PALLADIUM-CATALYZED C–H BOND FUNCTIONALIZATION OF HETEROCYCLES AND AMINES

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Enrico Tapire Nadres

August 2012

PALLADIUM-CATALYZED C–H BOND FUNCTIONALIZATION

OF HETEROCYCLES AND AMINES

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ABSTRACT

Palladium-catalyzed functionalization of C–H bonds is becoming an important synthetic tool that allows the preparation of desired substances in fewer steps and higher yields compared to traditional synthetic routes. The C–H bonds can be directly converted to C–C or C–heteroatom bonds. However, the ubiquity of C–H bonds in organic compounds can lead to problems in chemo- and regioselectivity.

In heterocycles, the control of regioselectivity of the reaction is governed by the difference in acidity of the heterocyclic ring C–H bonds. An economical method for the arylation of C–H bonds of pyrroles and furans by aryl chlorides was developed. The method employs a palladium acetate catalyst, 2-(dicyclohexylphosphino)biphenyl ligand, and an inorganic base. Electron-rich, electron-poor, and heterocyclic aryl chloride coupling partners can be used and arylated heterocycles are obtained in moderate to good yields.

The functionalization of sp^2 and sp^3 C–H bonds can be promoted by the use of directing groups that coordinate the Pd catalyst and activate the desired C–H functionalities. Use of $Pd(OAc)_2$ in conjunction with cesium acetate or potassium carbonate bases allows functionalization of sp^2 and sp^3 C–H bonds in amides possessing picolinic acid directing group. Stoichiometric silver additive is not required in contrast with previously published procedure. Arylations are effective for sp^2 as well as primary and secondary sp^3 C–H bonds. Alkylations of sp^2 C–H bonds are successful in most cases. Both primary and secondary alkyl iodides are reactive but secondary alkyl iodides afford low yields. Alkylation of sp^2 C–H bonds is low yielding and the reaction requires

further optimization. Alkyl and aryl iodides as well as benzyl bromides are reactive. Aryl and alkyl bromides afford no product.

Direct conversion of C–H bonds to C–N bonds was also developed. Pd-catalyzed method for pyrrolidine, indoline, and isoindoline formation by cyclization via C–H/N–H coupling is presented. The method employs a picolinamide directing group, $PhI(OAc)_2$ oxidant, and toluene solvent at 80–120 °C. Cyclization is effective for sp^2 as well as aliphatic and benzylic sp^3 C–H bonds.

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LIST OF ABBREVIATIONS

Alk	alkyl
Am	amyl
Ar	aryl
BINAP	1,1′-Binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*t*-butoxycarbonyl
bpy	2,2’-bipyridine
Bu	butyl
Bz	benzoyl
cod	cyclooctadiene
CMD	concerted metallation–deprotonation
Cy	cyclohexyl
dba	dibenzylacetone
DCE	dichloroethane
DCM	dichloromathane
DMA	dimethyl acetamide
DMSO	Dimethyl sulfoxide
DMF	dimethylformamide
dppm	diphenylphosphinobutane
dppf	diphenylphosphinoferrocenyl
Et	ethyl
EWG	electron-withdrawing groups
FG	Functional group
Ile	isoleucine
L	ligand
M	metal
Me	methyl
MS	molecular sieves
NHC	*N*-heterocyclic carbene
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	nosyl
Pd	palladium

Ph	phenyl
Piv	pivaloyl
Pr	propyl
RT	room temperature
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tol	tolyl
Tf	triflyl
Ts	tosyl

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CHAPTER 1

Mechanisms of Pd-catalyzed C–H Functionalizations

Palladium offers unparalleled versatility as a catalyst in the construction of organic molecules.[1] A variety of substrates can undergo cross-couplings, and the reactions are named depending on which starting materials are used (Scheme 1.1).[2]

Scheme 1.1. Pd-catalyzed cross coupling reactions

$$R^1\text{–}X \;+\; R^2\text{–}Y \xrightarrow{\text{Pd catalyst}} R^1\text{–}R^2$$

R^1–X (X=I, Br, Cl)	R^2–Y	Name of reaction
organohalides	alkenes	Heck[3]
organohalides	boronic acids	Suzuki–Miyaura[4]
organohalides	organotin	Stille–Migita–Kosugi[5]
organohalides	organosilicon	Hiyama[6]
organohalides	alkynes	Sonogashira[7]
organohalides	organozinc	Negishi[8]
organohalides	Grignard reagents	Kumada−Corriu–Tamao[9]
organohalides	amines	Buchwald–Hartwig[10]
arenediazonium salts	alkenes	Heck-Matsuda[11]
allylic compounds	nucleophiles	Tsuji-Trost[12]
C–X or C–H	C–H	Direct cross coupling[13]

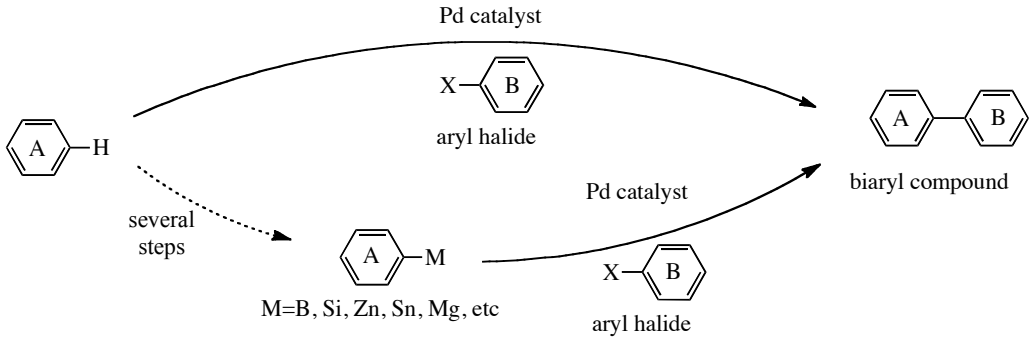
Palladium-catalyzed reactions are surprisingly chemoselective, tolerating different functionalities including carbonyl, carboxy, and hydroxy groups.[14] Many of palladium-catalyzed reaction methodologies are not moisture, air or acid/base sensitive. Enantioselective reactions have been developed.[15] The possibility of catalyst recovery and recyclability makes many palladium catalyzed reactions attractive on industrial scale.[16]

The power of Pd catalysis has been shown also in total synthesis.[17] Many total syntheses have been completed using at least one step that utilizes palladium catalyst.[18] Recently completed total syntheses that rely on Pd-based reaction for its key step includes bryostatin (Trost),[19] complestatin (Boger)[20] and piperarborenines (Baran).[21]

The practicality of Pd-catalyzed reactions has been demonstrated by performing the reactions on industrial scale.[22] For example, preparation of arylpiperazines, arylhydrazines, and diarylamines, which are common subunits and intermediates in pharmaceutical drugs, were successfully scaled up using Buchwald-Hartwig reaction.[23]

While methods such Suzuki and Stille are very powerful in terms of selectivity and mildness of reaction, the boronic acid and the organotin coupling partners have to be synthesized if they are not available from commercial sources. The use of organometallics as coupling partners involves additional steps in the synthetic sequence. Use of the C–H bond as functional group would allow shorter synthetic schemes by excluding the need to convert the starting materials to halides or organonometallic intermediates (Scheme 1.2).

Scheme 1.2. Cross coupling of arenes



I. Mechanisms of Pd-catalyzed C–H functionalizations

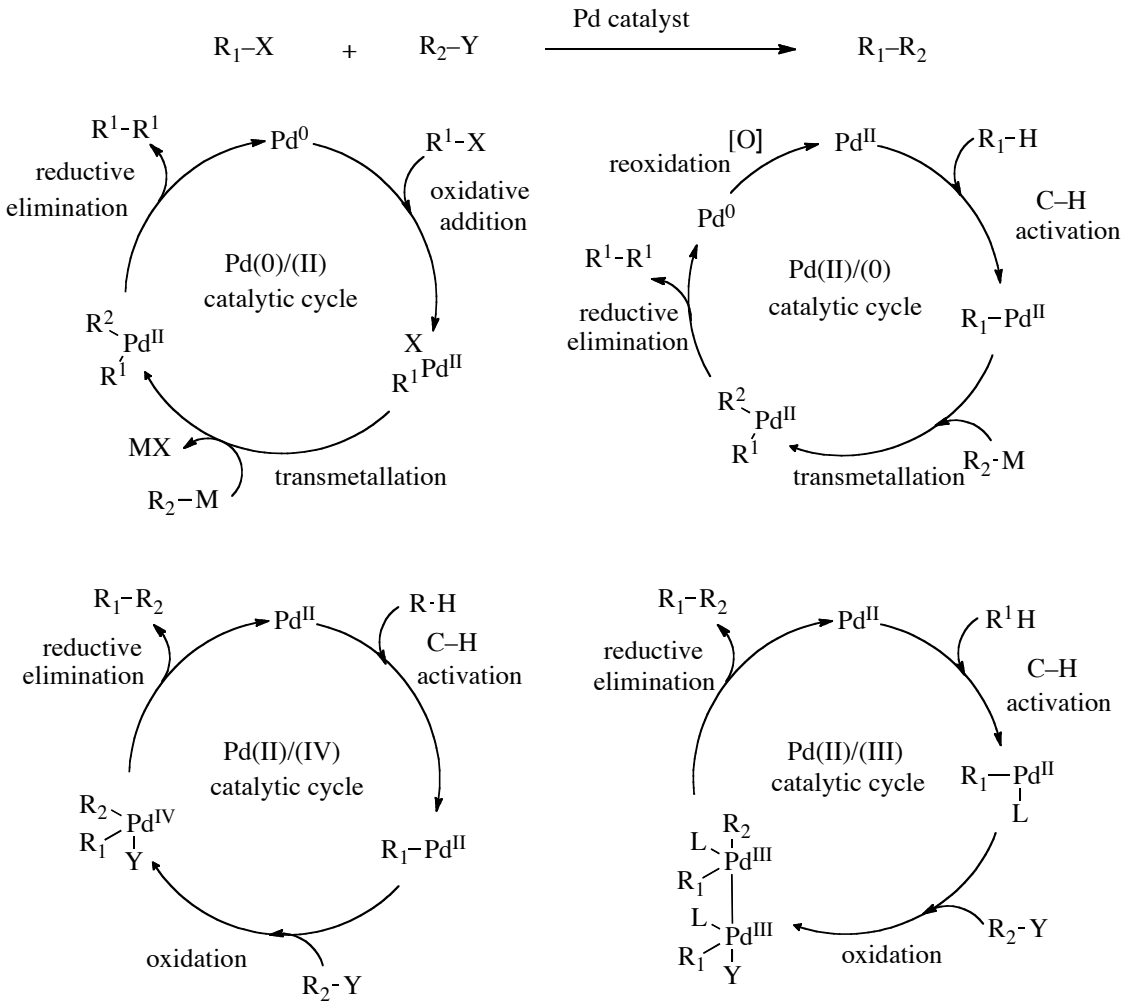
The straightforwardness of C–H activation methodologies can provide atom-economic and cost effective method of synthesis for desired compounds. Novel disconnections arising from C–H functionalization are also being discovered.[17] These synthetic advantages of C–H functionalization have led to the development of various methods that utilize palladium in different catalytic modes. General mechanisms of these methods are outlined in Scheme 1.3.[24]

In Pd (0)/(II) catalytic cycle mode, the organohalide undergoes oxidative addition to the Pd(0) complex, followed by transmetallation with an organometallic compound. Reductive elimination affords the product and regenerates the catalyst.[25] In Pd(II)/(0) cycle, Pd(II) species is introduced into the ring by a C–H activation process. Transmetalation of the organometallic compound follows. Reductive elimination generates the product and Pd(0) species. The Pd(0) species is reoxidized to the active Pd(II) form.

In the Pd (II)/IV) catalytic mode, the Pd(II) activates one of the C–H bonds of the substrate. The other organic fragment is introduced by oxidative addition to form Pd(IV) species. Reductive elimination forms the product and regenerates the catalyst.[26] Alternatively, the Pd(II) is oxidized to Pd (IV) by external oxidant prior to the C–H activation step.[27] In a related cycle, the Pd(II) species activates one of the C–H bonds of the substrate. This is followed by oxidation to form a bimetallic Pd(III)–Pd(III) species. Reductive elimination affords the product and regenerates Pd(II) species.[28]

Different methodologies have been developed to accommodate various substrates. Reaction conditions such as solvents, bases, oxidants, and other additives dictate the actual mechanism by which the C–H functionalization occurs.

Scheme 1.3. Different modes of reactions for Pd-catalyzed coupling reactions



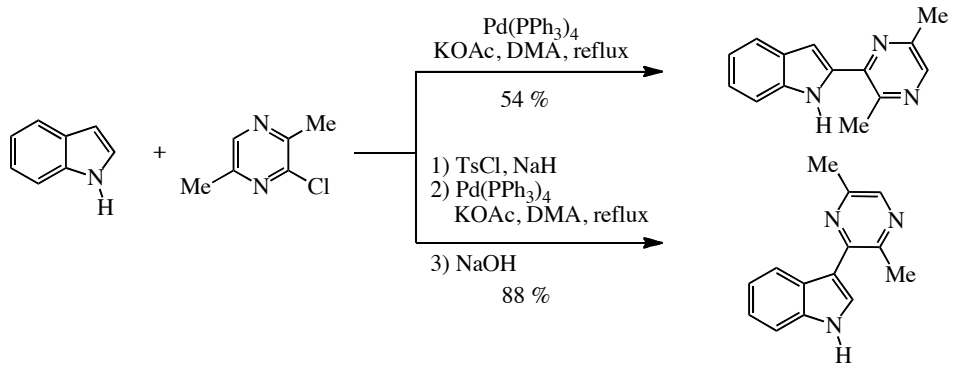
II. Pd(0)/(II) catalytic cycle

Early attempts of direct arylation of heterocycles such as pyrroles and indoles[29] involved the use of stoichiometric palladium as promoter of the reaction. Subsequently, catalytic version of indole arylation was developed using chloropyrazine coupling partners.[30]

Installation of aryl groups on indoles provides a challenge for direct C–H activation methodology since mixture of products from arylation at C–2 and C–3 positions is usually obtained. It is often necessary to use *N*-protected indoles since the use of free *N*H-indoles affords mainly *N*-arylated products. Various factors such as nature of substituents, substitution pattern on the indole nucleus, ligand, base, and solvent determines the regioselectivity of the arylation reaction.

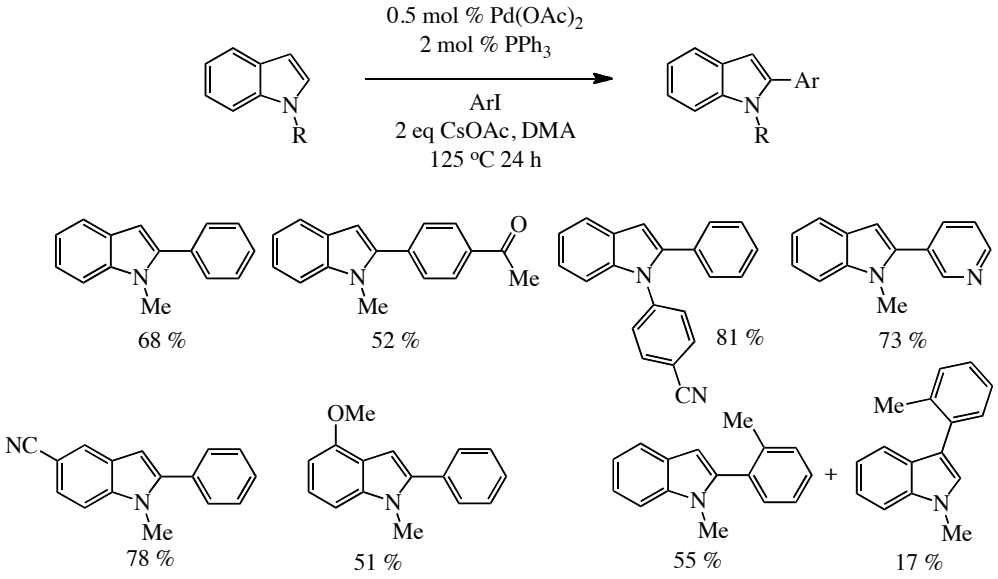
The Pd-catalyzed direct arylation of indoles by using 2-chloropyrazines as the coupling partners was reported in 1985 (Scheme 1.4).[30] The reaction is important since it demonstrated that arylation of indole can be performed regioselectively to give 2-arylindoles. The preference can be switched to provide the 3-arylated products by installing electron-withdrawing *N*–tosyl group.[31]

Scheme 1.4. Early examples of regioselective arylation of indoles



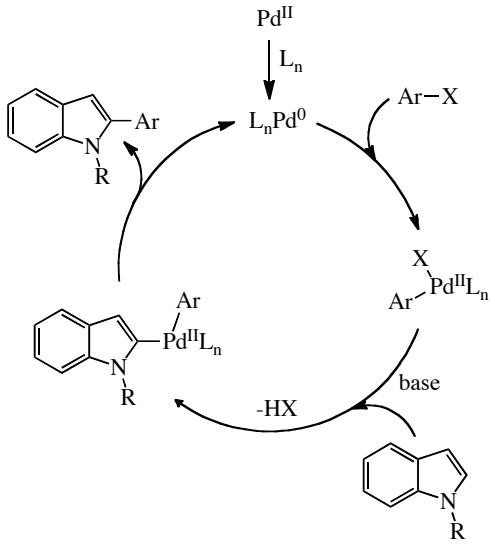
A more efficient Pd-catalyzed direct arylation method for indoles was developed in 2004. Using a combination of $Pd(OAc)_2$ and PPh_3 ligand, a wide variety of aryl iodides can be used in the arylation. (Scheme 1.5).[32] The reaction requires low catalyst loadings and the formation of by-products arising from homocoupling of aryl iodides was suppressed. However, a mixture of regioisomers was still observed, when aryl halides with *ortho*-substituents were used.

Scheme 1.5. Regioselective arylation of indoles



The mechanism of the arylation of heterocycles involves a Pd(0)/(II) catalytic cycle (Scheme 1.6). If Pd(II) precatalyst is used, phosphine will reduce it to Pd(0).[33] The aryl halide enters the cycle by oxidative addition[34] to the Pd(0) species[35] resulting in a Pd(II) complex. This is followed by base-assisted introduction of the Pd(II) moiety into the heterocycle. There are two mechanisms by which palladium may activate the heterocycle ring. First, electrophilic addition process may occur for some substrates. Second, the C–H activation may proceed by concerted deprotonation-metallation. Subsequent reductive elimination affords the product and regenerates Pd(0) catalyst.[36]

Scheme 1.6. General mechanism for the arylation of indoles with aryl halides

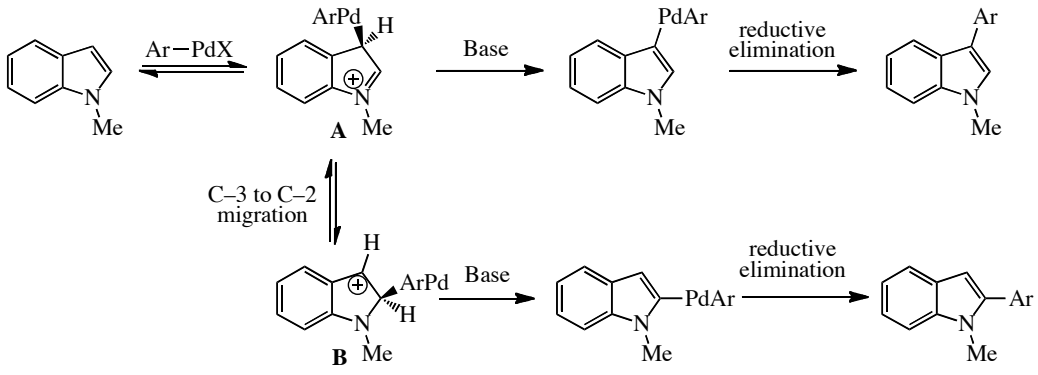


A. Electrophilic aromatic substitution (S_EAr) mechanism

1. Arylation of indoles

Installation of aryl groups on indoles provides a special challenge using direct C–H activation methodology since mixture of products from arylation of the C–2 and C–3 positions can be obtained. The mechanism of the indole arylation was elucidated using *N*-methylindole to explain the observed regioselectivity. It was found that there is a large kinetic isotope effect (k_H/k_D=1.6) for the arylation of C–3 position even if the aryl group was not installed there. A smaller k_H/k_D value of 1.2 was found for C–2 position.[37] Based on these observations, it was proposed that the mechanism of the reaction involves the electrophilic addition of Pd(II) to the more electron-rich C–3 position. The resulting organopalladium species can be deprotonated. Reductive elimination affords the C–3 arylated product. Alternatively, the Pd can migrate to the adjacent position and reductive elimination affords the C–2 arylated product (Scheme 1.7).

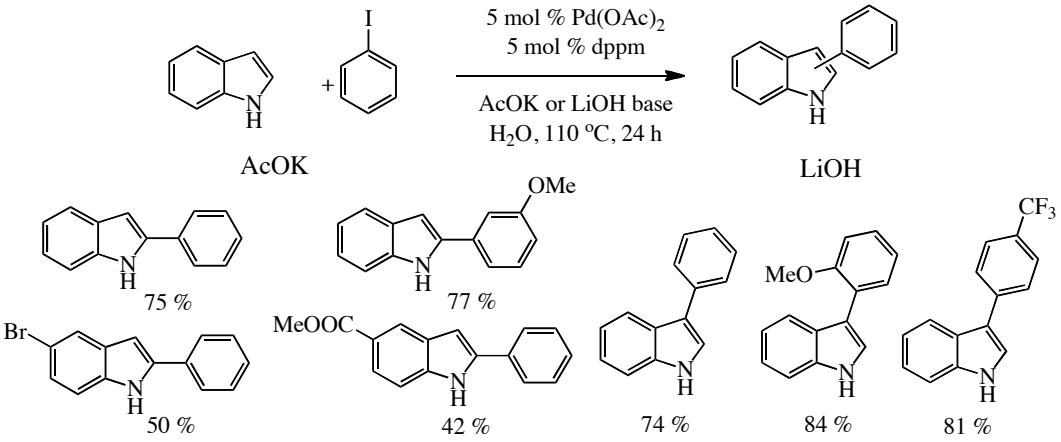
Scheme 1.7. Mechanism of indole arylation



The arylation regioselectivity is dependent on the base strength (Scheme 1.8).[38] When strong bases such as LiOH, NaOH or KOH were used, immediate deprotonation of

the organopalladium complex was achieved (Scheme 1.7, structure A), leading to 3–substituted product after reductive elimination. The use of weak bases such as carboxylates provides an opportunity for a C–3 to C–2 migration of the aryl group (Scheme 1.7, structure B), leading to 2–substituted indoles.

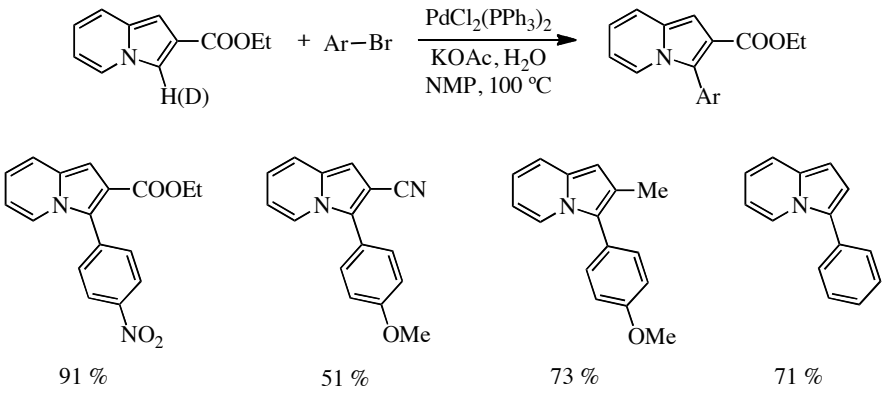
Scheme 1.8. Arylation of indoles



2. Arylation of indolizines

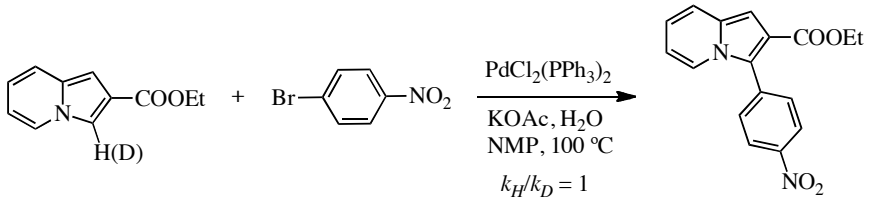
The first convenient general method for the synthesis of 3-arylindolizines was developed by means of direct arylation. Optimized conditions include catalytic amounts of $PdCl_2(PPh_3)_2$, KOAc (2 equiv), and H_2O (2 equiv) in NMP at 100 °C. Under these reaction conditions, a variety of substituted indolizines underwent smooth arylation in good to excellent yields (Scheme 1.9).[39] A variety of substituents are tolerated both on the indolizine and aryl halide. Notably, electron-rich bromoanisole underwent cross-coupling with both 2-cyanoindolizine and 2-methylindolizine.

Scheme 1.9. Arylation of indolizines



A kinetic isotope effect study was performed (Scheme 1.10). Deuterium-labeled 2-carboethoxyindolizine was subjected to the optimized reaction conditions. Experiments revealed that there is no isotope effect (k_H/k_D=1). This results excludes the C–H activation pathway and favors the electrophilic substitution pathway in which deprotonation event is not the rate limiting step.

Scheme 1.10. Deuterium isotope effect in the arylation of indolizines



Kinetic studies were also performed. Competition experiments were run between indolizine (**A**), 2-methylindolizine (**B**), and 2-carboethoxyindolizine (**C**). If the reaction proceeds by electrophilic substitution mechanism, electron-donating substituents at C-2 of indolizine would accelerate arylation at C-3, whereas electron-withdrawing groups

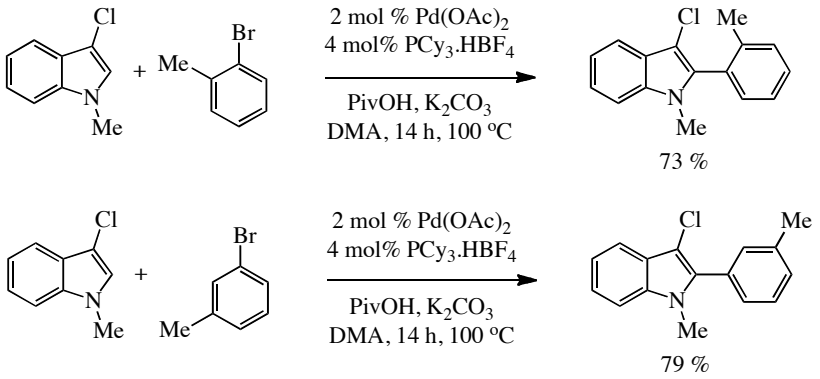
should slow down the reaction. The relative rates of Pd-catalyzed arylation of **A**:**B**:**C** were found to be 1.00:0.97:0.66. The EWG-substituted 2-carboethoxyindolizine underwent the slowest arylation, as expected; however, 2-methylindolizine was arylated slower than indolizine presumably due to steric bulk of methyl group. These results further support S_EAr mechanism.

B. The concerted metallation-deprotonation (CMD) mechanism

1. Arylation of indoles

Selective arylation of both 2– and 3–positions of indoles can be performed by blocking one of the positions with chloride substitutent (Scheme 1.11).[40] The chloro group can be removed by a Pd/C catalyzed hydrogenation after the arylation.

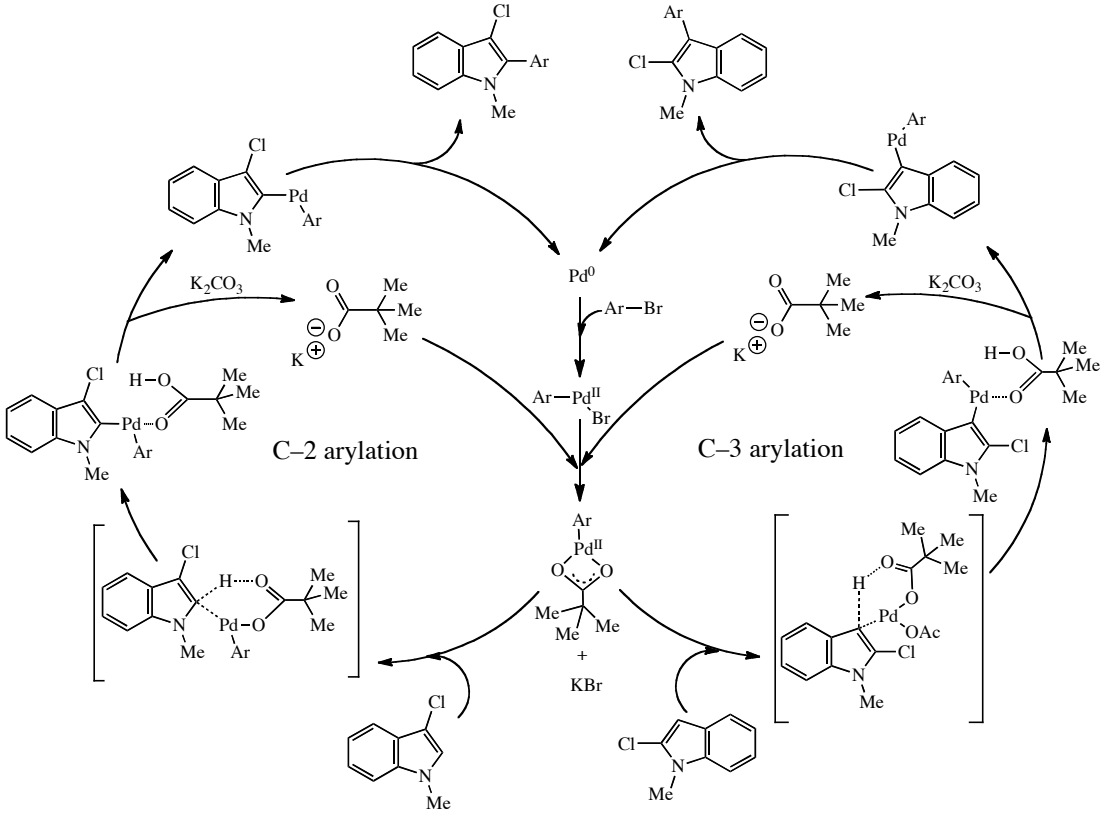
Scheme 1.11. Selective arylation f the C–2 and C–3 position of indole



The use of pivalic acid facilitates the removal of proton from the substrate and a concerted metallation–deprotonation (CMD) mechanism was proposed (Scheme 1.12).[41] The cycle starts with the oxidative addition aryl bromide to the Pd(0) species, followed

by ligand exchange. The active palladium species is introduced into the indole ring by a CMD process. The pivalate removes proton simultaneously with the formation of the carbon-palladium bond. Once the organopalladium species is formed, pivalic acid is released and deprotonated by the inorganic base, forming pivalate ion which can be reused for another cycle. Meanwhile, the palladium complex undergoes reductive elimination to form the product and regenerate the Pd(0) catalyst.

Scheme 1.12. Concerted metallation-deprotonation (CMD) mechanism for the arylation of indoles

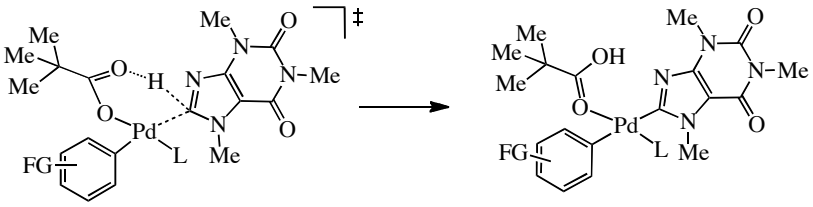


Addition of silver(I) salt in the reaction mixture removes the halide from the complex and enhances the reaction rate.[42] No special ligand was needed in this new method, but nitrobenzoate base was used.

2. Arylation of caffeine

The CMD mechanism was also proposed for the direct arylation of caffeine (Scheme 1.13).[43] In this mechanism, the cleavage of the C–H bond is favorable due to abstraction proton of the by pivalate ion which serves as shuttle from the substrate to the solid inroganic base.[44] Methodology operating by this mechanistic pathway was eventually developed for arylation of other heterocycles such as imidazoles and indoles.[45]

Scheme 1.13. Proposed mechanism for the direct arylation of caffeine

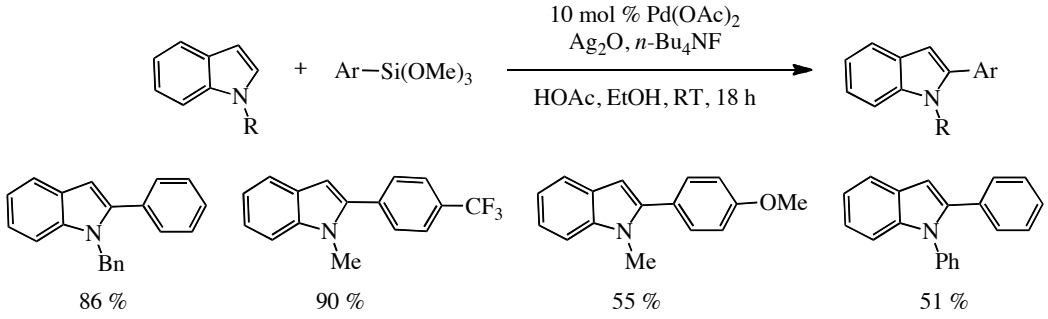


III. Pd(II)/(0) catalytic cycle

A. Arylation with organometallic compounds

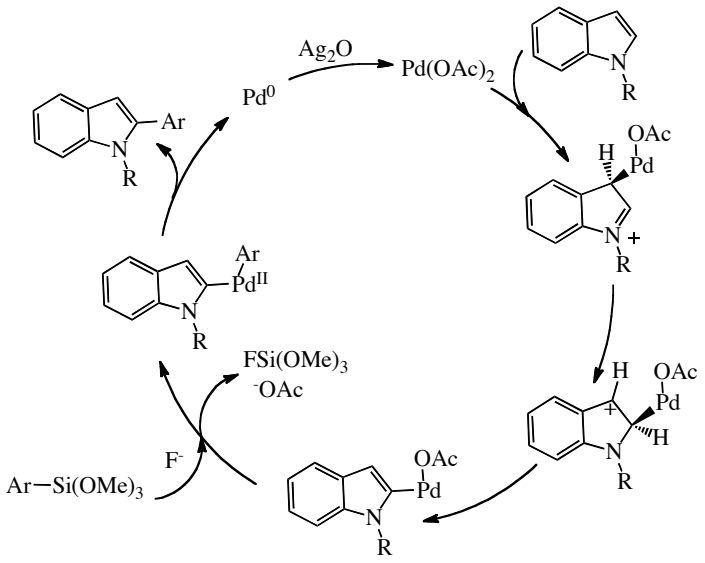
Arylation of indoles with siloxanes was performed in acidic medium at room temperature. The reaction proceeds efficiently when 10 mol % of $Pd(OAc)_2$ was used in combination with Ag_2O oxidant and tetrabutylammonium fluoride in ethanol (Scheme 1.14).[46] The reaction tolerates electron-deficient and electron-rich arylsiloxanes. Various indoles could also be arylated.

Scheme 1.14. Arylation of indoles with arylsiloxanes



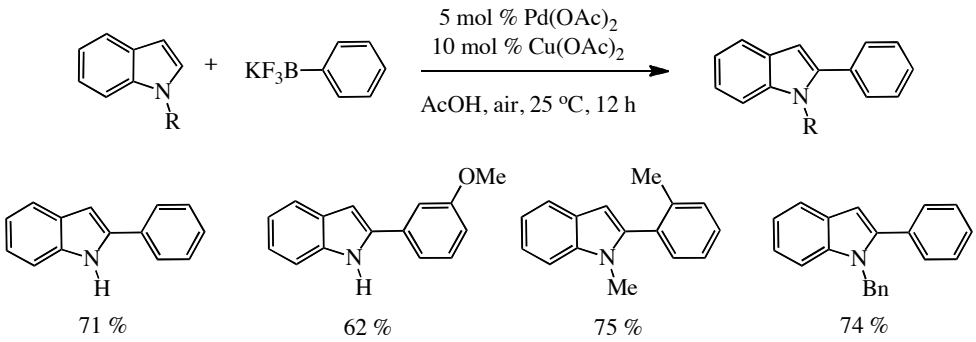
The proposed mechanism involves electrophilic substitution of the indole ring at the C–3 position, followed by migration of the palladium metal to the C–2 position (Scheme 1.15). Deprotonation affords an indoylpalladium(II) species which is transmetallated by the organosilicon compound. The subsequent reductive elimination generates the arylated indoles and Pd(0) species, which is oxidized with Ag_2O to the Pd(II).

