binds to the Lewis acidic Pd^{II} center prior to halide dissociation. This would lead to a five-coordinate intermediate **1c**.[10] Following the formation of this intermediate, the amide is deprotonated and the halide dissociates from the complex forming **1d**. This step is facilitated by decreased electron density at the palladium center. Increased electrophilicity of palladium encourages nucleophilic attack by the amide. Access to the palladium center is also

critical to successful ligand exchange. Thus, steric crowding about the metal slows this step. Accordingly, *ortho*-substituted substrates tend to exhibit slower reaction rates.

Alternatively, a dissociative ligand exchange mechanistic step (Figure 4) would involve the loss of the halide thus forming a cationic Pd^{II} intermediate **2**.[10] It is believed that an associative pathway is typically favored, but dissociation may be involved for reactions involving weakly nucleophilic, hindered amides.[10] Similarly, van Leeuwen proposed that dissociative ligand exchange occurs from **L11**-Pd^{II} complexes undergoing *cis/trans* isomerization.[12] As the leaving group ability of the halide/psuedohalide increases, the likelihood of the complex to undergo dissociative ligand exchange increases. Accordingly, since a triflate group is a very good leaving group and can stabilize a negative charge, aryl triflates are likely to follow a dissociative ligand exchange pathway. The ionization energy requirement for bromide complexes may also be low enough to favor this type of mechanism.[10]

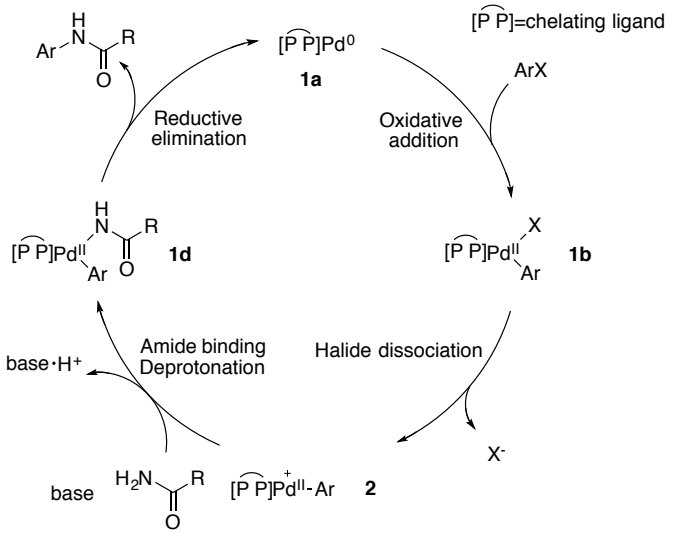


Figure 4. General catalytic cycle for palladium catalyzed amidation, illustrating a dissociative ligand exchange step.

The final step in both associative and dissociative mechanistic scenarios of palladium catalyzed amidation reactions is reductive elimination. This step regenerates Pd^0 and releases the N-aryl amide product. In both cases, reductive elimination is facilitated by decreased electron density at the palladium center produced by electron deficient ligands and electron-withdrawing substituents on the substituted halide.[13] The success of bidentate ligands is likely attributed to their effect on this reductive elimination step. Reductive elimination studies by Hartwig and co-workers have shown that a larger bite angle helps promote reductive elimination from amidate complexes.[14] This explains the greater success found with amidation reactions employing **L11** (111°) over **L16** (96°).[15]

Buchwald reported that the success of **L11** could be attributed to the *trans*-chelated intermediate (**1a-c**) about the palladium center.[16] X-ray crystallography unambiguously assigned the conformation of this intermediate. In this rare *trans*-chelating structure, the bite angle of **L11** is

150.7°, significantly larger than the calculated bite angle range of **L11** (97-135°). However, while it is known that a larger bite angle can promote this step, the details of reductive elimination a *trans*-complex are currently not fully understood. The product cannot reductively eliminate directly from the *trans*-amidate complex. In all likelihood, reductive elimination occurs following isomerization to the *cis* isomer or dissociation of one phosphine to give a three-coordinate intermediate.[17]

Much work has been done to determine how ligand geometry affects the rate of reductive elimination in palladium amidate intermediates. Since palladium is bound to the ancillary ligand at two sites, bidentate ligands restrict available conformations of the amidate complex. Specifically, they prevent the formation of a κ^2-amidate complex in which the amide is simultaneously bound to the palladium center through both the nitrogen and oxygen atoms.[14] This additional coordination in κ^2 intermediates slows reductive elimination due to the difficulty overcoming the Pd-O interaction. Instead, bidentate ligands force κ^1-amidate geometry (Pd-N bonding only), from which reductive elimination is not hampered by Pd-O coordination.

The rate-determining step in amidation reactions is dependent upon the choice of ligand. The reduced barrier to reductive elimination with bidentate ligands due to the κ^1-amidate conformation likely speeds up this step to the point it no longer becomes rate-limiting. Hartwig demonstrated that reductive elimination from Xantphos-Pd(Ph)-(PhNC(O)Me) is facile.[14] Thus ligand exchange is likely the slow step in these transformations. As

such, amidation reactions employing bidentate ligands are typically improved with electron-withdrawing groups on the aryl halide which favor this step.

2.2 Monodentate Ligands

Amidation reactions proceed through a similar mechanism when monodentate, rather than bidentate, ligands are used to effect the transformation, but there are a few critical differences. Monodentate ligands contain a single phosphine and only coordinate once to the palladium center. The nuances of the mechanism are strongly affected by the choice of reaction conditions, especially dealing with ancillary ligand choice. In cases employing bulky monodentate biaryl phosphine ligands, the ligand substituents must be carefully modified for application to amidation reactions. The numbering scheme for these dialkyl biaryl phosphine ligands is displayed in Figure 5. Figure 6 displays the role of each substituent in the general scaffold of a Buchwald ligand.

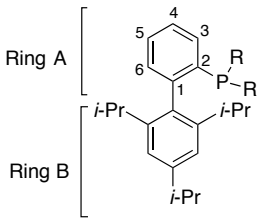


Figure 5. Numbering scheme for dialkyl biaryl phosphine ligands

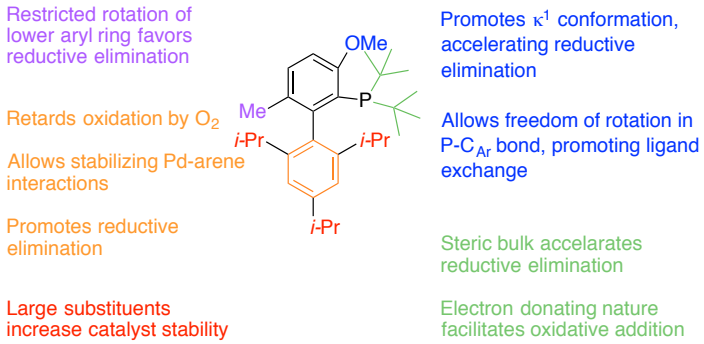


Figure 6. Role of key substituents of the dialkyl biaryl phosphine ligand scaffold.

Oxidative addition is still fast when monodentate ligands are employed, with the initial rate dependent on the nature of the halide moiety. Monodentate biaryl phosphine ligands introduced by the Buchwald group typically contain bulky alkyl substituents on the coordinating phosphine, which donate electron density to the palladium center, facilitating this step.

Following oxidative addition, the amide binds to the complex **3b** to give a four-coordinate intermediate as in Figure 7; alternatively, the halide can dissociate prior to amide binding giving a three coordinate intermediate **4** (Figure 8). However, a dissociative ligand exchange mechanism is unlikely in systems involving a monodentate ligand since the ionization energy is higher.[8] This cost is higher in monodentate systems than in bidentate systems since the palladium is coordinatively unsaturated when monodentate ligands are employed. As with bidentate ligands, ligand exchange is promoted through decreased electron density at the palladium center and access to the metal center. Accordingly, substituted aryl halides with electron-withdrawing substituents promote amide binding. Aryl

halides bearing *ortho*-substituents proceed slower through this step because of sterics.

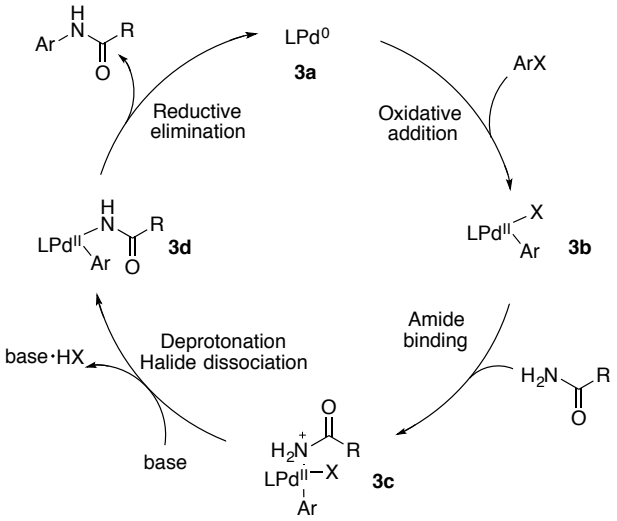


Figure 7. Proposed mechanism with an associative ligand exchange step for amidations utilizing monodentate ligands

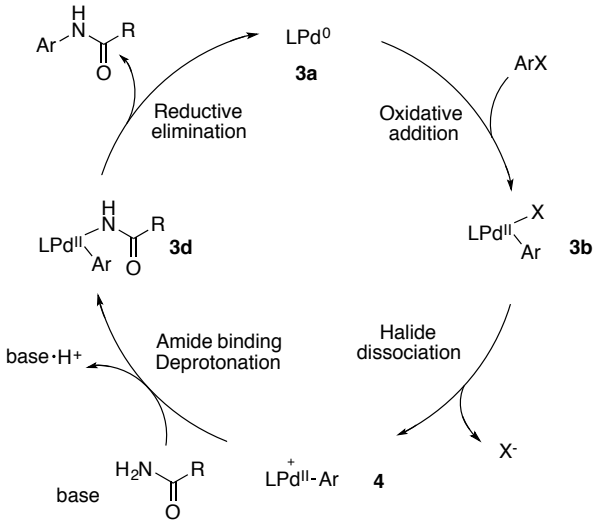


Figure 8. Proposed mechanism, including a dissociative ligand exchange step, for amidations involving a monodentate ligand.