Scheme 1.15. Mechanism of the arylation of indole with siloxanes



Arylboronic acid[47] and potassium aryltrifluorborates[48] can be used as a source of aryl group in Pd-catalyzed indole arylation (Scheme 1.16). Selective formation of 2-arylindoles was achieved using $O_2/Cu(OAc)_2$ system as oxidant.[48] TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) was also shown to be useful as a mild oxidant for this type of reactions. [47]

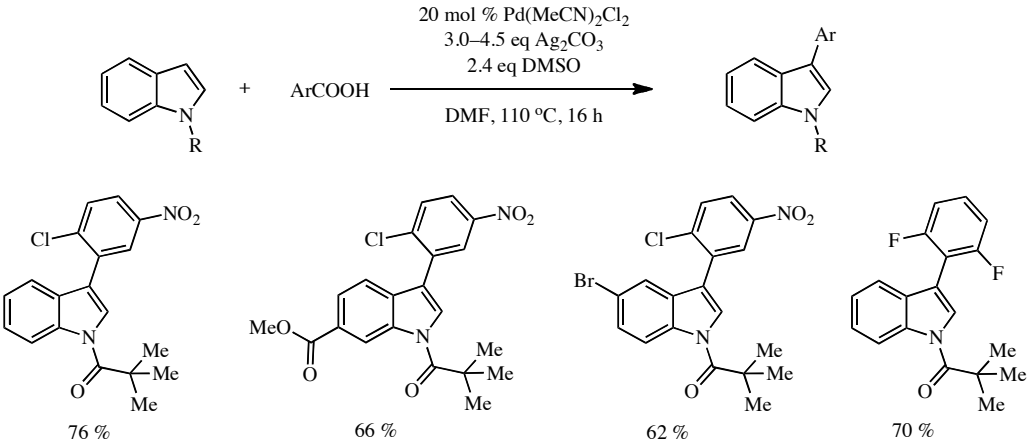
Scheme 1.16. Arylation of indoles with aryltrifluoroborates



B. Decarboxylative oxidation mechanism

Cheap and ubiquitous carboxylic acids were used as coupling partners for the Pd-catalyzed arylation.[49] When indoles were used as coupling partners in direct arylation reaction, high preference for the formation of 3-arylated indoles was observed. (Scheme 1.17).[50]

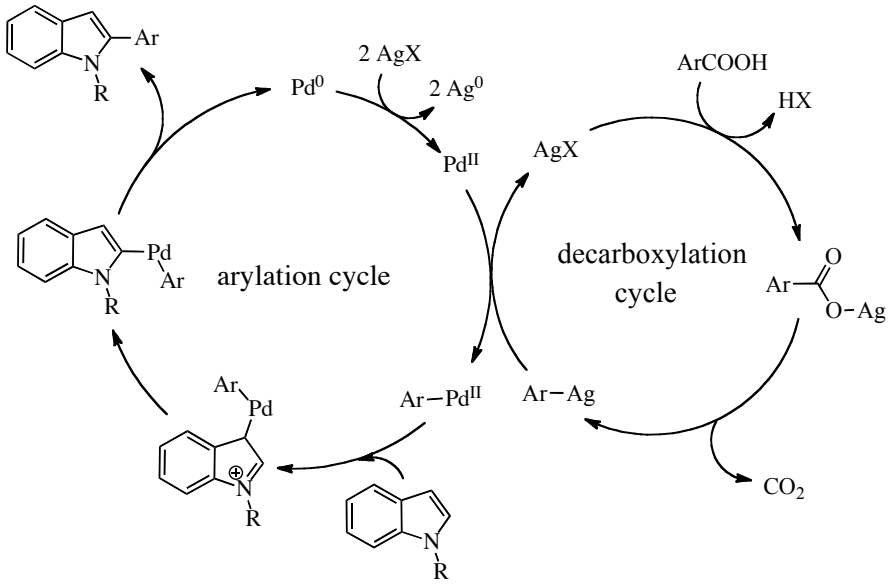
Scheme 1.17. Arylation of indoles with benzoic acids



The mechanism for the arylation involves two cycles (Scheme 1.18). One is for the generation of arylsilver(I) species from benzoic acids. The aryl group is then

transmetallated to generate arylpalladium(II) species, which is used in another cycle. The indole undergoes electrophilic palladation with arylpalladium(II) species at C–3 position. Migration of the aryl group to C–2 position follows. Reductive elimination affords the product and Pd(0) species, which is oxidized by Ag(I) to the catalytically active Pd(II) species.[50]

Scheme 1.18. Mechanism for decarboxylative arylation of indoles with benzoic acids

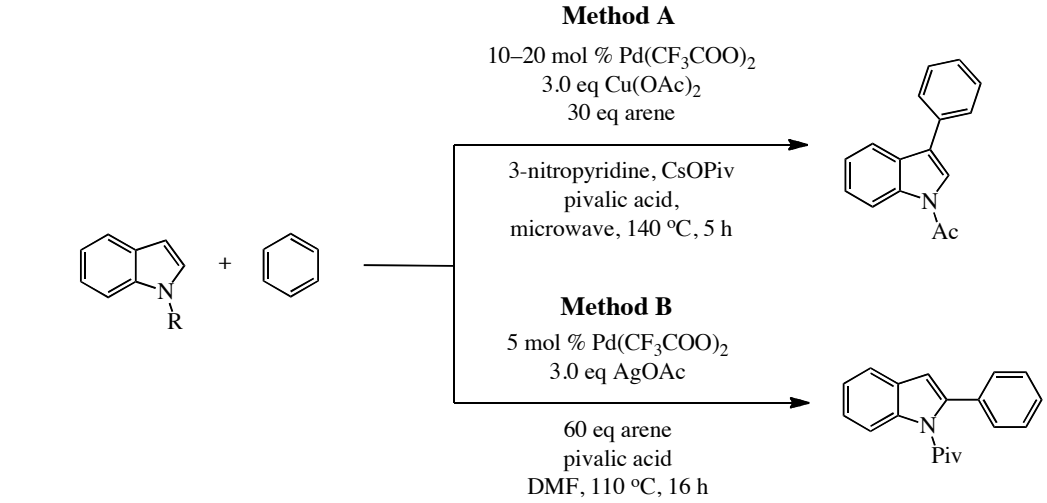


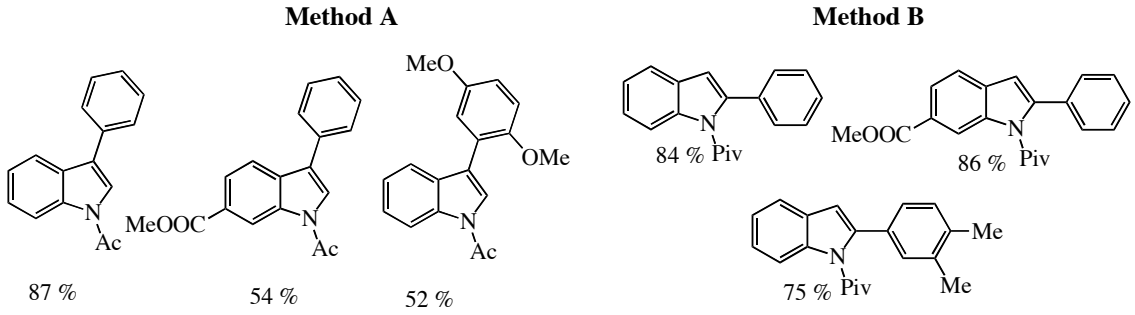
C. C–H/C–H coupling

A remarkable method for the coupling of two hydrocarbon species in which there is no need for the activation and prefunctionalization of both the aryl and the indole moieties has been developed. Early catalytic methodology involves the use of up to 20 mol % Pd catalyst, copper(II) acetate oxidant and 30 equivalents of arenes as arylating agents at 140 ^{o}C. This methodology affords products that are predominantly arylated at

the indole C–3 position.[51] Switching of the oxidant to silver(I) acetate reverses the regioselectivity preference and improves the overall reaction efficiency to give 2-aryl indoles with higher regioisomer ratio. (Scheme 1.19).

Scheme 1.19. Direct C–H/C–H cross coupling of indoles with arenes

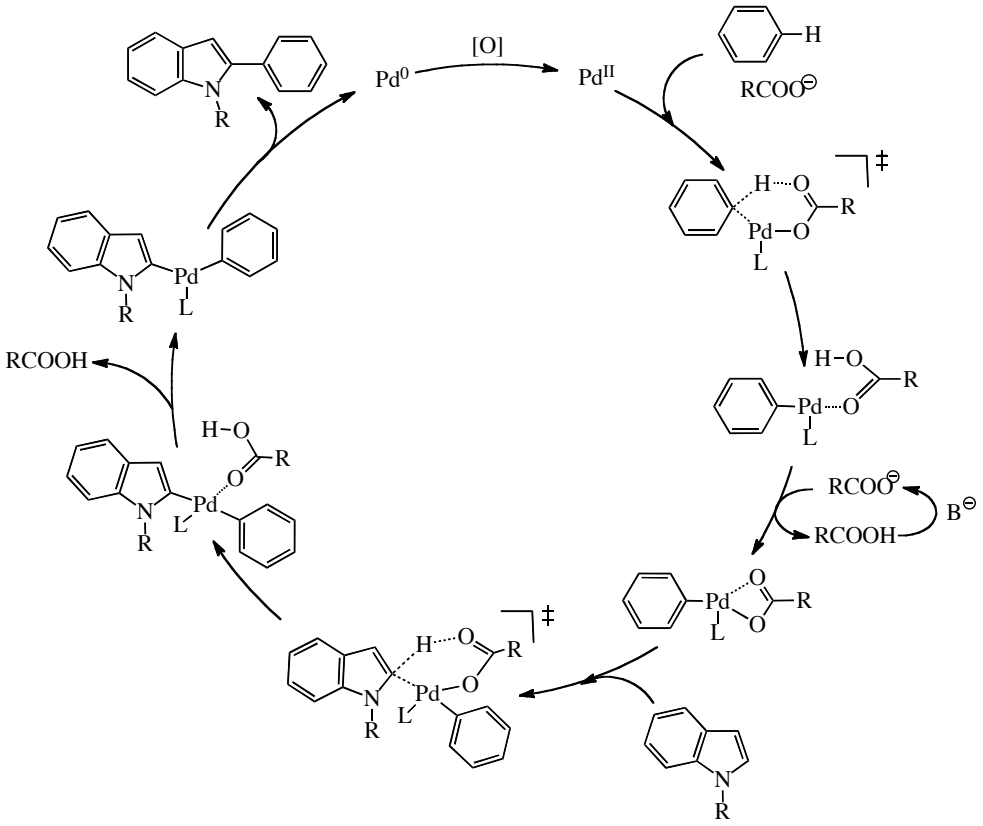




The mechanism of the reaction involves a succession of two C–H activations (Scheme 1.20).[51] The mechanism for the C–H activation of the arene follows the CMD pathway and retention of aromaticity is observed at the CMD transition state.[41a] The resulting arylpalladium(II) species reacts with indole by another CMD process.[52] Reductive elimination releases the product and Pd(0) species which is converted to the

active Pd (II) species by oxidants.[51] Higher rate of formation of the first arylpalladium(II) complex was ensured by using a large excess of the arene partner.

Scheme 1.20. General mechanism for the C–H/C–H cross coupling of indoles with arenes



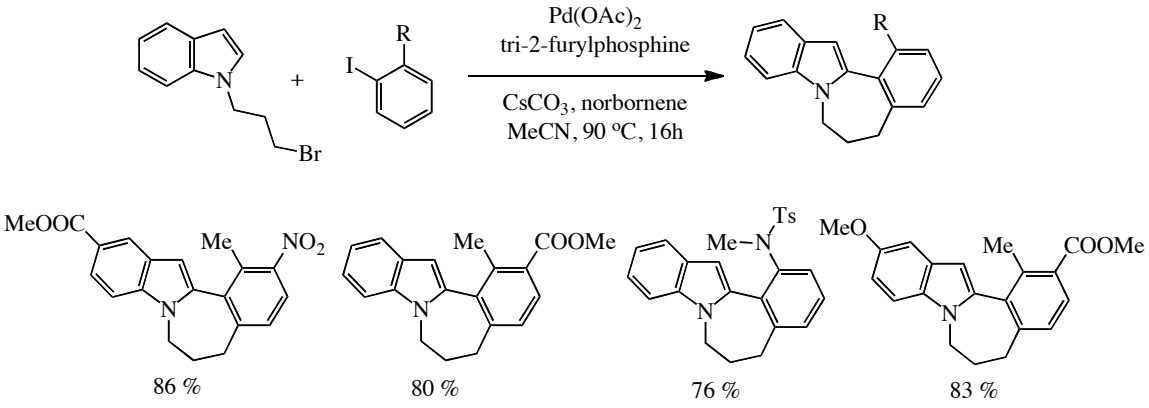
Other methods for C–H/C–H cross couplings were developed utilizing other combinations of arenes and heterocycles. Furans, thiophene, benzofuran, benzothiophene, xanthines, imidazoles, indolizines, pyridine-*N*-oxides anilines, and other arenes were used in direct arylations.[53] The method was also used in the synthesis of complex indoles[54] and dragmacidin D.[55]

IV. Pd(II)/(IV) and Pd(II)/(III) catalytic cycles

A. Arylation by Catellani reaction

Arylated indoles were synthesized by a cascade Pd-catalyzed arylation known as the Catellani reaction (Scheme 1.21).[56] The use of norbornene as cocatalyst in Pd-catalyzed C–H activation provided an elegant route for arylation.[57] Norbornene participates in the reaction by providing a rigid framework for the delivery of Pd-aryl complex at the C-2 position of indoles. Using this method, even bulky aryl iodide starting materials provide a single regioisomeric product.

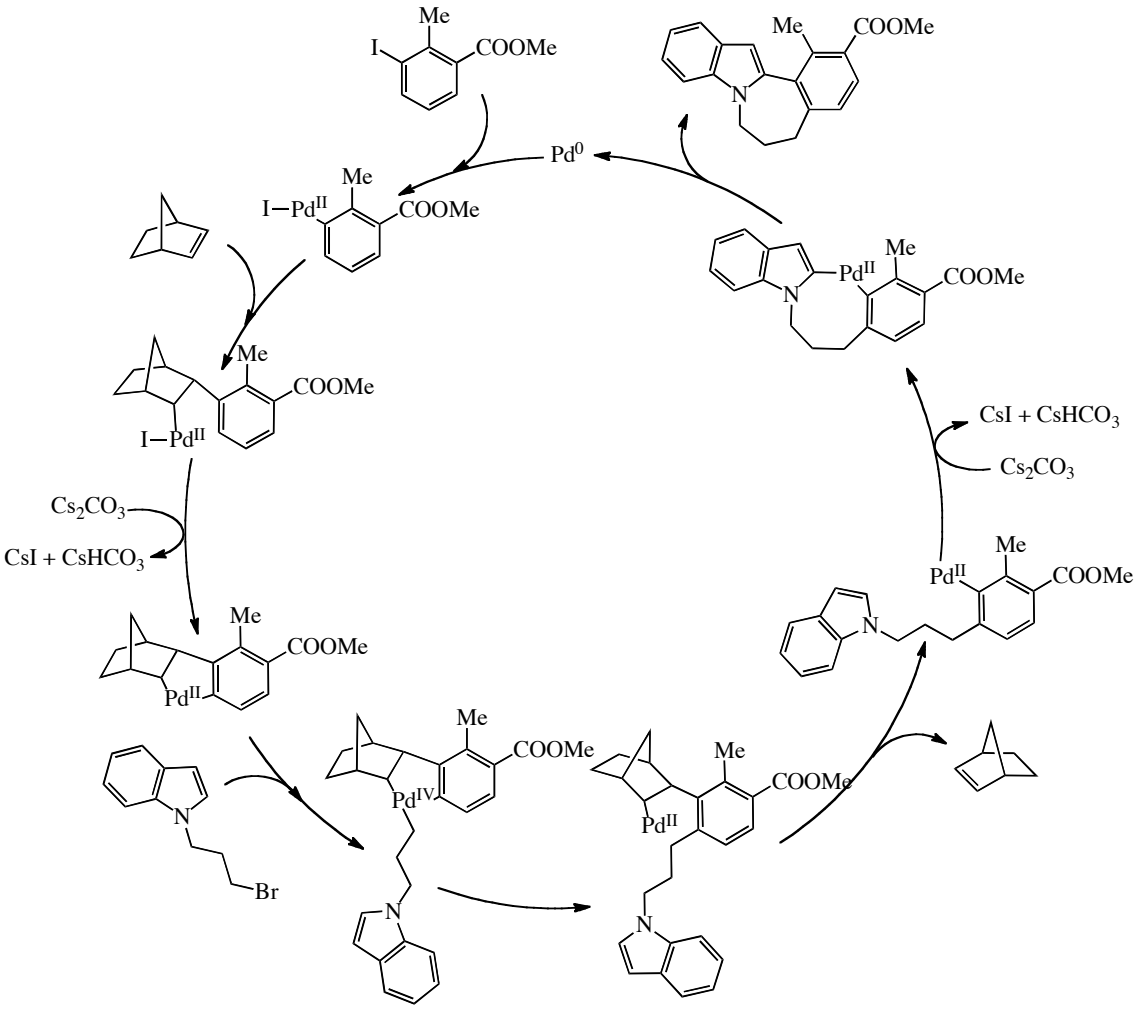
Scheme 1.21. Catellani reaction of indoles



The mechanism of the reaction was proposed by Lautens (Scheme 1.22).[56] The first step of the reaction is the oxidative addition of the aryl iodide to Pd(0) generating an arylpalladium (II) species. Norbornene participates in carbopalladation affording a norbornylpalladium(II) complex. The complex in the presence of base forms a five-membered palladacycle. The palladacycle reacts with aryl halide in another oxidative

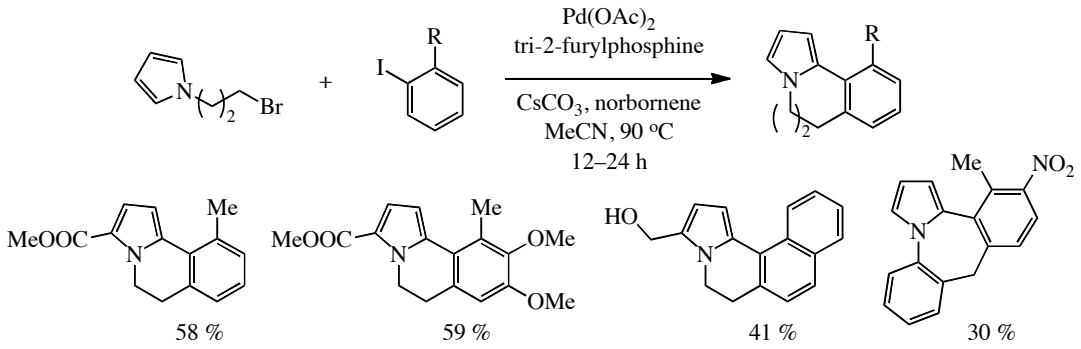
addition step, forming a palladium(IV) complex. Reductive elimination completes the alkylation segment of the reaction. The new norbornylpalladium(II) complex expels the norbornene, resulting in a new arylpalladium(II) species which undergoes intramolecular direct coupling in the presence of base. Reductive elimination affords product and regenerates the catalyst.

Scheme 1.22. Proposed mechanism for indole arylation via Catellani reaction



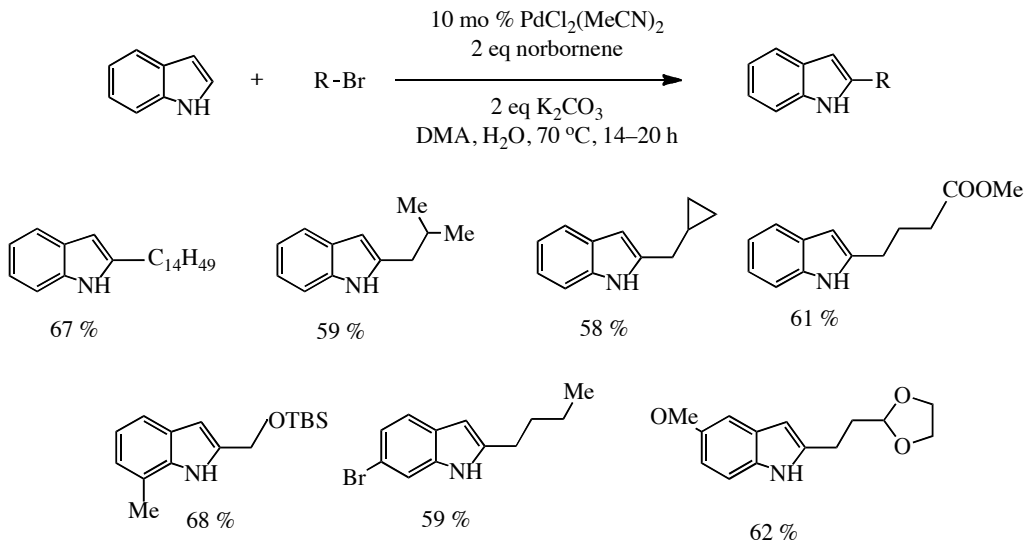
Regioselective arylation of nitrogen-containing heterocycles was developed using the same approach. The versatility of the new method was demonstrated by the synthesis of six-, seven-, and eight-membered ring-annulated pyrroles (Scheme 1.23) and azaindoles. Indazoles and triazoles were also used as substrates.[58] The methodology was expanded further to include sulfur-containing heterocycles such as thiophenenes and benzothiophenes.[59]

Scheme 1.23. Arylation of pyrroles via Catellani reaction



Intermolecular alkylation of free *N*H–indoles was also accomplished by the Catellani reaction. The reaction is regioselective, providing C–2 arylated products. The method tolerates a wide range of functional groups in indoles and alkyl bromides (Scheme 1.24).[60]

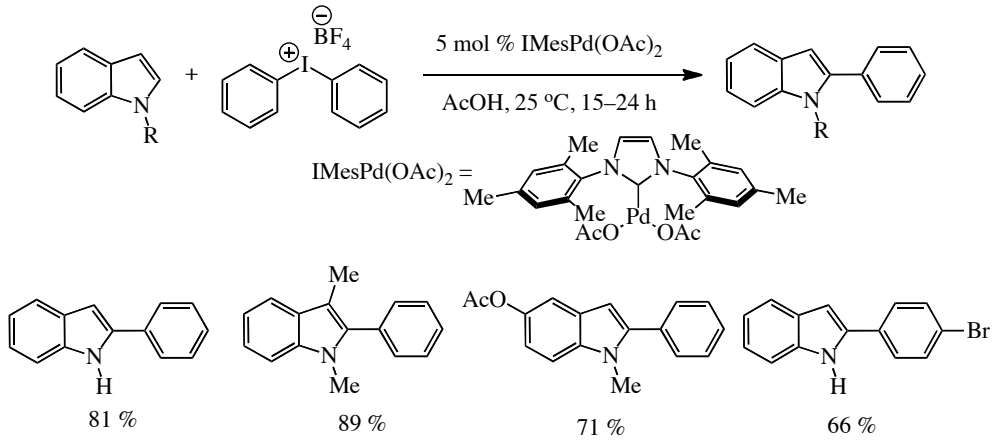
Scheme 1.24. Alkylation of indoles via Catellani reaction



B. Functionalization with hypervalent iodine compounds

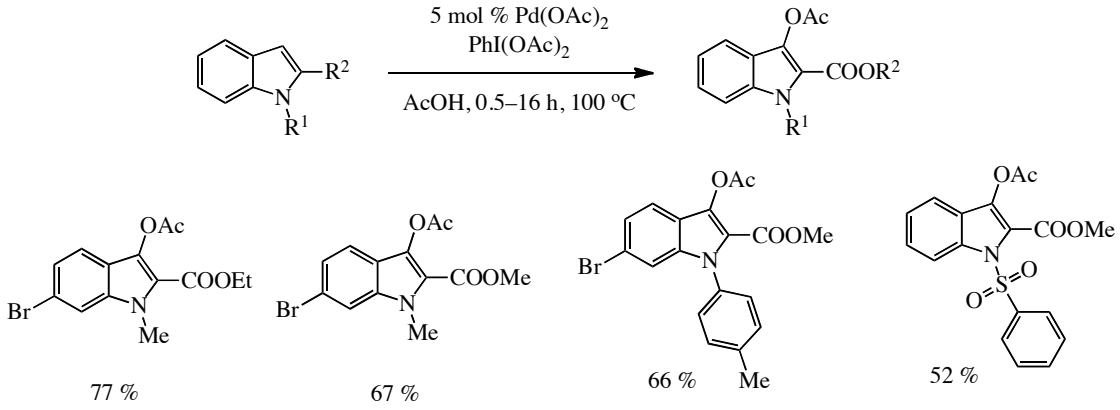
Hypervalent iodine reagents can be used as both oxidant and coupling partners in palladium-catalyzed reactions.[61] The use of diphenyliodonium salts provides a gentle and regioselective method for the arylation of indoles (Scheme 1.25).[62] The method operates at room temperature and exhibits C–2 selectivity even with free *N*H–indoles. Pyrroles can also be used as substrates. One drawback of the method is the limited commercial availability of diaryliodonium coupling partners.

Scheme 1.25. Pd-catalyzed C-2 arylation with diphenyliodonium salts



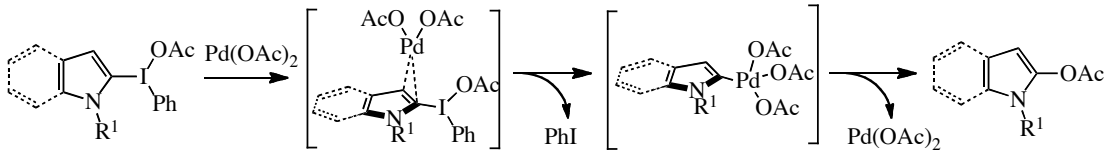
Other groups could be introduced into the heterocycle rings using hypervalent iodine as oxidants. Acetoxy group was introduced on the C–3 position of 2-carboxyindole ester using iodobenzene diacetate (Scheme 1.26).[63] Pyrroles could also be used as substrates. Acetoxylation of simple arenes using $PhI(OAc)_2$ as an oxidant have been reported.[64]

Scheme 1.26. Pd-catalyzed acetoxylation of indoles



Study of the mechanism of the reaction shows the initial formation of indolyliodonium acetates, which can be isolated (Scheme 1.27).[65] The next step in the reaction sequence is palladation. The regioselectivity of the palladation is due to the η^2-coordination of the iodonium heterocycle to the Pd(II) species prior to oxidative addition. The C–O bond is formed by reductive elimination.

Scheme 1.27. Mechanism for the palladation of indolyliodonium acetate



V. Summary and conclusions

The Pd-catalyzed functionalization of C–H bonds has been demonstrated to work well on heteroarenes. Organohalides, organoboron, and arenes could be used as arylating agents. Methods that have been developed provide an excellent way to introduce aryl, alkyl and a variety of other functional groups regioselectively. Both electrophilic substitution and CMD-type mechanisms have been proposed for C–H bond activation step.

Despite the remarkable advancements in the field of Pd-catalysis, further research is still needed to improve yield, selectivity, and generality of reaction. The research may include design of new catalysts, ligands, and oxidants.

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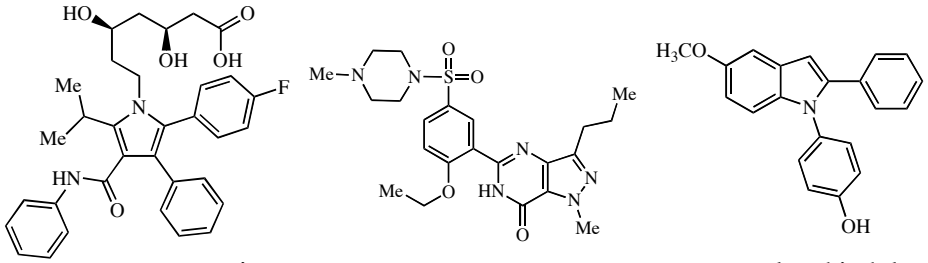
CHAPTER 2

Arylation of Furans and Pyrroles with Aryl Chlorides

I. Introduction

A. Arylated heterocycles in medicine, agriculture, and optoelectronics

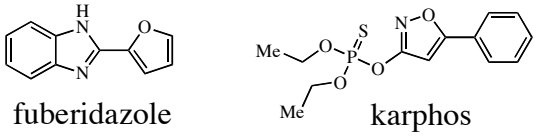
Many interesting and useful compounds contain a motif in which an aryl group is directly bound to a heterocycle.[1] Heterocycle-aryl linkage is very common in medicinal chemistry. Compounds with this substructure have been shown to exhibit versatile binding activities to receptors.[2] As a result, many drugs and other biologically active compounds contain at least one aryl–heterocycle bond. For example, the cholesterol lowering drug Lipitor (atorvastatin) has two aryl groups bound to a pyrrole ring.[3] Direct installation of these aryl rings may provide a shorter route in the synthesis of drugs. Other bioactive compounds with an arylated heterocycle motif is the erectile dysfunction drug sildenafil[4] and an anti-fertility indole derivative.[5]



atorvastatin (Lipitor) | sildenafil (Viagra) | an arylated indole (antifertility agent)

Figure 2.1. Biologically active compounds possessing arylated heterocycle moiety

Many agrochemicals possess an arylated heterocycle substructure. The fungicide fuberidazole has a benzimidazole ring directly linked to furan. The insecticide karphos has an arylated isoxazole carbon skeleton.



fuberidazole (fungicide) karphos (insecticide)

Figure 2.2. Examples of agrochemicals with arylated heterocycle backbone

Arylated heterocycles provides extended conjugation along the carbon backbone of liquid crystals which enhances electrical conductivity.[6] Substitution of the aryl rings with heterocycles in organic light-emitting diodes (OLEDs) results in more efficient optochemicals for lighting applications.[7]

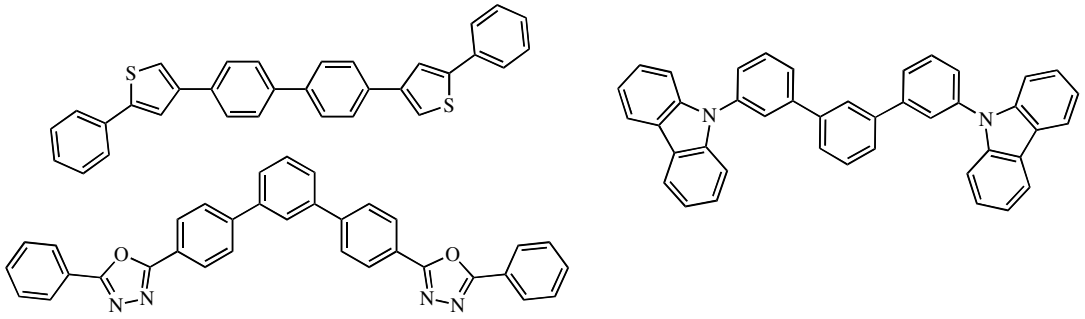


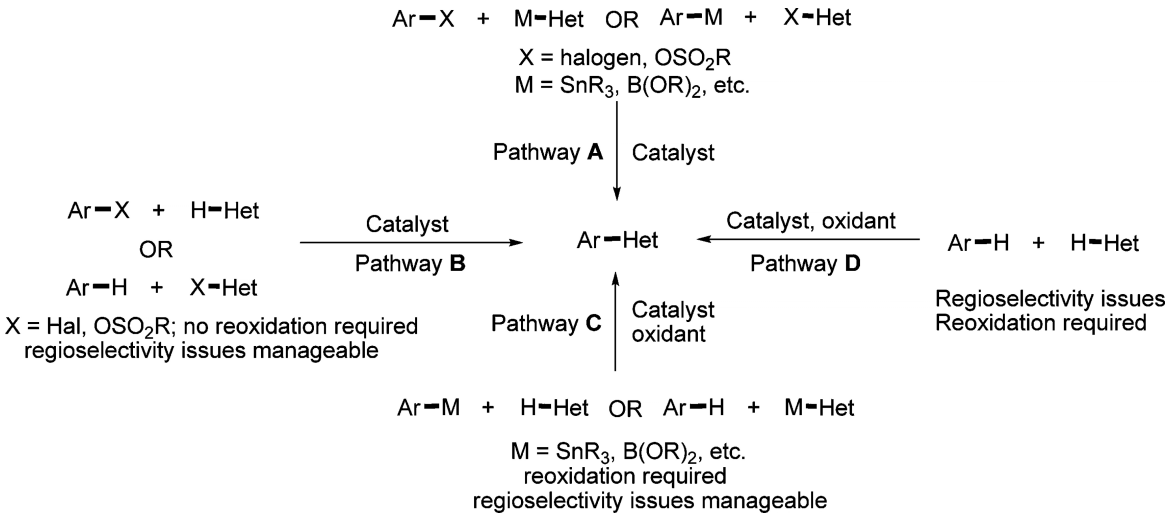
Figure 2.3. Heterocyclic liquid crystalline compounds

Arylated heterocycles have been shown to have a wide range of applications. The development of efficient synthetic methods leading to arylated heterocycles is therefore important.

B. Cross-coupling methods for the arylation of heterocycles

Transition-metal catalyzed cross-coupling methods that have been developed for creation of aryl-heteroaryl linkages are summarized in Scheme 2.1. One can couple either the aryl halide with heteroaryl metal reagent or aryl metal with heteroaryl halide (Pathway A).[8] This is the classical route for creation of sp^2–sp^2 carbon−carbon bonds. The advantages include excellent control of regioselectivity as well as extensively investigated chemistry that allows synthesis of nearly any structural motifs. However, the use of metallated reagents as coupling partners may involve separate preparation of organometallic compounds, thus lengthening synthetic sequences. This approach is not atom economic since the activating group will be removed later and formation of metal by-products may create disposal problems.

Scheme 2.1. Methods for heterocycle arylation



Coupling of an aryl halide with a heterocycle C−H bond or, rarely, arene with heteroaryl halide also can result in the formation of an arylated heterocycle (Pathway B).[9, 10] In this case, one can use readily available, stable heterocycles, and aryl halides, thus avoiding several synthetic steps and shortening synthetic schemes. Regioselectivity issues are manageable because most of heterocycle C−H bond arylations are regioselective.

The third possibility is the coupling of arylmetal with heterocycle or, rarely, arene with a heteroaryl metal reagent (Pathway C).[11] Carboxylates can be employed as arylmetal surrogates.[12] Although this method allows the use of stable and readily available heterocycles as one of the coupling components, several disadvantages are obvious compared with Pathway B. First, a stoichiometric reoxidant, typically a copper or silver salt, is often required for catalytic turnover generating heavy metal waste. Second, aryl metal reagents are often prepared from aryl halides, thus increasing total number of steps to the desired product.

The final possibility is the cross-coupling of heterocycle and arene C−H bonds (Pathway D).[13] Readily available arenes and heterocycles are used as the coupling partners. Consequently, Pathway D is the shortest route to the cross-coupled products since no functionalized intermediates need to be prepared. The potential problems include lack of regioselectivity with respect to simple arene coupling partners such as toluene and requirement for a stoichiometric oxidant. Additionally, a large excess of the arene component is often employed, decreasing the efficiency of the process. However, this

method appears to hold the most promise if the regioselectivity problems are solved and environmentally friendly oxidants such as oxygen[14] could be employed.

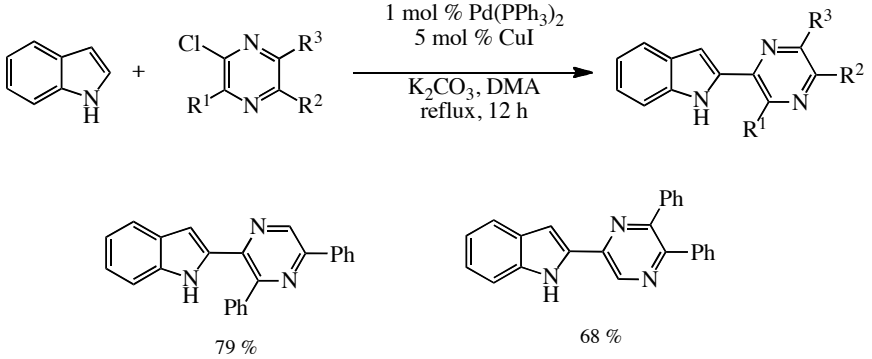
The above analysis shows that methodology following either Pathway B or Pathway D should result in the most efficient arylation processes. At this point, it is not obvious how to solve the regioselectivity issues for Pathway D, although in special cases cross-coupling selectivity has been obtained by employing tailored ligands on palladium.[15] While arylations according to pathway B are common, in most cases aryl bromide or iodide reagents have been employed and the methodology appears to be mature.[9, 10] In contrast, nonactivated aryl chlorides have been used rarely. [9d, e, 10b, c, 10e]

C. Arylation by aryl chlorides

Although cross coupling route is significantly shorter than traditional biaryl synthesis, improvements are still needed. Most of the developed methods use aryl iodides or bromides as electrophilic coupling partners. The scope and practicality can be improved by the use of cheaper and more chemically diverse aryl chlorides.[16]

A pioneering paper describing activated (electron-poor) aryl chloride use in heterocycle arylation was published in 1985 and is one of the first intermolecular direct heterocycle arylation examples.[9a] Chloropyrazines can be used to regioselectively arylate *NH*-indoles at the C-2 position if $Pd(PPh_3)_4$ catalyst is employed. Copper(I) additive improves the arylation yield. This modification is now widely used for such reactions (Scheme 2.2).

Scheme 2.2. Arylation of indole with aryl chloride

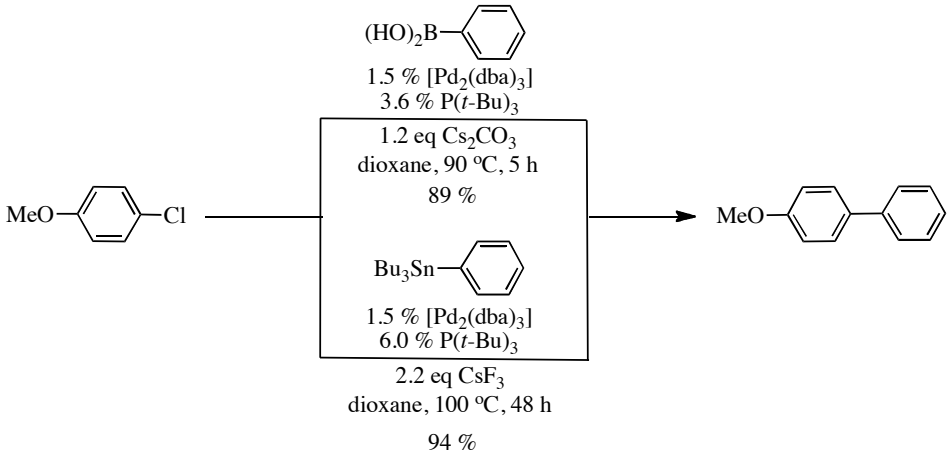


Use of aryl chlorides in such cross-coupling reactions has been limited because of the strength C–Cl bond that retards oxidative addition.[17] Oxidative addition of aryl halides to Pd is more favorable when the complex is more electron-rich by virtue of emplying suitable ligands.[18]

1. Phosphine ligands

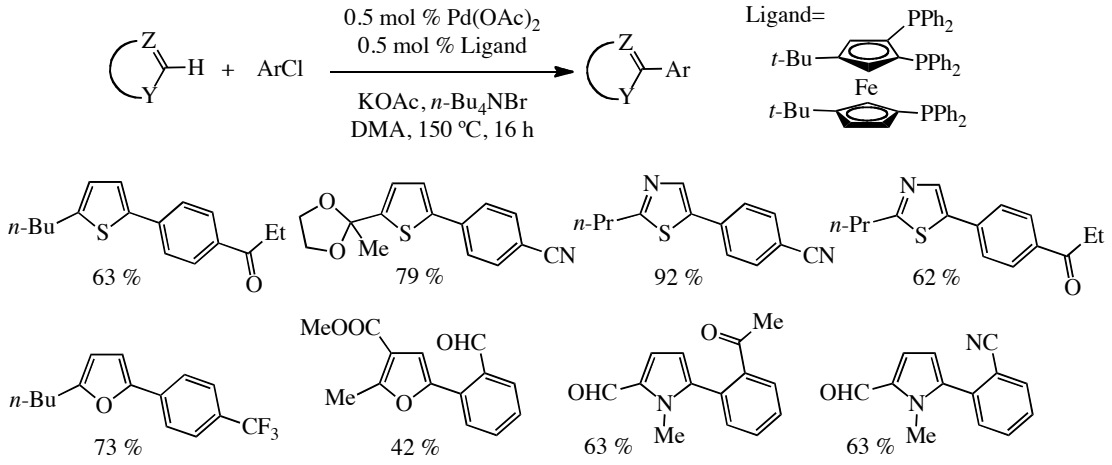
Use of ligands such as alkyl phosphines takes advantage of the strong σ-donating capability that increases the electron density around the metal center. The use of P(*t*-Bu)$_3$ as a ligand allowed the use of aryl chlorides in Suzuki[18] and Stille[19] reactions (Scheme 2.3).

Scheme 2.3. Palladium-catalyzed Suzuki and Stille reactions



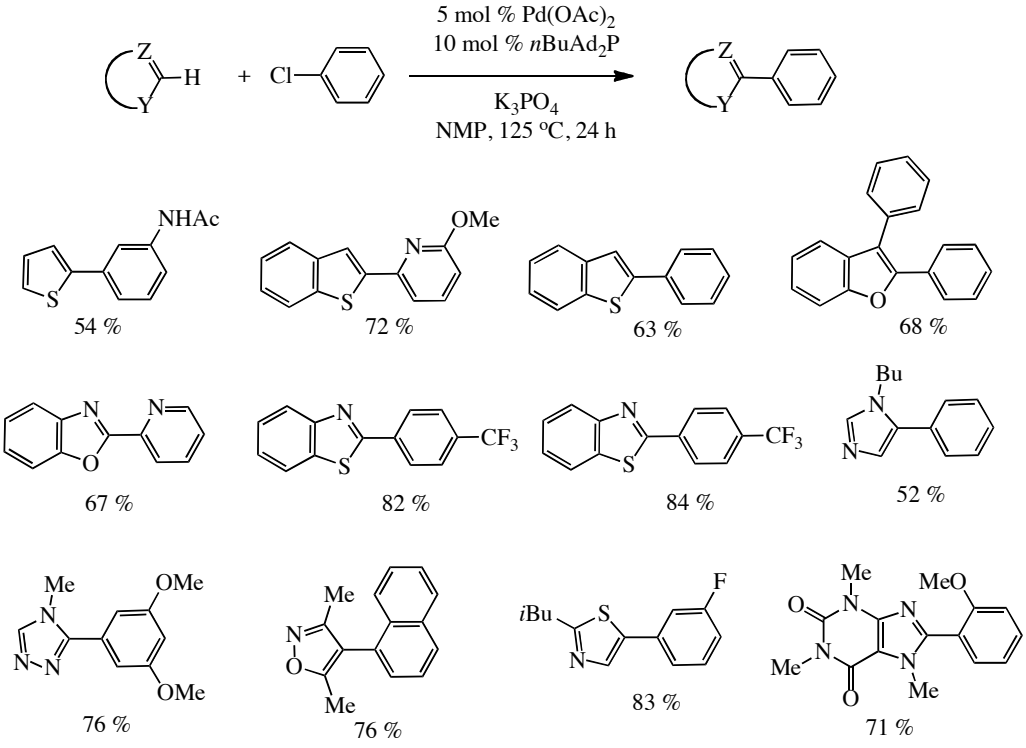
Several ferrocenylphosphane ligands were developed for arylation of heterocycles with aryl chlorides.[20] Although, the method needs only 0.1–0.5 mol % of Pd-ligand catalyst, the reaction is performed at 150 ºC (Scheme 2.4). The method is limited to aryl chlorides with electron withdrawing substituents and only examples of substituted furans, thiophenes, thiazoles and pyrroles were arylated.[21]

Scheme 2.4. Arylation of heterocycles with aryl chlorides at low catalyst loadings



Another phosphine that was developed as ligand for the utilization of aryl chlorides in Pd-catalyzed reactions is the *di*-(1-adamantyl)-*n*-butylphosphine (nBuAd$_2$P, cataCXium® A).[22] In the method developed in our group, this phosphine was used as a ligand for the arylation of five-membered ring electron-rich heterocycles (Scheme 2.5).[9e] The method is the general and can be used for a wide variety of electron rich heterocycles. Thiophene, benzothiophene, 1,2- and 1,3-oxazole derivatives, benzofuran, thiazoles, benzothiazole, 1-alkylimidazoles, 1-alkyl-1,2,4-triazoles, and caffeine can be arylated in good yields. Electron-rich, electron-poor, and heteroaryl chlorides can all be used. The method, however, fails for a number of substrate such as unprotected indoles, pyrroles and imidazoles. Indoles with *N*-tosyl or *N*-acyl protection failed to react. Low conversions and/or regioisomer mixtures were obtained. In the same study, *N*-phenylpyrrole and furan arylation resulted in low yields.

Scheme 2.5. General arylation method for electron-rich heterocycle

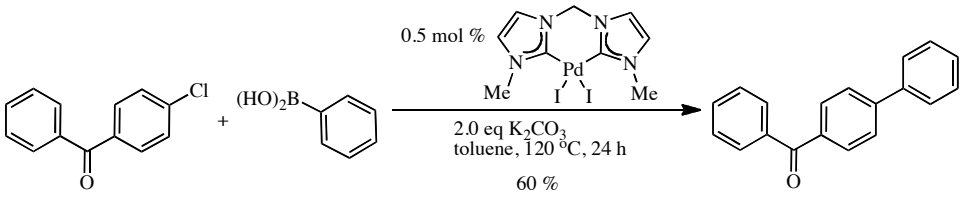


2. NHC ligands

N-Heterocyclic carbenes (NHC) are nucleophilic, carbon-based ligands that can be used as an alternative to phosphines as ligands for cross-coupling reactions. Initial experiments on a Pd-carbene complex showed that it can be used as a ligand for Pd-catalyzed Suzuki coupling of 4-chloroacetophenone with phenylboronic acid (Scheme 2.6).[23] Although the yield is low, this study prompted interest on NHC ligands for Pd-catalyzed reactions.[24] Eventually, more efficient NHC-based Pd catalyst was developed that can function at lower temperatures and can transform sterically hindered starting materials.[25] The new NHC ligands are effective in this reaction because of the combination of several factors which include their inherent electron-donating capability

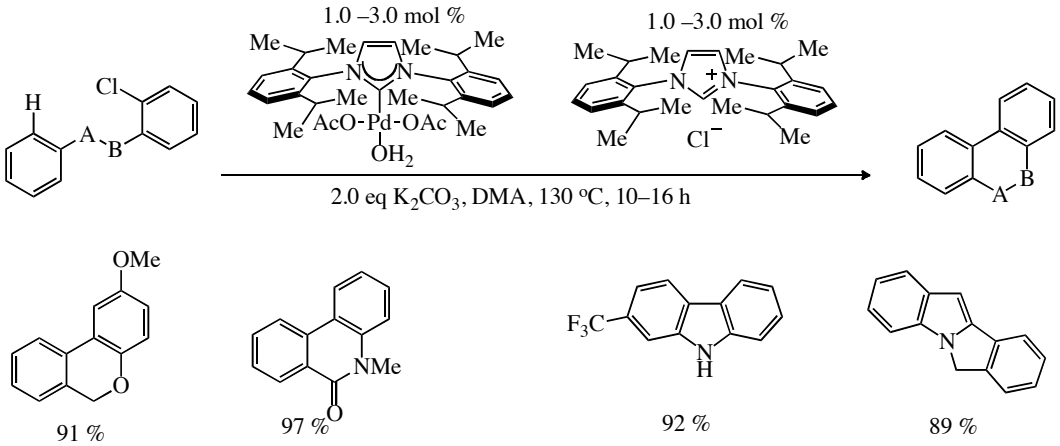
that enhances oxidative addition step, tight coordination to the Pd metal preventing formation of Pd black, and steric bulk around the metal that favors the formation of monocarbene species and promotes reductive elimination.[24b]

Scheme 2.6. NHC–Pd complex as a catalyst for Suzuki coupling



Early methods for direct arylation reactions that use NHC ligands for Pd-catalyzed coupling of aryl chloride features intramolecular bond formation (Scheme 2.7).[26] Five- to six-membered rings could be formed in this reaction. Arylation of the C–2 position of indole was successful. The addition of NHC salts prevented catalyst decomposition and lead to higher turnover number.

Scheme 2.7. Pd–NHC-catalyzed intramolecular cyclization of aryl chlorides



Direct arylation method for intermolecular arylation of azoles and indoles using an NHC (NHC 1) as a ligand were first developed for aryl iodides and bromides (Figure 2.4).[27] Diarylation of imidazole was accomplished by arylation (with ArI) of protected imidazole at C–2 position using NHC 1 as ligand followed by arylation (with ArCl) of the product at C–5 position using *n*BuAd$_2$P as a ligand.[28] As the design of the ligands is improved, activated aryl chlorides can be utilized to afford moderate yields when used as coupling partner for furan, thiophene, and thiazole (using NHC 2).[9p] Arylation of imidazoles with aryl chlorides afforded moderate yield using NHC 3, a catalyst with both NHC and phosphine as ligands (Scheme 2.8).[29]

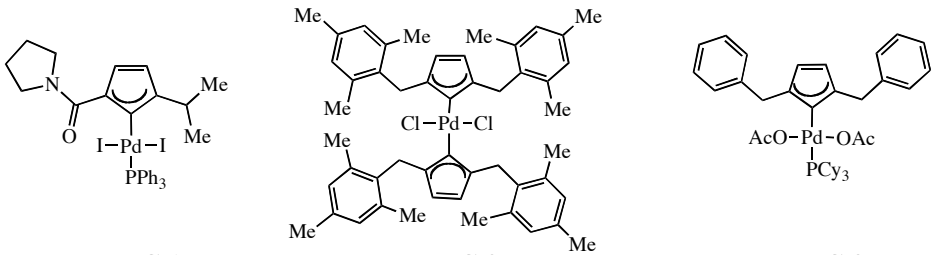
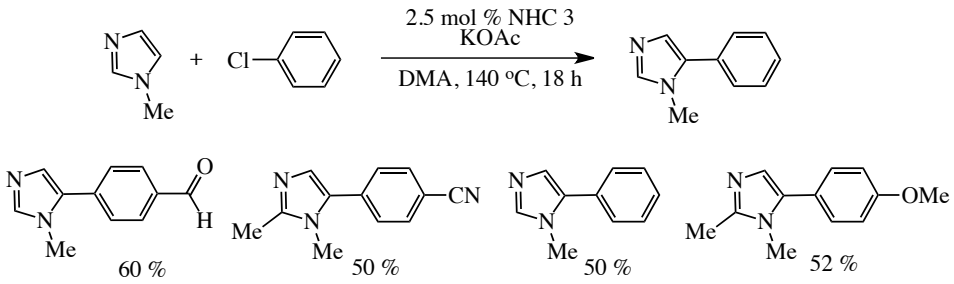


Figure 2.4. NHC ligands used in the direct arylation of heterocycles

Scheme 2.8. Arylation at C–5 position of imidazole with aryl chlorides

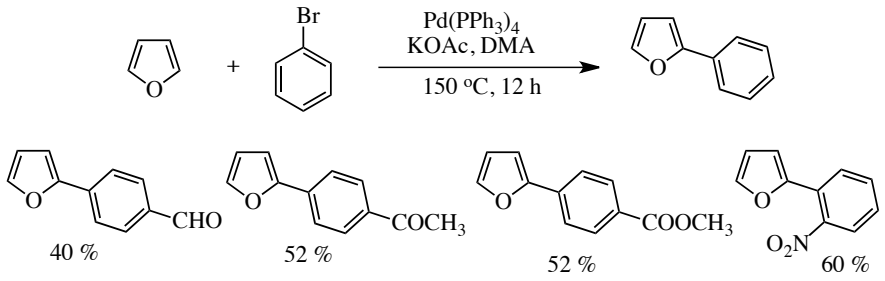


Several reports from other groups describe use of nonactivated aryl chlorides in heterocycle C−H bond arylations.[10b, c, 10e] Further improvement in the method however is necessary to include other biologically important heterocycles. Pyrrole and furan arylation by nonactivated aryl chlorides has been elusive.

D. Arylation of furans

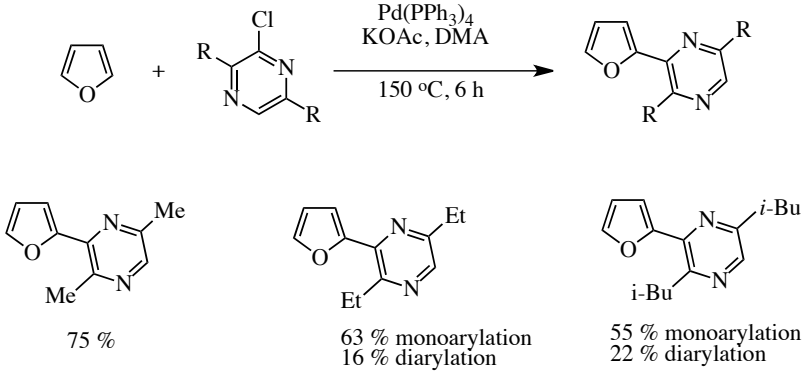
Arylation of heterocycles such as thiophene, benzofuran, benzothiophene, and furans was performed in the presence of tetrakis(triphenyl-phosphine)palladium catalyst, aryl bromides, potassium acetate base, and *N,N*-dimethylacetamide solvent under argon at 150 ^{o}C (Scheme 2.9).[10l] Only activated aryl bromides are reactive under the reaction conditions employed. Other heterocycles were arylated but furans afforded relatively low yields. The lower reactivity of furans towards arylation is a known challenge in C–H bond functionalization. General arylation method for arylation of furan by aryl chlorides was not available before our work.

Scheme 2.9. Arylation of furans by aryl bromides



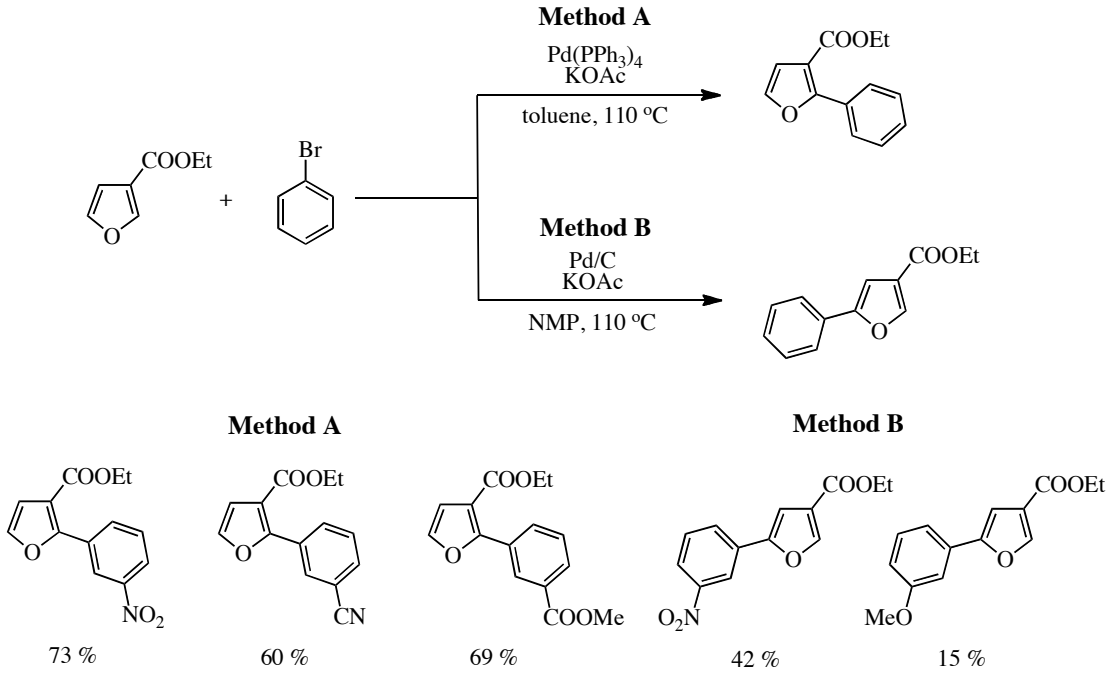
Methodologies that were developed earlier were effective only for activated aryl chlorides such as chloropyrazines. (Scheme 2.10).[30] The products were obtained in moderate to good yields, however, in most cases, as mixtures of monoarylated and diarylated furans.

Scheme 2.10. Arylation furans by chloropyrazines



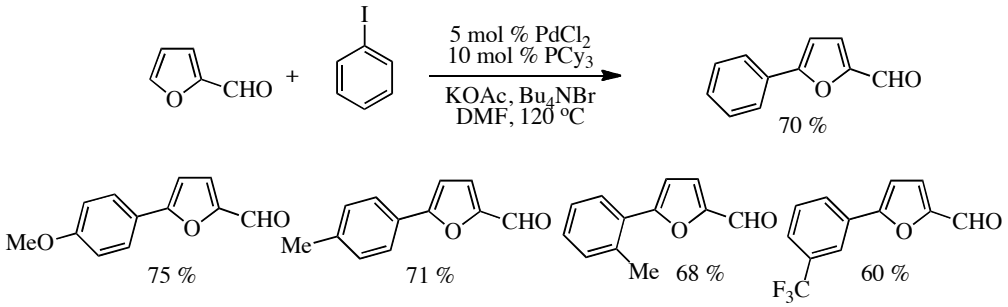
Regioselective method for arylation of ethyl furan-3-carboxylate was developed (Scheme 2.11).[10a] Arylation at the C–5 position was observed using Pd/C in combination with polar aprotic solvent such as NMP. In contrast, arylation at the more sterically hindered C–2 position was observed if palladium-phosphine complex was used as a catalyst in nonpolar solvent such as toluene. Only activated aryl bromides were used.

Scheme 2.11. Regioselective arylation of ethyl furan-3-carboxylate



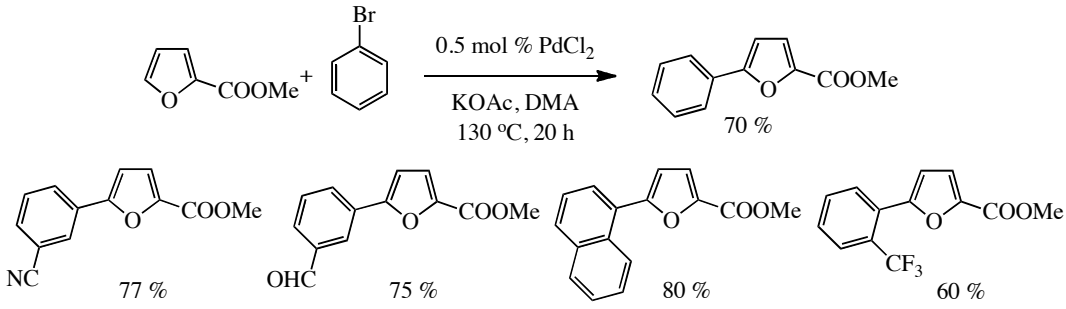
In order to prevent formation of product mixtures, arylation methods developed used only furans that are substituted at the 2-position. A $PdCl_2$ catalyst and tricyclohexylphosphine ligand was used together with KOAc base and Bu_4NBr additive in DMF at 120 °C (Scheme 2.12).[31] Substitution at the 5-position was observed. Non-activated and hindered aryl iodides can be employed. Aryl bromides and heteroaryl bromides were also effective arylating agents. In another method, Pearlman's catalyst ($Pd(OH)_2$ on carbon) was used for the arylation of 2-furaldehyde with bromobenzene, giving product in a good yield.

Scheme 2.12. Arylation of 2-furaldehyde with aryl iodides



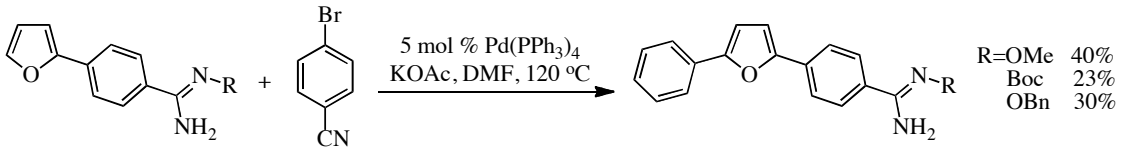
Arylation of 2-methylfuroate was also demonstrated. The method employed 0.005 mol % of $Pd(OAc)_2$ and does not require any ligand (Scheme 2.13).[32] Many aryl bromides were shown to be reactive. In addition, the products were utilized as starting materials for decarboxylative arylation of furans.

Scheme 2.13. Arylation of methyl 2-furoate with aryl bromides



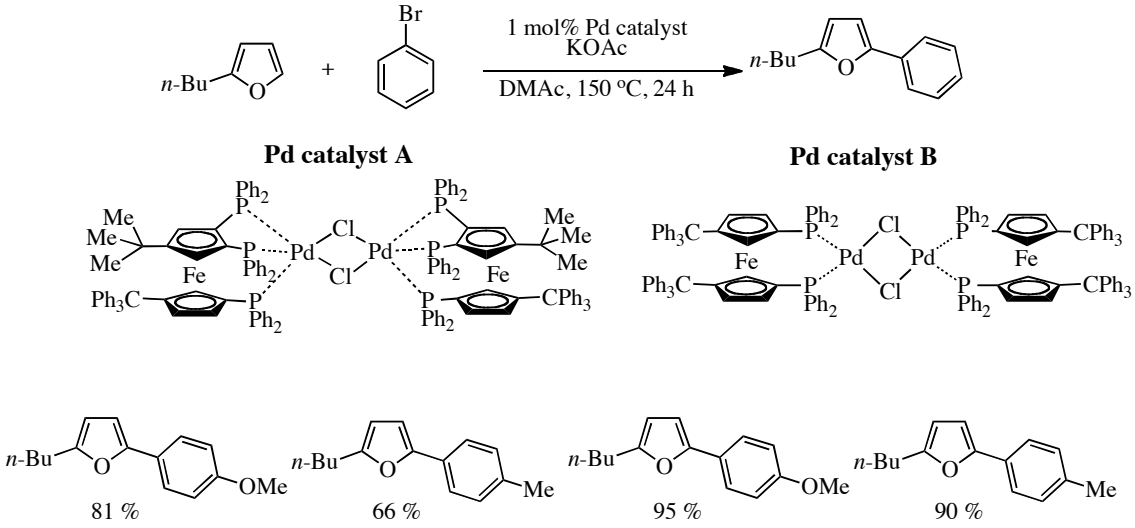
Other types of furans that were prepared using direct arylation method include the metabolite of prodrug 2,5-bis(4-*O*-methoxyaminophenyl)furan (Scheme 2.14).[33] The method was compatible with various amidoxime functional groups.

Scheme 2.14. Arylation of 2-arylfuran by an aryl bromide



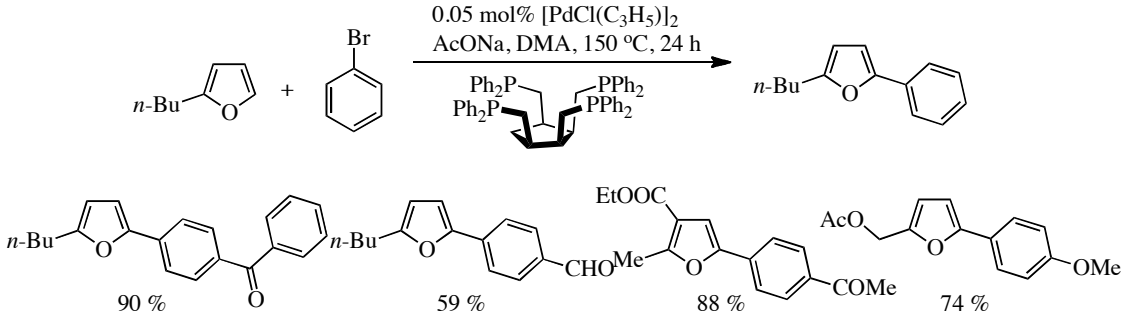
Nature of palladium source has a significant effect on the yield of furan arylation. The complex of palladium with ferrocenyl polyphosphine ligands was found to be effective for the arylation of 2-(*n*-butyl)furan by aryl bromides (Scheme 2.15).[34] Other palladium sources such as $Pd(PPh_3)_4$, $Pd(OH)_2$, $PdCl_2/2PCy_3$ and $Pd(OAc)_2$ provided significantly lower yield. The backbone of the ferrocenyl-based phosphine ligands provides a rigid scaffold for the catalyst during the reaction.

Scheme 2.15. Arylation of 2-(*n*-butyl)furan using Pd with ferrocenyl-based ligand



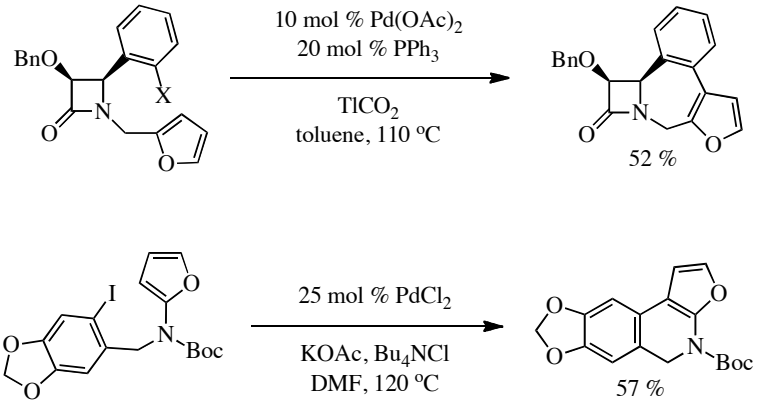
Method for the arylation of furan by aryl bromides using Pd catalyst system at low catalyst loadings was also developed. The method used 1,2,3,4,-tetrakis((diphenylphosphino)methyl)cyclopentane ligand (Scheme 2.16).[35] Various aryl bromides were reactive under the reaction conditions.

Scheme 2.16. Arylation of furans with aryl bromides at low catalyst loadings



Intramolecular version of direct furan arylation was developed to generate polycyclic ring scaffold for natural product synthesis. Arylation at the 3-position was enforced by the topological location of the arylating group that is geared towards the reaction with C–H bond at the 3-position. Palladium-catalyzed direct furan arylation was used in the synthesis of ß-lactam antibiotic intermediate (Scheme 2.17).[36] Direct furan arylation is used for the preparation of an intermediate for the total synthesis of γ-lycorane (Scheme).[37]

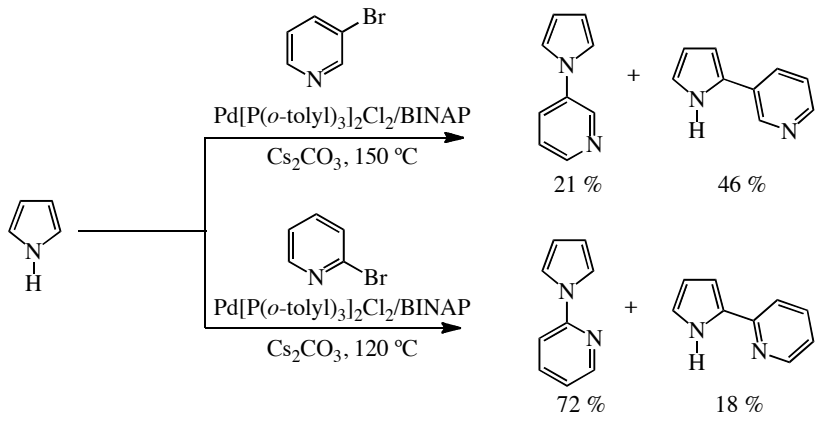
Scheme 2.17. Intramolecular arylation of furan at the C–3 position



E. Arylation of pyrroles

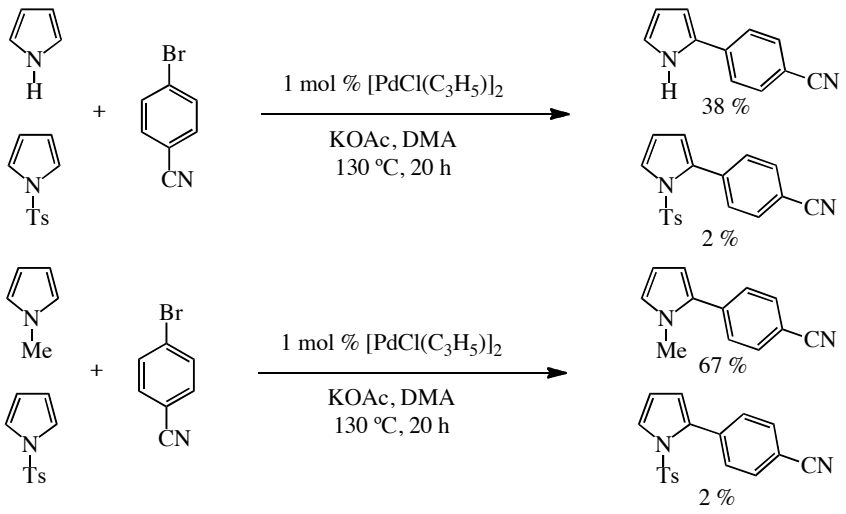
Arylation of pyrroles has an additional challenge if compared with other heterocycles. In addition to polyarylation and competing C–2 and C–3 arylation, a more acidic *N*-H reacts faster than the C–H bonds under many arylation conditions. The main product of the reaction is *N*-arylated species, and only rarely significant proportion of C–arylated product is obtained (Scheme 2.18).[38]

Scheme 2.18. Pd-catalyzed arylation of free *N*–H pyrroles



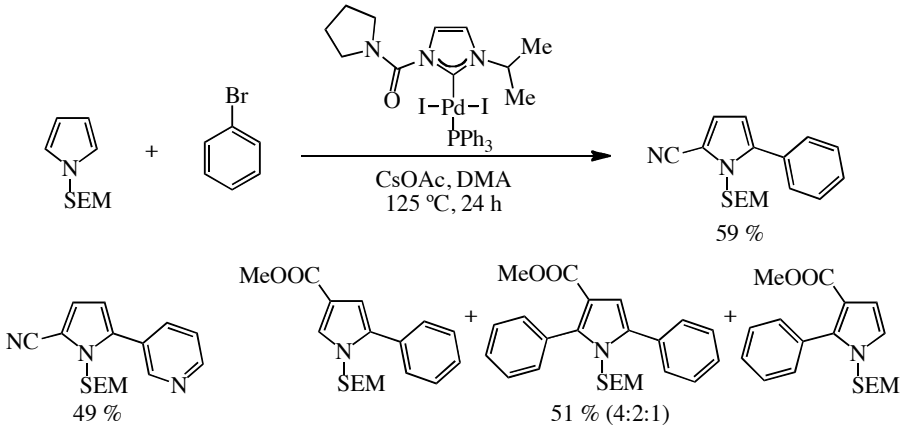
In order to obtain the C–arylation product, the *N*–H functionality of pyrroles is usually protected. Pyrroles with alkyl substituent on nitrogen were found to be more reactive than free *N*–H pyrroles, which in turn are more reactive than *N*–tosyl heterocycles (Scheme 2.19). Electron-withdrawing protecting groups slow down the arylation. However, installation of electron withdrawing protecting group becomes necessary since most of the readily available protecting groups for nitrogen render the pyrrole rings more electron deficient. The challenge is choosing the optimal protecting group that will protect the nitrogen but will still permit C–arylation.

Scheme 2.19. Competitive experiments for arylation of pyrroles



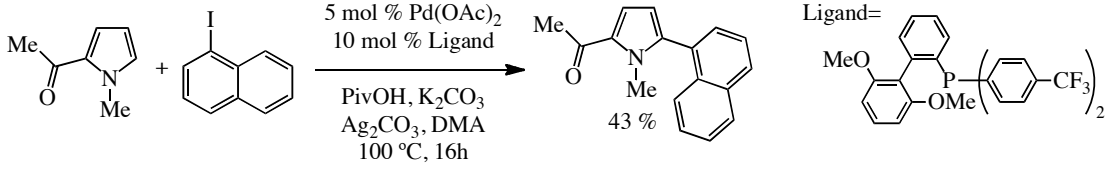
Arylation of SEM-protected pyrroles (SEM=2-(trimethylsilyl)ethoxymethyl) was performed using Pd complex with NHC (*N*-heterocyclic carbene) ligand (Scheme 2.20).[27] Three examples of SEM-protected pyrroles were reported, all with moderate yields. Mixtures of arylated products were obtained.