Increased rotation around the P-C_{Ar} bond at position 2 of ring A (Figure 5) lowers the barrier to ligand exchange due to the favorable conformations for amide association that can be achieved. Computational studies demonstrated that the lowest energy conformation for amide binding

places the palladium moiety over or away from the lower biaryl ring.[10] The importance of this freedom of bond rotation was demonstrated through reactions with analogous ligands with the methoxy group at C2 on ring A substituted for a methyl group, which has a larger A-value. These analogous ligands with the larger *ortho*-methyl group were not nearly as successful in effecting amidation. In fact, **L3**, an **L6** analog with methyl groups on ring A of the biaryl backbone, provided only 12% yield when used to carry out amidation. **L6**, on the other hand, afforded the product in 99% yield.[18]

Beyond allowing for increased bond rotation to accelerate ligand exchange, the *ortho*-methoxy group at C3 is critical to catalyst stability and may promote reductive elimination. The Buchwald group carried out computational studies to demonstrate the importance of an *ortho*-substituent on the aryl ring A. They reported that amidate intermediates prefer to adopt a κ^2 structure when the ligand lacks this *ortho* substituent.[11] As with bidentate ligands, this κ^2 conformation hinders reductive elimination due to the need to overcome the additional Pd-O interaction. A substituent at the 6-position of ring A also aids with reductive elimination because it restricts rotation of aryl ring B. This conformational rigidity favors the release of the aryl amide product.[19]

One modern biaryl phosphine ligand, **L10**, involves a slightly altered mechanism due to the drastically modified electronic nature of the phosphine moiety. With P-bound 3,5-(bis)trifluoromethyl substituents, the palladium in the amidate complex **3c** is highly electrophilic. This changes the

favored geometry of the amidate; thus the κ^2 intermediate becomes kinetically favored.[10] It is likely that the palladium center is electron deficient enough that reductive elimination proceeds unimpeded despite the κ^2 amidate complex geometry. The success of **L10** in effecting amidations can likely be primarily attributed to the facilitation of the ligand exchange step. The strongly electron withdrawing trifluoromethyl-substituents encourage the nucleophilic nitrogen of the amide to bind through the decrease in electron density at the palladium center.

The Hartwig group carried out mechanistic studies and determined that reductive elimination was hampered by reduced nucleophilicity of the heteroatom bound to palladium, suggesting that this step may be rate limiting in amidations when some dialkyl biaryl phosphine ligands are employed.[17] However, newer modifications of the original biaryl scaffold may increase the rate of reductive elimination to the point it is no longer rate-limiting. The bulky nature of the alkyl substituents on the phosphine facilitates this step in the Buchwald ligand scaffold. In modern Buchwald-type ligands bearing a methoxy group at C2 and a methyl group at the 6-position on the aryl ring A, along with bulky alkyl substituents on the phosphine, ligand exchange is likely the slow step in this mechanistic scenario.[10] The strong dependence of the reaction rate on the nature of the halide/psuedohalide disfavors a mechanism in which reductive elimination is rate-limiting.[11]

Chapter 3

Early Amidation Studies

3.1 Intramolecular Amidation

In 1996, the Buchwald group published the first successful amidation reactions using aryl halides with tethered acetamide substrates.[20] They obtained highest yields and shortest reaction times when using $Pd_2(dba)_3$/ 2 (2-furyl)$_3$P as the catalyst and Cs_2CO_3 as the base (Figure 9). This method required high catalyst loadings and was slower than the analogous amine reactions; however, high yields could be obtained using select substrates. Optimal success was obtained when forming five-membered rings (**5a, b**); six-membered rings could also be formed, albeit in low yields (**5c**). Of note, no detectable product formation was observed when seven-membered ring formation was attempted. All reactions were run with electronically neutral aryl substrates. Trials to apply these conditions to intermolecular coupling were unsuccessful. NMR experiments indicated that the oxidative addition product of 5-bromo-*m*-xylene and $Pd_2(dba)_3$/P(*o*-tolyl)$_3$ failed to coordinate to N-methyl acetamide.

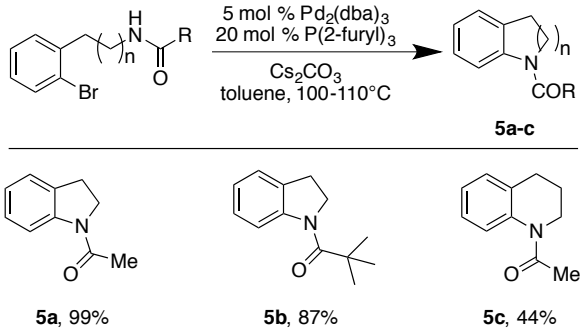


Figure 9. Initial intramolecular amidation conditions on tethered acetamide substrates

They carried out similar trials with N-benzamides of the type displayed in Figure 10. These proved to be slightly more challenging substrates. These reactions took considerably longer (42-91 hours) and gave lower yields. Optimal results were obtained using a $Pd_2(dba)_3$/ 2 o-tolyl$_3$P catalyst system when K_2CO_3 was employed as the base (Figure 10). This protocol was most effective for the formation of six-membered rings, such as **6b**.

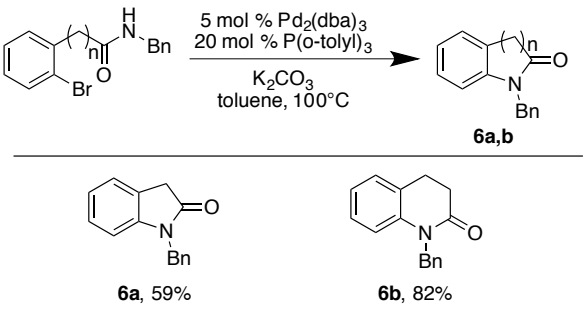


Figure 10. Intramolecular cyclization conditions for benzamide substrates.

Following numerous reports of varied ligands in C-N bond formation in amination chemistry, the Buchwald group returned to the corresponding amidation reactions in hopes of expanding the scope of this reaction. Using

chelating ligands, they were able to decrease the amount of palladium required (from 10 mol % to 3.3 mol %) and expand the substrate scope to include secondary amides and carbamates (Figure 11).[21] For the first time, seven-membered rings (**7a**,**c**) were formed in high yields (79-90%); this reaction provided the best results when **L11** was used as an ancillary ligand. They also found **L14** and $Pd(OAc)_2$ to be a particularly effective catalyst system, requiring lower catalyst loading compared to previous transformations (3.3 mol % Pd, 5 mol % **L14**) and resulting in good yields. These conditions also applied to substrates that cyclized to form five, six, and seven membered rings and carried acetyl (**6a**, **7a**), carboxybenzyl (**7b**), and t-butyloxycarbonyl (boc) (**7c**) groups at the N-position. Depending on the substrate, optimal success was realized by varying the chelating ligands (**L11**, **L12, L13**, **L14**).

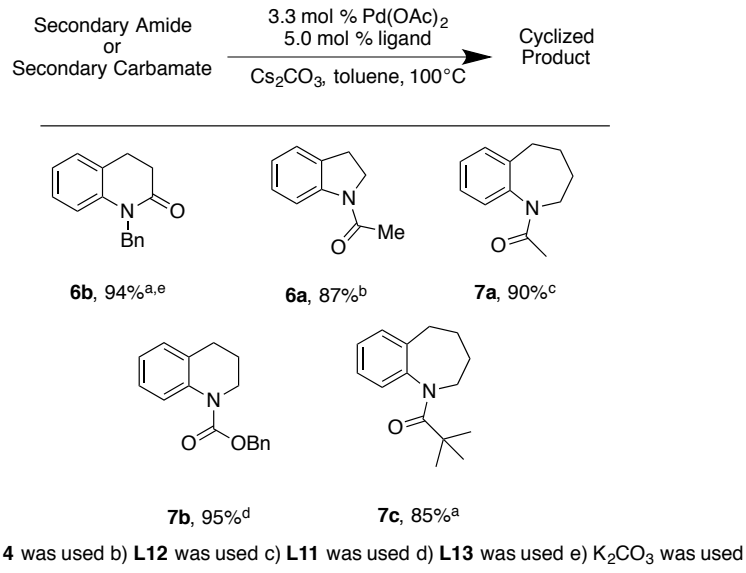


Figure 11. Intramolecular amidation of secondary amides through the use of chelating ligands.

3.2 Intermolecular Studies

In 1999, Shakespeare *et al.* sought to expand palladium catalyzed amidation reactions to the more challenging intermolecular reaction.[22] Their work began with reacting lactams with aryl bromides because the pK_as of lactams are similar to indole, which Mann and Hartwig previously coupled with aryl bromides.[23] Additionally, the modified pK_a values resulting from varied ring size allowed for investigations into possible reactivity differences. This transformation was carried out with a Pd^{II} source, $Pd(OAc)_2$, and the bidentate catalyst **L16**. The conditions are shown in Figure 12. While this reaction gave good yields with a variety of substituted bromobenzenes, electron-rich (**8c**) and electron-neutral (**8d**) substrates required longer reaction times to proceed to completion. They found the transformation to be highly efficient when working with five-membered lactams (**8a**,**b**), but four, six, and seven-membered rings were significantly less reactive. This difference in reactivity cannot be accounted for strictly by pK_a differences, although the higher pK_as of the larger rings may inhibit coordination of the anion to the catalyst due to low anion concentration.[24] Different conformations of the larger rings may affect their ability to effectively coordinate to the catalyst.

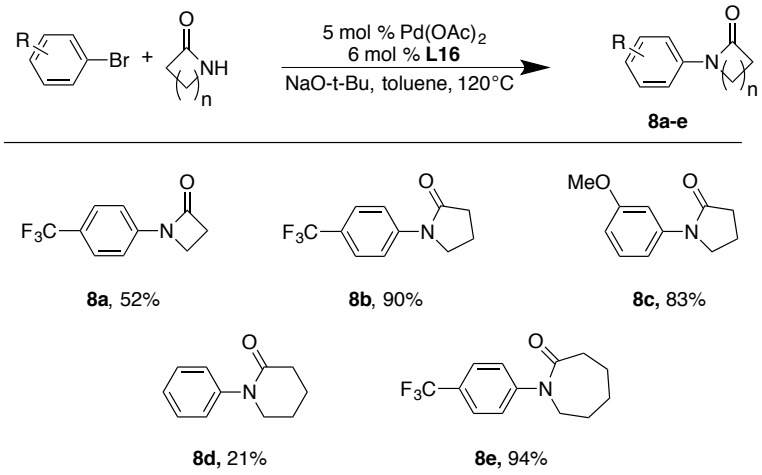


Figure 12. Intramolecular amidation of aryl bromides with lactams of varied size.

The Hartwig group applied a similar method to the formation of carbamates to form Boc-protected aniline derivatives using P(*t*-Bu)$_3$ and $Pd_2(dba)_3$ (Figure 13).[25] They obtained the highest conversions when using NaOPh as a base rather than Cs_2CO_3 or NaO-*t*-Bu. Additionally, a 2:1 ratio of ligand to palladium was found to be beneficial. Aryl bromides activated by electron withdrawing substituents (**9d**) were the optimal substrates. Only moderate yields were obtained when the electron density on the aryl bromide was increased through an electron-donating substituent such as a methoxy group (**9e**).