Scheme 2.20. Arylation of SEM-protected pyrroles

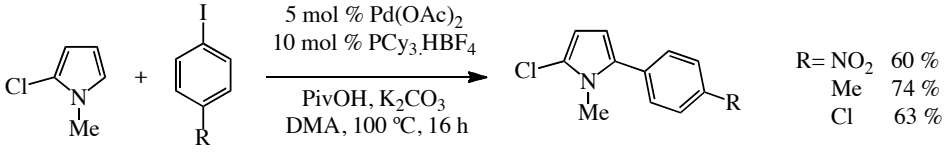


Arylation of pyrroles were performed using an electron deficient bulky phosphine ligand. Arylation of other heterocycles such as benzothiophene, thiophenes, thiazoles, furans, pyrazole, triazoles, and imidazole by aryl iodides were also effective. However, moderate yield in direct arylation of *N*-methylpyrrole was obtained using the same method (Scheme 2.21).[39] Slightly better yields for *N*-benzylpyrroles were obtained using a combination of electron-rich tricyclohexylphosphine ligand and aryl iodide coupling partner (Scheme 2.22).[9k]

Scheme 2.21. Arylation of pyrroles under Pd-catalysis with electron-deficient phospine

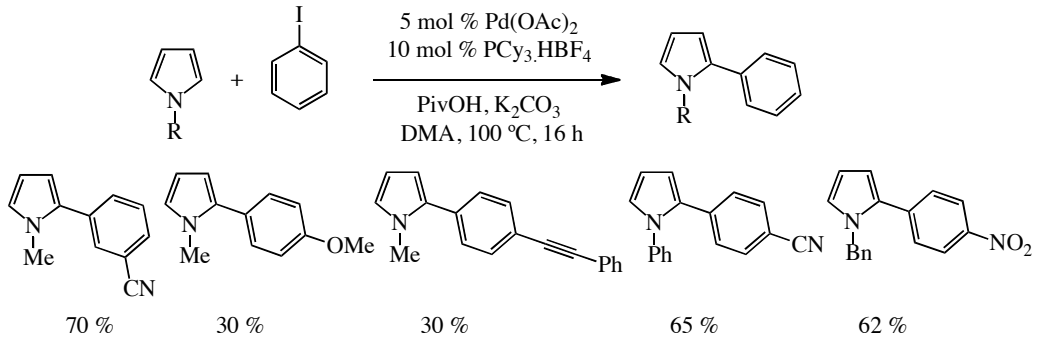


Scheme 2.22. Arylation of pyrroles under Pd-catalysis with electron-rich phosphine



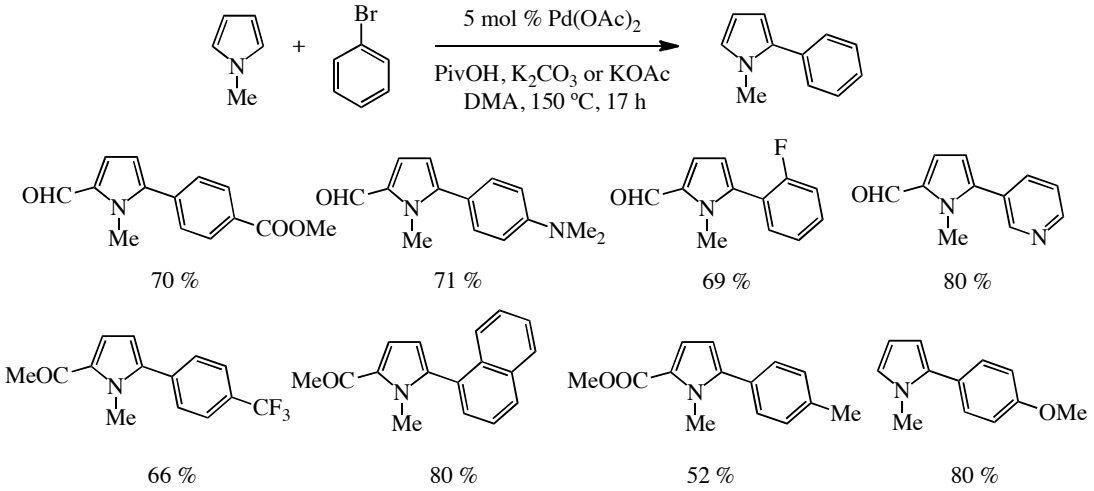
Several other conditions were reported to be effective for arylation of *N*–arylated and alkylated pyrroles. A variety of aryl iodide coupling partners could be used. However, the method uses stoichiometric amount of silver acetate base (Scheme 2.23).[9q]

Scheme 2.23. Pd-catalyzed arylation of pyrroles with aryl iodides



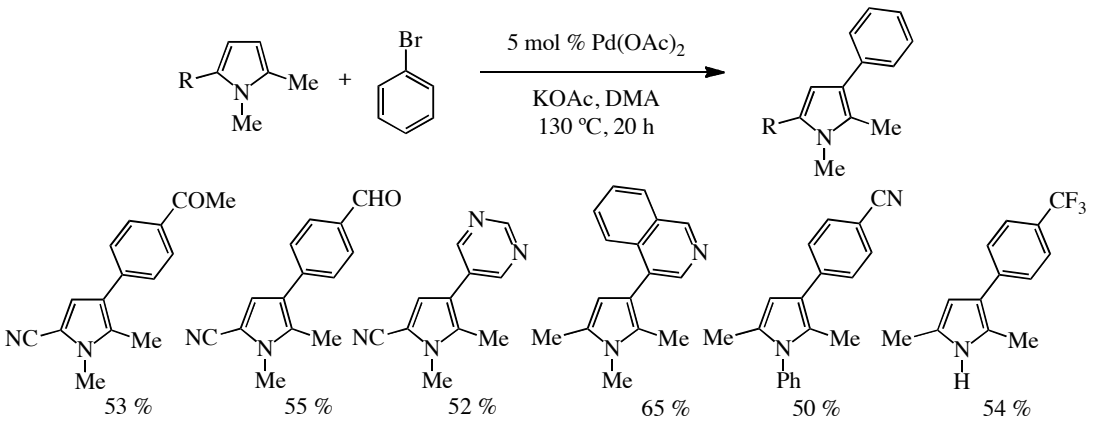
Another economical method for palladium-catalyzed C–2 and C–5 arylation of pyrroles was developed (Scheme 2.24).[40] The method did not require the use of ligand. Potassium carbonate or potassium acetate bases were employed. A wide variety of aryl bromides can be used. However, arylation of only *N*-methylpyrroles were reported.

Scheme 2.24. Ligand-free Pd-catalyzed arylation of *N*-methylpyrrole



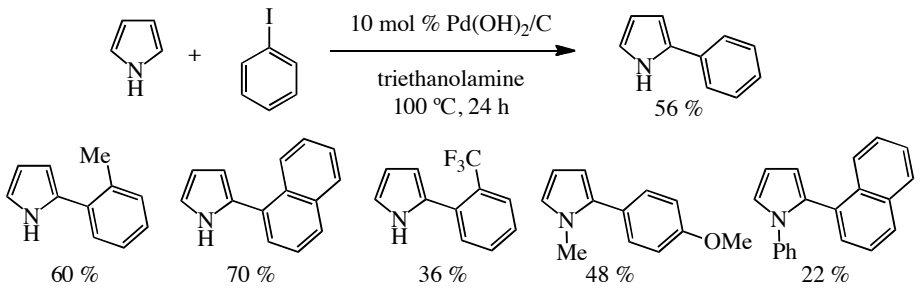
Arylation at the C–3 or C–4 positions of pyrroles was also demonstrated. The method used palladium acetate catalyst, potassium acetate base and dimethylacetamide solvent (Scheme 2.25).[41] Pyrroles containing substitution at N–1, C–2, and C–5 positions were found to be susceptible to arylation at other positions. Aryl bromides with electron-rich and electron-poor substituents can be used in the reaction. *N*–Phenyl and -methyl pyrroles containing electron-withdrawing groups were arylated.

Scheme 2.25. Ligand-free Pd-catalyzed C–3 and C–4 arylation of pyrroles



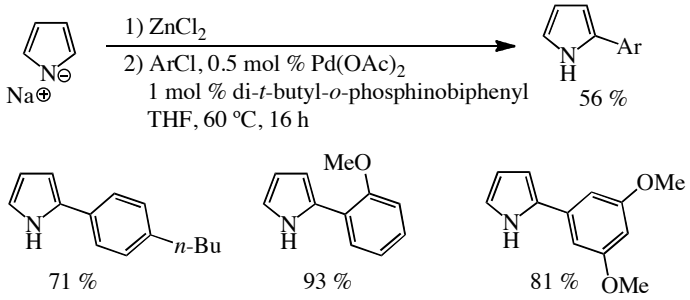
Arylation of unprotected *N*-H pyrroles were also demonstrated utilizing phenyl iodide under $Pd(OAc)_2$ catalysis, cesium acetate base, and DMA solvent at 125 ºC (Scheme 2.26).[91] No ligand was employed in the method, and although the yield is low, *N*–arylation was not reported. Other successful C–selective arylation of free *N*–H pyrroles with aryl iodides utilize a combination of $Pd(OH)_2/C$ and triethanolamine at 100 ºC. This method however, gave lower yield for pyrroles with substituents on the nitrogen.[42]

Scheme 2.26. Direct arylation of pyrroles in triethanolamine



Pyrrole salt of zinc prepared *in situ* from the reaction of pyrrolyl sodium with zinc chloride was reported to be effectively arylated and perfluoroalkylated at the C–2 position with organohalides.[43] However, in this study the products were not purified and only GC yields were reported. Later, the tactic of using zincated pyrroles as starting materials for the arylation was further developed so that more arylating agents could be used (Scheme 2.27).[9d] The method mostly used aryl bromides. Only three examples of aryl chloride use were provided. The success of the method is due to the use of the electron-rich, bulky phosphine ligands such as 2-(di-*tert*-butylphosphino)biphenyl. In most cases, arylation occurs at the C–2 position. In some cases, however, the *N*–arylation occurs if 2-(dicyclohexylphosphino)biphenyl ligand is used.

Scheme 2.27. Arylation of pyrrole salt by aryl chlorides



At this point, there are many methods developed for direct arylation of heterocycles. Most of these methods use aryl bromides and aryl iodides as coupling partners, and few examples rely on aryl chlorides. Our laboratory has developed a general method for arylation of electron-rich heterocycles.[9e] However, the method does not work for furans and pyrroles. This study was undertaken to fill that gap in the scope of the arylation method. We report here a method for arylation of furans and *N*-substituted pyrroles by aryl chlorides.

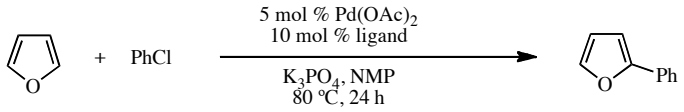
II. Results and Discussions

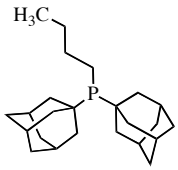
A. Furan arylation

1. Optimization of ligand

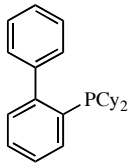
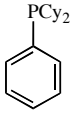
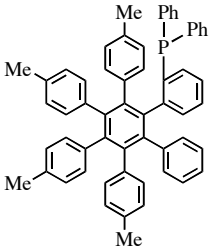
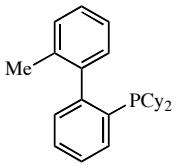
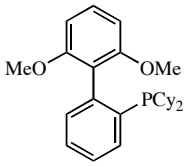
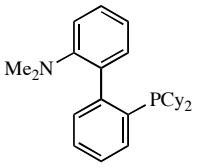
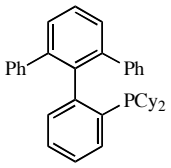
The initial optimization involved testing of phophine ligands (Table 2.1). Ligands such as dicyclohexylphenyl-, tricyclohexyl-, and *n*-butyldi-1-adamantylphosphine were not effective. A bowl-shaped triarylphosphine[44] afforded 51% conversion to the monoarylated product (entry 5). The best ligand for the furan arylation was found to be 2-(dicyclohexylphosphino)biphenyl (entry 2). Appreciable amount of the diarylated product was seen in the reaction mixture. Adjusting the temperature to 100 ^{o}C and increasing the amount of solvent prevents overarylation and increases the GC yield. Other Buchwald-type ligands were also tested. Ligands that contain electron-releasing substituents (entry 6) and those that provide extra chelation (entries 7 and 8) afford less conversion than the unsubstituted ligand (entry 2). Introduction of other phenyl rings in the ligand to increase bulk did not improve the yield (entry 12).

Table 2.1. Screening of ligand for coupling of furan with chlorobenzene[a]



Entry	Ligand	% GC Yield (isolated)
1		< 2 %

Continuation of Table 2.1

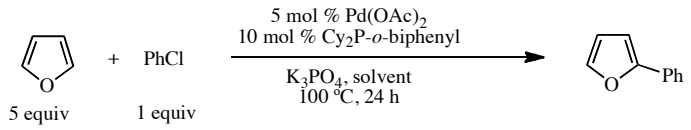
Entry	Ligand	% GC Yield (isolated)
2		67 % monoarylation 15 % diarylation 86 % monoarylation[b] Trace diarylation
3		3 %
4	Cy_3P	< 2 %
5		51 %
6		32 %
7		53 %
8		28 %
9		67 %

[a]Conditions: Furan (5 equiv), PhCl (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_3PO_4 (2 equiv), NMP (1 mL), stir for 24 h at 80 °C. [b]2 mL NMP, 100 °C.

2. Optimization of solvent

Solvent optimization is shown in Table 2.2. The best solvent for the arylation of furan is NMP (*N*-methylpyrrolidine, entry 1). Other polar solvents afford very low conversion.

Table 2.2. Optimization of solvent for coupling of furan with chlorobenzene.[a]



Entry	Solvent	GC conversion
1	NMP	86 % monoarylation Trace diarylation
2	THF	< 2 %
3	DMA	16 % monoarylation
4	DMPU	< 2 %

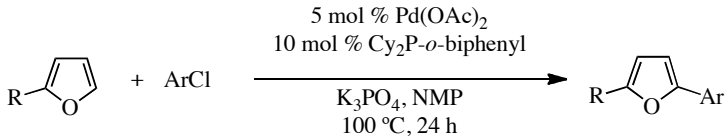
[a]Conditions: Furan (5 equiv), PhCl (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_3PO_4 (2 equiv), solvent (1 mL), 24 h, 100 °C.

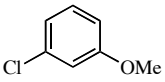
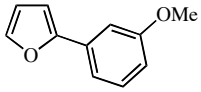
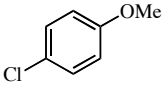
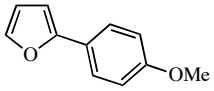
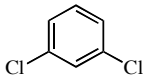
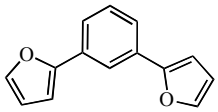
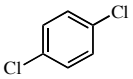
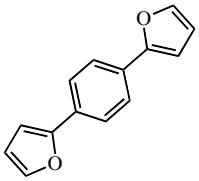
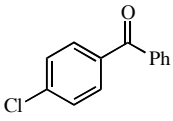
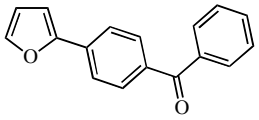
3. Arylation of furans by aryl chlorides

Furan arylation results are presented in Table 2.3. The scope with regards to furan that can be arylated is wide. Simple furan as well as furans with electron-donating and electron-releasing substituents can be arylated. Furan (entries 1–5), furan-2-carboxylic acid ethyl ester (entries 6–7), and 2-methylfuran (entries 8–10) were successfully arylated.

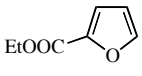
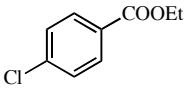
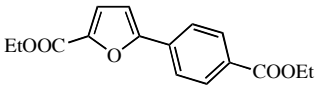
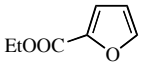
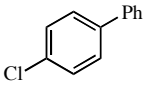
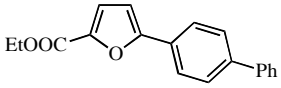
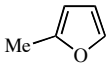
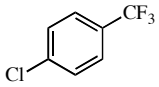
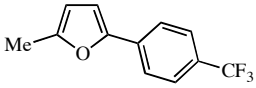
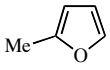
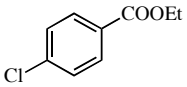
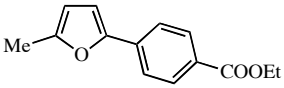
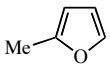
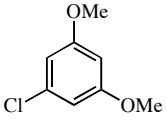
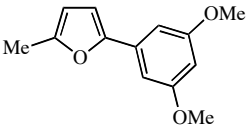
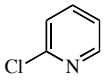
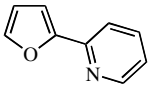
A wide variety of aryl chlorides can be utilized for arylation. Electron-rich (entries 1–2) as well as electron-poor aryl chlorides (entries 3–6, 8–9) are reactive. Dichloroarenes can be reacted with furan resulting in substances possessing several heterocyclic moieties (entries 3–4). Heterocyclic aryl chlorides such as 2-chloropyridine are competent arylating reagents (entry 11). Yields range from moderate to good. Several equivalents of furan are typically employed to avoid diarylation. For monosubstituted furan arylation, excess of aryl chloride is used.

Table 2.3. Furan arylation[a]



Entry	Furan	Aryl Chloride	Product	Yield, %
1				92
2				71
3				82
4				75
5				78

Continuation of Table 2.3

Entry	Furan	Aryl Chloride	Product	Yield, %
6[b]				63
7[b]				54
8				76
9				50
10				54
11				53

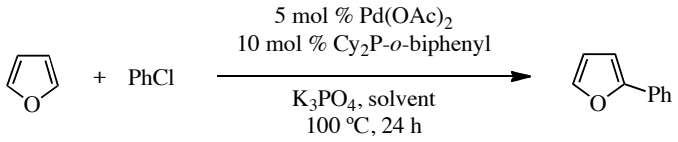
[a] Conditions: 5 mol % $Pd(OAc)_2$, 10 mol % Cy_2P-*o*-biphenyl, K_3PO_4 (2 equiv), furan (5 equiv), aryl chloride (1 equiv), NMP solvent, 24 h at 100 °C; isolated yield. [b] Furan (1 equiv), aryl chloride (5 equiv). Yields are the average of two runs.

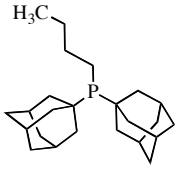
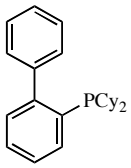
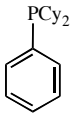
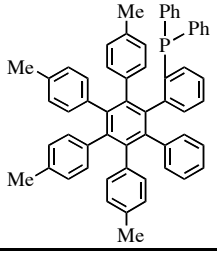
B. Pyrrole arylation

1. Ligand optimization

A short ligand optimization was undertaken for the arylation of *N*-methylpyrrole with chlorobenzene. Dicyclohexylphenyl- and tricyclohexylphosphine afforded moderate conversions to the product while butyldi-1-adamantylphosphine was inefficient. The best results were obtained by employing 2-(dicyclohexylphosphino)biphenyl ligand that was used for subsequent reactions (entry 2).

Table 2.4. Ligand screening for coupling of *N*-methylpyrrole with chlorobenzene[a]



Entry	Ligand	Conversion [%]
1		31
2		70
3	PCy_3	13
4		13
5		69

[a]Conditions: 1-methyl-1H-pyrrole (5 equiv), PhCl (1 equiv), $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), K_3PO_4 (2 equiv), NMP (1 mL), 24 h at 125 °C.

2. Arylation of pyrroles by aryl chlorides

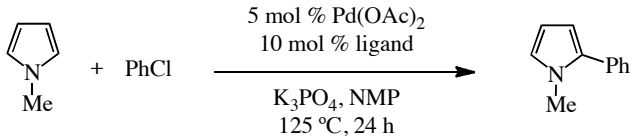
Pyrroles can be arylated by aryl chlorides using palladium acetate and 2-(dicyclohexylphosphino)biphenyl in NMP as solvent at 125 ºC (Table 2.5). DMPU occasionally provides better yield than NMP (Entry 5). The scope of the arylation of pyrroles by aryl chlorides is shown in Table 2.5.

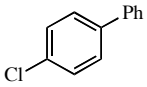
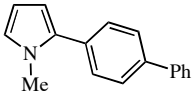
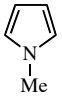
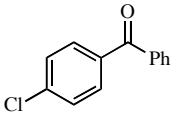
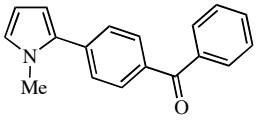
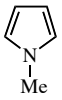
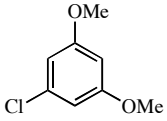
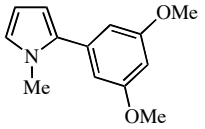
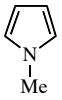
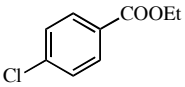
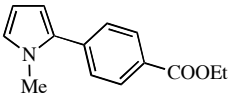
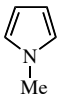
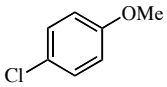
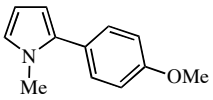
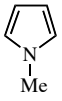
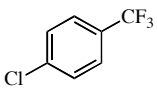
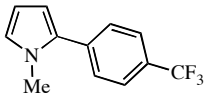
A wide variety of pyrroles could be arylated by the method developed. In most cases, excess of *N*-methylpyrrole is used to avoid diarylation. *N*-Methylpyrroles with both electron-withdrawing (entries 10 and 11) and phenyl groups (entry 9) are reactive. 1-Methyl-2-phenylpyrrole is also reactive and can be *p*-tolylated in 63% yield (entry 9). 1-Methylpyrrole-2-carboxylic acid ethyl ester is arylated in moderate yields (entries 10 and 11). Arylation of *N*-phenylpyrrole was also successful (entry 12).

The method displays wide functional group tolerance for aryl chlorides. Both electron-rich (entries 5, 9, 11) and electron-poor (entries 2, 4, 6) aryl chlorides are reactive. Introduction of two *N*-methylpyrrole functionalities is possible if *m*-dichlorobenzene is employed (entry 8) and 1,3-bis(1-methyl-1*H*-pyrrol-2-yl)benzene was obtained in 72% yield.

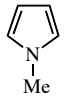
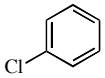
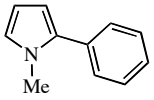
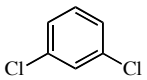
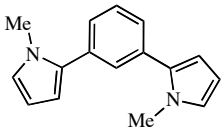
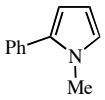
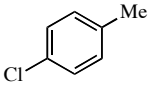
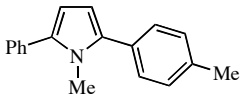
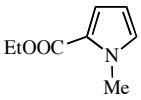
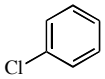
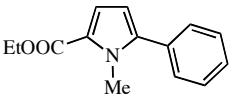
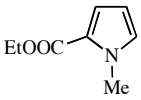
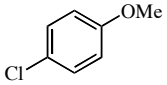
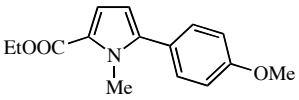
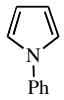
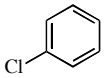
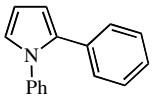
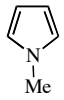
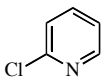
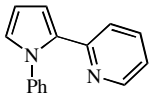
Functional groups such as ketone (entry 2) and ester (entry 4) are tolerated. Heteroaryl chlorides such as 2-chloropyridine are reactive (entry 13)

Table 2.5. Pyrrole arylation[a]



Entry	Pyrrole	Aryl Chloride	Product	Yield, %
1				56
2				51
3				50
4				78
5[b]				70
6				60

Continuation of Table 2.5

Entry	Pyrrole	Aryl Chloride	Product	Yield, %
7				60
8				72
9[c]				63
10[c]				53
11[c]				53
12[c]				42
13				53

[a]Conditions: 5 mol % $Pd(OAc)_2$, 10 mol % Cy_2P-*o*-biphenyl, 2 equiv K_3PO_4, aryl chloride (1 equiv), pyrrole (5 equiv), NMP solvent, 24 h at 125 °C; isolated yield. [b] DMPU solvent. [c] Pyrrole (1 equiv), aryl chloride (3 equiv). Yields are the average of two runs.

III. Conclusions

We have demonstrated the arylation of pyrroles and furans by aryl chlorides. The method employs a palladium acetate catalyst, 2-(dicyclohexylphosphino)biphenyl ligand, and an inorganic base. Electron-rich, electron-poor, and heterocyclic aryl chloride coupling partners can be used and arylated heterocycles are obtained in moderate to good yields. Unfortunately, it appears that at this point arylation by unactivated aryl chlorides requires extensive optimization of reaction conditions for every substrate class to determine optimal ligand, base, and solvent. *N*-Arylation of pyrroles is preferred to *C*-arylation if unactivated aryl chloride coupling partners are employed. Further investigations are required to solve these problems.

VI. Experimental details

A. General considerations

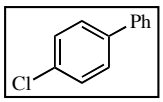
Reactions were performed in 4-dram vials with PTFE caps. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Preparative TLC was performed on Analtech 02015 plates, 20 x 20 cm, 2000 μm thick, with fluorescent indicator. GC analyses were performed on a Shimadzu CG-2010 chromatograph equipped with a Restek column (Rtx®-5, 15m, 0.25 mm ID). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a GE QE-300 or JEOL EC-500 NMR using residual solvent or TMS peaks as a reference. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument.

B. Materials

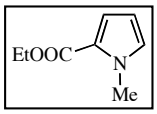
Palladium acetate was used as received. Powdered K_3PO_4, anhydrous NMP, anhydrous DMPU, and 2-(dicyclohexylphosphino)biphenyl were stored under argon.

The following starting materials were obtained from commercial sources and were used without further purification. DMA, DMF, potassium phosphate, 1,4-dioxane, 1,4-dichlorobenzene, 1,3-dichlorobenzene, 3-chloropyridine, ethyl 2-furoate, 2-methylfuran, cyclohexylacetylene, 3-chloroanisole, 3-methylindole, 1-phenylpyrrole, furan, 3-chlorotoluene, 3-chloroanisole, 4-chloroanisole, (4-chlorophenyl)(phenyl)methanone, 4-chlorobenzotriflouride, 5-chloro-m-xylene, 1-chloro-3,4-dimethylbenzene,

triphenylphosphine, 2-(dicyclohexyl-phosphino)biphenyl, butyldi-1-adamantylphosphine, sodium bicarbonate, concentrated hydrochloric acid, 1,2-dimethylindole, methyl 3-chlorobenzoate, chlorobenzene, 1-chloro-3,5-dimethoxybenzene, and ethyl-4-chlorobenzoate. 1-Methyl-1*H*-pyrrole was distilled prior to use.



4-Chlorobiphenyl. A procedure developed by Beller was used.[45] Outside the glovebox, a 12-dram vial equipped with a magnetic stir bar was charged with phenylboronic acid (10.0 mmol, 1.22 g), 1-bromo-4-chlorobenzene (11.0 mmol, 2.1 g), and triphenylphosphine (1.0 mmol, 260 mg, 10 mol %). The vial was flushed with argon, capped and placed inside a glovebox followed by addition of K_3PO_4 (20.0 mmol, 4.25 g), anhydrous NMP (20 mL), and $Pd(OAc)_2$ (0.5 mmol, 110 mg, 5 mol %). The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min and placed in heating block (125 °C) for 24 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate (10 mL). The suspension was filtered through filter paper. The solids were washed with ethyl acetate (5 mL). The filtrate was concentrated under vacuum to a volume of about 5 mL. The mixture was absorbed on silica gel and subjected to flash chromatography (hexane/ethyl acetate 95/5). After concentration of the fractions containing the product, the residue was dried under reduced pressure (40 °C) to yield crude product. The crude compound was dissolved in hot ethanol followed by dropwise addition of water until cloudiness appeared. After standing overnight the solution was filtered to give pure 4-chlorobiphenyl (1.59 g, 86 %). This compound is known.[46] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.51 (m, 4H), 7.47–7.40 (m, 4H), 7.39–7.36 (m, 1H).



Ethyl 1-methyl-1*H*-pyrrole-2-carboxylate. A procedure developed by Jones was used.[47] *N*-methylpyrrole (25 mmol, 2.23 mL) was added to THF (25 mL) under argon at -78 ^{o}C followed by dropwise addition of a solution of *n*-BuLi (25 mmol, 10 mL of a 2.5 M solution). The reaction mixture was stirred for 5 minutes, warmed to room temperature and stirred under Ar for 14 h. The resulting lithiated *N*-methylpyrrole solution was added dropwise to a solution of ethyl chloroformate (25 mmol, 2.37 mL) in THF (20 mL) at 0 ^{o}C. The reaction mixture was stirred for 90 min and water (20 mL) was added to quench the reaction. The layers were separated and the aqueous layer was extracted with diethyl ether (3 X 20 mL). The organic layers were combined and dried with $MgSO_4$. After filtration and evaporation to a volume of about 5 mL, the crude product was subjected to flash chromatography using pentane-diethyl ether eluent. Clear oil (1.96 g, 51 %) was obtained after evaporation of the solvent. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (dd, *J*=4.0, 1.7 Hz, 1H), 6.76–6.75 (m, 1H), 6.10–6.09 (m, 1H), 4.27 (q, *J*=7.0 Hz, 2H), 3.91 (s, 3H), 1.34 (t, *J*=7.0 Hz, 3H).

C. General procedure for the determination of the amount of the analyte by internal standard method

The response factor of the compounds analyzed was determined by preparing a mixture of the dodecane internal standard (1 mmol, 179 mg), analyte (1 mmol of pure arylated indole, pyrrole or furan), and dichloromethane (4 mL). This mixture was analyzed by GC and the response factor was determined from the ratio of the area of the internal standard and the analyte. Internal standard (dodecane, 197 mg, 1 mmol) was added to the reaction mixture to be analyzed. The mixture was diluted with dichloromethane to 4 mL. An aliquot was filtered through a pad of Celite and analyzed

by GC. The amount of the product formed was determined from the area of dodecane standard, product, and response factor obtained above.

D. Furan arylation

1. Optimization of ligand

Outside the glovebox, a 4-dram vial equipped with a magnetic stir bar was charged with furan (5 mmol) and chlorobenzene (1 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added ligand (0.10 mmol, 10 mol %), K_3PO_4 (2.0 mmol, 425 mg), and anhydrous NMP (1 mL). The mixture was shaken and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 5 mol %) was added. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min, placed in heating block (100 ^oC), and stirred vigorously for 24 h. The reaction mixture was allowed to cool to room temperature and amount of the product was analyzed by GC using internal standard method. The ligand optimization results are shown in Table 2.1.

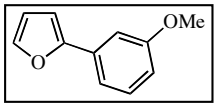
2. Optimization of the solvent

Outside the glovebox, a 4-dram vial equipped with a magnetic stir bar was charged with furan (5 mmol) and chlorobenzene (1 mmol). The vial was flushed with argon, capped, and placed inside a glovebox. To this mixture was added 2-(dicyclohexylphosphino)biphenyl (0.10 mmol, 10 mol %), K_3PO_4 (2.0 mmol, 425 mg), and anhydrous solvent (1 mL). The mixture was shaken and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 5 mol %) was added. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min, placed in heating block (100 ^oC), and stirred vigorously for 24 h.

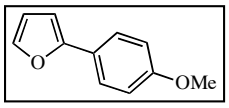
The reaction mixture cooled to room temperature and the amount of the arylated product was determined by internal standard method. The solvent optimization results are shown in Table 2.2.

3. General procedure for the arylation of furans

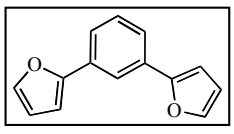
Outside the glovebox, a 4-dram vial equipped with a magnetic stir bar was charged with furan and chloroarene. The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (2.0 mmol, 425 mg), and anhydrous NMP (2 mL). The mixture was shaken and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 5 mol %) was added. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min and placed in heating block (100 ^oC) for 24 h. The reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (50 mL). Resulting suspension was filtered. The filtrate was concentrated under vacuum to a volume of about 2 mL. The mixture was absorbed on silica gel and subjected to column chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure (40 °C) to yield a pure arylated furan. The yields listed in Table 2.3 are the average of two runs.



2-(3-Methoxyphenyl)furan (Table 2.3, Entry 1): Palladium acetate (11.4 mg, 0.05 mmol), furan (0.47 mL, 5.0 mmol), 3-chloroanisole (147 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 95/5), 167 mg (93 % yield) of a light yellow oil was obtained. A second experiment under the same conditions gave 90 % yield. This compound is known.[48] R_f = 0.23 (hexanes/ethyl acetate 95/5). ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 7.39 (s, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.11–7.07 (m, 2H), 6.70 (d, J=8.0 Hz, 2H), 6.41 (s, 1H), 6.15–6.13 (m, 1H), 3.31 (s, 3H).

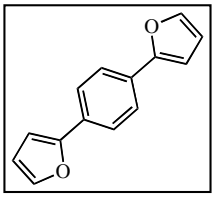


2-(4-Methoxyphenyl)furan (Table 2.3, Entry 2): Palladium acetate (11.4 mg, 0.05 mmol), furan (0.47 mL, 5.0 mmol), 4-chloroanisole (165 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes) 149 mg (73 %) of white powder were obtained. A second experiment under the same conditions gave 68 % yield. This compound is known.[46] R_f=0.24 (hexanes). ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.61–7.58 (m, 2H), 7.15–7.13 (m, 1H), 6.77–6.75 (m, 2H), 6,34 (d, J=4.0 Hz), 6.18–6.16 (m, 1H), 3.25 (s, 3H).

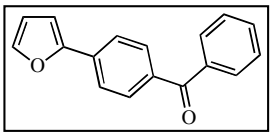


1,3-Di(furan-2-yl)benzene (Table 2.3, Entry 3): Palladium acetate (11.4 mg, 0.05 mmol), furan 0.94 mL, 10.0 mmol), 1,3-dichlorobenzene (159 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes), pure fractions were combined and the solvent was

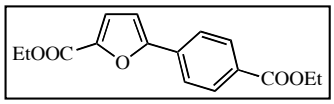
evaporated. The impure fractions were combined, concentrated, and subjected to another column chromatography step (hexanes). The pure fractions were combined and after evaporation of the solvent more product was obtained. A total of 184 mg (80 % yield) of a pale yellow oil was obtained. A second experiment under the same conditions gave 83 % yield. R_f = 0.48 (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.99–7.98 (m, 1 H), 7.55 (dd, *J*=7.4 Hz, 1.7 Hz, 2 H), 7.48 (d, *J*=1.7 Hz, 1H), 7.39–7.37 (m, 2H), 6.70 (d, *J*=3.4 Hz, 2H), 6.49–6.47 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 153.7, 142.2, 131.3, 129.0, 122.7, 119.1, 111.7, 105.4. FT-IR (neat, cm^{-1}) ν 1614, 1503, 1220, 1156, 1012. Anal. Calcd for $C_{14}H_{10}O_2$ (210.23 g/mol): C, 79.98; H, 4.79; Found: C, 79.80; H, 4.79.



1,4-Di(furan-2-yl)benzene (Table 2.3, Entry 4): Palladium acetate (11.4 mg, 0.05 mmol), furan (0.5 mL, 5.0 mmol), 1,4-dichlorobenzene (72 mg, 0.5 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes), fractions containing the desired compound were combined and the solvent was evaporated affording white powder (103 mg, 72 %). A second experiment under the same conditions gave 76 % yield. R_f = 0.28 (hexanes). This compound is known.[46] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.69 (s, 4H), 7.48 (dd, *J*=1.8, 0.9 Hz, 2H), 6.67 (dd, *J*=3.4, 0.9 Hz, 1H), 6.48 (dd, *J*=3.4, 1.8 Hz, 1H).

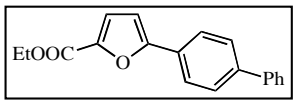


(4-(Furan-2-yl)phenyl)(phenyl)methanone (Table 2.3, Entry 5): Palladium acetate (11.4 mg, 0.05 mmol), furan (0.47 mL, 5.0 mmol), (4-chlorophenyl)(phenyl)methanone (238 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes), pure fractions were combined and the solvent was evaporated. The impure fractions were combined, solvent was evaporated, and the impure product was recrystallized from hexanes. A total of 205 mg (75 % yield) of pale yellow crystalline product was obtained. A second experiment under the same conditions gave 80 % yield. R_f = 0.07 (hexanes). This compound is known.[49] ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.77–7.69 (m, 2H), 7.73–7.72 (m, 2H), 7.53–7.51 (m, 2H), 7.14–7.12 (m, 1H), 7.27–7.04 (m, 3H), 6.39–6.37 (m, 1H), 6.12–6.10 (m, 1H).

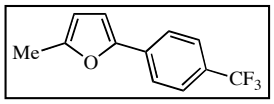


Ethyl 5-(4-(ethoxycarbonyl)phenyl)furan-2-carboxylate (Table 2.3, Entry 6): Palladium acetate (11.4 mg, 0.05 mmol), ethyl 2-furoate (143 mg, 1.0 mmol), ethyl 4-chlorobenzoate (800 mg, 5.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL), reaction temperature 125 °C. The reaction mixture was loaded directly onto the column. After column chromatography (hexanes/ethyl acetate 95/5), fractions containing the desired compound were combined and the solvent was evaporated leaving a white powder (178 mg, 61 % yield). A second experiment under the same conditions gave 64 % yield. R_f = 0.10 (hexanes/ethyl acetate 95/5), mp=48–49 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.05 (d, J=8.6 Hz, 2H),

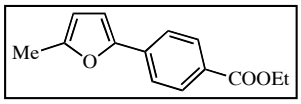
7.80 (d, *J*=8.6 Hz, 2H), 7.22 (d, *J*=3.7 Hz, 1H), 6.82 (d, *J*=3.7 Hz, 1H), 4.38–4.34 (m, 4H), 1.39–1.36 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 166.0, 158.7, 156.1, 144.7, 133.3 130.4, 130.1, 124.5, 119.8, 108.7, 61.1, 61.2, 14.4, 14.3. FT-IR (neat, cm^{-1}) *v* 1718, 1708, 1301, 1265, 1177, 1141, 1100, 1021. Anal calcd for $C_{16}H_{16}O_5$ (288.3 g/mol): C, 66.66; H, 5.59; Found: C, 67.14; H, 5.26.