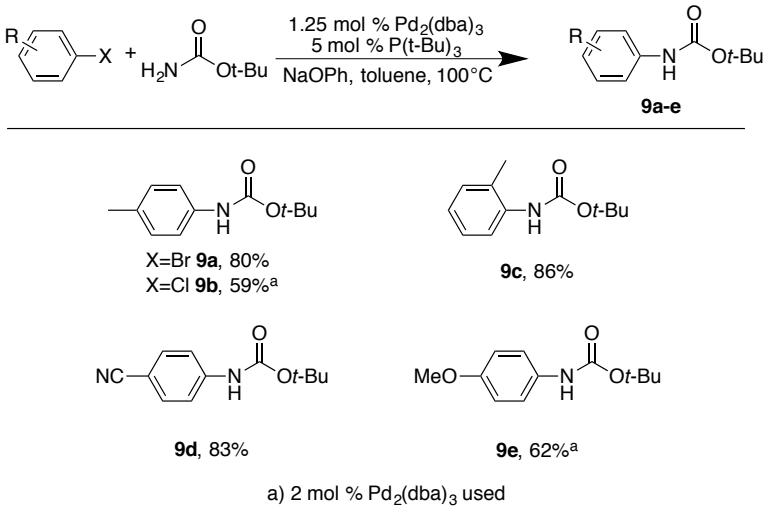


Figure 13. Intermolecular amidation with t-butyl carbamate

Wang devised a regioselective synthesis of aryl hydrazides by reacting aryl bromide derivatives with *t*-butylcarbazate.[26] Initial conditions afforded a mixture of four regioisomeric products corresponding to coupling at the two different nitrogens in the *t*-butylcarbazate (**10a**, **10c**), and two dimeric compounds resulting from exhaustive coupling of **10** with *t*-butylcarbazate (Figure 14). Optimized conditions, shown in Figure 15, suppressed the dimeric products and allowed the amidation products **10a** and **11a-c** to predominate in a 23:1 ratio. Further studies were conducted to understand the role substituents on the aryl halide played in product formation. Aryl bromides bearing electron-withdrawing *para*-substituents gave the highest yields (81-83%) of amidation products (**10a, 11a**) while the *meta*-substituted analogs provided the lowest yields (**11c**, 16-26%). Based on Hartwig's investigations,[27] it was found that unactivated aryl bromides could only undergo this amidation reaction upon modification of the palladium source from $Pd(OAc)_2$ to $Pd_2(dba)_3$, however, the yield remained low (**11b**,

18%). Added *ortho*-substituents favor the amination product over the amidation product likely due to increased steric bulk (**11d**). The authors proposed that the more nucleophilic site on the *t*-butylcarbazate, the amino portion, coordinates to the palladium center and then undergoes an intramolecular rearrangement to give the corresponding amidation product. However, this intramolecular rearrangement may be hindered in the case of *ortho*-substituted substrates.

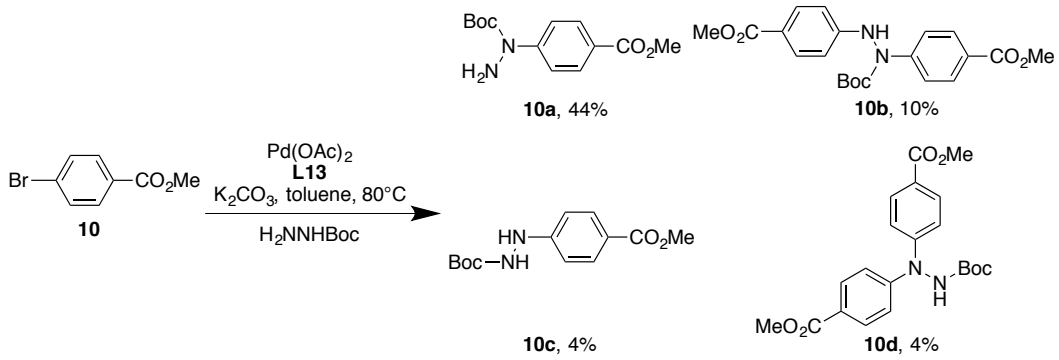
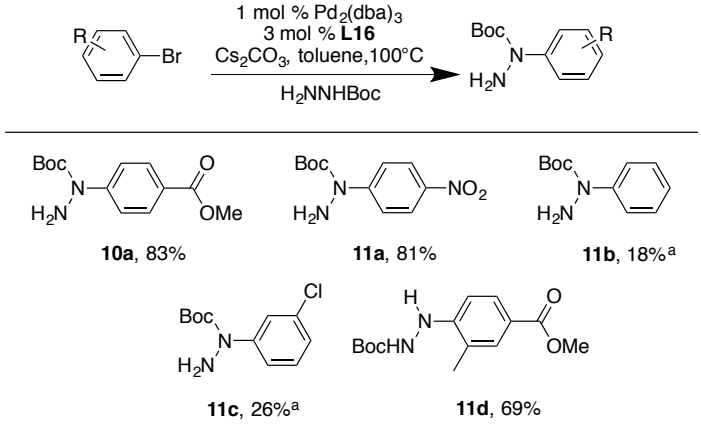


Figure 14. Initial reaction conditions to form aryl hydrazides from t-butylcarbazate, affording a mixture of four products.



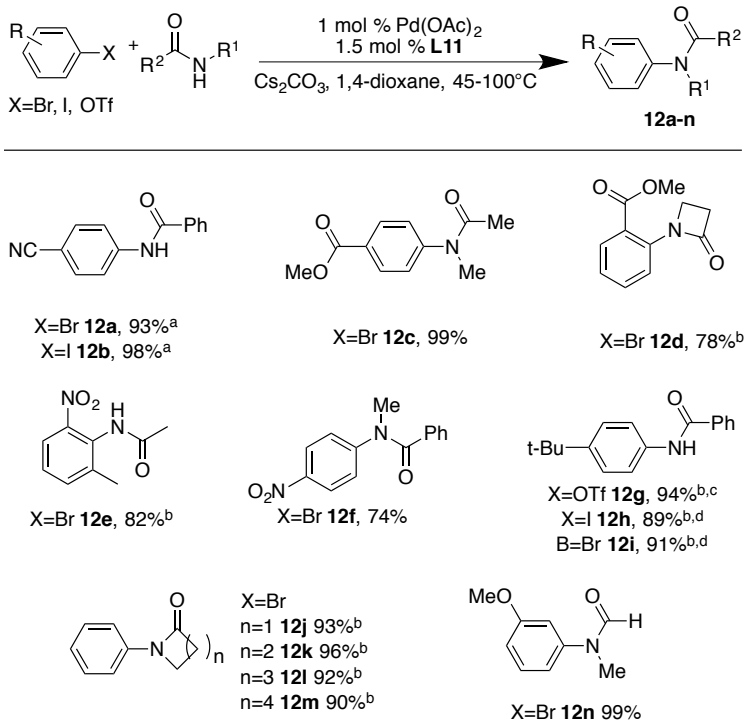
a(R)-(-)-1-[(S)-2-(diphenylphosphino)ferrocenyl]ethyldi-*t*-butylphosphine was used

Figure 15. Optimized conditions that resulted in the suppression of dimeric products and afforded the major regioisomer in a 23:1 ratio.

Chapter 4

General Amidation Studies

The Buchwald group described the first general intermolecular amidation reactions between aryl halides and amides in 2000. Through the use of **L11** (Xantphos), the reaction proceeded with good functional group tolerance and good to excellent yields (Figure 16).[28] Their catalyst system expanded the work of Shakespeare[22], which was limited to the coupling of five-membered ring lactams, to include four to seven membered lactams (**12d,j-m**). They found increased success with $Pd_2(dba)_3$ rather than $Pd(OAc)_2$ on less activated substrates (**12g-m**). However, despite significant improvements in generality to previous work, the substrate scope of this reaction was limited. Unactivated aryl chlorides, o-substituted electronically neutral aryl halides, and electron-rich aryl halides were not efficient in these transformations. Secondary acyclic amides other than N-methylformamide and sulfonamides proceeded slowly with unactivated aryl halides.



a) THF as solvent b) $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$ (1 mol % Pd refers to 0.5 mol % $Pd_2(dba)_3$) c) 4 mol % Pd d) 2.5 mol % Pd

Figure 16. Palladium catalyzed amidation of aryl substrates through the use of a chelating ligand.

Two years later, the Buchwald group published continued exploration of the intermolecular reaction conditions.[16] They found that careful control of the catalyst loading and reaction concentration was critical in amidation of less reactive substrates (Figure 17). For challenging substrates, lower concentrations (0.125-0.5M rather than 1M) and higher catalyst loadings proved beneficial to the reaction. Simply increasing the catalyst loading without lowering the concentration was found to increase formation of the aryl group exchange byproduct, formed via exchange between the aryl group bound to Pd^{II} and the phenyl group of the phosphine ligand, and quicker catalyst decomposition. Modification of the reaction conditions offered an expanded substrate scope with regard to the aryl halide. Activated aryl

moieties with electron-withdrawing groups at *ortho*-, *meta*-, or *para*-positions could now be effectively coupled with primary amides, secondary amides, carbamates, and sulfonamides (**13e**). Unactivated or deactivated aryl halides are also valid substrates under carefully selected conditions (**13a-d**). For example, sterically hindered aryl halides with electron-donating substituents effectively reacted under these carefully selected conditions (**13a,b**).

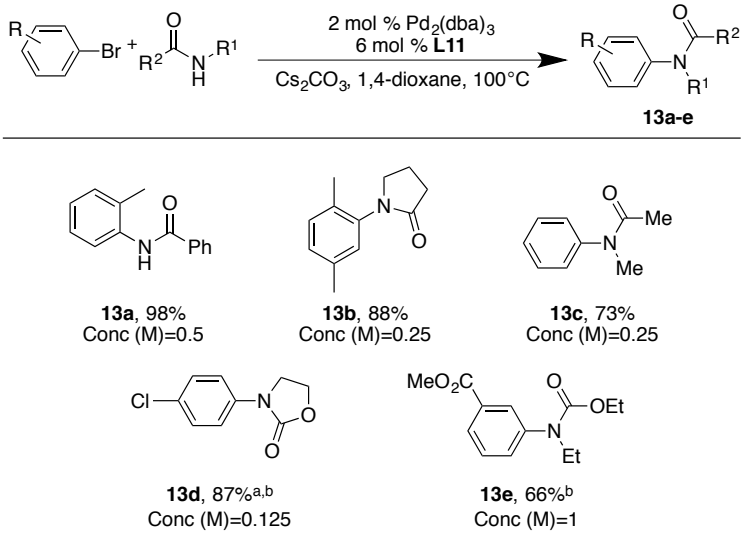
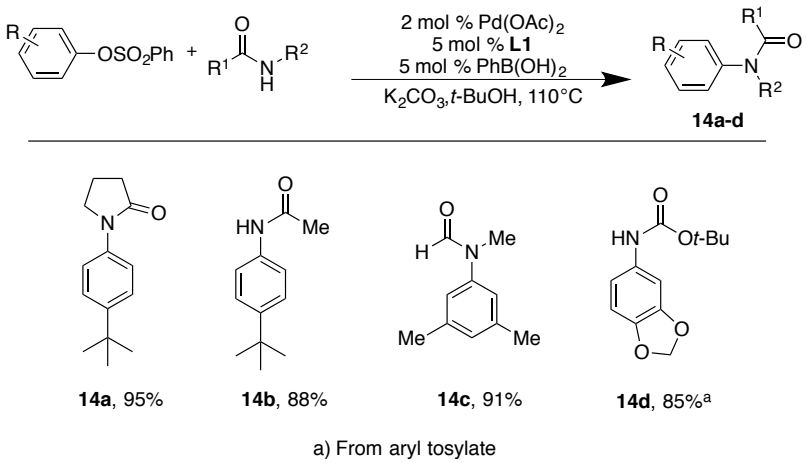


Figure 17. Expanded substrate scope for amidations with chelating ligand L11.

Following the success of the newly developed XPhos (**L1**) ligand in amination reactions, this ligand was applied to couple amide substrates with aryl benzenesulfonates and aryl tosylates.[29] For the first time, this intermolecular transformation was effected with a monodentate dialkylbiarylphosphine, rather than a bidentate chelating ligand, such as **L11**. Reactions of pyrrolidinone, primary amides, *N*-methyl formamide, and *N*-Boc

amide with aryl benzenesulfonates and aryl tosylates all coupled in excellent yields in the presence of **L1** (Figure 18). These conditions tolerated electron-donating substituents on the aryl substrate (**14a-d**). A catalytic amount of phenyl boronic acid was required to facilitate reduction of the Pd^{II} precatalyst to the active Pd^0 species. This reaction proceeded most efficiently in *t*-BuOH with K_2CO_3 as base at 110°C.



a) From aryl tosylate

Figure 18. First intermolecular amidations effected by a monodentate dialkyl biaryl phosphine ligand.

4.1 Expansion to Chlorine Substrates

Aryl chlorides are the most attractive substrates for cross-coupling reactions since they are the least expensive of the aryl halides and most readily available. However, they have proved to be the most challenging substrates for cross coupling chemistry.[25, 30] The difference in reactivity between various halides can be advantageous for selective coupling.[31] Indeed, aryl bromides can be selectively coupled in good yields in the presence of a chlorine substituent.[11, 32] Expansion of amidation reactions to

include chlorine substrates was only possible following more detailed mechanistic studies.[17, 23]

One of the first successful expansions of the amidation methodology to chloride substrates was carried out with enaminones in 2000.[33] This was possible by applying recent work on palladium-catalyzed couplings of aryl halides with less nucleophilic nitrogen sources, along with a newly developed catalyst system designed by the Buchwald group.[34] The **L5**/$Pd_2(dba)_3$ catalyst system was originally designed to improve the generality of amination reactions but proved useful in an amidation-type reactions as well. **L5**, a commercially available ligand, allowed for an efficient transformation of aryl bromides and chlorides of varying electronic states into N-aryl vinylogous amides (Figure 19).[33] Reactions of sterically hindered enaminones proved slower than unhindered analogues, but these transformations were still accomplished in good yields. For example, when the sterically hindered enamide **15** was reacted with an electron-rich aryl bromide, this transformation took 48 hours but afforded the desired product in 90% yield (**16a**). Important for potential applications to medicinal chemistry, the reaction could also be applied for the one-pot formation of heterocycles such as **17** (Figure 20).

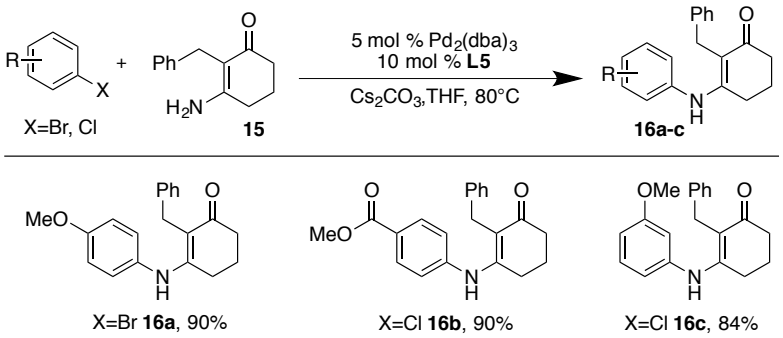


Figure 19. Coupling of a aryl bromides and chlorides with a sterically hindered enaminone.

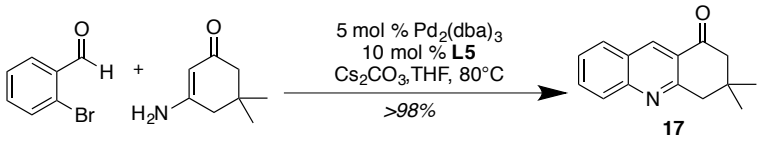


Figure 20. One-pot heterocycle synthesis from enaminones.

The Buchwald group also designed an effective ligand for the amidation of aryl chlorides based on several mechanistic observations.[11] First attempts for the use of a monodentate phosphine ligand in this reaction with **L1** and **L2** gave the desired product but in very poor yields (<10%). They postulated that increasing the bulk of the phosphine-containing aromatic ring would improve catalysis due to the aforementioned effect on reductive elimination. Indeed, **L3**, with four methyl groups on the upper ring, proved to be much more effective, resulting in high yields for a wide range of aryl chloride substrates. Further studies indicated that only the *ortho*-methyl group at C2 is critical to the activity of this ligand. They postulate that this substituent plays a key role in orchestrating the conformation of intermediates and catalyst stability.

A few years later, the Buchwald group improved the scope of this reaction by revisiting the ligand design. As discussed previously, they found that substituting the methyl group at the *ortho* position with a methoxy group increased the activity of the catalyst system which led them to publish the so-called BrettPhos (**L7**) ligand for amidation.[35] **L7** proved to be an effective ligand for amidations with aryl chloride substrates.[18] The effectiveness of this catalyst system was improved further through the modification of the phosphine-bound cyclohexyl substituents to bulkier *t*-butyl groups to give **L6**. The bulkier t-butyl groups on the phosphine are believed to assist with reductive elimination due to sterics and to promote oxidative addition due to their electron donating nature. Using the water-mediated catalyst preactivation method[36] with **L6**, $Pd(OAc)_2$, and K_3PO_4 in *t*-BuOH to react 2-chlorotoluene with acetamide, the desired product was afforded in a 99% GC yield in only 40 minutes (Figure 21). These proved to be quite general reaction conditions, with success for electron-rich and electron-poor aryl chlorides. Important for potential biological applications, amides containing furans, pyridines, and thiophenes were all coupled effectively (**18e,f**).

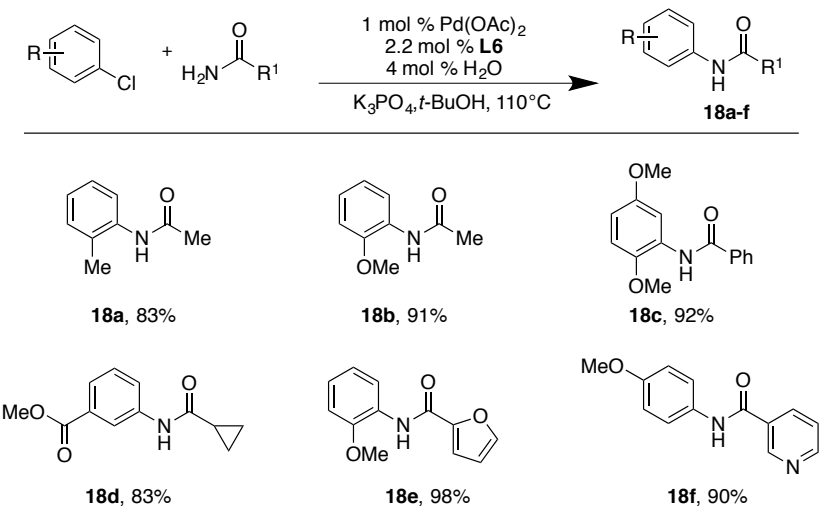


Figure 21. Amidation effected by the water-mediated catalyst preactivation method of $Pd(OAc)_2$ and L6

4.2 Urea Coupling

Due to the similar nucleophilic nature of amides and ureas, arylation of urea substrates was a natural progression of the aforementioned amidation chemistry. The N-aryl and N-heteroaryl urea motif is common in biologically active targets such as anion binding receptors.[37] Accordingly, these molecules are quite important in drug development.[38] Outside of medicinal chemistry, these substituted ureas offer promise as new materials.[39] However, typical synthetic routes to substituted ureas often involve hazardous and toxic intermediates.[40] Through the expansion of amidation conditions to urea substrates, these substituted ureas with diverse applications can be synthesized under much more mild conditions.

Buchwald's general amidation conditions[16] were applied to urea substrates very shortly after they were reported. Through the use of $Pd_2(dba)_3$, **L11**, and Cs_2CO_3 in dioxane, a variety of aryl halides can be

converted to diarylureas (Figure 22).[32] The diarylurea product predominates over the monoarylurea product, even with a two-fold excess of urea. Several phosphine ligands were screened for this reaction, including P(*o*-Tol)$_3$, **L16**, **L12**, and **L11**, but only **L11** was found to be promote this transformation. This is an efficient method for the synthesis of N,N'-diarylureas and N-aryl-N'-phenylureas; although valuable, substrates remain limited to *para*-substituted aryl bromides (**19a-c**).

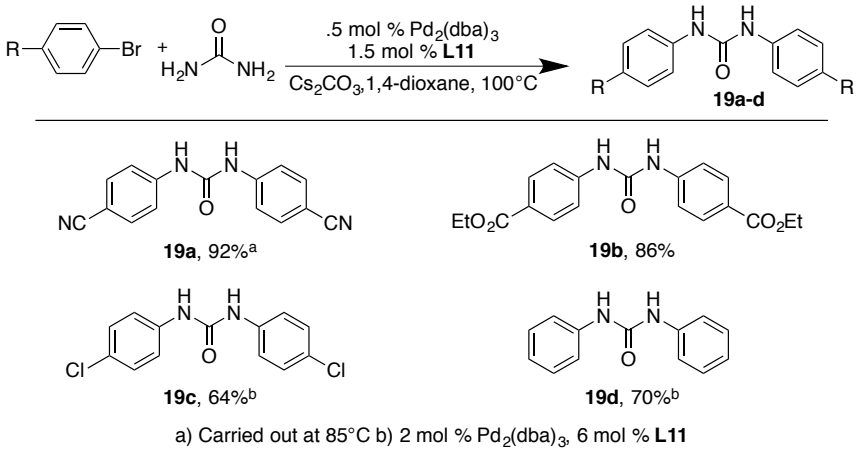


Figure 22. Application of amidation conditions to form symmetric diarylureas

With the goal of improved urea arylation, the Beletskaya group tested a series of xanthene-based bidentate ligands in palladium-catalyzed reactions.[41] They sought to speed up reductive elimination through electron-withdrawing substituents on the Xantphos backbone. They found that 3,5-$(CF_3)_2$Xantphos effected diarylation of ureas more effectively than **L11**. Using this ligand, the arylation of urea with unactivated aryl halides proceeded with yields of 62-98% (Figure 23). *o*-Substituted aryl bromides

gave the highest yields (**20a**) while *p*-substituted aryl bromides resulted in moderate yields (**19c, 20b**).