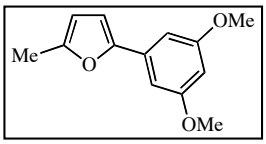
Ethyl 5-(biphenyl-4-yl)furan-2-carboxylate (Table 2.3, Entry 7): Palladium acetate (11.4 mg, 0.05 mmol), ethyl 2-furoate (143 mg, 1.0 mmol), 4-chlorobiphenyl (508 mg, 3.0 mmol), 2-(dicyclohexylphosphino)-biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was loaded directly onto the column. After column chromatography (hexanes/ethyl acetate 95/5), fractions containing the desired compound were combined and the solvent was evaporated leaving yellowish powder (282 mg). The impure product was recrystallized from hexanes giving 155 mg (52 %) of a beige powder. A second experiment under the same conditions gave 55 % yield. R_f =0.13 (hexanes/ethyl acetate 95/5), mp= 95–96 °C (pentane). ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.68–7.65 (m, 2H), 7.41–7.37 (m, 4H), 7.22–7.19 (m, 2H), 7.15–7.12 (m, 2H), 6.26 (d, *J*=3.4 Hz, 1H), 4.14 (q, *J*=7.5 Hz, 2H), 1.04 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 158.3, 157.1, 144.5, 141.5, 140.4, 128.8, 128.6, 128.0, 127.5, 127.0, 125.2, 119.6, 106.8, 60.4, 14.1. FT-IR (neat, cm^{-1}) *v* 1722, 1479, 1302, 1284, 1271, 1218, 1153, 1022. Anal. Calcd for $C_{19}H_{16}O_3$ (292.33 g /mol): C, 78.06; H, 5.52; Found: C, 78.14; H, 5.54.



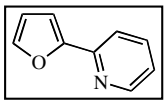
2-Methyl-5-(4-(trifluoromethyl)phenyl)furan (Table 2.3, Entry 8): Palladium acetate (11.4 mg, 0.05 mmol), 2-methylfuran (0.47 mL, 5.0 mmol), 4-chlorobenzotrifluoride (199 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes), 189 mg (76 %) of a white powder was obtained. A second experiment under the same conditions gave 76 % yield. R_f = 0.62 (hexanes). This compound is known.[50] ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.39–7.32 (m, 4H), 6.31 (d, J = 3.4 Hz, 1H), 5.79 (m, 1H), 1.98 (s, 3H).



Ethyl 4-(5-methylfuran-2-yl)benzoate (Table 2.3, Entry 9): Palladium acetate (11.4 mg, 0.05 mmol), 2-methylfuran (0.5 mL, 5.0 mmol), ethyl 4-chlorobenzoate (159 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 98/2), fractions containing the desired compound were combined and the solvent was evaporated affording white powder (107 mg, 50 % yield). A second experiment under the same conditions gave 50 % yield. R_f = 0.14 (hexanes/ethyl acetate 98/2), mp=52–53 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.03–8.01 (m, 2H), 7.67–7.65 (m, 2H), 6.67–6.65 (m, 1H), 6.09–6.08 (m, 1H), 4.37 (q, J=6.9 Hz, 2H), 2.38 (s, 3 H), 1.40 (t, J=6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.5, 153.4, 151.4, 135.1, 130.1, 128.3, 122.9, 108.4, 108.3, 61.0, 14.5, 13.9. FT–IR (neat, cm^{-1}) ν 1699, 1610, 1274, 1178, 1103, 1024. Anal. Calcd for $C_{14}H_{14}O_3$ (230.09 g /mol): C, 73.03; H, 6.13; Found: C, 72.95; H, 6.12.



2-(3,5-Dimethoxyphenyl)-5-methylfuran (Table 2.3, Entry 10): Palladium acetate (11.4 mg, 0.05 mmol), 2-methylfuran (0.5 mL, 5.0 mmol), 1-chloro-3,5-dimethoxybenzene (508 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous DMPU (2.0 mL). After column chromatography (hexane/ethyl acetate 98/2), fractions containing the desired compound were combined and the solvent was evaporated affording 282 mg (56 % yield) of a yellowish oil. A second experiment under the same conditions gave 52 % yield. R_f = 0.09 (hexane/ethyl acetate 98/2). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.79 (d, J=2.3 Hz, 2H), 6.52 (d, J=3.2 Hz, 1H), 6.35–6.33 (m, 1H), 6.04–6.03 (m, 1H), 3.8 (s, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.1, 152.1, 133.0, 107.8, 106.6, 101.5, 99.4, 55.5, 31.0, 13.9. FT-IR (neat, cm^{-1}) ν 1592, 1551, 1485, 1426, 1336,1227, 1203, 1155, 1023. Anal calcd for $C_{13}H_{14}O_3$ (218.25 g /mol): C, 71.54; H, 6.47; Found: C, 71.79; H, 6.29.



2-(Furan-2-yl)pyridine (Table 2.3, Entry 11): Palladium acetate (11.4 mg, 0.05 mmol), furan (5.0 mmol, 0.45 mL), 2-chloropyridine (124.7 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After column chromatography (pentane/diethyl ether 95/5), 82 mg (52 %) of a colorless oil was obtained. A second experiment under the same conditions gave 53 % yield. This compound is known.[51] R_f = 0.15 (pentane/diethyl ether 95/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.60–8.56 (m, 1H), 7.73–7.67 (m, 2H), 7.54–7.53 (m, 1H), 7.16–7.13 (m, 1H), 7.06–7.05 (m, 1H), 6.54–6.52 (m, 1H).

E. Pyrrole arylation

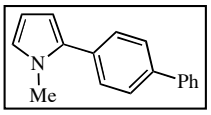
1. Optimization of ligand

Outside the glovebox, a 4-dram vial equipped with a magnetic stir bar was charged with *N*-methylpyrrole (5 mmol) and chlorobenzene (1 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added ligand (0.10 mmol, 10 mol %), K_3PO_4 (2.0 mmol, 425 mg), and anhydrous NMP (1 mL). The mixture was shaken and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 5 mol %) was added. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min, placed in heating block (100 ^oC), and stirred vigorously for 24 h. The reaction mixture was allowed to cool to room temperature and amount of the product was analyzed by GC using internal standard method. The ligand optimization results are shown in Table 2.4.

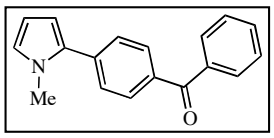
2. General procedure for pyrrole arylation

Outside the glovebox, a 4-dram vial equipped with a magnetic stir bar was charged with pyrrole and chloroarene. The vial was flushed with argon, capped, and placed inside a glovebox. To this mixture was added 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (2.0 mmol, 425 mg), and anhydrous *N*-methylpyrrolidone (2 mL). The mixture was shaken and $Pd(OAc)_2$ (0.05 mmol, 11 mg, 5 mol %) was added. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min, placed in heating block (125 °C) and stirred vigorously for 24 h. The reaction mixture was allowed to cool to room temperature and then diluted with ethyl acetate (50 mL). Resulting suspension was filtered. The filtrate was concentrated under

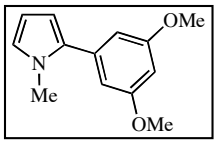
vacuum to a volume of about 2 mL. The mixture was absorbed on silica gel and subjected to column chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure (40 ^{o}C) to yield a pure arylated pyrrole. The yields listed in Table 2.5 are the average of two runs.



2-(Biphenyl-4-yl)-1-methyl-1*H*-pyrrole (Table 2.5, Entry 1): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), 4-chlorobiphenyl (192 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 95/5), pure fractions were combined and solvent was evaporated leaving white crystals. The impure fractions were combined, concentrated and subjected to another column chromatography step (hexanes/ethyl acetate 95/5). The pure fractions were combined and the solvent was evaporated. A total of 136 mg (57 % yield) of white crystalline product was obtained. A second experiment under the same conditions gave 54 % yield. The compound is known.[52] R_f = 0.51 (hexanes/ethyl acetate 95/5). ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.52–7.45 (m, 4H), 7.34–7.32 (m, 2H), 7.25–7.22 (m, 1H), 7.15–7.14 (m, 2H), 6.49–6.46 (m, 2H), 6.38 (dd, *J*=6.3 Hz, 3.5 Hz, 1H), 2.94 (s, 3H).

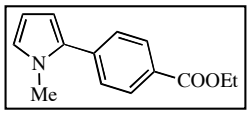


(4-(1-Methyl-1*H*-pyrrol-2-yl)phenyl)(phenyl)methanone (Table 2.5, Entry 2): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), (4-chlorophenyl)(phenyl)methanone (192 mg, 1.0 mmol), 2-(dicyclohexylphosphino)-biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 95/5), fractions containing the desired compound were combined and the solvent was evaporated affording 186 mg of crude product. The crude compound was recrystallized from hexanes giving 96 mg (55 %) of a yellowish powder. A second experiment under the same conditions gave 47 % yield. R_f = 0.15 (hexanes/ethyl acetate 95/5), mp=75–76 ^{o}C (hexanes). ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.79–7.76 (m, 4H), 7.20–7.18 (m, 2H), 7.14–7.13 (m, 1H), 7.09–7.06 (m, 2H), 6.45–6.44 (m, 1H), 6.41–6.39 (m, 1H), 6.32–6.31 (m, 1H), 2.94 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 195.2, 138.5, 137.7, 135.8, 133.6, 132.0, 130.7, 130.2, 128.4, 128.3, 125.3, 110.8, 108.9, 34.7. FT–IR (neat, cm^{-1}) ν 1653, 1602, 1475, 1446, 1319, 1310, 1277, 1186, 1059. Anal. Cald for $C_{18}H_{15}NO$ (261.32 g/mol): C, 82.73; H, 5.79; N, 5.36; Found: C, 82.60; H, 5.88, N, 5.24.

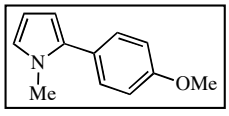


2-(3,5-Dimethoxyphenyl)-1-methyl-1*H*-pyrrole (Table 2.5, Entry 3): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), 1-chloro-3,5-dimethoxybenzene (185 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 90/10), fractions containing the desired compound were combined and the solvent

was evaporated. The crude compound was subjected to preparative TLC (2 plates, hexanes/ethyl acetate 90/10, R_f = 0.30) giving 120 mg (52 % yield) of a viscous yellow oil. A second experiment under the same conditions gave 48 % yield. ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 6.64 (d, J=2.3 Hz, 2H), 6.54–6.52 (m, 1H), 6.49–6.47 (m, 1H), 6.45–6.43 (m, 1H), 6.34–6.32 (m, 1H), 1.66 (s, 6H), 1.54 (s, 3H). ^{13}C NMR (125 Mz, C_6D_6, ppm) 161.3, 136.0, 134.7, 123.8, 109.4, 108.3, 107.2, 99.5, 54.8, 34.5. FT-IR (neat, cm^{-1}) v 1592, 1465, 1421, 1279, 1204, 1154, 1065. Anal cald for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45; Found: C, 71.89; H, 6.79; N, 6.48.

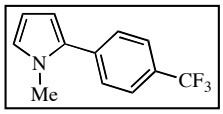


Ethyl 4-(1-methyl-1*H*-pyrrol-2-yl)benzoate (Table 2.5, Entry 4): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), ethyl-4-chlorobenzoate (188 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After two successive column chromatographies (both hexanes/ethyl acetate 95/5 eluent), 180 mg (78 % yield) of a white powder was obtained. A second experiment under the same conditions gave 78 % yield. R_f = 0.19 (hexanes/ethyl acetate 95/5). This compound is known.[53] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.08–8.06 (m, 2H), 7.49–7.46 (m, 2H), 6.77–6.76 (m, 1H), 6.34–6.33 (m, 1H), 6.22–6.23 (m, 1H), 4.39 (q, J=7.4 Hz, 2H), 3.71 (s, 3H), 1.41 (t, J=7.4 Hz, 3H).

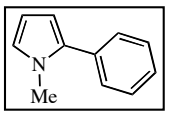


2-(4-Methoxyphenyl)-1-methyl-1*H*-pyrrole (Table 2.5, Entry 5): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), 4-chloroanisole (131 mg, 1.0 mmol), 2-(dicyclohexylphos-

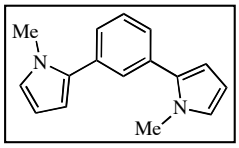
phino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous DMPU (2.0 mL). After column chromatography (hexanes/ethyl acetate 95/5), 131 mg (71 % yield) of a white powder was obtained. R_f=0.38 (hexanes/ethyl acetate 95/5). A second experiment under the same conditions gave 69 % yield. This compound is known.[54] ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.22–7.19 (m, 2H), 6.79–6.76 (m, 2H), 6.46 (dd, *J*=3.5 Hz, 1.7 Hz, 1H), 6.42–6.41 (m, 1H), 6.40–6.38 (m, 1H), 3.31 (s, 3H), 3.03 (s, 3H).



1-Methyl-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (Table 2.5, Entry 6): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), 4-chlorobenzotrifluoride (201 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes), fractions containing the desired compound were combined and the solvent was evaporated. The crude compound was subjected to another column chromatography (hexanes/ethyl acetate 99/1). The fractions with the product were combined and the solvent was evaporated giving 165 mg (60 %) of a viscous yellow oil. A second experiment under the same conditions gave 61 % yield. This compound is known.[55] R_f = 0.23 (hexanes). ^{1}H NMR (400 MHz, C_6D_6, ppm) δ 7.32 (d, *J*=8.2 Hz, 2H), 7.04 (d, *J*=8.2 Hz, 2H), 6.38–6.36 (m, 1H), 6.33–6.32 (m, 1H), 6.29–6.27 (m, 1H), 2.86 (s, H).

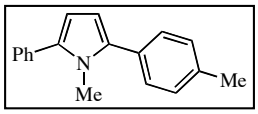


1-Methyl-2-phenyl-1*H*-pyrrole (Table 2.5, Entry 7): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.40 g, 0.44 mL), chlorobenzene (136 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 99/1), 113 mg (62 %) of white powder was obtained. A second experiment under the same conditions gave 58 % yield. This compound is known.[55] R_f = 0.28 (hexanes/ethyl acetate 95/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.42–7.38 (m, 4H), 7.32–7.25 (m, 1H), 6.73 (dd, J=4.6, 2.8 Hz, 1H), 6.25–6.23 (m, 1H), 6.22–6.20 (m, 1H), 3.67 (s, 3H).

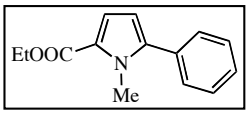


1,3-Bis(1-methyl-1H-pyrrol-2-yl)benzene (Table 2.5, Entry 8): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-2-phenyl-1*H*-pyrrole (1.0 mL, 10.0 mmol), *m*-dichlorobenzene (175 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (850 mg, 2.0 mmol), and anhydrous NMP (3.0 mL). After column chromatography (hexanes/ethyl acetate 96/4), fractions containing the desired compound were combined and the solvent was evaporated. The crude compound was subjected to another column chromatography (hexanes/ethyl acetate 96/4) giving 140 mg (73 %) of a yellowish oil. A second experiment under the same conditions gave 70 % yield. R_f = 0.16 (hexanes/ethyl acetate 96/4). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.52–7.51 (m, 1H), 7.49–7.46 (m, 2H), 7.41–7.39 (m, 1H), 6.80–6.79 (m, 2H), 6.34–6.33 (m, 2H), 6.29–6.28 (m, 2H), 3.76 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 134.5, 133.6, 128.9, 128.5, 127.1, 123.0, 109.0,

108.0, 35.3. FT-IR (neat, cm^{-1}) υ 1604, 1490, 1091. Anal calcd for $C_{16}H_{16}N_2$ (236.3 g/mol): C, 81.32; H, 6.82; N, 11.85; Found: C, 81.16; H, 6.81; N, 11.69.

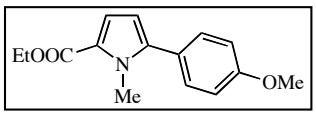


1-Methyl-2-phenyl-5-*p*-tolyl-1*H*-pyrrole (Table 2.5, Entry 9): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-2-phenyl-1*H*-pyrrole (1.0 mmol, 141 mg), 4-chlorotoluene (380 mg, 3.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). After column chromatography (hexanes/ethyl acetate 95/5), fractions containing the desired compound were combined and solvent was evaporated. The crude compound was recrystallized (hexanes/ethyl acetate 99/1) giving 140 mg (63 %) of white crystals. A second experiment under the same conditions gave 63 % yield. R_f = 0.27 (hexanes/ethyl acetate 95/5), mp=154–155 °C. ^{1}H NMR (500 MHz, C_6D_6, ppm) δ 7.40–7.37 (m, 2H), 7.32–7.30 (m, 2H), 7.23–7.19 (m, 2H), 7.11–7.09 (m, 1H), 7.03 (d, *J*=8.2, 2H), 6.51 (s, 2H), 3.15 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 137.0, 136.6, 136.1, 134.2, 131.3, 129.1, 128.8, 128.7, 128.4, 126.5, 109.3, 109.0, 33.6, 20.8. FT-IR (neat, cm^{-1}) ν 1548,1490, 1468, 1331. Anal calcd for $C_{18}H_{17}N$ (217.26 g/mol): C, 87.41; H, 6.93; N, 5.66; Found: C, 87.25; H, 7.26; N, 5.61.

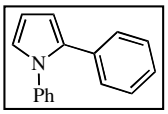


Ethyl 1-methyl-5-phenyl-1*H*-pyrrole-2-carboxylate (Table 2.5, Entry 10): Palladium acetate (11.4 mg, 0.05 mmol), ethyl 1-methyl-1*H*-pyrrole-2-carboxylate (1.0 mmol, 159 mg), chlorobenzene (0.30 mL, 3.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After column chromatography (hexanes/ethyl acetate 95/5), 119 mg

(51 % yield) of a colorless oil was obtained. A second experiment under the same conditions gave 55 % yield. This compound is known.[56] R_f = 0.38 (hexanes/ethyl acetate 95/5) ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.45–7.38 (m, 5H), 7.04 (d, *J*=4.0 Hz, 1H), 6.21 (d, *J*=4.0, 1H), 4.30 (q, *J*=7.0 Hz, 2H), 3.88 (s, 3H), 1.37 (t, *J*=7.0 Hz, 3H).

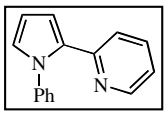


Ethyl 5-(4-methoxyphenyl)-1-methyl-1*H*-pyrrole-2-carboxylate (Table 2.5, Entry 11): Palladium acetate (11.4 mg, 0.05 mmol), ethyl 1-methyl-1*H*-pyrrole-2-carboxylate (1.0 mmol, 160 mg), 1-chloro-4-methoxybenzene (0.37 mL, 3.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After column chromatography (hexanes/ethyl acetate 95/5), 145 mg (52 %) of a white powder was obtained. A second experiment under the same conditions gave 54 % yield. This compound is known.[48] R_f = 0.14 (hexanes/ethyl acetate 95/5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.31 (d, *J*=8.9 Hz, 2H), 7.02 (d, *J*=4.0, 1H), 6.96 (d, *J*=8.9 Hz, 2H), 6.15 (d, *J*=4.0 Hz, 1H), 4.29 (q, *J*=6.9 Hz, 2H), 3.85 (s, 6H), 1.36 (t, *J*=6.9 Hz, 3H).



1,2-Diphenyl-1*H*-pyrrole (Table 2.5, Entry 12): Palladium acetate (11.4 mg, 0.05 mmol), 1-phenyl-1*H*-pyrrole (1.0 mmol, 141 mg), chlorobenzene (0.37 mL, 3.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After column chromatography (hexanes), 95 mg (44 %) of a white powder was obtained. A second experiment under the same conditions gave 40 % yield. This compound is known.[55] R_f = 0.22 (hexanes). ^{1}H NMR (500 MHz,

$CDCl_3$, ppm) δ 7.35–7.15 (m, 10H), 6.97 (dd, *J*=2.8, 1.8 Hz, 1H), 6.47 (dd, *J*=3.4, 1.8 Hz, 1H), 6.39 (dd, *J*=3.4, 2.8 Hz, 1H).



2-(1-Methyl-1*H*-pyrrol-2-yl)pyridine (Table 2.5, Entry 13): Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1*H*-pyrrole (5.0 mmol, 0.45 mL), 2-chloropyridine (119.6 mg, 1.0 mmol), 2-(dicyclohexylphosphino)biphenyl (35 mg, 0.10 mmol, 10 mol %), K_3PO_4 (425 mg, 2.0 mmol), and anhydrous NMP (2.0 mL). The reaction mixture was directly adsorbed onto the silica column. After column chromatography (hexanes/ethyl acetate 95/5), 88 mg (54 %) of a colorless oil was obtained. A second experiment under the same conditions gave 51 % yield. This compound is known.[56] R_f = 0.15 (hexanes/ethyl acetate 95/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56–8.54 (m, 1H), 7.64–7.60 (m, 1H), 7.52–7.50 (m, 1H), 7.07–7.04 (m, 1H), 6.73–6.72 (m, 1H), 6.57–6.55 (m, 1H), 6.18–6.17 (m, 1H), 3.99 (s, 3H).

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CHAPTER 3

Palladium-catalyzed C–H Bond Arylation and Alkylation of Amines

I. Introduction

Transition-metal-catalyzed functionalization of C–H bonds is becoming an important synthetic tool that allows to create carbon-carbon bonds efficiently.[1] Preparation of desired substances can be carried out in fewer steps and higher yields compared to traditional synthetic routes. The atom economy of the reactions are improved, while the formation of byproducts and reaction waste are minimized. Palladium was shown to be the most versatile among the transition metals that catalyze the transformation.[2] Other transition metals that were shown to be effective for these types of reactions include rhodium,[3] cobalt,[4] nickel,[5] iron,[6] copper,[7] and ruthenium.[8]

However, the ubiquity of C–H bonds in organic compounds can lead to problems in chemo- and regioselectivity. In heteroarenes, the control of regioselectivity of the reaction is governed by the difference in acidity of the heterocyclic ring C–H bonds. The selectivity in many substituted arenes can be tuned by the electronic differences of the C–H bonds. For other arenes, the presence of directing groups ensures regioselectivity.

A. Directed functionalizations

The functionalization of unreactive C–H bonds can be promoted by the use of directing groups that can deliver the Pd catalyst to the desired site.[9] The key mechanistic

feature of these reactions is the capability of the substrate to form an intramolecular coordination complex that subsequently forms five- to seven-membered palladacycles (Figure 3.1).[10] Once this key intermediate is formed, other groups could participate in the reaction by transmetallaion, oxidative addition or coordination with the metal.[11] Reductive elimination forms the C–C, C–O, C–X or C–N bonds.

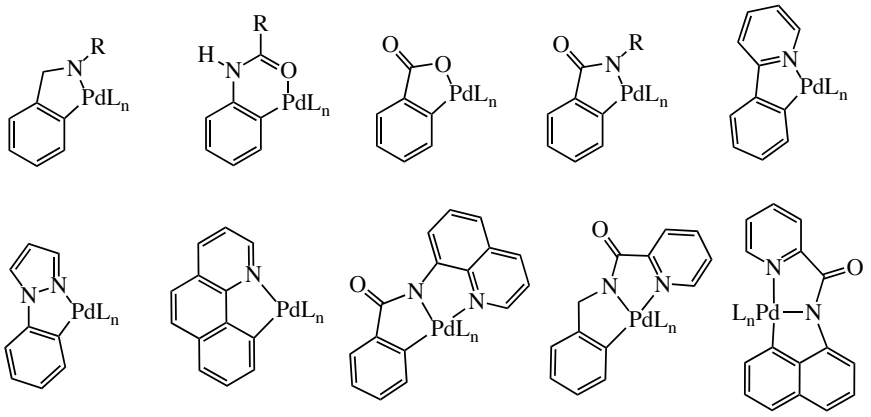


Figure 3.1. Organopalladium intermediates in the functionalization of various directing group-containing aromatic compounds

Directing groups could be a built-in moiety in structures such as pyridines,[12] pyrazoles,[12a] ketones[13] and carboxylic acids.[2h] Auxiliary that can act as directing group could be installed. Amines[14] and carboxylates[15] could be converted to amides, carbonyl groups to imines[16] and oximes,[17] and phenols to carbamates[2p] for more effective C–H functionalization reaction. After the reaction, the auxiliary can be removed or transformed to other functional groups.[18]

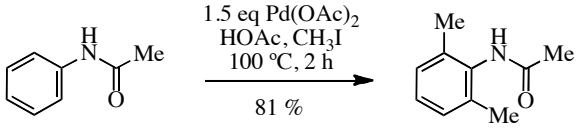
The presence of directing groups was shown to be compatible with many Pd-catalyzed reactions. The methods based on Pd(0)/(II), Pd(II)/(0), and Pd (II)/(III) or

(II/IV) catalysis benefit from the directing group by enhancement of regioselectivity and general promotion of C–H activation step.[19]

B. Functionalization of sp^2 C–H bonds

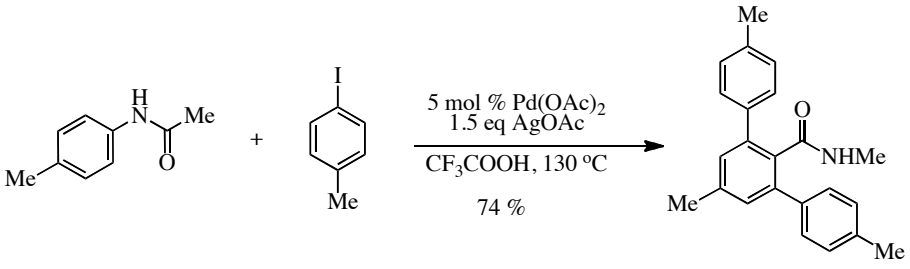
Many directing groups has been found to be efficient in arylation of *ortho* sp^2 C–H bonds. Early example demonstrated that acetanilides can be alkylated by alkyl iodides in the presence of stoichiometric palladium acetate (Scheme 3.1).[20]

Scheme 3.1. Alkylation of anilides



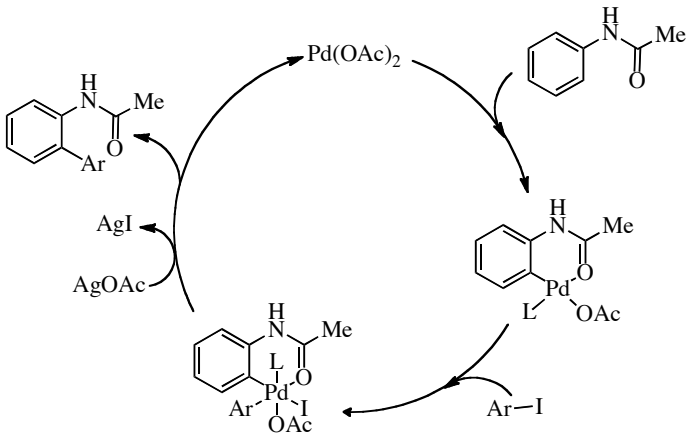
Catalytic arylation version of the reaction was then developed in our group. Anilides were arylated with aryl iodides (Scheme 3.2).[21] The reactions are fastest in trifluoroacetatic acid. Silver acetate is required for the removal of iodide from reaction mixture to achieve catalytic turnover.[9b]

Scheme 3.2. Palladium catalyzed arylation of anilides



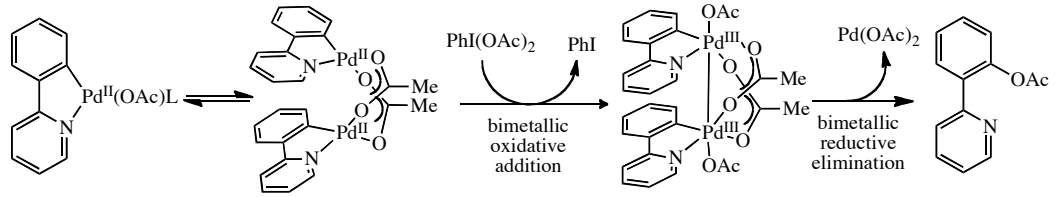
The mechanism of the reaction involves initial coordination of the palladium with the directing group (Scheme 3.3).[22] The key step in this type of reaction is the ability of the substrate to form a six-membered palladacycle following C–H activation. The arylating agent then oxidatively adds to the palladium center forming a high energy Pd(IV) intermediate. Reductive elimination followed by anion exchange forms the product and regenerates the catalyst.

Scheme 3.3. Mechanism of the arylation of anilides



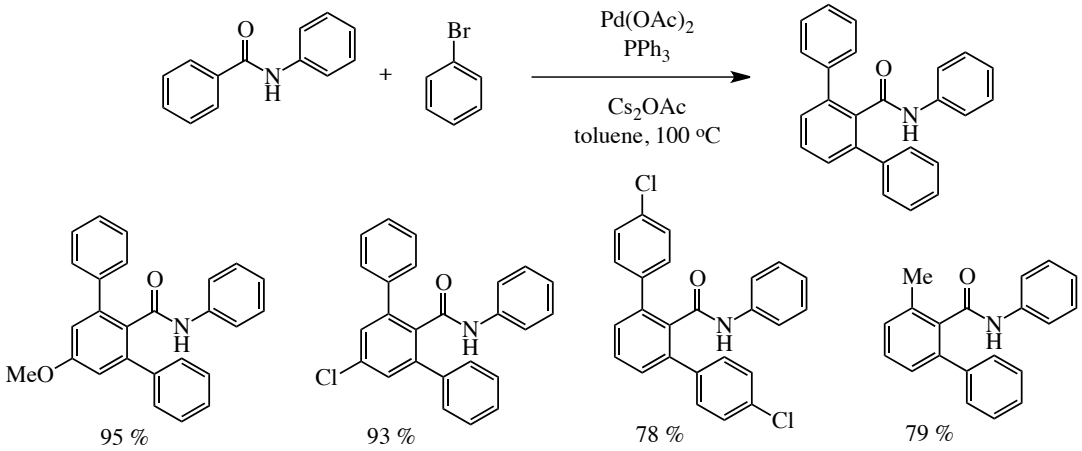
In a related reaction, evidence implicates the involvement of a dinuclear Pd(III) complex (Scheme 3.4).[23] Isolation and kinetic analysis pointed to the bimetallic Pd(III) as the competent catalyst for the reaction and excluded the participation of Pd(IV) in the mechanism. [23c]

Scheme 3.4. Reductive elimination from bimetallic Pd(III)–Pd(III) complex



Benzamides could be used as a directing group for the installation of aryl groups in the *ortho*-position of benzanilides by Pd-catalyzed cross coupling with aryl triflates and bromides (Scheme 3.5).[15a] The method used PPh_3 ligand and Cs_2CO_3 base under inert atmosphere. Although the yield is good, the reaction is restricted to benzanilides. Simple amide such as *n*-propylbenzamide provided lower yield.

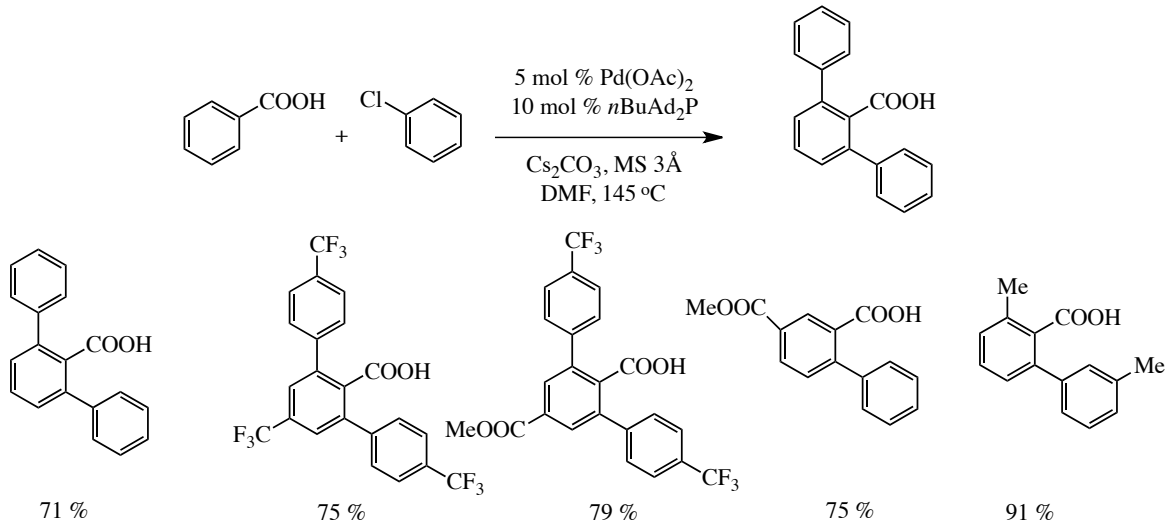
Scheme 3.5. Arylation of benzamides with aryl bromides or triflates



Arylation of anilides possessing different *N*-acyl substitutents such as acetyl, [24] propionyl,[25] and pivaloyl, [26] was successful. A wide variety of aryl iodides can be utilized in the reaction. Coupling with vinyl bromide was also successful.[26] Arylation with iodonium salts[27] and boronic acids[28] is also possible.

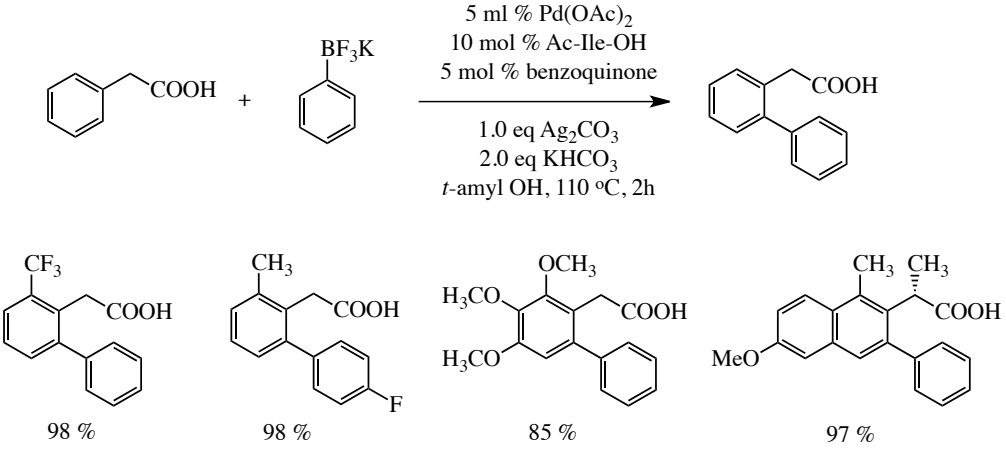
Carboxylic acid was also shown to be useful for Pd-catalyzed directed *ortho*-arylation. Methods for installation of aryl groups on benzoic acids using economical aryl chlorides were developed (Scheme 3.6).[2h] The success of the method is due to the use of bulky, electron-rich *n*BuAd$_2$P ligand that promotes the oxidative addition of aryl chlorides. The method proceeds through Pd(0)/(II) catalytic cycle. This method provides an efficient way of forming biphenyl after decarboxylation.

Scheme 3.6. Arylation of free carboxylic acid with aryl chlorides



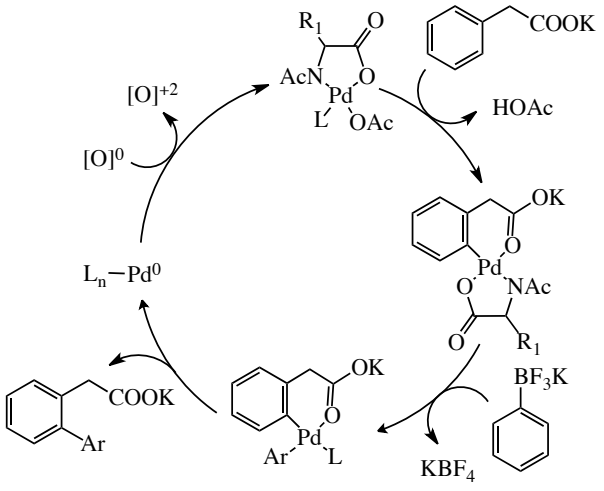
Successful Pd-catalyzed arylation of phenylacetic acids with aryltrifluoroborates was achieved using amino acid derivative ligand and Ag_2CO_3 oxidant (Scheme 3.7).[29] The reaction is fast and high yielding and tolerates many functional groups. Alkylation of sp^2 and sp^3 C–H with boronic acids were assisted by 2-pyridyl group with copper(II) acetate as an oxidant. [30]

Scheme 3.7. Arylation of phenylacetic acid with aryltrifluoroborates



Mechanism of the reaction involves a Pd(II)/(0) catalytic cycle (Scheme 3.8). The substrate enters the cycle by coordination with the Pd-amino acid ligand complex. Transmetallation followed by reductive elimination releases the product. This mechanism features the use of Ag_2CO_3 oxidant to reoxidize Pd(0) to the active Pd(II) species.