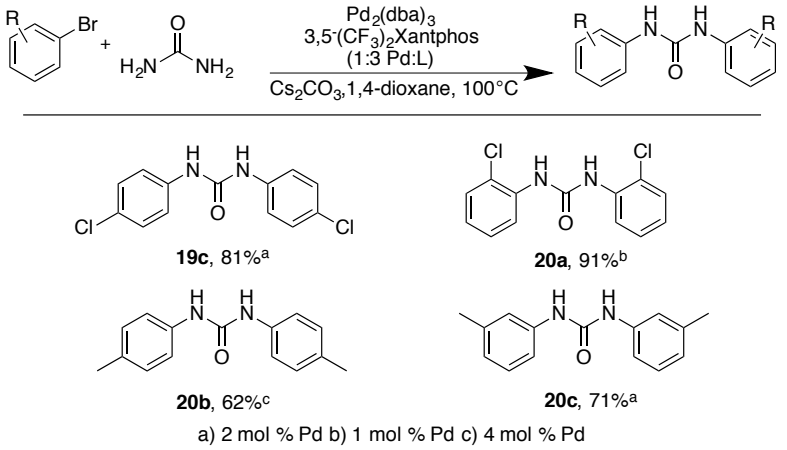


Figure 23. Formation of diarylureas through an electron-deficient L11 analog

The Abad group designed a regioselective method for the preparation of pyrinin-2-yl ureas using **L11**. For the first time, chloro-substituted starting materials were utilized in a palladium-catalyzed ureidation.[42] Optimal conditions are displayed in Figure 24. They were able to couple to a variety of substrates, including both aryl and aliphatic ureas. Initial reactions produced a number of side-products, displayed in Figure 24, so extensive optimization was carried out. A screen of base additives indicated that Cs_2CO_3 and NaO*t*-Bu were most effective, giving highest conversion and shortest reaction time, along with the smallest amount of side-products. The use of $Pd(OAc)_2$ reduced the amount of amine produced through an unwanted reduction (amines **23** and **24** in Figure 24). Reducing the amount of ligand below 6 mol % or lowering the temperature below 100°C decreased

the conversion. The presence of an equimolar amount of water with respect to the base was found to improve the reaction to give a nearly quantitative yield. Through these carefully selected conditions, side-product formation was suppressed to a large extent. Reactivity studies demonstrated that the 2-position of the pyridine is particularly reactive.

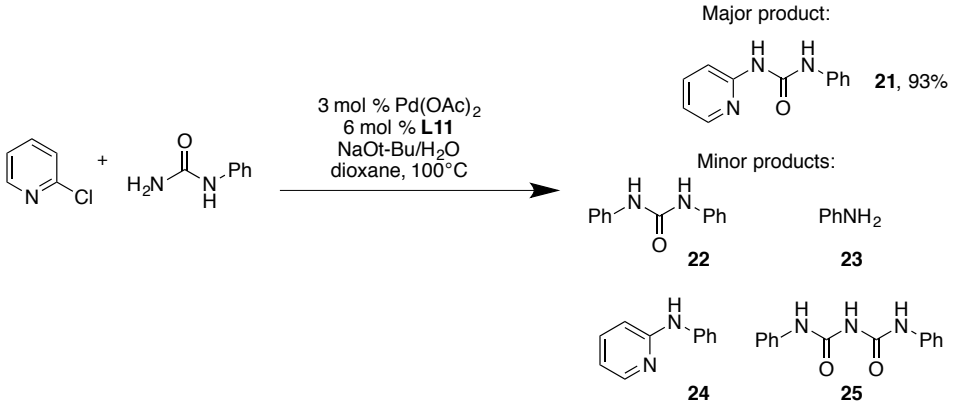


Figure 24. Regioselective preparation of pyrinin-2-yl ureas from chloro-substituted pyridines

McLaughlin *et al.* expanded this methodology to allow for the synthesis of cyclic ureas- a class of pharmaceutically important heterocyclic compounds. This regioselective protocol allows for the preparation of a variety of imidazopyridinones (**26a-c**) and benzoimidazolones (**26d-f**) from *o*-chloro-N-substituted arylamines in yields ranging from 70% to 99% (Figure 25).[43] After the discovery that **L11** promoted this reaction efficiently, they examined bis-(diphenylphosphino)butane (DPPB), a less expensive bidentate phosphine with a similar bite angle. Following substantial optimization, this transformation very efficiently provided imidazopyridinones from a series of pyridines when reduced catalyst loading

of 1 mol % $Pd(OAc)_2$ and 2 mol % DPPB was used (Figure 25). Unfortunately, this system was ineffective for the less activated *o*-haloanilines. They were forced to switch to the more expensive, yet highly active, XPhos (**L1**) ligand, for these more challenging substrates.

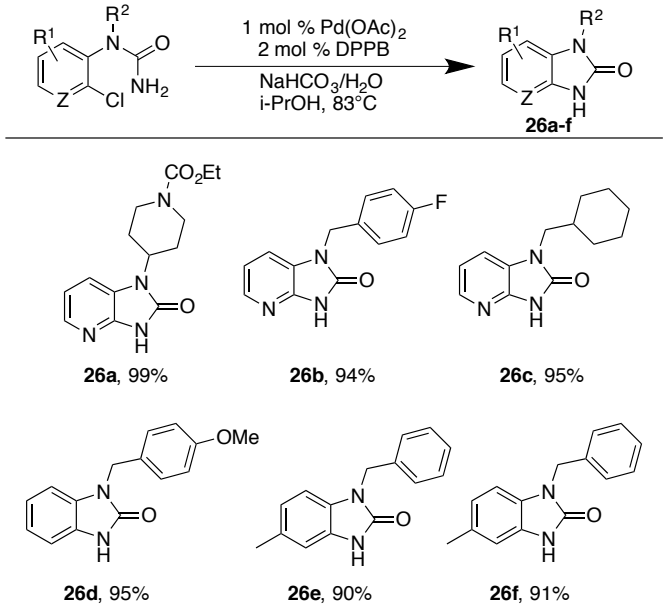


Figure 25. Use of a relatively inexpensive chelating ligand to form cyclic ureas

In 2009, Kotecki et al. reported an important breakthrough in palladium-catalyzed amidation through the synthesis of unsymmetrically substituted ureas using the nonproprietary ligand BippyPhos (**L9**).[44] The nonproprietary nature of **L9** makes it an especially attractive ligand for urea couplings in the pharmaceutical arena because of its lower associated costs. The Buchwald biaryl phosphine ligands have proven useful in these types of reactions; however, their proprietary nature makes them expensive and likely to slow drug development. With this in mind, several nonproprietary

ligands were screened for the coupling of aryl halides with ureas. The catalyst system employing **L9** with $Pd_2(dba)_3$ proved to be the most efficient, resulting in almost quantitative yields of the desired substituted urea. Thorough optimization expanded the reaction scope to include aryl chloride substrates with comparable efficiency to aryl bromides. The optimized conditions are displayed in Figure 26. These conditions enjoy high functional group tolerance and work well with both electron-deficient and electron-rich substrates (**27a-h**). The primary limitation to these conditions is the low conversion and formation of byproducts observed with sterically hindered aryl halides. For instance, when 2-chloro-1,3-dimethylbenzene was subjected to these amidation conditions, no product was detected (**27f**).

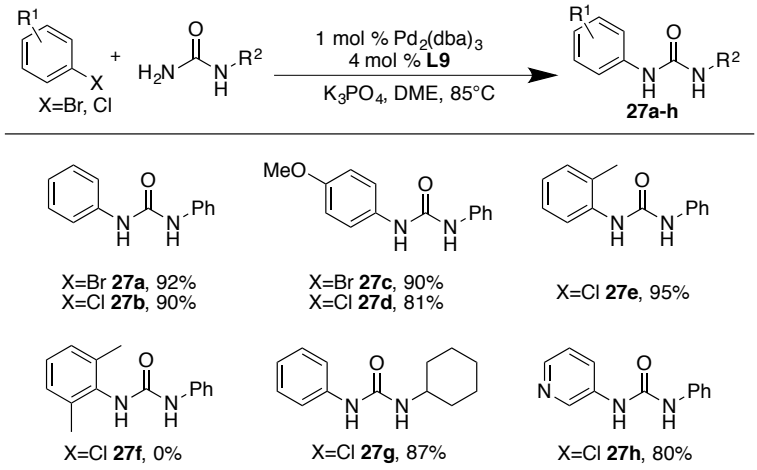
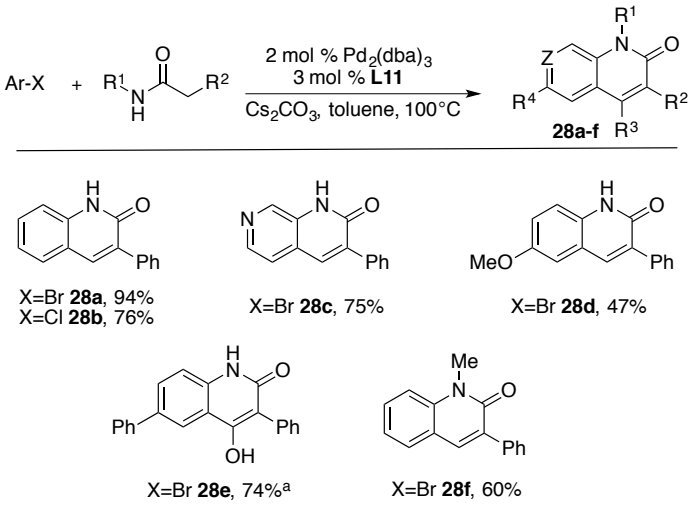


Figure 26. Formation of unsymmetrically substituted ureas though the employment of nonproprietary ligand L9

4.3 Formation of Bicyclic Heterocycles from Amides

In 2004, palladium-catalyzed amidation was used to devise a one-pot synthesis of naphthyridinones and quinolinones via a tandem amidation and

aldol condensation.[45] The enolizable carbon functionality of the o-carbonyl substituted aryl halide complicates this reaction as this moiety can undergo a competing α-arylation.[46] Buchwald's relatively mildly basic coupling conditions[16, 28] minimized the formation of the α-arylation by-product. Accordingly, the cross-coupling and subsequent dehydration reaction proceeded in only a few hours and gave good yields of the isolated products (Figure 27). This cascade reaction sequence offers much potential in the diversity of products. Both aryl bromides and aryl chlorides were effective coupling partners, but aryl chlorides required longer reaction times and resulted in slightly lowered yields (**28a**: 94%, 2 h, **28b**: 76%, 6h). Electron-rich aryl bromides could be transformed into the desired product but the yield was moderate (**28d**). The secondary amide *N*-methyl-2-phenrylacetamide performed well in this reaction, giving **28f** in a 60% yield, although this was the only secondary amide that was effective. Some substrates needed to be heated to reflux following the initial cross-coupling reaction in order to complete the cyclization (**28e**).



a) After initial cross-coupling, the reaction mixture was heated to reflux

Figure 27. Scope of reaction to form naphthyridinones and quinolinones through a tandem amidation/aldol condensation.

Recently, the Clark group applied palladium-catalyzed amidation to substituted heterocycles in order to derive a facile synthesis of imidazo-[4,5-b]pyridines and –pyrazines.[47] This method allowed for quick access to products with a wide range of substituents at N1 and C2. Ligand screening experiments were carried out to couple the *p*-methoxybenzyl substrate and formamide to form **29a**. The desired product was formed when **L3**, **L6**, **L7** and **L9** were employed, with the highest yields obtained in reactions involving **L3** and **L6**. Potassium phosphate and *tert*-butanol, previously shown to be successful in these types of transformations,[11] worked well; the desired product was formed in under 4 hours in all cases. Under these optimized conditions, a wide range of substrates was tested to explore the scope of the reaction. Several pyridines were reacted with formamide to explore the tolerance of these conditions to N1 substitution; representative products **29a-f** are shown in Figure 28. The reaction produced the desired

products in good to excellent yields when the N1 position was substituted with various benzyl derivatives (**29a-c**). Notably, an aryl chloride was tolerated under these conditions (**29d**). The reaction proceeded efficiently with N1 alkyl substituents (**29e**) and N1 chiral substituents (**29f**).

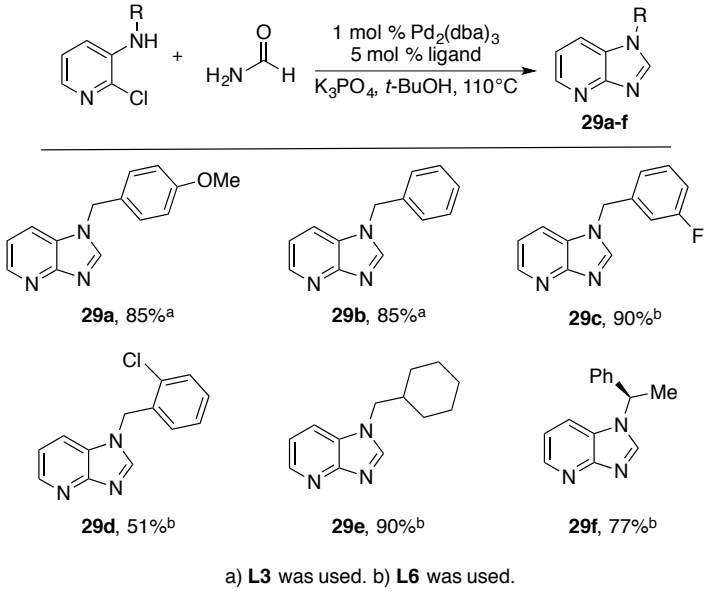
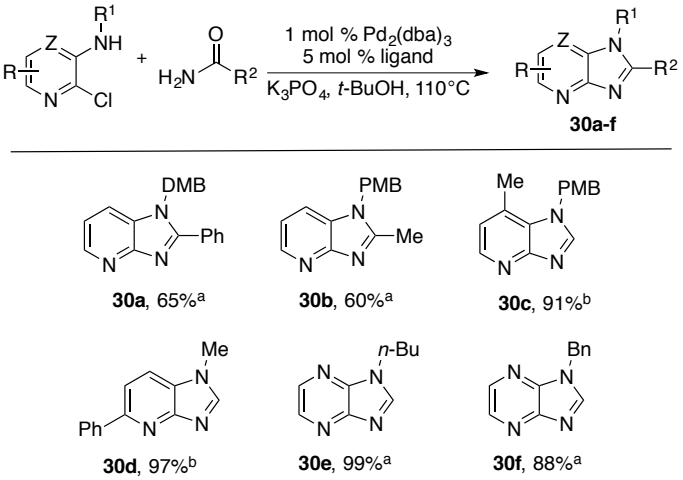


Figure 28. Scope of reaction, relative to varied substitution at N1.

Following successful demonstration of the tolerance of N1 substitution on pyridine substrates, the Clark group performed further experiments to couple varied amides with substituted pyridine and pyrazine substrates to explore the scope of the reaction conditions (Figure 29). Substitution at the 4- and 6-positions was well tolerated, providing the desired products in excellent yields (**30c**,**d**). Replacing formamide with benzamide or acetamide to give a substituent at the C2 position was slightly more challenging, but still afforded the product in an acceptable yield (**30a,b**). Pyrazine substrates (**30f**) reacted especially quickly, yielding the

desired product up to 8-fold faster than the pyridine analogs. Presumably, this is due to more facile oxidative addition with the electron-deficient pyrazine moiety.[47]



a) **L6** was used. b) **L3** was used.

Figure 29. General conditions for the formation of imidazo[4,5-b]pyridines and -pyrazines with varied substituents at the N1 and C2 positions.

Following success in these heterocycle-forming reactions, the Clark group explored the use of alternative ligands. Although effective, the monodentate ligands **L3** and **L6** are relatively expensive and can be difficult to obtain. Instead, bidentate phosphine ligands were evaluated. Long reaction times and low conversions were observed with **L12** and **L13**; **L11** resulted in optimal success. The use of **L11** required an extensive solvent screen. Previous studies have shown that alcoholic solvents result in little to no conversion when bidentate ligands are employed.[18, 35, 48] In an aprotic solvent, the reaction failed to go to completion despite extended reaction time. Presumably, an increase in solvent polarity aids conversion due to greater reactant solubility and stabilization of intermediates during

dehydration. Under this idea, polar aprotic solvents such as DMF, NMP, and diglyme were examined. However, full conversion was still not observed. The previous success of these transformations in *tert*-butanol indicated that a protic solvent might be necessary to mediate cyclization. The combination of these results led to the development of a mixed solvent system. Using 10:1 *tert*-amyl alcohol (*t*-amOH)/1,4-dioxane and **L11**, the desired product was isolated in 93% yield in only 6 hours.

With these optimized conditions, the scope of the reaction was explored. The modified conditions gave high yields with a variety of N1 substituents (Figure 30). Notably, the new conditions improved the yield of the 2-chlorobenzyl substrate, as it selectively coupled and was isolated in a 79% yield (**29d**). These modified conditions now tolerated electron-deficient N1 substituents (**31b**). A primary goal in switching to the bidentate ligand **L11** was to improve the amide scope of the reaction (Figure 31). With monodentate ligands, modification of the C2 substituent was limited to a methyl or phenyl group through the use of acetamide and benzamide, respectively. With these reagents, the desired products (**30a**,**b**) were obtained in moderate yields (60-65%). However, the new protocol improved the yield of the acetamide product (**30b**) to 83% and the benzamide product (**30a**) to 78%. Incomplete or no cyclization was observed when cyclohexanecarboxamide and trans-cinnamide were used as coupling partners under the previous conditions; however, these amides produced the

desired product in 44% and 97% yields, respectively, under the modified conditions. Pyrazines continued to perform well, providing **30f** in 95% yield.

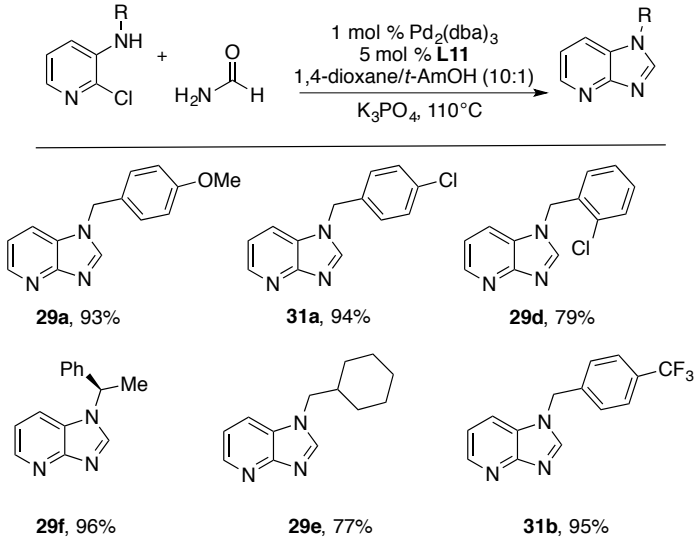


Figure 30. Modified conditions for the formation of imidazo[4,5-b]pyridines carrying N1 substituents.

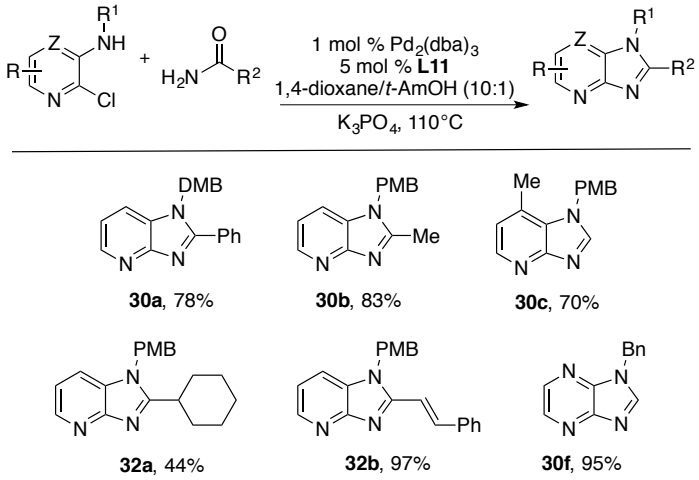


Figure 31. Reaction scope for the formation of imidazo[4,5-b]pyridines and -pyrazines with new protocol.

4.4 Formation of Enamides

Enol triflates can often substitute for aryl halides in a wide range of palladium-catalyzed reactions, including C-N bond forming reactions.[49] In

2003, Wallace reported a simple synthesis of enamides through the extension of palladium-catalyzed amidation to enol triflate substrates.[50] This transformation was efficient when carried out with **L11** and Cs_2CO_3 (Figure 32). Other bidentate ligands gave little to no desired product. At higher temperatures (80°C), isomerization of the double bond occurred and a 1:1 mixture of products was observed. To counteract this issue, the temperature was lowered to 40-50°C and the reaction time was limited to 8 hours. While lower temperatures and shorter reaction time facilitated stereoselective synthesis, only moderate conversion was observed. With substrates unable to isomerize, longer reaction time and higher temperatures resulted in complete consumption of the starting material and afforded high yields of the enamide. This reaction requires electron-withdrawing substituents (**33d**) or conjugation (**33a-c,e**) in order to provide useful product formation. Accordingly, the formation of **33f** was not detected from subjecting the appropriate starting materials to the same conditions. Similar to amidation of aryl halides, acyclic secondary amides were found to be unreactive. Selective coupling an enol triflate in the presence of an aryl bromide is effective, resulting in only the enamide product that retains the bromide.