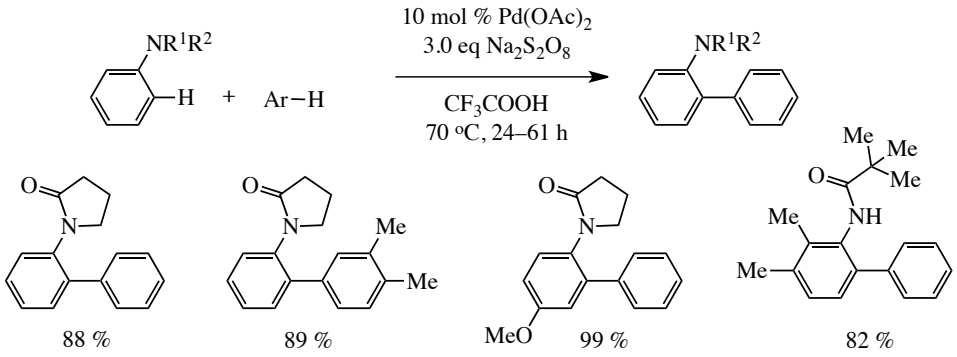
Scheme 3.8. Mechanism for the arylation of phenylacetic acid with aryltrifluoroborates



Carboxylic acids can be converted to hydroxamic acids to provide an auxiliary with stronger coordination, which was used to deliver aryl and alkyl groups to sp^2 and sp^3 C–H bonds.[31] Carbonyl groups can be converted to imines prior to C–H arylation to give an auxiliary that works two fold: electron-withdrawing group activates the ring towards palladation, and directing group increases regioselectivity of the reaction.[16] Acetoxy group was installed on *ortho*-position of anilides using potassium persulfate as an oxidant[32] and on phenylalanine and ephedrine using peroxyanhydride as an oxidant.[33] Boryl group could also be installed using *N*-arylbenzamide directing group and silver oxidant.[34]

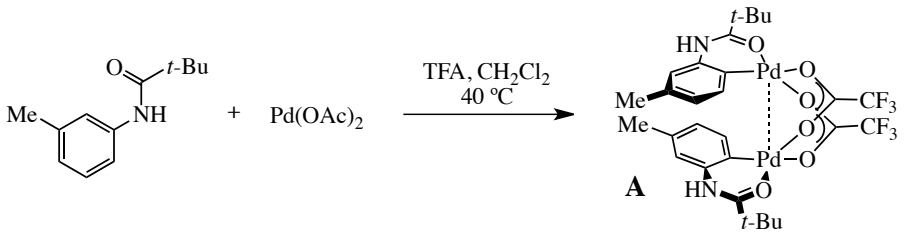
The directing influence of auxiliaries can be utililized for C–H/C–H bond coupling. Arylation of different amides with simple arenes were achieved using cheap sodium persulfate oxidant (Scheme 3.9).[14b] A method that uses O_2 as a terminal oxidant was also developed.[35] The dual activation of C–H bonds in *ortho*-position of benzamides and *para*-position of monosubstituted arenes were achieved by using *N*-fluorobenzenesulfonimide oxidant.[15b]

Scheme 3.9. Dual C–H/C–H arylation of anilides



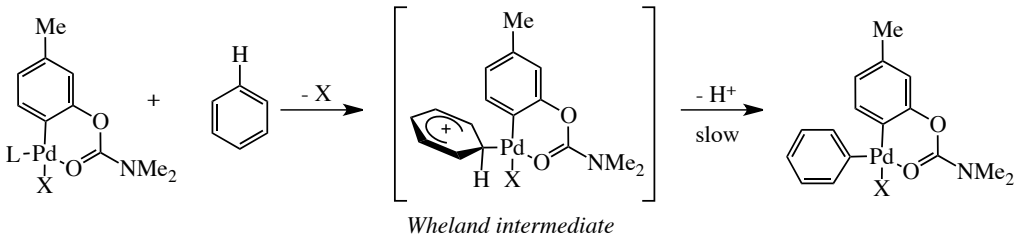
The proposed mechanism of the reaction involves two discrete C–H bond activations.[2p] The first C–H bond activation forms a dimeric cyclopalladated product (Scheme 3.10, compound A), which exhibits a weak Pd–Pd interaction as seen from its crystal structure.[14b]

Scheme 3.10. Cyclopalladation of anilide



The second C–H bond activation occurs either by CMD mechanism or S_EAr mechanism. In CMD mechanism, electron-deficient arenes should undergo arylation faster since their C–H bonds are more acidic.[36] However, the trend of arene reactivity observed for arylation of *O*-phenylcarbamate is different (*o*-dichlorobenzene << benzene << *o*-dimethoxybenzene), leading the authors to favor S_EAr mechanism.[2p] Competition experiments revealed that benzene reacts faster than deuterated benzene (k_H/k_D=3.9) suggesting that the process occurs in two steps (Scheme 3.11). First step is the electrophilic reaction of the Pd complex with arene to yield Wheland intermediate, followed by rate-limiting proton abstraction to form the Pd σ-complex.

Scheme 3.11. Proposed reaction pathway for the second C–H bond activation



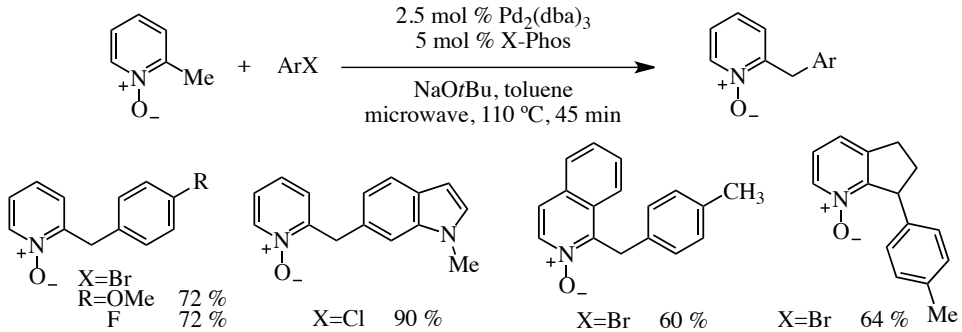
Wheland intermediate

C. Functionalization of sp^3 C–H bonds

The functionalization of unactivated sp^3 C–H bonds is more difficult than that of an sp^2 C–H bonds.[37] The presence π-orbitals in sp^2 systems may provide an initial precoordination site to the transition metal. This assistance does not happen in sp^3 systems. Aryl–metal bonds are generally stronger than alkyl–metal bonds.[38] Furthermore, formation of C–C bond by reductive elimination is easier between aryl groups than between alkyl groups due to less steric hindrance, more favorable orbital interation[39] and lack of competing ß-elimination in aryl structures [40]

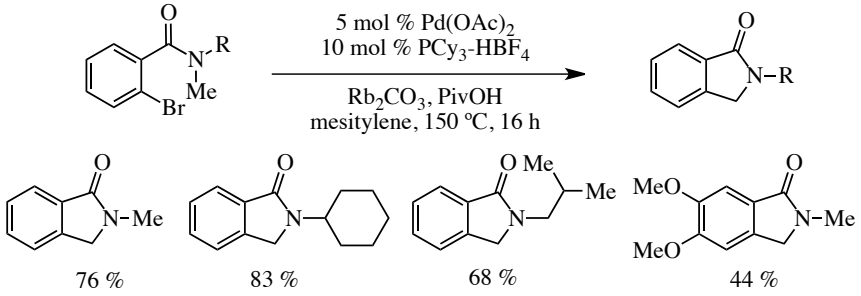
Early studies on sp^3 C–H bond activation were performed on molecules featuring a specific types of C–H bonds. Benzylic and allylic sp^3 C–H became an easy target for method development due to their higher reactivity. In the case of allylic and benzylic systems, the unsaturated bond becomes a precoordination site for the Pd catalyst. This reactivity pattern has been exhibited in the arylation of 2-methylpyridine *N*-oxide where aryl groups from aryl bromides are preferentially installed on the benzyl C–H bond (Scheme 3.12).[41]

Scheme 3.12. Benzylic sp^3 C–H arylation

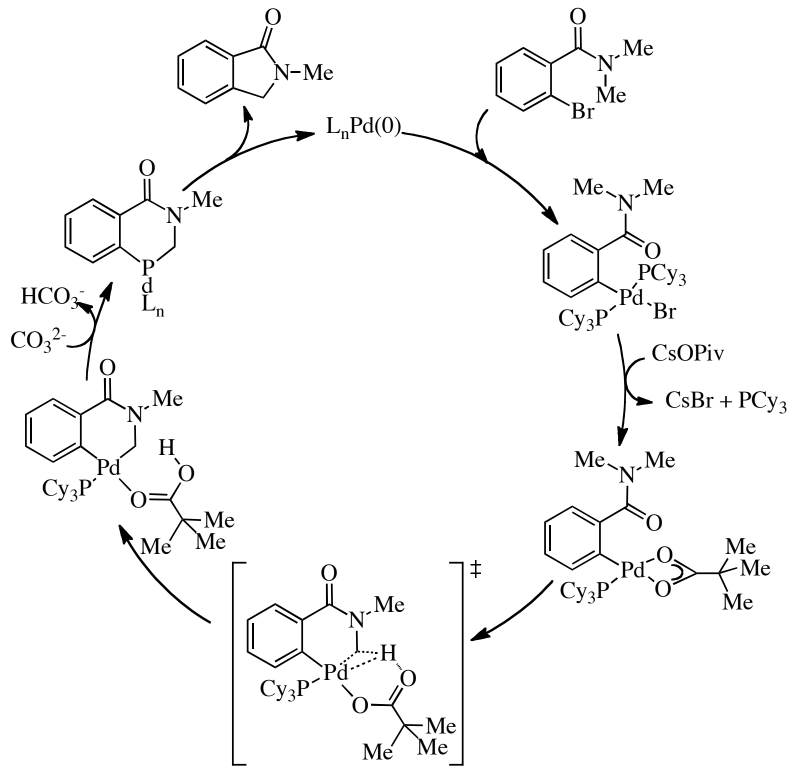


Functionalization of an sp^3 C–H bond adjacent to a heteroatom is relatively easy. Syntheses of isoindole derivatives were accomplished by cyclization of *N*–methyl amides (Scheme 3.13).[42] The proposed mechanism of the reaction is shown in Scheme 3.14. Oxidative addition is facilitated by electron-rich phosphine ligands. The next step is ligand exchange with pivalate, followed by palladation *via* CMD mechanism. Finally, reductive elimination affords the heterocycle product.

Scheme 3.13. Arylation of C–H bond adjacent to a heteroatom

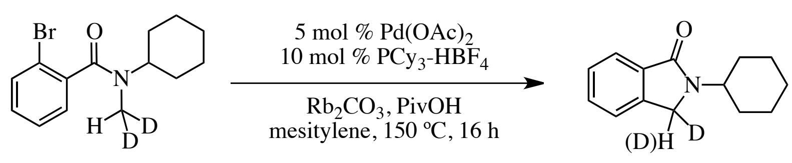


Scheme 3.14. Mechanism for the arylation of sp^3 C–H bonds adjacent to heteroatoms



The observed kinetic isotope effect (k_H/k_D) is 3.4. This shows that the C–H bond cleavage is the rate determining step (Scheme 3.15).

Scheme 3.15. Kinetic isotope effect for the arylation of sp^3 C–H adjacent to a heteroatom

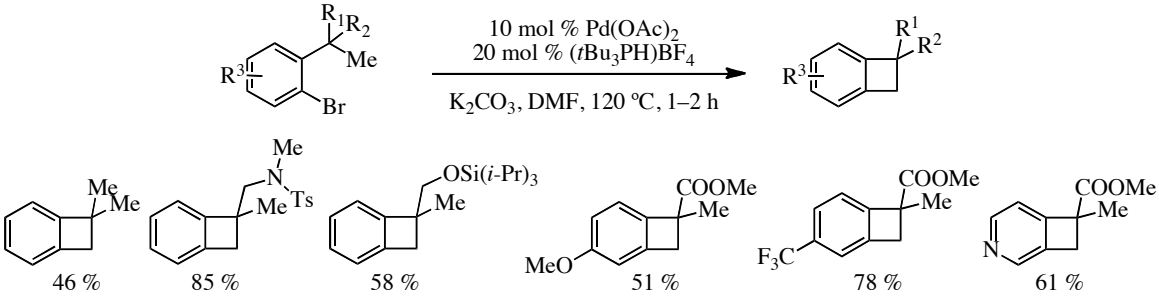


The activation of sp^3 C–H bonds adjacent to quaternary centers has also been a focus of research. The activation is usually triggered by coordination of the metal to a directing group or by oxidative addition, which holds the metal in close proximity to the

C–H bonds that will be activated. Activation of C–H bonds in this case is easy due to entropic considerations and the impossibility of ß-H elimination from the organometallic intermediates.

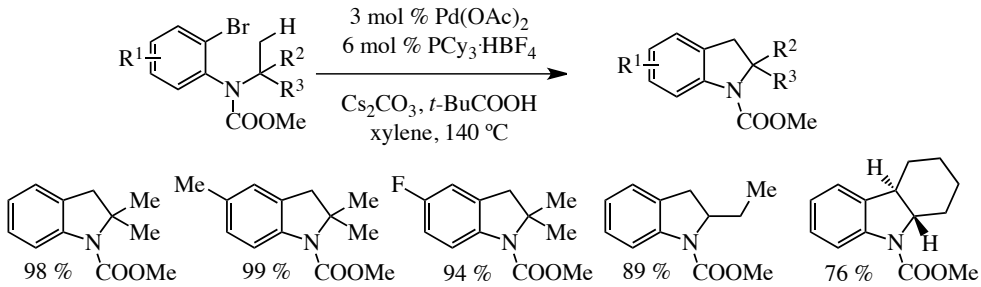
Benzocyclobutenes were synthesized by C–H activation of methyl groups connected to a tertiary center (Scheme 3.16).[43] Palladium was introduced in the molecule by oxidative addition of the aryl bromide. The base assisted the removal of the proton resulted in palladacycle formation. The final product is formed in reductive elimination step.

Scheme 3.16. Synthesis of benzocyclobutanes from activation of sp^3 C–H next to a tertiary center



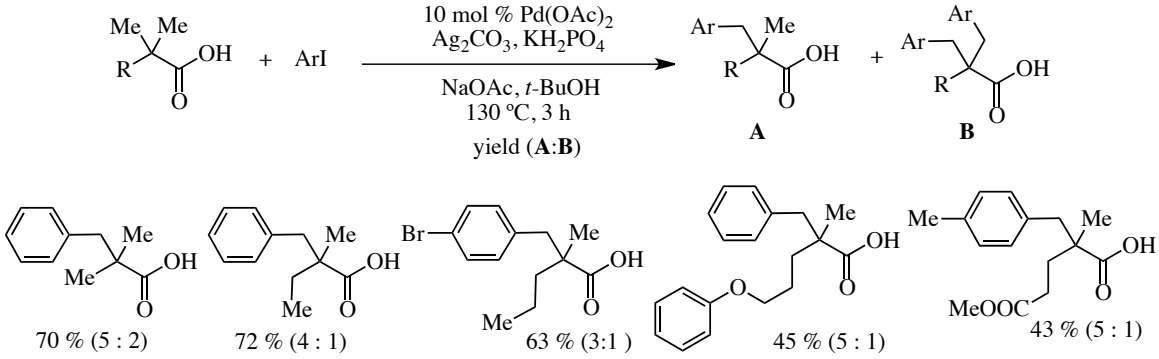
A method for synthesis of indoline derivatives from *N*-alkyl-2-bromoanilines was also developed (Scheme 3.17).[44] Cyclization can also be performed with aryl iodides or chlorides. Primary and secondary sp^3 C–H bonds are reactive.

Scheme 3.17. Synthesis of indolines from activation of sp^3 C–H bonds



Regioselectively functionalization of sp^3 C–H bonds can be performed with the assistance of a directing group. Intermolecular arylation of sp^3 C–H of carboxylic acids was accomplished under Pd catalysis using aryl iodides. The carboxylate group acts as a directing group (Scheme 3.18).[45]

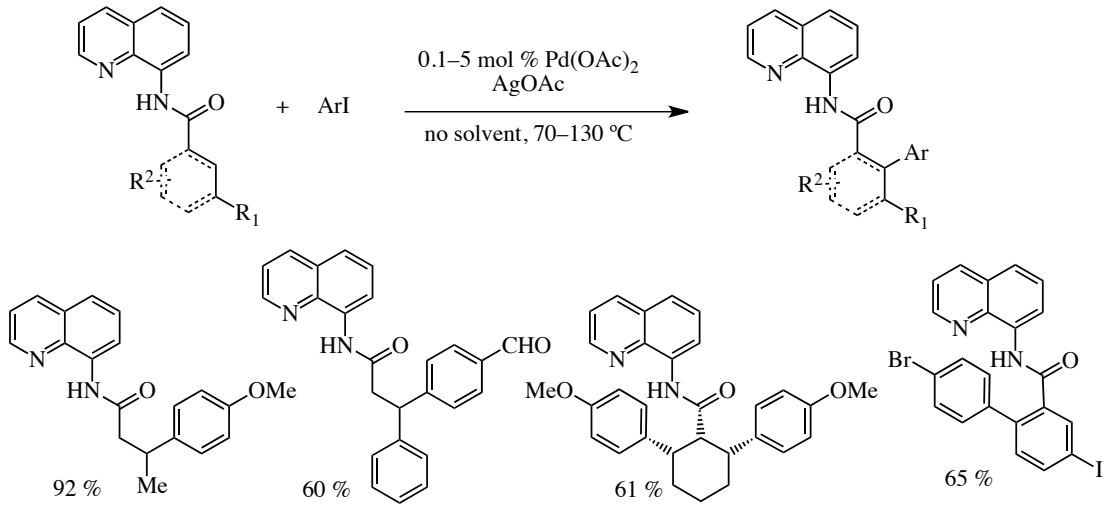
Scheme 3.18. Intermolecular arylation of carboxylic acid



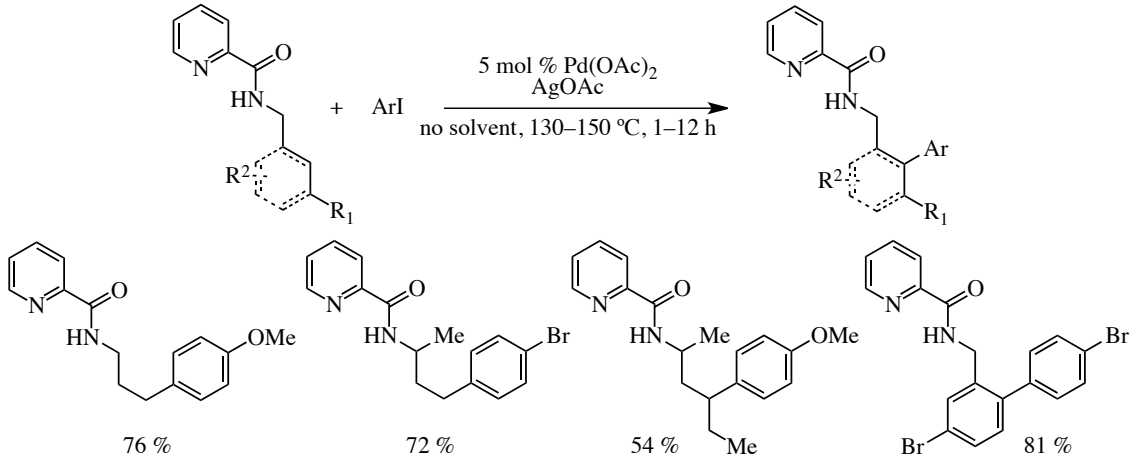
Other palladium-catalyzed C–H functionalization methods for olefination, carbonylation, and arylation for sp^3 C–H bonds have been developed by employing perfluoroaniline auxiliaries.[2j, 46] Pyridine has been utilized a directing group for sp^3 C–H bond alkylation by alkylboronic acids and in aerobic sp^3 C–H bond olefination.[47]

Until recently, most of the published examples of sp^3 C-H bond functionalization involve methyl groups that are next to unsaturated bonds, tertiary carbon centers or heteroatoms. Functionalization of secondary sp^3 C–H bonds are rare. The arylation of the β-position of carboxylic acid (Scheme 3.19) and the γ- postion of amine (Scheme 3.20) derivatives were successfully performed in our group by employing an 8-aminoquinoline or picolinic acid auxiliary, catalytic $Pd(OAc)_2$, stoichiometric AgOAc, and an aryl iodide coupling partner.[48]

Scheme 3.19. Arylation of carboxylic derivatives of 8-aminoquinoline

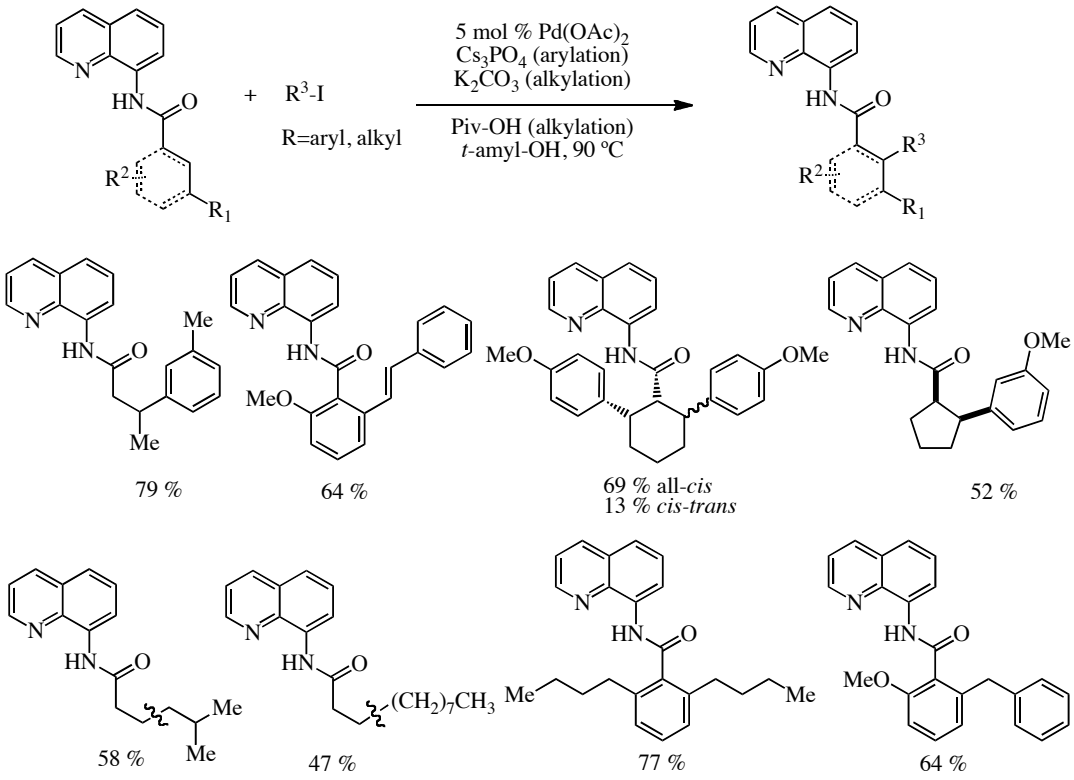


Scheme 3.20. Arylation of picolinamides



A number of auxiliaries were investigated for carboxylic acid β-arylation. It was shown that silver salts can be replaced by simple inorganic bases.[49] Omission of silver allowed catalytic alkylation of sp^2 and sp^3 C–H bonds (Scheme 3.21).

Scheme 3.21. Functionalization of carboxylic derivatives of 8-aminoquinoline



Several other groups have used this methodology for synthetic purposes. Corey has used the 8-aminoquinoline auxiliary to arylate sp^3 C–H bonds in amino acid derivatives.[50] Chen has employed the methodology for the total synthesis of Celogentin C.[51] Carbocycles have been constructed by using 8-aminoquinoline directing group.[52] Alkynylation of sp^3 C–H bonds has also been accomplished by employing 8-aminoquinoline auxiliary.[53] Picolinic acid directing group has also been used by Chen in arylation of γ-positions of amines culminating in the synthesis of obafluorin.[51] However, the γ-arylation of amine C–H bonds that does not require a stoichiometric silver additive has not yet been disclosed. Similarly, γ-alkylation of amine C–H bonds has not been reported yet.

In this study, methods for picolinic acid-directed arylation of 8-naphtylamine was developed. The method uses $Pd(OAc)_2$ catalyst and silver acetate base. Method for the γ-alkylation and arylation of picolinamides that does not require silver additives was also developed.

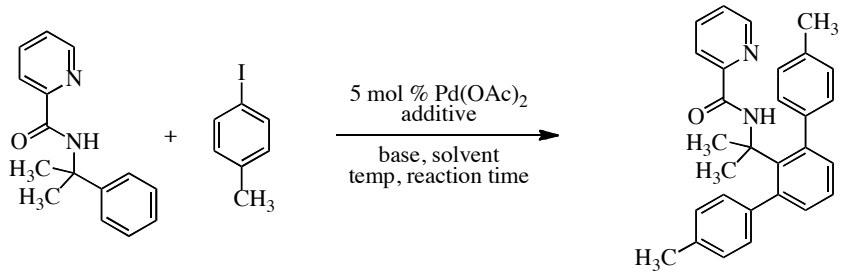
II. Results and discussions

A. Arylation of sp^2 and sp^3 C–H bonds

1. Optimization of reaction conditions

Based on our previous results with carboxylic acid derivative functionalization, the initial optimization experiments were aimed at replacing silver acetate with other stoichiometric additives for arylation of cumylamine picolylamide (Table 1). Sodium acetate (entries 1–2), potassium phosphate (entries 4 and 6), and cesium carbonate (entry 5) bases were inefficient. Potassium carbonate afforded good yields, but best results were obtained with cesium acetate in *t*-amyl alcohol (entry 12). Addition of 10 mol % of $CuBr_2$ allowed to achieve full conversion to diarylation product (entry 13). Thus, the optimized arylation conditions include 4 equivalents of CsOAc base in *t*-amyl alcohol solvent, 5 mol % $Pd(OAc)_2$, 10 mol % $CuBr_2$, and 4 equivalents of ArI at 140 °C.

Table 3.1. Optimization for arylation of picolinamides



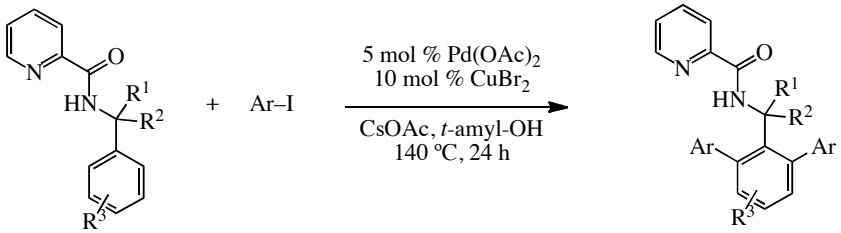
0.5 mmol 4 mmol

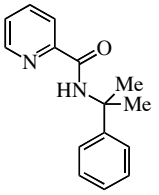
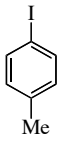
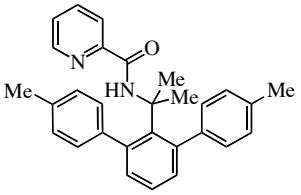
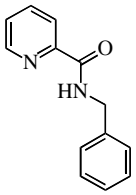
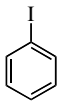
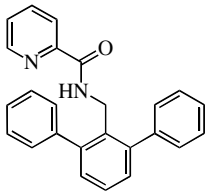
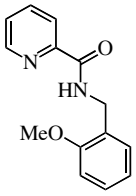
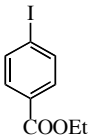
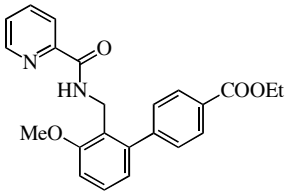
Entry	Reaction conditions	% GC Yield (isolated)
1	4 eq NaOAc, 2 mL MeCN, 60 °C, 16 h	0
2	4 eq NaOAc, 2 mL toluene, 140 °C, 16 h	10
3	4 eq CsOAc, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	30
4	2 eq K_3PO_4, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	15
5	2 eq Cs_2CO_3, 1.6 mL toluene, 0.4 mL MeCN, 140 °C, 16 h	15
6	3 eq K_3PO_4, 1.6 mL *t-a*myl alcohol, 0.4 mL H_2O, 90 °C, 16 h	70
7	3 eq K_2CO_3, 2 mL *t*-amyl alcohol, 90 °C, 20 h	80
8	4 eq K_2CO_3, 2 mL *t*-amyl alcohol, 110°C, 24 h	90 (86)
9	4 eq K_2CO_3, 2 mL *t*-amyl alcohol, 140°C, 24 h	80
10	4 eq CsOAc, 1 mL *t*-amyl alcohol, 110°C, 24 h	85
11	4 eq CsOAc, 1 mL *t*-amyl alcohol, 140°C, 24 h	90
12	10 % $CuBr_2$, 4 eq CsOAc, 1 mL *t*-amyl alcohol, 110°C, 24 h	75 (70)
13	**10 % $CuBr_2$, 4 eq CsOAc, 1 mL *t*-amyl alcohol, 140°C, 24 h**	**99 (99)**

2. Arylation of *N*-benzylpicolinamides

The optimized conditions were applied to arylation of a number of picolinamides (Table 3.2). Benzylamine derivatives are arylated in excellent yields (entries 1-3). Diarylated products are obtained if unsubstituted benzylamines are employed (entries 1-2).

Table 3.2. Arylation of sp^2 C–H bonds[a]



Entry	Picolinamide	Aryl iodide	Arylated Picolinamide	% Yield[b]
1				99 % 86 %[c]
2				99 %
3				92 %

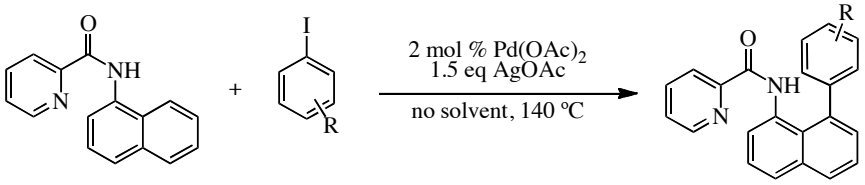
[a] aryl or alkyl picolinamide (1 mmol), aryl iodide (4 mmol), $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (10 mol %), CsOAc (4 mmol), 140 °C, 24 h. [b] Yields are isolated yields. [c]No $CuBr_2$.

3. Arylation of 1-(*N*-naphthylpicolinamide)

A method for the preparation of 8-aryl-1-aminonaphthalenes which uses silver salt additive was developed earlier. The transformation is achieved by heating the substrate, $Pd(OAc)_2$ catalyst, and aryl iodide with AgOAc as halide scavenger, with no solvent at 140 ºC for 24 h (Table 3.3). The products are obtained in excellent yields.

A wide variety of aryl iodides can be used for the arylation. Aryl iodides with electron-donating groups (entry 2) give excellent result. Hydrolyzable ester functionality (entry 4) on the arylating agent remains intact and the product can be obtained in very good yield. Aryl iodides with electron-withdrawing groups such as chloride (entry 5) and bromide (Table 1, entry 6) are reactive. Arylation with 4-iodonitrobenzene and 2-methyliodobenzene did not give any product, in good agreement with other Pd-catalyzed arylation methods.[54]

Table 3.3. Arylation of 1-(*N*-naphthylpicolinamide)

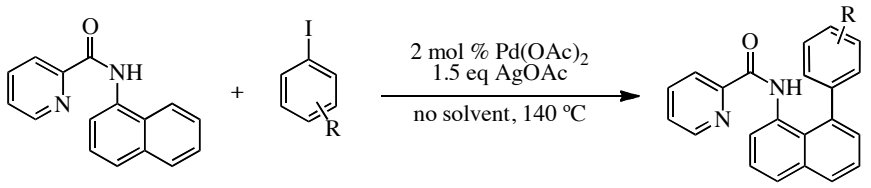


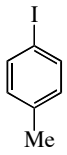
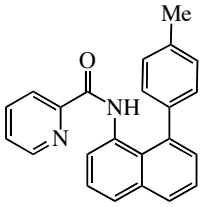
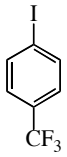
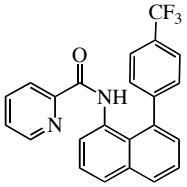
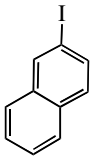
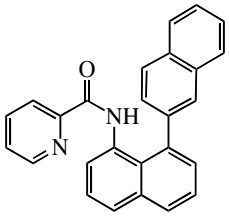
Entry	R	% Yield[b]
1	4-*tert*-Butyl	99
2	4-OMe	98
3	3-OMe	99
4	4-COOEt	92
5	3-Cl	98
6	4-Br	82

[a] 0.5 mmol picolinamide, 1.5 mmol aryl iodide, 5 mol % $Pd(OAc)_2$, 1.5 mmol AgOAc, [b] Yields are isolated yields.

The yield of the reaction is very good if the arylation is performed on larger scale (Table 3.4). Products were obtained on gram-scale after chromatography.

Table 3.4. Gram-scale arylation of 1-(*N*-naphthylpicolinamide)[a]

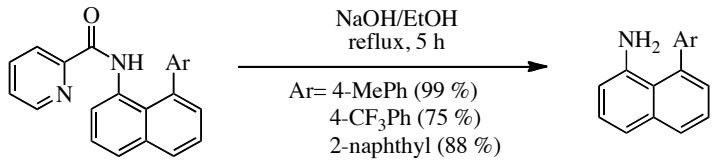


Entry	Aryl iodide	Product	Yield, %
1			91
2			84
3[c]			65

[a] picolinamide (40 mmol), aryl iodide (160 mmol), $Pd(OAc)_2$ (2 mol %), AgOAc (60 mol %), 140 °C, 24 h. [b] Yields are isolated yields. [c] 3-Napthyl iodide (120 mmol)

The products from these reactions were used to obtain hindered amines. Picolinic acid auxiliary can be efficiently removed by hydrolysis using alcoholic NaOH under reflux to give 8-aryl-1-aminonaphthalene. (Scheme 3.22)

Scheme 3.22. Directing group removal



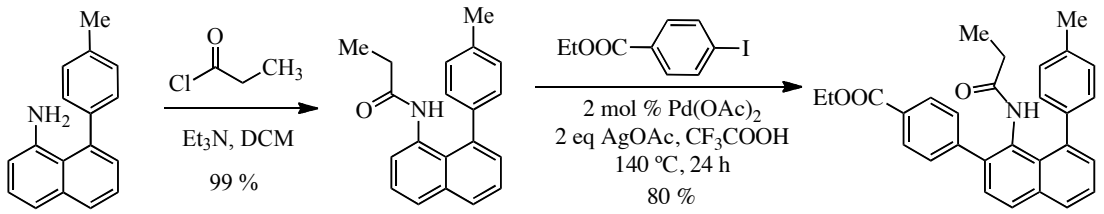
The 8-aryl-1-aminonaphthalenes are useful as intermediates for the synthesis of various ligands.[55] Previously available method for their preparation requires several steps, which include metallation, functional group modification, and cross coupling.[55b, 56] Direct lithiation of functional groups with acidic protons limit the scope of substrates for which these methods can be used.[55c, 57] In the Pd-catalyzed direct arylation method that we developed, route to 8-aryl-1-aminonaphthalenes is at least two steps shorter than the existing methods.

Bulky amines can be useful as starting materials for the synthesis of ligands for transition metal catalysts used in various applications. Bulky diimines formed from the condensation with diketones are effective for propylene oligomerization.[58] Diimines can be further converted to imidazolium salts that can be deprotonated to form *N*-heterocyclic carbenes.[59]

The 8-aryl-1-aminonaphthalenes were subjected to another round of arylation to obtain a more complex carbon scaffold not readily accessible by other methods. As an

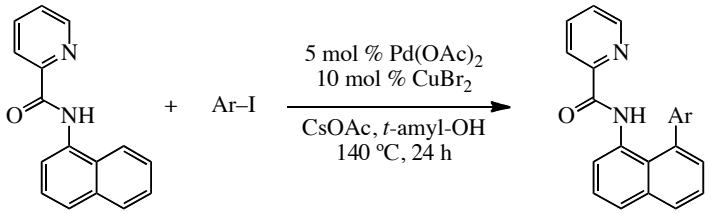
illustration, the amino group was reacted with propionyl chloride to form an amide. Propionamide group was demonstrated to direct aryl groups to the *ortho*-position of the ring.[48] The 8-arylnaphthalene propionamide was subjected to arylation with ethyl 4-iodobenzoate under palladium catalysis with stoichiometric silver and trifluoroacetic acid as a solvent giving a diarylated naphthylamide in 80 % yield. The ester functionality remained intact (Scheme 3.23).