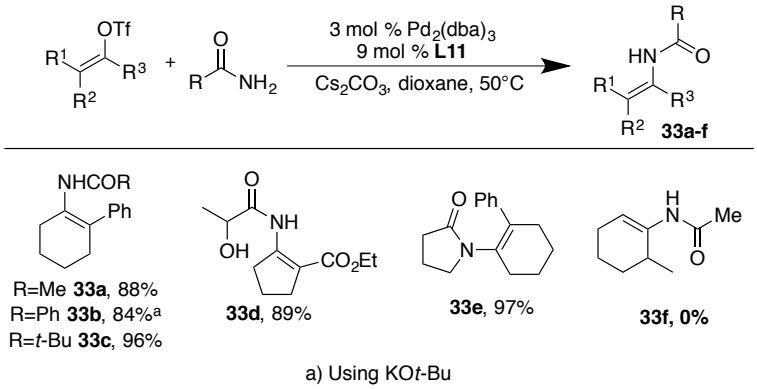


Figure 32. General conditions for the regioselective synthesis of enamides

An analogous reaction was carried out with enol tosylates by Klapars *et al*.[51] However, these substrates proved more challenging because the tosylates are orders of magnitude less reactive than the corresponding triflates due to leaving group ability.[52] Enol-tosylates are attractive reagents since they are typically less expensive then triflates and exist as crystalline solids, which simplifies purification and isolation. Monodentate phosphine ligands gave poor to moderate yields, while chelating bidentate ligands were much more successful. **L11** effectively catalyzed only sterically unhindered substrates, while **L15** proved to be a more universal ligand. This is the first application of **L15** as an ancillary ligand for palladium-catalyzed C-N coupling reactions. The choice of base was found to be substrate dependant, with K_2CO_3 working best for less hindered vinyl tosylates and K_3PO_4 preferred for more hindered tosylates, as in Figure 33. $Pd_2(dba)_3$ proved to be the ideal palladium source, giving increased reaction rates and higher conversions than $Pd(dba)_2$ or $Pd(OAc)_2$. As with enol triflate substrates, isomerization proved to be an issue even after the coupling reaction was

complete. A higher ratio of the desired product to the unwanted isomer was observed with bulkier amides and shorter reaction times. For example, enamide **34a**, with a methyl substituent from the original amide, formed in a 10:1 Z/E ratio. Enamide **34b**, on the other hand, formed in a much higher proportion of the desired isomer due to the replacement of the methyl group with a bulky *tert*-butyl substituent (>50:1 Z/E). While these amidations tolerate steric hindrance well, the substrate scope of this reaction is limited to enol tosylates with an aryl substituent or an electron-withdrawing group at the β-position of the double bond.

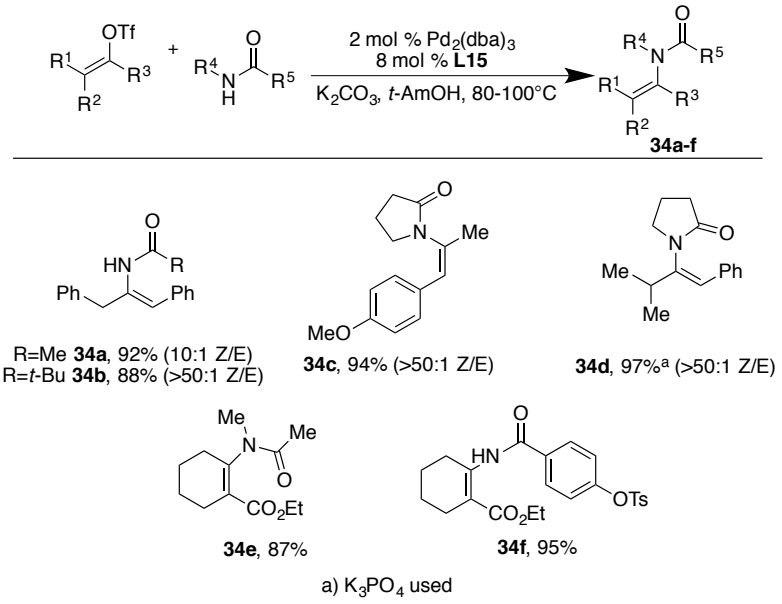


Figure 33. Coupling of enol tosylates through a chelating ligand L15.

The Willis group expanded the substrate scope of this reaction through ligand screening. Originally, monodentate phosphine ligands were thought to be ineffective. However, under optimized conditions, **L2** was found to give the desired product from both enol triflates and enol tosylates

in high yields (Figure 34).[53] Alkyl, aryl, and alkenyl amides all coupled in good yields, along with carbamates (**35a-f**). Product decomposition was observed when the reaction was carried out at temperatures higher than 80°C in *t*-BuOH. Previously, effective substrates conjugation or an electron withdrawing substituent required. With this catalyst system, the amidation of enol sulfonates proved to be successful on substrates that do not contain an activating substituent.

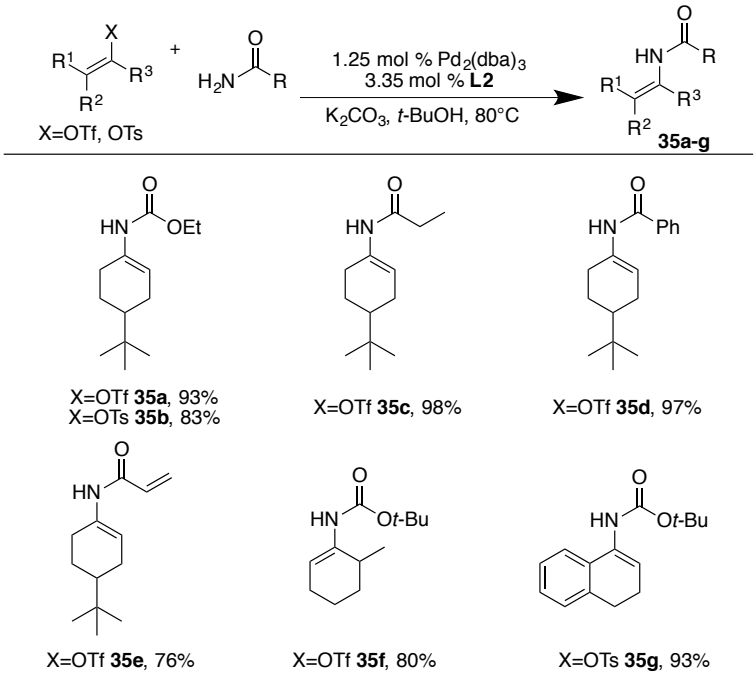


Figure 34. Application of a monodentate ligand to enamide formation from enol-triflates and enol-tosylates.

4.5 Coupling with Secondary Amides

Acyclic secondary amides have proven to be a challenging substrate class due to their low nucleophilicity (relative to hydroxide) and large size. As a result, previous catalyst systems that worked well for the coupling of

amides, ureas, carbamates and sulfonamides have largely failed on acyclic secondary amides.[16, 20-21, 28] Recently, a new ligand, JackiePhos (**L10**), was designed specifically for amidations of secondary amides following synthetic, mechanistic, and computational studies.[10] The critical elements of this ligand include an *ortho*-methoxy group on the biaryl scaffold and two strong electron-withdrawing P-bound 3,5-(bis)trifluoromethylphenyl groups. The electron-deficient nature of this ligand helps to facilitate amide binding, the rate-limiting step.

Reaction optimization for amidations with **L10** provided desired products with a wide range of substrates in good yields. The use of a nonpolar solvent such as toluene was found to be critical. Use of 3Å molecular sieves improved product yields by preventing hydrolysis of the amide by adventitious water. The precatalyst $[Pd(allyl)Cl]_2$ was chosen as the palladium source for its ease of use. Electron-deficient, electron-neutral, and moderately electron-rich aryl nonaflates all reacted efficiently under these conditions (Figure 35). Aryl nonaflates coupled selectively in the presence of a chlorine substituent (**36g**). Due to their resistance to hydrolysis, aryl nonaflates were the substrate of focus but aryl triflates were also shown to be effective.

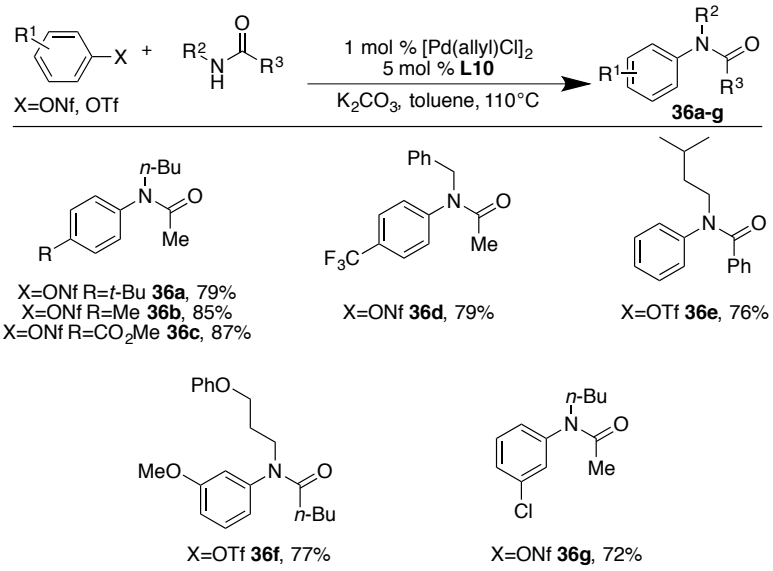


Figure 35. Optimized conditions for the coupling of secondary amides with aryl nonaflates and aryl triflates through the use of L10.

This methodology was expanded to chlorine substrates through increased reaction temperature and a change of base from K_2CO_3 to Cs_2CO_3 (Figure 36). This reaction became more challenging with hindered amides (**37b**), but provided good yields for less bulky coupling partners.

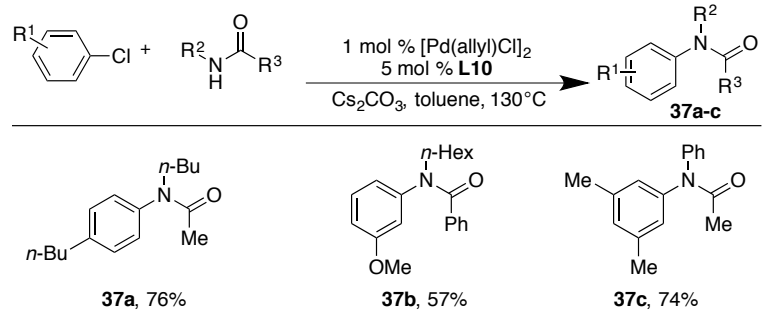


Figure 36. Pd-catalyzed coupling of secondary amides with aryl chlorides

The JackiePhos ligand also improved the scope of reactions with secondary carbamates, ureas, and sulfonamides (Figure 37). Substituted

ureas remained difficult substrates but did couple with electron-deficient nonaflates (**38a**). Secondary carbamates and secondary sulfonamides proved to be highly efficient substrates under the new conditions. This development was significant because it was the first cross-coupling of N-alkyl carbamates (**38b**) and the first intermolecular coupling of N-alkyl acyclic sulfonamides (**38c**).

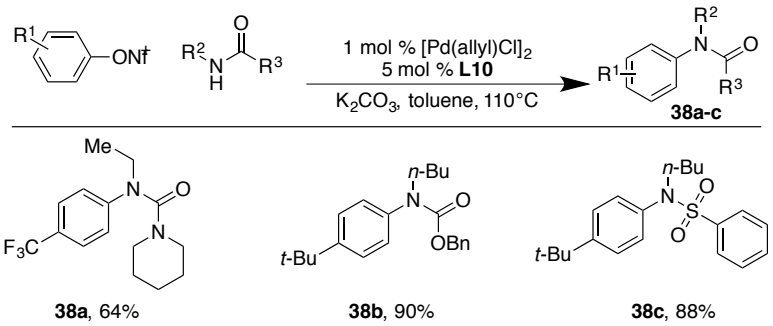


Figure 37. Pd-catalyzed coupling of aryl nonaflates with secondary ureas, carbamates, and sulfonamides.

Chapter 5

Applications

From the beginning, synthetic chemists realized the power of this transformation and harnessed C-N amidation for drug development and the synthesis of biologically important molecules. In 1998, Snider *et. al*. reported the total synthesis of (-)-Asperlicin, a cholecystokinin (CCK) receptor antagonist, using a palladium-catalyzed intramolecular cyclization between a carbamate residue and an indole as the key transformation (Figure 38).[54] This CCK antagonist is a useful investigative tool and offers therapeutic potential in pancreatic disorders. Additionally, methodology developments in amide coupling have allowed rapid synthesis of diaryl benzamide derivatives. These compounds display biological activity as nuclear receptor binding agents.[55] Another biological molecule of interest, a TRPV1 receptor antagonist, was synthesized through the novel palladium-catalyzed amidation of a substituted urea with an indazole employing the nonproprietary ligand **L9**.[56] Attractive pharmaceutical molecules, these receptor antagonists offer a non-NSAID, nonopiate alternative to pain relief. These amidation conditions were also employed to synthesize a class of biologically significant molecules: amide substituted purine derivatives.[57] These purine derivatives were found to exhibit anti-HIV integrase activity.

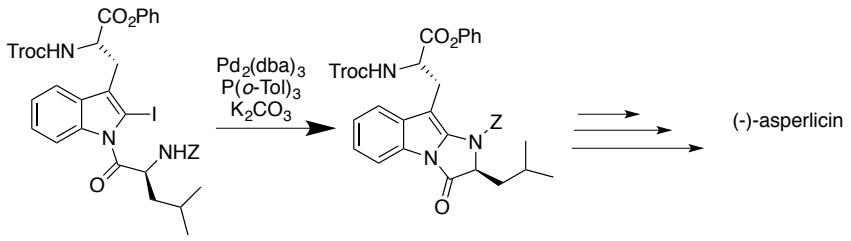


Figure 38. Palladium-catalyzed amidation as key step in (-)-asperlicin synthesis.

The expansion of amidation conditions to heterocycle substrates is critical to biological and pharmaceutical applications of this methodology. Much work on the derivation of improved amidation conditions began with a focus on the synthesis of imidazo[4,5-b]pyridines. Derivatives of this moiety possess a broad range of biological activity. They have been shown to exhibit anticancer,[58] antiviral,[59] and several other important therapeutic properties.[60] For instance, many derivatives displayed inhibitory properties against serine/threonine kinases that are overexpressed in numerous cancers.[61] One derivative has been shown to possess activity at two receptors, an angiotensin II type 1 receptor and peroxisome proliferator-activated receptor-γ, which play a role in cardiovascular risk factors.[62] Other derivatives may also help prevent stroke or septic shock through their activity as selective nitric oxide synthase inhibitors.[63]

Access to this imidazo[4,5-b]pyridine core laid the foundation for a facile synthesis of the natural product pentosidine (Figure 39). Increased levels of this advanced glycation end product (AGE) have been observed in patients with diabetes, end-stage renal failure, kidney dysfunction, and various aging disorders.[64] The characteristic fluorescence of pentosidine

makes it a useful biomarker for these diseases as it is easily measured in the body. However, a regioselective synthesis has proven challenging; early synthetic methods have been low yielding, required 18-19 steps, or began with expensive *o*-diaminopyridine starting materials.[65] However, optimized Buchwald-Hartwig amidation conditions allowed for the total synthesis of pentosidine from 3-amino-2-chloropyridine in only 6 steps.[66]

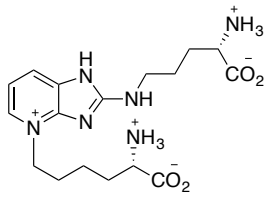


Figure 39. The natural product Pentosidine, featuring an imidazo[4,5-b]pyridine core.

Chapter 6

Conclusions

This review summarizes advances in palladium-catalyzed amidation chemistry, pioneered by John Hartwig and Stephen Buchwald. Mechanistic investigations that led to more efficient catalyst systems are discussed, along with how these advanced ligands expanded the substrate scope. A facile and efficient synthesis of amide bonds is desirable due to their ubiquity in natural products and pharmaceuticals. Palladium-catalyzed reactions offer the scalability, efficiency, and functional group tolerance to fulfill this need. This review increases the practicality of amidation applications through the concise analysis of previous work. Through this collection of progress in the field, this review will aid in reaction sequence development. As such, palladium-catalyzed amidation conditions holds promise in the advancement of synthetic and medicinal chemistry.

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Summary of Capstone Project

Stephen Buchwald and John Hartwig, two pioneers in the field of organometallic chemistry, separately developed conditions for the palladium-catalyzed formation of carbon-nitrogen bonds in 1995 through the reaction of amines with aryl substrates bearing halogen substituents. These conditions, now known as Buchwald-Hartwig amination conditions, are extremely applicable in the formation of aryl substituted amines. Shortly after, these conditions were expanded from amine substrates to amide substrates. This reaction proved more challenging but promising due to the potential utility of the product.

The synthesis of amide bonds is attractive due to the ubiquitous nature of these linkages in biological systems. Amide bonds link amino acid building blocks to form proteins. Accordingly, amide bond formation is a critical tool in natural product synthesis. Additionally, an extensive collection of pharmaceuticals contains amide bonds. For example, Atorvastatin, the top-selling drug in the United States in 2012 that is prescribed to lower blood cholesterol, contains a key amide linkage.

The Buchwald-Hartwig amidation reaction is an extremely useful method to form these amide bonds. Through the use of a palladium catalyst, phosphine ligand and base, a wide range of aryl substrates with halogen substituents can be coupled with amides. In practice, the choice of ligand, base, solvent, temperature, and catalyst loading are all highly dependent upon the functional groups on the aryl substrate and the selected amide. In

this review, I sought to explore previous advances in amidation reactions and understand how various changes in conditions affect the reaction.

In order to develop a strong understanding of why and how changes in the reaction conditions affect the scope of the reaction, I investigated the mechanism of the reaction. Both bidentate and monodentate phosphine ligands prove useful in these transformations. Bidentate ligands coordinate at two sites to the palladium to form the active catalyst species; this is typically accomplished through two phosphine groups in the ligand. Monodentate ligands, with only one phosphine, coordinate once to the metal to form the active catalyst. The general catalytic cycle that the reaction proceeds through is essentially the same with both types of ligands, but there are a few critical differences. It is important to understand these differences when selecting the ancillary ligand or designing a new ligand to effect a specific transformation.

My understanding of the effects of varied conditions on the scope of reaction began by applying amidation conditions in my own laboratory work. Goals to synthesize pentosidine, an important natural product, drove my initial work with amidation reactions. Through a one-pot amidation, the imidazo[4,5-b]pyridine core of this natural product could be synthesized from accessible and cheap starting materials. Imidazo[4,5-b]pyridines are bicyclic nitrogen-containing aromatic compounds. Due to the pervasiveness of this scaffold in biological systems, we focused on improving the synthesis of these heterocycles with varied substituents. We began to explore a wide

variety of solvents, bases, ligands, pyridine substrates, and amides to carry out this one step transformation.

I sought to expand these laboratory investigations of conditions through literature research into prior studies. In general, advances in amidations have not followed a linear progression toward a single, advanced method, with each new study an improvement upon previous ones. Instead, newer publications typically provide additional "tools" for the synthetic chemist and broaden the range of viable substrates and conditions. However, in the beginning, when amidation reactions were initially published, each subsequent publication essentially improved upon this brand-new method. For this reason, I present my review in loosely chronological order, with a greater focus on more recent studies that are more applicable. When considering each development, I included the scope of the reaction and limitations of the specified conditions.

I chose to consider amidations with ureas and aryl chlorides separately due to the applicable, yet challenging, nature of both types of molecule. The aryl and heteroaryl substituted urea motif is common in biological systems, but typical synthetic routes to these molecules involve hazardous and toxic chemicals. Aryl chlorides are much cheaper and more readily available reagents than the corresponding aryl bromides or iodides. However, aryl chlorides prove to be the most difficult substrates in cross-coupling reactions. These substrates typically require longer reaction times and give lower yields. In early amidation studies, aryl chlorides completely

failed to couple and no desired product was detected. Due to this practicality of both aryl chlorides and ureas, expansion of amidations to both ureas and aryl chlorides was a step-wise, yet important, breakthrough in amidation chemistry.

I also provided a separate discussion of amidations with heterocycles substrates due to the practicality of reactions with heterocycles, their unique reactivity, and our group's focus on these substrates. The inclusion of nitrogen in the aromatic ring modifies the reactivity at various positions. This can make these substrates more reactive toward certain transformations, but it can also increase susceptibility toward unwanted side reactions. Developing conditions toward modular heterocycle synthesis and functionalization is useful in medicinal chemistry. For example, sixty imidazo[4,5-b]pyridine derivatives were recently tested for inhibitory activity against serine/threonine kinases that are overexpressed in many cancers. Step-wise modification of the heterocycle scaffold would allow easy access to derivatives in similar studies.

Through extensive research into published explorations of amidation chemistry, I found that both monodentate and bidentate ligands formed effective catalyst systems. Additionally, the substrate scope of these reactions is quite extensive. Conditions to tolerate many solvents, varied temperatures (as low as room temperature), a range of aryl substrates, different bases, and both primary and secondary amides have all been developed and improved in the last decade. The diversity of the aryl group is

significant. Successful coupling partners include aryl substrates bearing a range of halogen or psuedohalogen substituents, heteroaryl substrates, sterically hindered aryl halides, and aryl halides of any electronic state.

Due to the biological significance of amide bonds and the potential utility in pharmaceuticals, the desire for a facile synthesis of amides bearing aryl substituents clearly exists. Additionally, palladium-catalyzed reactions offer the scalability, efficiency, and functional group tolerance to fulfill this need. However, practical application of this method relies on the ability to easily tailor the method to a specific set of constraints. This project increases the feasibility of amidation application because it aids in reaction sequence development. Whether developing starting materials, synthesizing natural products, or working in drug design, this review will assist synthetic endeavors to develop conditions. Rather than carrying out extensive optimization studies, this collection and analysis of previous work will help chemists quickly select effective conditions, based on given limitations, such as deactivating functional groups. This holds promise for the field of medicinal chemistry, as a way to speed drug development and natural product syntheses.

Countless reviews on Buchwald-Hartwig aminations increased the practicality of this C-N bond forming sequence. As a result, aminations are now key steps in many syntheses, including biological molecules and pharmaceuticals. Similarly, I hope to expand the viability of the related, yet

chemically distinct, amidation sequence through the publication of this review.