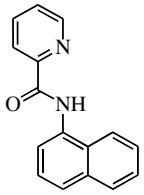
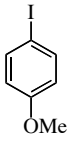
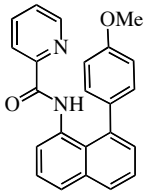
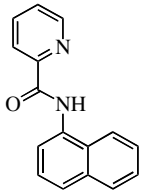
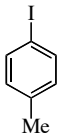
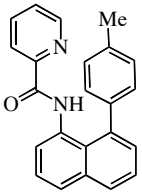
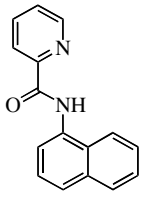
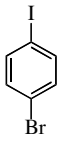
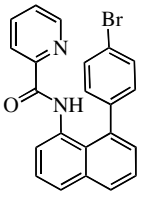
Scheme 3.23. Arylation at different positions of the ring



The above described method uses stoichiometric silver base. A more practical approach for the synthesis of 8-aryl-1-aminonaphthalenes would replace the silver salt aditive with simple inorganic bases. The developed silverless method was used for the arylation of naphthyl picolinamides (Table 3.4). The yields for arylation are comparable (entry 3) or slightly lower (entry 3) than those using silver additives.

Table 3.5. Palladium-catalyzed arylation of sp^2 C–H bonds[a]

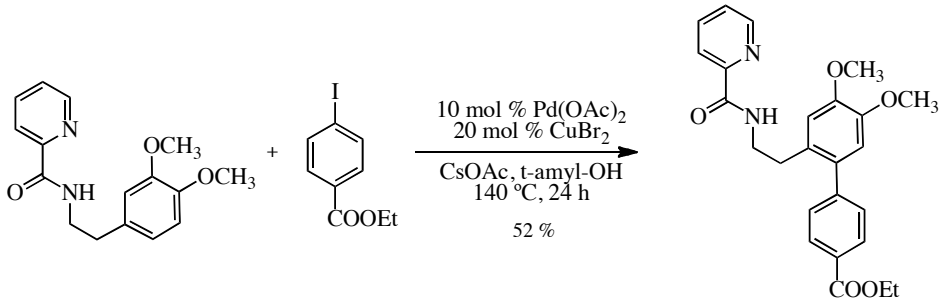


Entry	Picolinamide	Aryl iodide	Arylated Picolinamide	% Yield[b]
1				73 %
2				75 %
3				84 %

[a] picolinamide (1 mmol), aryl iodide (4 mmol), $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (10 mol %), CsOAc (4 mmol), 140 °C, 24 h. [b]Yields are isolated yield. [c]no $CuBr_2$

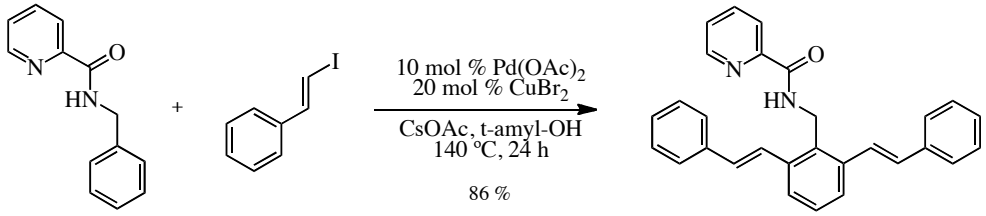
Other structures that could be arylated by the method include phenethylamine derivatives, which are arylated in moderate yield, presumably due to requirement for less favorable six-membered palladacycle intermediate (Scheme 3.24). In contrast, the previous benzylamine arylation methodology developed in our laboratory is not applicable to arylation of phenethylamines.[14a]

Scheme 3.24. Arylation of picolinamide of phenethylamine derivative



Iodostyrene can also be employed in couplings affording dialkenylation product in good yield (Scheme 3.25). 2-Iodotoluene was unreactive as shown before for arylations proceeding via high-valent palladium intermediates.[24]

Scheme 3.25. Vinylation of *N*-benzylpicolinamide



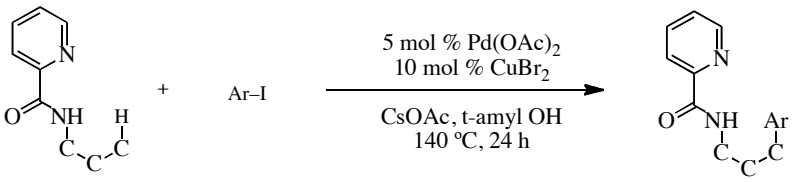
The scope of aryl iodides that can be used in silverless Pd-catalyzed arylation is reasonably wide. Ester (Table 3.2, entry 3; Table 3.5, entry, 4; Scheme 3.14) and bromine (Table 3.4, entry 3) substituents are well-tolerated.

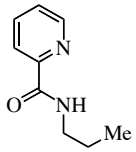
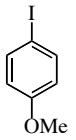
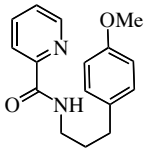
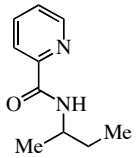
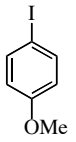
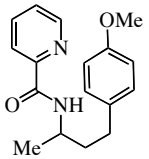
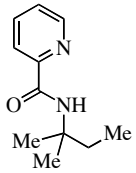
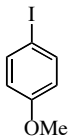
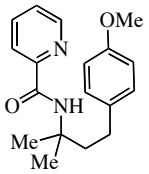
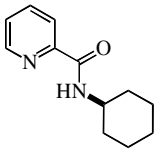
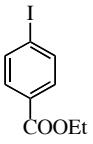
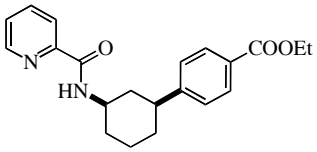
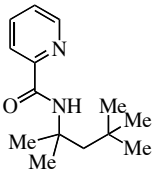
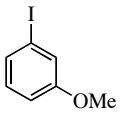
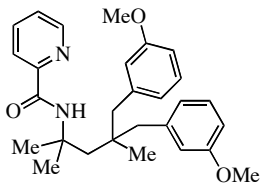
4. Arylation of sp^3 C–H bonds

Arylation of unactivated sp^3 C-H bonds is also successful (Table 3.5). Comparison of the arylation yields for propyl (entry 1), *s*-butyl (entry 2), and 2-(2-methylbutyl) derivatives shows that the reaction is most efficient for the substrates possessing the most α-methyl groups. This is most likely due to Thorpe-Ingold effect.[60]

Arylation of a secondary aliphatic C–H bonds is also feasible and proceeds in moderate to good yields (entry 11). An amide derived from *t*-octylamine is arylated in low yield. A mixture of mono- and diarylation products are obtained, with functionalization occurring at δ-positions (entry 5). Six-membered palladacycle intermediate may be responsible for less efficient arylation.

Table 3.6. Arylation of alkyl picolinamides[a]



Entry	Picolinamide	Ar–I	Product	Yield %
1				51 %
2				75 %
3				91 %
4				81 %
5[b,c]				29 %

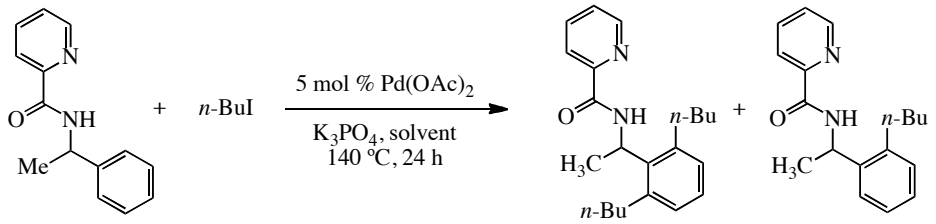
[a] Picolinamide (1 mmol), ArI (4 mmol), $Pd(OAc)_2$ (5 mol%), $CuBr_2$ (10 mol%), CsOAc (4 mmol), *t*-amyl alcohol solvent, 24 h at 140 °C. Yields are isolated yields. [b] $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (20 mol%). [c] Monoarylation product also isolated (13%).

B. Alkylation of sp^2 and sp^3 C–H bonds

1. Optimization of the solvent

The *N*-(1-phenylethyl)picolinamide was alkylated by iodobutane under $Pd(OAc)_2$ catalysis and K_3PO_4 base (Table 3.6). The best solvents for the reaction were found to be hexafluoroisopropanol and water. Water was used in further reactions due to its low cost.

Table 3.7. Alkylation of picolinamides – optimization of solvent[a]



A **B**

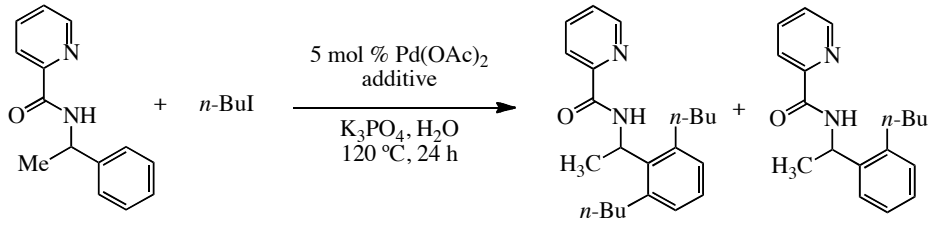
Entry	Solvent	% GC Yield [b]	
		A	**B**
1	CF_3CH_2OH	26	19
2	$CF_3CH(OH)CF_3$	52	29
3	CH_3COOH	36	13
4	Piv-OH	20	5
5	H_2O, *m*-xylene	50	24
6	H_2O	47	23
7	**H_2O (0.15 mL)**	**50**	**14**

[a] *N*-(1-phenylethyl)picolinamide (1 mmol), *n*-BuI (4 mmol), $Pd(OAc)_2$ (5 mol%), base (4 mmol), solvent (2.0 mL), 24 h at 140 °C. [b] Dodecane as internal standard

2. Optimization of the additive

Different additives (10 mol %) were added to the reaction mixture for the alkylation of *N*-(1-phenylethyl)picolinamide (Table 3.7). Analysis by GC revealed that the best additive is 10 % $CuBr_2$, giving full conversion of the starting material to 95 % dialkylated and 5 % monoalkylated product.

Table 3.8. Alkylation of picolinamides – optimization of the additive



A **B**

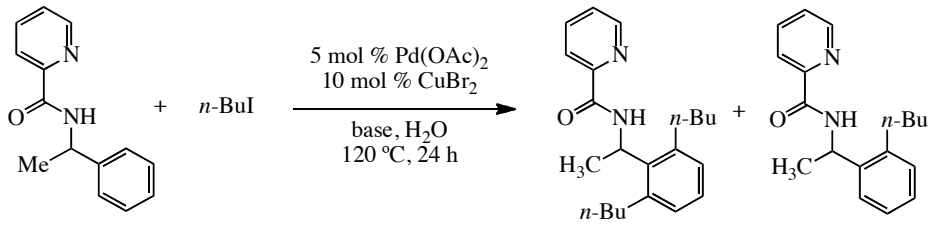
Entry	Additive	% GC Yield [b]	
		A	**B**
1	No additive	45	15
2	**10 % $CuBr_2$**	**95**	**5**
3	20 % $CuBr_2$	76	14
4	10 % $Cu(NO_3)_2$	65	17
5	20 % $Cu(NO_3)_2$	95	4
6	10 % $CuCl_2$	55	20
7	10 % $CuCO_3$	58	19
8	10 % CuOAc	84	10
9	10 % MnO_2	70	17

[a] *N*-(1-phenylethyl)picolinamide (0.5 mmol), *n*-BuI (2 mmol), $Pd(OAc)_2$ (5 mol%), additive , K_3PO_4 (2 mmol), H_2O (0.15 mL), 24 h at 120 °C.
[b] Dodecane as internal standard

3. Optimization of the base

Different bases were used in optimization (Table 3.8). Analysis by GC showed that potassium carbonate is the best base for the alkylation, giving complete conversion to dialkyated *N*-(1-phenylethyl)picolinamide.

Table 3.9. Alkylation of picolinamides – optimization of the base



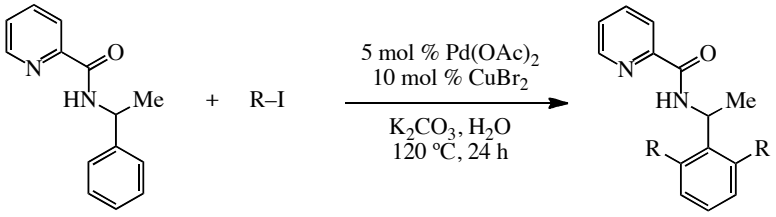
Entry	Base	% GC Yield [b]	
		A	**B**
1	K_3PO_4	95	5
2	Na_3PO_4	49	20
3	**K_2CO_3**	**99**	**0**
4	Na_2CO_3	54	20
5	Cs_2CO_3	28	10
6	CsOAc	7	14
7	K_2HPO_4	32	10
8	NaOAc	6	18

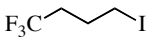
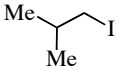
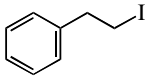
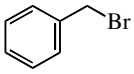
[a] *N*-(1-phenylethyl)picolinamide (0.5 mmol), *n*-BuI (2 mmol), $Pd(OAc)_2$ (5 mol%), base (2 mmol), H_2O (0.15 mL), 24 h at 120 °C.
[b] Dodecane as internal standard

4. Alkylation of sp^2 and sp^3 C–H bonds

α-Methylbenzylamine derivatives can be alkylated by various alkyl iodides (Table 3.9). Butyl iodide (entry 1), 4,4,4-trifluorobutyl iodide (entry 2), isobutyl iodide (entry 3), and 2-phenethyl iodide (entry 4) can be used in alkylation affording products in good yields. Benzylation can be performed by employing benzyl bromide (entry 5).

Table 3.10. Alkylation of *N*-(1-phenylethyl)picolinamide[a]

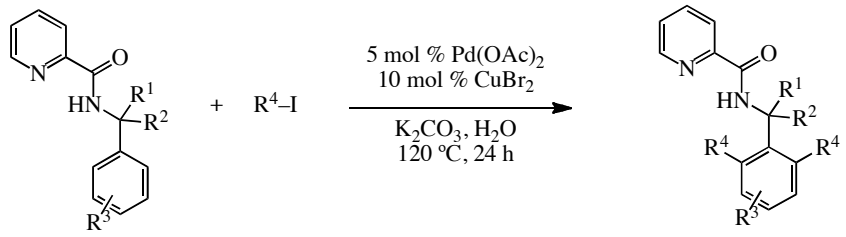


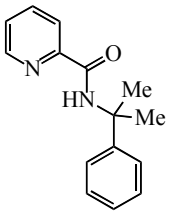
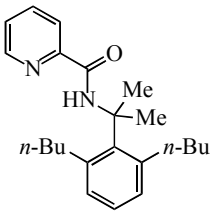
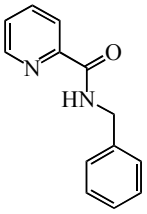
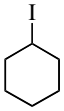
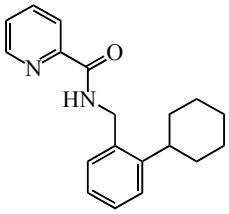
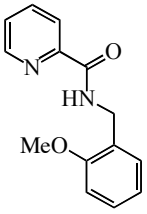
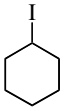
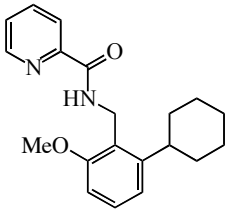
Entry	R–I	% Yield [b]
1[d]	*n*-Bu–I	99 %
2		79 %
3		92 %
4		86 %
5[d]		85 %

[a] aryl or alkyl picolinamide (1 mmol), aryl iodide (4 mmol), $Pd(OAc)_2$ (10 mol %), $CuBr_2$ (20 mol %), K_2CO_3 (4 mmol), H_2O (0.30 mL), 120 °C, 24 h. [b] Yields are isolated yields. [δ] $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (10 mol %)

The picolinamide derivative of α,α-dimethylbenzylamine (Table 3.10) was alkylated with *n*-butyl iodide in good yield (Entry 1). Lower catalyst loading was used in this reaction. However, if butyl iodide was replaced with butyl bromide, no product was obtained. Unexpectedly, secondary alkyl iodides are also reactive. Cyclohexylation of benzyl picolinamide affords a 20% yield of monoalkylation product in addition to 14% of dialkylation (entry 2). Similarly, methoxybenzylamine derivative gives the product in 14% yield (entry 9).

Table 3.11. Alkylation of picolinamides[a]

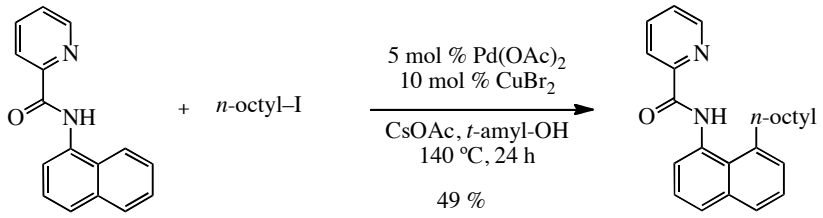


Entry	Picolinamide	R–I	Product	Yield[b]
1[c, d]		*n*-Bu–I		54 %
2[e]				20
3				14

[a] Picolinamide (1 mmol), alkyl iodide (4 mmol), $Pd(OAc)_2$ (10 mol %), $CuBr_2$ (20 mol %), K_2CO_3 (4 mmol), H_2O (0.30 mL), 120 °C, 24 h. [b] Yields are isolated yields. [c] $Pd(OAc)_2$ (5 mol %), $CuBr_2$ (10 mol %). *δ*-Monoalkylation product also isolated (14 %), 6 equiv of *n*-BuI used. [e] Dialkylation product also isolated (11 %).

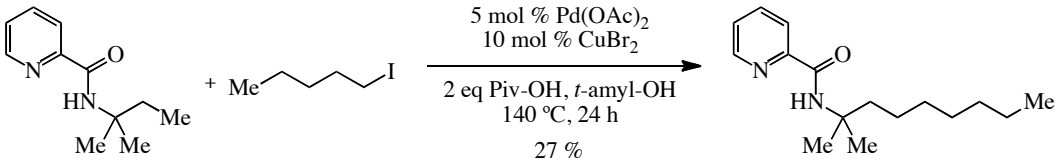
A procedure for alkylation of *N*-(naphthalen-1-yl)picolinamide was also developed by using cesium acetate in combination with *t*-amyl alcohol solvent (Scheme 3.26). The method does not use stoichiometric silver. The *N*-(naphthalen-1-yl)picolinamide was alkylated by *n*-octyl iodide in moderate yield

Scheme 3.26. Alkylation of *N*-(naphthalen-1-yl)picolinamide



The alkylation of unactivated sp^3 C-H bonds is inefficient. Reaction of 2-(2-methyl)butylamide of picolinic acid with *n*-amyl iodide yielded only 27% of the product (Scheme 3.27). However, this is the first example of γ-alkylation of an aliphatic amine derivative.

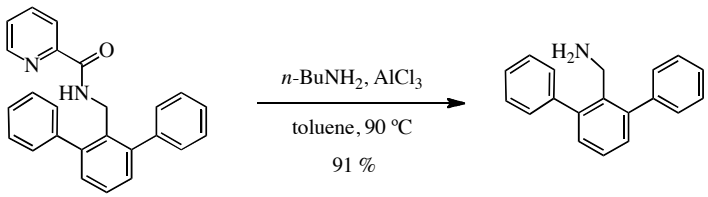
Scheme 3.27. Alkylation of alkylpicolinamide



C. Removal of directing group

The picolinamide directing group can be easily removed by transamidation. Heating picolylamide of 2,6-diphenylbenzylamine with $AlCl_3$ and butylamine in toluene afforded 91% yield of 2,6-diphenylbenzylamine (Scheme 3.28).[61]

Scheme 3.28. Cleavage of directing group



III. Conclusions

An extension of the previously published amine γ-arylation method has been developed. Use of palladium catalyst in conjunction with cesium acetate or potassium carbonate bases allows for a simple functionalization of sp^2 and sp^3 C–H bonds in amides possessing picolinic acid directing group. Stoichiometric silver additive is not required in contrast with our previously published procedure.[26] Arylations are effective for sp^2 as well as primary and secondary sp^3 C–H bonds. Alkylations of sp^2 C–H bonds are successful in most cases. Both primary and secondary alkyl iodides are reactive but secondary alkyl iodides afford low yields. Alkylation of sp^2 C–H bonds is low-yielding and the reaction requires further optimization. Alkyl and aryl iodides as well as benzyl bromides are reactive. Aryl and alkyl bromides afford no product.

IV. Experimental details

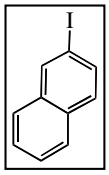
A. General considerations

Flash chromatography was performed on 60Å silica gel. Preparative TLC was performed on TLC plates, 20 x 20 cm, 2000 μm thick, with fluorescent indicator. Residual solvent peak was used as a reference in ^{1}H NMR and ^{13}C NMR spectra. Melting points are uncorrected.

B. Materials

The following starting materials were obtained from commercial sources and were used without further purification: picolinic acid, triethylamine, dichloromethane, ethyl chloroformate, $MgSO_4$, hexanes, ethyl acetate, 2-phenylpropan-2-amine, 1-phenylethanamine, benzylamine, 1-naphthyl-amine, pyridine, triphenylphosphite, H_2SO_4, (2-methoxyphenyl)methanamine, 2-(3,4-dimethoxyphenyl)ethanamine, 2-methylbutan-2-amine, 2-aminobutane, 1-propylamine, 1-pentylamine, cyclohexylamine, 2,4,4-trimethylpentan-2-amine, palladium(II) acetate, copper(II) bromide, cesium acetate, *tert*-amyl alcohol, iodo-4-methylbenzene, iodobenzene, 1-iodo-4-methoxybenzene, 1-bromo-4-iodobenzene, ethyl 4-iodobenzoate, 4-iodo-1,1'-biphenyl, iodoethane, 1,1,1-trifluoro-4-iodobutane, 1-iodo-2-methylpropane, (2-iodoethyl)benzene, benzyl iodide, octyl iodide, iodobutane, iodocyclohexane, iodopentane, aluminum chloride, toluene, 1-naphthylamine, pyridine, picolinic acid, triphenylphosphite, dichloromethane, sulfuric acid, sodium bicarbonate, methanol, 2-bromonaphthalene, tetrahydrofuran, *n*-butyllithium solutions (2.0 N in cyclohexane and 2.5 N in hexane), iodine, sodium

thiosulfate, sodium iodide, magnesium sulfate, palladium acetate, silver acetate, celite, hexanes, ethyl acetate, 4-*t*-butyliodobenzene, 4-iodoanisole, 3-iodoanisole, ethyl 4-iodobenzoate, 1-chloro-3-iodobenzene, 1-bromo-3-iodobenzene, 4-iodotoluene, 4-iodobenzotrifluoride, sodium hydroxide, ethanol, triethylamine, propionyl chloride.

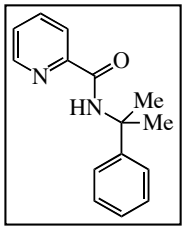


2-Iodonaphthalene. 2-Bromonaphthalene (20.7 g, 100 mmol) was dissolved in anhydrous tetrahydrofuran (100 mL) under argon. The mixture is cooled to -78 °C and a solution of n-BuLi in hexanes (2.5 N, 44 mL) was added dropwise. The mixture is stirred at -78 °C and after two hours, iodine (200 mmol, 50.6 g) in tetrahydrofuran (100 mL) was added. After 30 minutes, the mixture was warmed to room temperature and stirred overnight. Then, a solution of sodium thiosulfate (110 mmol, 17.4 g) and sodium iodide (110 mmol, 15.0 g) in water (100 mL) was added. The organic layer was collected and the aqueous layer was washed with dichloromethane. The combined organic layers were dried with magnesium sulfate. The solvent was evaporated and the resulting crude product was subjected to chromatography using hexanes as solvent. This compound is known.[62] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.25 (s, 1H), 7.81–7.78 (m, 1H), 7.74–7.69 (m, 2H), 7.58–7.56 (m, 1H), 7.52–7.48 (m, 2H).

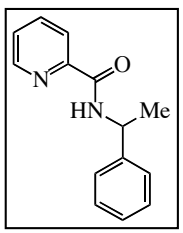
C. General procedure for the preparation of the picolinamides from amines[63]

Picolinic acid (35 mmol, 4.3 g) and triethylamine (70 mmol, 9.70 mL) was dissolved in dry dichloromethane (80 mL). The solution was cooled to 0 °C then, ethyl chloroformate (35 mmol, 3.3 mL) was added and the mixture was stirred for 30 minutes. The amine (20 mmol) was added and the suspension was stirred for one hour. The

solution was warmed to room temperature and stirred for 24 hours. After the reaction is complete, water (100 mL) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dry dichloromethane. The organic layers were combined, dried with $MgSO_4$, concentrated, and loaded in a silica column with hexanes/ethyl acetate mixture as eluent.

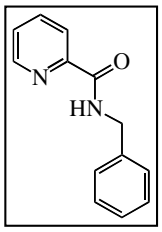


***N*-(2-Phenylpropan-2-yl)picolinamide** (S01) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-phenylpropan-2-amine (20 mmol, 2.7 g). After chromatography (hexanes/ethyl acetate 70/30), white crystalline material was obtained (4.44 g, 93 % yield). R_f = 0.40 (hexanes/ethyl acetate 70/30), mp=87–88 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.54 (m, 1H), 8.48 (*br* s, 1H), 8.15–8.13 (m, 1H), 7.84–7.80 (m, 1H), 7.48–7.45 (m, 2H), 7.44–7.40 (m, 1H), 7.36–7.31 (m, 2H), 7.25–7.21 (m, 1H), 1.85 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 150.6, 147.9, 146.9, 137.5, 128.5, 126.8, 126.1, 124.9, 122.0, 55.7, 29.3. FT-IR (neat, cm^{-1}) ν 3381, 1682, 15.13, 1570, 1436, 1384, 1365, 1280. Anal. Calcd for $C_{29}H_{28}N_2O$ (420.55 g/mol): C, 74.97; H, 6.71; N, 11.66; Found: C, 75.02; H, 6.71; N, 11.62.

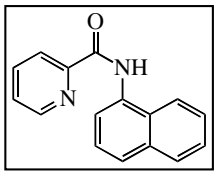


***N*-(1-Phenylethyl)picolinamide** (S02) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 1-phenylethanamine (20 mmol, 2.42 g). After chromatography (hexanes/ethyl acetate 70/30), white crystals were obtained (4.35 g, 96 % yield). R_f = 0.31 (hexanes/ethyl acetate 70/30). This

compound is known.[64] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.52 (m, 1H), 8.32 (bd, 1H), 8.20–8.18 (m, 1H), 7.84–7.80 (m, 1H), 7.41–7.38 (m, 3H), 7.36–7.31 (m, 2H), 7.28–7.23 (m, 1H), 5.38–5.26 (m, 1H), 1.62 (d, *J*=6.87 Hz, 3H).

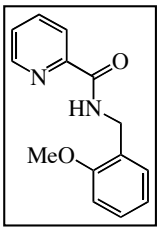


***N*-Benzylpicolinamide** (S03) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and benzylamine (20 mmol, 2.14 g). After chromatography (hexanes/ethyl acetate 60/40), white crystals were obtained (3.81 g, 90 % yield). R_f = 0.36 (hexanes/ethyl acetate 60/40). This compound is known.[65] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.51 (m, 1H), 8.37 (*br* s, 1H), 8.23 (d, *J*=7.8 Hz, 1H), 7.87–7.83 (m, 1H), 7.43–7.40 (m, 1H), 7.38–7.32 (m, 4H), 7.30–7.26 (m, 1H), 4.67 (d, *J*=6.0 Hz, 2H).

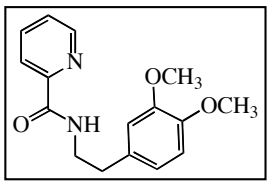


***N*-(Naphthalen-1-yl)picolinamide** (S04) 1-Naphthyl-amine (7.2 g, 50 mmol) in pyridine (10 mL) was added dropwise for 15 minutes to a stirring solution of picolinic acid (6.2, 50 mmol) in pyridine (14 mL) heated to 50 °C. Triphenylphosphite (13 mL, 50 mmol) was then, added to the resulting mixture was stirred at 110 °C for 4 hours. The mixture was cooled, and then distilled water (50 mL) and dichloromethane (50 mL) was added. The mixture was then placed in a 500 mL Erlenmeyer flask and 150 mL of aqueous H_2SO_4 (concentrated H_2SO_4/water 1/1 v/v) added. The mixture was shaken and the layers were separated. The organic layer was washed with aqueous H_2SO_4 (2 X 100 mL). The acidic aqueous layers were combined and neutralized with solid sodium bicarbonate. The tan solids formed were filtered and washed thoroughly with distilled water, then recrystallized in methanol to

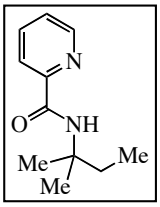
obtain tan needles (10.9 g, 87 % yield). This compound is known.[66] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.77 (s, 1H), 8.70 (d, J = 8.2 Hz, 1 H), 8.36 (d, J = 8.2 Hz, 1 H), 8.36 (d, J = 7.8 Hz, 1 H), 8.09 (d, J = 8.2 Hz, 1 H), 7.95–7.88 (m, 2 H), 7.70 (d, J = 8.2 Hz, 1 H), 7.61–7.50 (m, 4 H).



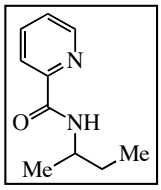
***N*-(2-Methoxybenzyl)picolinamide** (S05) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and (2-methoxyphenyl)methanamine (20 mmol, 2.74 g). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (3.2 g, 71 % yield). R_f = 0.34 (hexanes/ethyl acetate 60/40). This compound is known.[67] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.52 (m, 1H), 8.45 (*br* s, 1H), 8.21–8.19 (m, 1H), 7.85–7.77 (m, 1H), 7.35 (dd, J=7.45, 1.7 Hz, 2H), 7.27–7.24 (m, 2H), 6.93–6.88 (m, 2H), 4.67 (d, J=6.30 Hz, 2H), 3.88 (s, 3H).



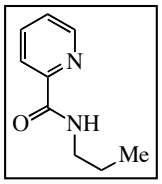
***N*-(3,4-Dimethoxyphenethyl)picolinamide** (S06) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-(3,4-dimethoxyphenyl)ethanamine (20 mmol, 3.62 g). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (5.56 g, 97 % yield). R_f = 0.30 (hexanes/ethyl acetate 60/40). This compound is known.[68] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52–8.51 (m, 1H), 8.21–8.16 (m, 2H), 7.87–7.82 (m, 1H), 7.43–7.39 (m, 1H), 6.84–6.78 (m, 3H), 3.87–3.85 (m, 6H), 3.74–3.69 (m, 2H), 2.91–2.87 (m, 2H).



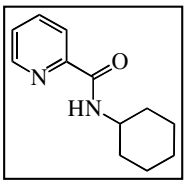
***N*-(*tert*-Pentyl)picolinamide** (S07) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-methylbutan-2-amine (20 mmol, 1.74 g). After chromatography (hexanes/ethyl acetate 70/30), colorless liquid was obtained (3.77 g, 98 % yield). R_f = 0.55 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52–8.51 (m, 1H), 8.19–8.16 (m, 1H), 7.97 (bs, 1H), 7.85–7.81 (m, 1H), 7.41–7.38 (m, 1H), 1.87 (q, J=7.3 Hz, 2H), 1.45 (s, 6H), 0.92 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 150.8, 147.8, 137.4, 125.9, 121.7, 53.7, 33.0, 26.4, 8.5. FT-IR (neat, cm^{-1}) v 2969, 1677, 1520, 1463, 1433, 1363, 1284. Anal. Calcd for $C_{11}H_{16}N_2O$ (192.26 g/mol): C, 68.72; H, 8.39; N, 14.57; Found: C, 68.20; H, 8.44; N, 14.33.



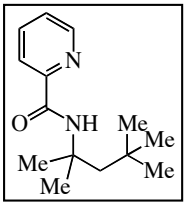
***N*-(*sec*-Butyl)picolinamide** (S08) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-aminobutane (20 mmol, 1.46 g). After chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (3.27 g, 92 % yield). R_f = 0.35 (hexanes/ethyl acetate 70/30). This compound is known.[26] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56–8.55 (m, 1H, 8.21 (d, J=7.79 Hz, 1H), 7.87–7.83 (m, 2H), 7.35–7.40 (m, 1H), 4.15–4.08 (m, 1H), 1.65–1.58 (m, 2H), 1.26 (d, J=6.41 Hz, 3H), 0.97 (t, J=7.5 Hz, 3H).



***N*-Propylpicolinamide** (S09) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 1-propylamine (20 mmol, 1.18 g). After chromatography (hexanes/ethyl acetate 70/30), colorless liquid was obtained (3.11 g, 95 % yield). R_f = 0.31 (hexanes/ethyl acetate 70/30). This compound is known.[7] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.21 (d, *J*=7.8 Hz, 1H), 8.15 (*br* s, 1H), 7.86–7.82 (m, 1H), 7.35–7.40 (m, 1H), 3.46 (q, *J*=6.41 Hz, 2H), 1.71–1.64 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H).



***N*-Cyclohexylpicolinamide** (S10) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and cyclohexylamine (20 mmol, 4.2 g). After chromatography (hexanes/ethyl acetate 70/30), white needles were obtained (4.3 g, 98 % yield). R_f = 0.32 (hexanes/ethyl acetate 70/30). This compound is known.[13b] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.22–8.20 (m, 1H), 7.96 (*br* d, *J*=3.7 Hz, 1H), 7.86–7.82 (m, 1H), 7.43–7.40 (m, 1H), 4.01–3.94 (m, 1H), 2.04–2.00 (m, 2H), 1.80–1.75 (m, 2H), 1.68–1.63 (m, 1H), 1.49–1.19 (m, 5H).



***N*-(2,4,4-Trimethylpentan-2-yl)picolinamide** (S11) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2,4,4-trimethylpentan-2-amine (20 mmol, 2.58 g). After column chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained 3.2 g, 62 % yield). R_f = 0.56 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, *J*=4.01 Hz, 1H), 8.18 (d, *J*=8.02, Hz, 1H), 8.12

(bs, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.1, 151.0, 148.9, 137.4, 125.8, 121.7, 54.7, 52.0, 31.8, 31.6, 29.2. FT-IR (neat, cm^{-1}) ν 2956, 1681, 1522, 1464, 1432, 1365, 1228, 998. Anal. Calcd for $C_{14}H_{22}N_2O$ (234.34 g/mol): C, 71.76; H, 9.46; N, 11.95; Found: C, 71.46; H, 9.29; N, 11.86.

D. Arylation of sp^2 and sp^3 C–H bonds

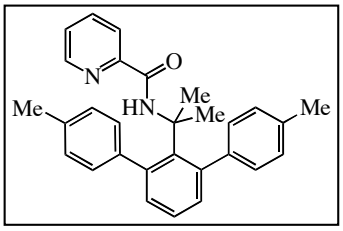
1. Optimization of the reaction condition

A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 246 mg) and 1-iodo-4-methylbenzene (4 mmol, 896 mg). The corresponding test reagents such as additive, base (4 mmol) and solvent was added to this mixture The resulting suspension was stirred in an oil bath at the specified temperature. After the designated time, the reaction mixture was cooled, and diluted with 4 mL dichloromethane and analysed by GC-MS. The results are shown in Table 3.1.

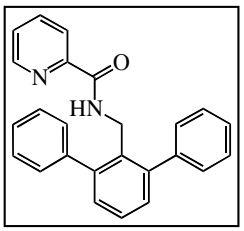
2. General procedure for arylation of sp^2 and sp^3 C–H bonds

A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), picolinamide (1 mmol), aryl iodide (4 mmol), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. The reaction mixture was then extracted with dichloromethane (4 mL) three times. The extracts were combined, filtered through pad of cotton, concentrated, and then loaded onto a chromatography column with hexanes/ethyl acetate mixture as eluent. The

solvent from the fractions containing the desired compound was evaporated to give the product.



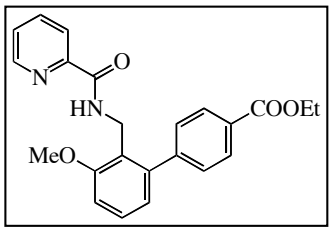
***N*-(2-(4,4''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)propan-2-yl)-picolinamide** (Table 3.2, Entry 1). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 246 mg), 1-iodo-4-methylbenzene (4 mmol, 896 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), tan powder (425 mg, 99 % yield) was obtained. R_f = 0.45 (hexanes/ethyl acetate 70/30), mp=164–165 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.21–8.20 (m, 1H), 7.99–7.97 (m, 1H), 7.76–7.72 (m, 1H), 7.58 (*br* s, 1H), 7.31–7.28 (m, 1H), 7.17–7.13 (m, 5H), 7.02 (d, *J*=7.33 Hz, 2H), 6.90 (d, *J*=7.33 Hz, 2H), 2.25 (s, 6H), 1.60 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 150.7, 147.1, 143.4, 141.8, 141.7, 136.9, 135.7, 132.8, 128.7, 128.2, 125.4, 124.9, 121.5, 57.5, 33.4, 21.2. FT-IR (neat, cm^{-1}) *v* 3369, 1679, 1527, 1444, 1224, 1042, 824. Anal. Calcd for $C_{29}H_{28}N_2O$ (420.55 g/mol): C, 82.82; H, 6.71; N, 6.66; Found: C, 82.47; H, 6.69; N, 6.55.



***N*-([1,1':3',1''-Terphenyl]-2'-ylmethyl)picolinamide** (Table 3.2, Entry 2). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1 mmol, 212 mg), iodobenzene (4 mmol, 816 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C

for 24 hours. After chromatography (hexane/ethyl acetate 70/30), white needles (360 mg, 99 % yield) were obtained. R_f = 0.34 (hexanes/ethyl acetate 70/30), mp=119–120 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.44–8.43 (m, 1H), 7.98–7.96 (m, 1H), 7.78–7.72 (m, 2H), 7.43–7.29 (m, 14H), 4.49 (d, J=5.04 Hz, 2H) ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.9, 149.8, 147.9, 143.9, 141.2, 137.1, 132.7, 129.8, 129.1, 128.3, 127.5, 127.4, 125.9, 122.0, 39.4. FT-IR (neat, cm^{-1}) ν 3378, 1678, 1510, 1464, 1435, 1000. Anal. Calcd for $C_{25}H_{20}N_2O$ (364.44 g/mol): C, 82.39; H, 5.53; N, 7.69; Found: C, 82.50; H, 5.45; N, 7.68.

When bromobenzene (4 mmol, 628 mg) was used as an arylating agent, < 5% of the product was detected by GC-MS.

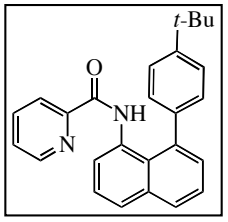


Ethyl 3'-methoxy-2'-(picolinamidomethyl)-[1,1'-biphenyl]-4-carboxylate (Table 3.2, Entry 3). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-methoxybenzyl)picolinamide (1 mmol, 247 mg), iodobenzene (4 mmol, 816 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 60/40), white needles (353 mg, 92 % yield) were obtained. R_f = 0.33 (hexanes/ethyl acetate 60/40), mp=163–164 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.48 (m, 1H), 8.33–8.36 (m, 1H), 8.16–8.13 (m, 1H), 8.10–8.07 (m, 2H), 7.81–7.76 (m, 1H), 7.43–7.41 (m, 2H), 7.38–7.31 (m, 2H), 6.96 (d, J=7.79 Hz, 1H), 6.89 (dd, J=7.79, 0.92 Hz, 1H), 4.58 (d, J=5.50 Hz, 2H), 4.37 (q, J=7.3 Hz, 2H), 3.94 (s, 3H), 1.38 (t, J=7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6,

163.4, 158.8, 150.3, 148.1, 145.3, 143.0, 137.3, 129.6, 129.5, 128.7, 126.0, 123.6. 122.5, 122.3, 110.2, 61.0, 56.0, 38.6, 14.5. FT-IR (neat, cm^{-1}) *v* 3396, 1709, 1668, 1584. 1512, 1462, 1271, 1176, 1023. Anal. Calcd for $C_{23}H_{22}N_2O_4$ (390.43 g/mol): C, 70.75; H, 5.68; N, 7.17; Found: C, 70.86; H, 5.65; N, 7.16.

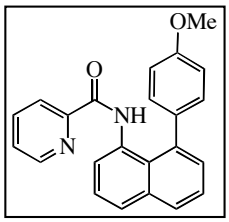
3. General procedure for the arylation of *N*-(naphthalen-1-yl)picolinamide using $Pd(OAc)_2$ catalyst and AgOAc base

A 2-dram screw-cap via was charged with $Pd(OAc)_2$ (2 mol%, 6 mg), AgOAc (166 mg, 1 mmol), aryl iodide (2 mmol), and *N*-(naphthalen-1-yl)picolinamide (0.5 mmol, 125 mg). The resulting solution was stirred at 140 ^oC for 24 hours. The reaction mixture was then diluted with dichloromethane (2 mL), filtered through pad of celite, concentrated, then loaded in a chromatography column with hexane/ethyl acetate mixture as an eluent.

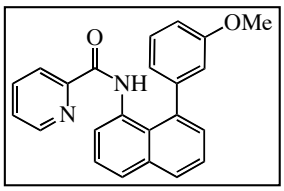


***N*-(8-(4-*tert*-Butylphenyl)naphthalen-1-yl)picolinamide** (Table 3.3, Entry 1): *N*-(naphthalen-1-yl)picolinamide (124, 0.5 mmol), 4-*t*-butyliodobenzene (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 80/20), the solvent was evaporated to give white powder (190 mg, 99 % yield). R_f = 0.34 (hexanes/ethyl acetate 80/20), mp=136–137 °C. ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 9.60 (s, 1H), 8.32–8.18 (m, 2H), 8.11–8.10 (m, 1H), 7.88 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.81–7.73 (m, 1H), 7.59–7.55 (m, 2H), 7.50–7.47 (m, 2H), 7.36–7.34 (m, 3H), 7.31–7.28 (m, 1H), 7.21–7.17 (m, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7, 149.8, 149.7, 147.6, 139.6, 137.8, 137.1, 135.6, 133.1, 130.7, 128.9, 128.4, 126.3, 126.0, 125.9, 125.2, 124.8, 122.3, 121.9, 34.3, 31.3 (one peak missing). FT-IR (neat, cm^{-1}) *v* 1690,

1521, 1495, 820, 767, 745, 665. Anal. Calcd for $C_{26}H_{24}N_2O$ (289.0 g/mol): C, 82.70; H, 6.36; N, 7.36; Found: C, 82.07; H, 6.20; N, 7.33.

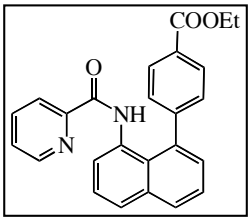


***N*-(8-(4-methoxyphenyl)naphthalen-1-yl)picolinamide** (Table 3.3, Entry 2): *N*-(naphthalen-1-yl)picolinamide (127 mg, 0.5 mmol), 4-iodoanisole (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (176 mg, 98 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30), mp=107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.71 (s, 1H), 8.30–8.28 (dd, J = 7.8, 1.4 Hz, 1H), 8.20–8.19 (d, J = 5.0, 1H), 8.11 (d, J = 7.8, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.86 (dd, J = 8.2, 0.9 Hz, 1H), 7.80–7.56 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.34–7.30 (m, 4H), 6.75–6.67 (m, 2H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 158.9, 150.1, 147.5, 137.4, 137.0, 135.5, 135.1, 133.1, 130.7, 130.4, 128.6, 126.4, 126.0, 125.8, 125.0, 122.3, 122.0, 113.6, 55.0. FT-IR (neat, cm^{-1}) ν 1683, 1494, 1515, 1433, 1243, 1176, 1036, 824. Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.4 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.68; H, 5.09; N, 7.78.

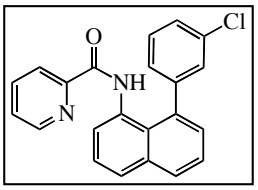


***N*-(8-(3-methoxyphenyl)naphthalen-1-yl)picolinamide** (Table 3.3, Entry 3): *N*-(naphthalen-1-yl)picolinamide (125 mg, 0.5 mmol), 3-iodoanisole (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (178 mg, 99 % yield). R_f = 0.30 (hexanes/ethyl acetate 70/30), mp=99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm)

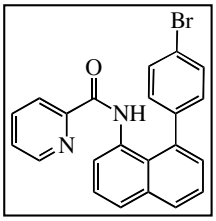
δ 9.60 (s, 1H), 8.23–8.18 (m, 2H), 8.10–8.08 (m, 1H), 7.88 (dd, J = 8.2, 1.4 Hz, 1H), 7.82–7.75 (m, 2H), 7.60–7.56 (m, 1H), 7.47 (dd, J = 8.2 Hz, 7.3 Hz, 1H), 7.34–7.31 (m, 2H), 7.07–7.04 (m, 2H), 6.91–6.93 (m, 2H), 6.52–6.49 (m, 1H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.21, 159.4, 149.9, 147.5, 144.2, 137.6, 137.1, 135.5, 132.9, 130.3, 129.2, 128.9, 126.6, 126.0, 125.9, 125.3, 125.0, 123.1, 121.9, 121.7, 114.0, 113.3, 55.2. FT-IR (neat, cm^{-1}) v 1682, 1521, 1577, 1498, 1427, 1215, 1160, 1041, Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.4 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.69; H, 5.10; N, 7.83.



Ethyl 4-(8-(picolinamido)naphthalen-1-yl)benzoate (Table 3.3, Entry 4): *N*-(naphthalen-1-yl)picolinamide (122 mg, 0.5 mmol), ethyl 4-iodobenzoate (122 mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (179 mg, 92 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30), mp=83–83°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.35 (s, 1H), 8.12–8.10 (m, 2H), 8.06 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.83–7.80 (m, 3H), 7.76–7.70 (m, 1H), 7.60–7.56 (m, 1H), 7.50–7.46 (m, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.24–7.22 (m, 1H), 4.29 (q, J = 7.3, 2H), 1.32 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.3, 162.0, 149.6, 147.7, 147.5, 137.1, 136.8, 135.5, 132.5, 130.2, 129.4, 129.2, 128.8, 126.9, 126.2, 125.9, 125.4, 125.0, 123.8, 122.0, 60.8, 14.5 (one missing peak). FT-IR (neat, cm^{-1}) v 1710, 1682, 1495, 1266, 1102, Anal. Calcd for $C_{25}H_{20}N_2O_3$ (396.4 g/mol): C, 75.74; H, 5.08; N, 7.07; Found: C, 75.63; H, 5.05; N, 7.00.



***N*-(8-(3-chlorophenyl)naphthalen-1-yl)picolinamide** (Table 3.3, Entry 5): *N*-(naphthalen-1-yl)picolinamide (135 mg, 0.5 mmol), 1-chloro-3-iodobenzene (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 80/20), the solvent was evaporated to give white powder (190 mg, 98 % yield). R_f = 0.30 (hexanes/ethyl acetate 80/20), mp=120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.50 (s, 1H), 8.30 (d, J = 4.6 Hz, 1H), 8.18 (dd, J = 7.8, 0.9 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.89 (dd, J = 8.2, 1.4 Hz, 1H), 7.82–7.76 (m, 2H), 7.60–7.56 (m, 1H), 7.49–7.47 (m, 2H), 7.37–7.34 (m, 1H), 7.28 (dd, J = 7.4, 1.4 Hz, 1H), 7.18–7.15 (m, 1H), 7.01–6.96 (m, 1H), 6.92–6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.9, 149.6, 147.5, 144.7, 137.2, 136.2, 135.5, 134.2, 132.6, 130.4, 129.3, 129.1, 129.0, 127.8, 126.8, 126.2, 126.1, 125.2, 125.0, 123.3, 122.0. FT-IR (neat, cm^{-1}) ν 1684, 1526, 1498, 1432, 998, 819, 794, 766, 698. Anal. Calcd for $C_{22}H_{15}ClN_2O$ (358.8 g/mol): C, 73.64; H, 4.21; N, 7.81; Found: C, 73.89; H, 4.09; N, 7.76.

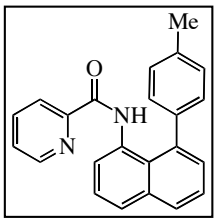


***N*-(8-(4-bromophenyl)naphthalen-1-yl)picolinamide** (Table 3.3, Entry 6): *N*-(naphthalen-1-yl)picolinamide (121 mg, 0.5 mmol), 1-bromo-3-iodobenzene (mg, 2 mmol), AgOAc (166 mg, 1.0 mmol) and $Pd(OAc)_2$ (4.4 mg, 0.01 mmol). After column chromatography (hexanes/ethyl acetate 70/30), the solvent was evaporated to give white powder (161 mg, 82 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30), mp=134–135°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.56 (s, 1H), 8.32–8.30 (m, 1H), 8.21–8.20 (m, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.3, 0.9 Hz, 1H), 7.84–7.80 (m, 2H), 7.61–7.57 (m, 1H), 7.50-7.46 (m, 1H), 7.42–7.39

(m, 1H), 7.32–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 149.5, 147.9, 141.9, 137.2, 136.4, 135.6, 132.6, 131.3, 130.9, 130.5, 129.2, 129.7, 126.3, 126.2, 125.0, 123.2, 122.0, 121.4 (one missing peak). FT-IR (neat, cm^{-1}) v 1687, 1498, 1433, 1009, 818, 765. Anal. Calcd for $C_{22}H_{15}BrN_2O$ (403.3 g/mol): C, 65.52; H, 3.75; N, 6.95; Found: C, 65.10; H, 3.54; N, 6.82.

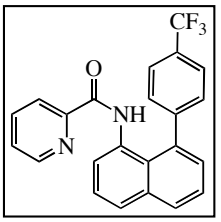
4. General procedure for the scaled-up arylation of *N*-(naphthalen-1-yl)picolinamide

In a 100 mL round bottom flask with magnetic stir bar, the following chemicals are combined: *N*-(naphthalen-1-yl)picolinamide (1eq), iodoarene (4 eq), AgOAc (1.5 eq) and $Pd(OAc)_2$ (2 mol %). The flask is sealed with rubber septum and the heated with stirring at 140 °C for 24 hours. After the reaction is complete, the mixture is cooled and 150 mL of ethyl acetate was added. The mixture was filtered and the filtrate was washed with an equivalent volume of brine. The layers were separated and the aqueous solution was extracted with ethyl acetate (2 X 50 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated. The residue was subjected to chromatography to give pure compound.

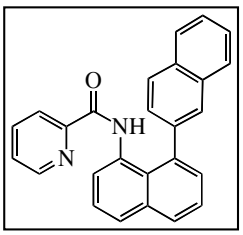


***N*-(8-*p*-tolylnaphthalen-1-yl)picolinamide** (Table 3.4, Entry 1): *N*-(naphthalen-1-yl)picolinamide (5.1 g, 20.5 mmol), 4-iodotoluene (17.5 g, 80.3 mmol), AgOAc (5.1 g, 30.5 mmol) and $Pd(OAc)_2$ (101 mg, 0.45 mmol). After column chromatography (hexanes/ethyl acetate 90/10 then hexanes/ethyl acetate 65/35), the solvent was evaporated to give light brown crystals (6.45 g, 91 % yield). R_f = 0.50 (hexanes/ethyl acetate 65/35), mp=123–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.61 (s, 1H), 8.23 (dd, J = 7.7, 1.5 Hz, 1H), 8.18–8.16 (m, 1H), 8.10–8.08 (m, 1H), 7.86 (dd, J = 8.4, 1.5 Hz, 1H), 7.80–7.74 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 4H), 6.96 (d, J = 7.7 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 150.0, 147.4, 139.9, 137.8, 137.0, 136.6, 135.6, 133.0, 130.5, 129.2, 128.9, 128.6, 126.5, 126.0, 125.7, 125.1, 125.0, 122.6, 121.9, 21.2. FT-IR (neat, cm^{-1}) v 1689, 1493, 1433, 814, 764, 751, 716, 697. Anal. Calcd for $C_{23}H_{18}N_2O$ (388.4 g/mol): C, 81.63; H, 5.36; N, 8.28; Found: C, 81.54; H, 5.35; N, 8.23.



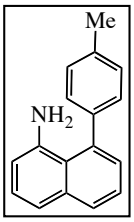
***N*-(8-(4-(trifluoromethyl)phenyl)naphthalen-1-yl)picolinamide** (Table 3.4, Entry 2): *N*-(naphthalen-1-yl)picolinamide (12.4 g, 50 mmol), 4-iodobenzotrifluoride (27.2 g, 100 mmol), AgOAc (12.45 g, 75 mmol) and $Pd(OAc)_2$ (224 mg, 1.0 mmol). After column chromatography (hexanes/ethyl acetate 65/35), the solvent was evaporated to give light orange crystals (16.26 g, 84 % yield). R_f = 0.48 (hexanes/ethyl acetate 70/30), mp = 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.34 (s, 1H), 8.15 (d, J = 4.1 Hz, 1H), 8.09–8.07 (m, 2H), 7.93 (dd, J = 8.2, 2.3 Hz, 1H), 7.84 (dd, J = 8.2, 1.3 Hz, 1H), 7.79–7.75 (m, 1H), 7.62–7.58 (m, 1H), 7.52–7.48 (m, 3H), 7.39 (d, J = 7.8 Hz, 2H), 7.34–7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 149.3, 147.6, 146.7, 137.3, 136.3, 135.6, 132.4, 130.5, 129.5, 129.1, 128.7, 127.0, 126.3, 125,5, 125.1, 124.9, 124.8, 124.1, 122.7, 121.9. FT-IR (neat, cm^{-1}) v 1670, 1491, 1320, 1185, 1141, 1111, 1070, 1058, 1018. Anal. Calcd for $C_{23}H_{15}F_3N_2O$ (392.4 g/mol): C, 70.40; H, 3.85; N, 7.14; Found: C, 70.59; H, 3.65; N, 7.14.



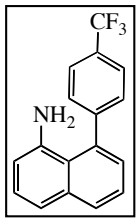
***N*-(1,2'-binaphthyl-8-yl)picolinamide** (Table 3.4, Entry 3): *N*-(naphthalen-1-yl)picolinamide (8.68 g, 35 mmol), 2-iodonaphthalene (26.7 g, 105 mmol), AgOAc (8.71 g, 52.5 mmol) and $Pd(OAc)_2$ (392 mg, 1.75 mmol). After column chromatography (dichloromethane/ethyl acetate 50/50), the solvent was evaporated and the residue obtained was recrystallized from methanol to give light brown crystals (8.5 g, 65 % yield). R_f = 0.32 (dichloromethane/ethyl acetate 50/50), mp = 155–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.56 (s, 1H), 8.31 (dd, J = 7.8, 1.4 Hz, 1H), 8.03 (s, 1H), 7.94–7.87 (m, 3H), 7.81 (dd, J = 8.3, 0.9 Hz, 1 H), 7.61–7.47 (m, 6H), 7.41–7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1, 149.4, 146.8, 140.7, 137.6, 136.6, 135.5, 133.8, 133.1, 132.7, 130.7, 129.0, 128.1, 128.0, 127.7, 127.6, 127.4, 126.4, 126.3, 126.1, 125.8, 125.7, 125.1, 125.0, 122.3, 121.5. FT-IR (neat, cm^{-1}) v 1692, 1496, 818, 763, 746, 657, 615. Anal. Calcd for $C_{26}H_{18}N_2O$ (374.4 g/mol): C, 83.40; H, 4.85; N, 7.48; Found: C, 83.19; H, 4.88; N, 7.39.

5. General procedure for the hydrolysis of the arylated picolinamides

8-*p*-Arylnaphthalen-1-amine was dissolved in ethanolic NaOH solution (NaOH in EtOH/H_2O 10/1) then refluxed for 6 hours. The reaction mixture is cooled and diluted with an equal volume of water. The product was then extracted with dichloromethane (3 X 60 mL). The combined organic layers were combined, dried with $MgSO_4$ and concentrated. The crude compound was subjected to column chromatography and the fractions containing the product were combined and the solvent was evaporated to give pure arylated naphthylamine.

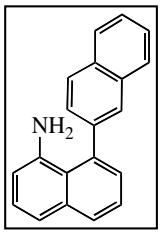


8-*p*-Tolylnaphthalen-1-amine (Scheme 3.12). *N*-(8-*p*-tolylnaphthalen-1-yl)picolinamide (10.1 g, 30 mmol), ethanolic NaOH solution (12 g NaOH, 300 mmol in 120 mL EtOH/ H_2O 10/1 v/v). After chromatography (hexane/ethyl acetate/triethylamine 94/5/1), beige crystals were obtained (7.0 g, quantitative yield). R_f = 0.16 (hexane/ethyl acetate/triethylamine 94/5/1), mp=73–74.°C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.75 (d, J = 8.1 Hz, 1H), 7.38–7.22 (m, 7H), 7.13 (d, J = 7.0 Hz, 1H), 6.60 (d, J = 7.3 Hz, 1H), 3.74 (s, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.8, 140.6, 138.4, 137.3, 135.9, 129.2, 128.8, 128.6, 128.4, 126.6, 124.7, 121.0, 119.1, 111.4. FT-IR (neat, cm^{-1}) ν 3490, 3393. 1615, 1579, 1522, 821, 767. Anal. Calcd for $C_{17}H_{15}N$ 233.3 g/mol): C, 87.52; H, 6.48; N, 6.00; Found: C, 87.44; H, 6.42; N, 5.96.



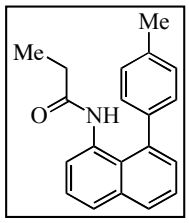
8-(4-(trifluoromethyl)phenyl)naphthalen-1-amine (Scheme 3.12). *N*-(8-(4-(trifluoromethyl)phenyl)- naphthalene-1-yl)picolinamide (16.3 g, 42 mmol), ethanolic NaOH solution (16.8 g NaOH, 420 mmol in 200 mL EtOH/H_2O 10/1 v/v). After chromatography (hexane/ethyl acetate/triethylamine 94/5/1), beige crystals were obtained (9.0 g, 75% yield). R_f = 0.21 (hexane/ethyl acetate/triethylamine 94/5/1), mp=108–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.80 (dd, J = 8.2, 0.9 Hz, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.56 (d, 7.8 Hz, 2 H), 7.41–7.28 (m, 3H), 7.12 (dd, J = 8.7, 1.4, 1H), 6.64 (dd, J = 8.7, 1.4 Hz, 1H), 3.56 (s, 2 H).^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.3, 143.4, 136.9, 135.9, 129.8, 129.5, 128.5, 126.9, 125.7, 125.0, 124.7, 123.0, 120.4, 119.4, 111.8. FT-IR (neat, cm^{-1}) ν 3707,

3618, 2973, 2922, 2865, 2844, 1323, 1057, 1032, 1015. Anal. Calcd for $C_{17}H_{12}F_3N$ (287.3 g/mol): C, 71.07; H, 4.21; N, 4.88; Found: C, 71.23; H, 4.12; N, 4.82.



1,2'-binaphthyl-8-amine (Scheme 3.12). *N*-(1,2'-binaphthyl-8-yl)picolinamide (8.23 g, 22 mmol), ethanolic NaOH solution (8.8 g NaOH, 220 mmol in 100 mL EtOH/ H_2O 10/1 v/v). After chromatography (hexane/dichloromethane 50/50), very light brown crystals were obtained (5.2 g, 88% yield). R_f = 0.26 (hexane/dichloromethane 50/50), mp=113–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.91–7.84 (m, 4H), 7.81–7.79 (m, 1H), 7.57–7.51(m, 3H), 7.41–7.26 (m, 3H), 7.22–7.20 (m, 1H), 6.60 (dd, J = 7.3, 1.4 Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.9, 141.3, 138.3, 136.0, 132.9, 132.6, 128.9, 128.7, 128.2, 128.0, 127.9, 127.6, 127.5, 126.8, 126.7, 126.4, 124.7, 120.9, 119.1, 111.3. FT-IR (neat, cm^{-1}) ν 3707, 3681, 2972, 2922, 2865, 2844, 1055, 1032, 1014. Anal. Calcd for $C_{20}H_{15}N$ (269.2 g/mol): C, 89.19; H, 5.61; N, 5.20; Found: C, 8.39; H, 5.56; N, 5.18.

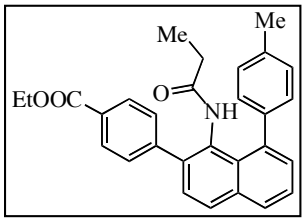
6. Installation of the propanamide auxiliary



***N*-(8-*p*-Tolylnaphthalen-1-yl)propionamide** (Scheme 3.13). 8-*p*-Tolylnaphthalen-1-amine (2.02 g, 8.7 mmol) and triethylamine (1.34 mL, 9.57 mol) were dissolved in dichloromethane (35 mL) and the resulting mixture was cooled in an ice bath. Propionyl chloride (1.55 mL, 17.4 mmol) in dichloromethane (10 mL) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 24 h. After this period, the reaction mixture was diluted with water (25 mL) and the layers were separated. The organic layer was

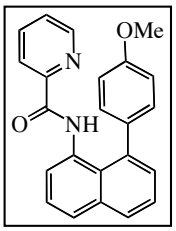
dried with $MgSO_4$, concentrated and subjected to column chromatography (hexane/ethyl acetate 75/25) to give 2.50 g (99 % yield) of white powder. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (d, J = 7.1 Hz, 1H), 7.85 (dd, J = 8.2, 1.4, 1H), 7.81 (d, J =7.8 Hz, 1H), 7.50–7.42 (m, 2H), 7.33–7.28 (m, 4H), 7.26–7.25 (m, 1H), 7.15 (s, 1H), 2.45 (s, 3H), 1.57 (q, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.5, 140.6, 137.7, 136.8, 135.2, 133.3, 129.9, 129.4, 129.0, 126.1, 125.7, 124.7, 124.0, 121.2, 30.5, 21.3, 9.4. FT-IR (neat, cm^{-1}) v 1651, 1378, 1219.

7. Arylation of naphthyl propanamide

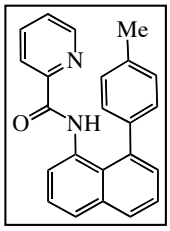


Ethyl 4-(1-propionamido-8-*p*-tolylnaphthalen-2-yl)benzoate (Scheme 3.13). A 2-dram screw-cap via was charged with $Pd(OAc)_2$ (5 mol%, 6 mg) AgOAc (166 mg, 1 mmol), ethyl 4-iodobenzoate (0.52 g, 2 mmol), *N*-(8-*p*-Tolylnaphthalen-1-yl)propionamide (149.9 mg, 0.5 mmol), and trifluoroacetic acid (0.5 mL). The resulting solution was stirred at 110 ^{o}C for 3 h. The reaction mixture was then diluted with dichloromethane (2 mL), filtered through pad of celite and concentrated. Purification by chromatography (hexane/ethyl acetate 80/20) gave white powder (180 mg, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.00 (d, J = 8.2 Hz, 2H), 7.94–7.89 (m, 2H), 7.50–7.45 (m, 2H), 7.40 (d, J = 8.2 Hz, 2H), 7.30 (dd, J = 7.2, 0.7 Hz, 1H), 7.26–7.21 (m, 4H), 6.38 (s, 1H), 4.36 (q, J =7.3 Hz, 2H), 2.40 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H), 1.22 (q, J = 7.4 Hz, 2H), 0.57 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.6, 166.6, 145.7, 142.0, 138.6, 138.4, 136.6, 135.1, 131.0, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.9,

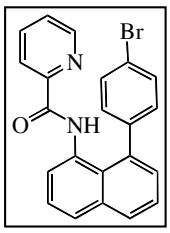
125.4, 61.0, 29.1, 21.2, 14.5, 9.0. FT-IR (neat, cm^{-1}) *v* 3710, 3680, 2956, 2844, 1716, 1662, 1266, 1055, 1033, 1014.



***N*-(8-(4-Methoxyphenyl)naphthalen-1-yl)picolinamide** (Table 4, Entry 1) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1 mmol, 247 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexanes/ethyl acetate 50/50) a beige powder (240 mg, 70 % yield) was obtained. R_f = 0.31 (hexane/ethyl acetate 50/50), mp=107–108 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.71 (s, 1H), 8.30–8.28 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.20–8.19 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.86 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.86 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.80–7.56 (m, 2H), 7.59–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.34–7.30 (m, 4H), 6.75–6.67 (m, 2H), 3.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 158.9, 150.1, 147.5, 137.4, 137.0, 135.5, 135.1, 133.1, 130.7, 130.4, 128.6, 126.4, 126.0, 125.8, 125.0, 122.3, 122.0, 113.6, 55.0 (signal for one carbon is missing). FT-IR (neat, cm^{-1}) *v* 1683, 1494, 1515, 1433, 1243, 1176, 1036, 824. Anal. Calcd for $C_{23}H_{18}N_2O_2$ (354.40 g/mol): C, 77.95; H, 5.12; N, 7.90; Found: C, 77.68; H, 5.09; N, 7.78.

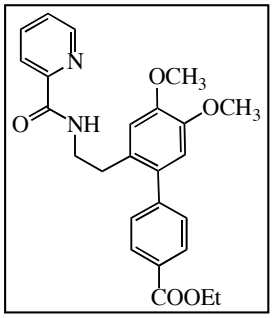


***N*-(8-(*p*-Tolyl)naphthalen-1-yl)picolinamide** (Table 4, Entry 2) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1 mmol, 251 mg), 1-iodo-4-methylbenzene (4 mmol, 872 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 h. After chromatography (hexane/ethyl acetate 70/30), pale yellow crystals 256 mg (70 % yield) was obtained. R_f=0.47 (hexanes/ethyl acetate 70/30), mp=123–124 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.61 (s, 1H), 8.23 (dd, J = 7.7, 1.5 Hz, 1H), 8.18–8.16 (m, 1H), 8.10–8.08 (m, 1H), 7.86 (dd, J = 8.4, 1.5 Hz, 1H), 7.80–7.74 (m, 2H), 7.58–7.54 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.24 (m, 4H), 6.96 (d, J = 7.7 Hz, 2H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 150.0, 147.4, 139.9, 137.8, 137.0, 136.6, 135.6, 133.0, 130.5, 129.2, 128.9, 128.6, 126.5, 126.0, 125.7, 125.1, 125.0, 122.6, 121.9, 21.2. FT-IR (neat, cm^{-1}) ν 1689, 1493, 1433, 814, 764, 751, 716, 697. Anal. Calcd for $C_{23}H_{18}N_2O$ (338.4 g/mol): C, 81.63; H, 5.36; N, 8.28; Found: C, 81.54; H, 5.35; N, 8.23.



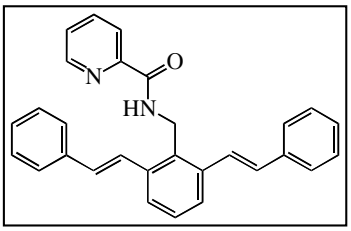
***N*-(8-(4-Bromophenyl)naphthalen-1-yl)picolinamide** (Table 3.4, Entry 3) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 251 mg), 1-bromo-4-iodobenzene (4 mmol, 1.13 g), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hr. After chromatography (hexane/ethyl acetate 80/20), light brown powder (342 mg, 84 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 80/20), mp=134–135 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.56 (s, 1H), 8.32–8.30 (m, 1H), 8.21–

8.20 (m, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.91 (dd, J = 8.3, 0.9 Hz, 1H), 7.84–7.80 (m, 2H), 7.61–7.57 (m, 1H), 7.50–7.46 (m, 1H), 7.42–7.39 (m, 1H), 7.32–7.28 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.0, 149.5, 147.9, 141.9, 137.2, 136.4, 135.6, 132.6, 131.3, 130.9, 130.5, 129.2, 129.7, 126.3, 126.2, 125.0, 123.2, 122.0, 121.4 (one missing peak). FT-IR (neat, cm^{-1}) v 1687, 1498,1433, 1009, 818, 765. Anal. Calcd for $C_{22}H_{15}BrN_2O$ (403.27 g/mol): C, 65.52; H, 3.75; N, 6.95; Found: C, 65.10; H, 3.54; N, 6.82.

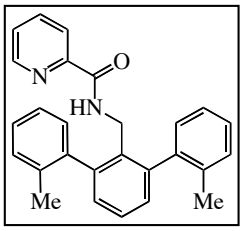


Ethyl 4',5'-dimethoxy-2'-(2-(picolinamido)ethyl)-[1,1'-biphenyl]-4-carboxylate (Scheme 3.14). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 265 mg), ethyl 4-iodobenzoate (4 mmol, 1.10 g), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 80/20), white powder (342 mg, 84 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 80/20), mp=133–134 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.49 (m, 1H), 8.14–8.11 (m, 1H), 8.06–8.03 (m, 2H), 7.97–7.95 (m, 1H), 7.84–7.80 (m, 1H), 7.42–7.37 (m, 3H), 6.86 (s, 1H). 6.72 (s, 1H), 4.34 (q, J=7.33 Hz), 3.87 (s, 3H), 3.86 (s, 3H), 3.52 (q, J=7.33 Hz, 2H), 2.85 (t, J=7.33 Hz, 2H), 1.41 (t, J=7.33 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 164.2, 149.9, 148.7, 148.0, 147.4, 146.2, 137.5, 133.6, 129.6, 129.1, 128.5, 126.3, 122.3, 113.1, 112.7, 61,1, 56.1, 56.0, 40.6, 32.6, 14.5 (signal for one carbon is missing). FT-IR (neat, cm^{-1}) v 3364, 1706, 1666, 1520, 1502, 1440, 1272, 1237, 1212, 1139, 1097, 1032.

Anal. calcd for $C_{25}H_{26}N_2O_5$ (434.48 g/mol): C, 69.11; H, 6.03; N, 6.45; Found: C, 69.08; H, 5.95; N, 6.44.

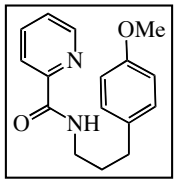


***N*-(2,6-Di((*E*)-styryl)benzyl)picolinamide** (Scheme 3.15). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-cyclohexylpicolinamide (1 mmol, 194 mg), (*E*)-(2-iodovinyl)benzene (4 mmol, 0.922 g), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 h. After chromatography (hexane/ethyl acetate 70/30), tan needles (269 mg, 86 % yield) were obtained. R_f = 0.35 (hexanes/ethyl acetate 70/30), mp=145–146 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.41 (m, 1H), 8.23–8.21 (m, 1H), 8.14–8.12 (m, 1H), 7.82–7.78 (m, 1H), 7.61–7.53 (m, 8H), 7.40–7.34 (m, 6H), 7.27–7.24 (m, 2H), 7.02 (d, *J*=16.03 Hz, 2H), 4.98 (d, *J*=5.50 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 149.8, 148.1, 138.3, 137.4, 137.3, 132.5, 132.4, 128.7, 128.5, 127.9, 126.9, 126.2, 126.0, 125.9, 122.4, 37.4. FT-IR (neat, cm^{-1}) *v* 3395, 1677, 1515, 964. Anal. calcd for $C_{29}H_{24}N_2O$ (416.51g/mol): C, 83.63; H, 5.81; N, 6.73; Found: C, 83.89; H, 5.70; N, 6.57.

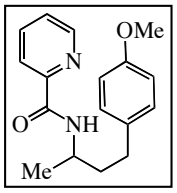


***N*-((2,2''-Dimethyl-[1,1':3',1''-terphenyl]-2'-yl)methyl)picolinamide.** A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1 mmol, 224 mg), 2-iodotoluene (4 mmol, 872 mg), CsOAc (4 mmol,

794 mg) and *tert*-amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 h. After cooling an aliquot of the reaction mixture was diluted with ethyl acetate and passed though silica plug. GC-MS analysis indicated that no product was formed.

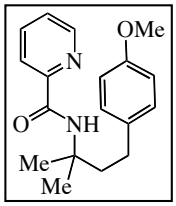


***N*-(3-(4-Methoxyphenyl)propyl)picolinamide** (Table 3.5, Entry 1) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-propylpicolinamide (1 mmol, 199 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), yellowish oil (168 mg, 56 % yield) was obtained. R_f = 0.19 (hexanes/ethyl acetate 70/30). This compound is known.[7] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, *J*=4.58 Hz, 1H), 8.18 (d, *J*=8.02 Hz, 1H), 8.09 (*br* s, 1H), 7.82–7.80 (m, 1H), 7.40–7.38 (m, 1H), 7.11 (d, *J*=8.02 Hz, 2H), 6.81 (d, *J*=8.02 Hz, 2H), 3.76 (s, 3H), 3.50–3.46 (m, 2H), 2.68–2.64 (m, 2H), 1.97–1.94 (m, 2H).

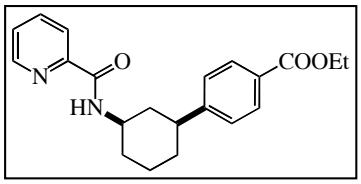


***N*-(4-(4-Methoxyphenyl)butan-2-yl)picolinamide** (Table 5, Entry 2) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 221 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), K_2CO_3 (4 mmol, 794 mg) and *tert*-amyl alcohol (2.0 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), pale yellow oil (255 mg, 75 % yield) was obtained. R_f = 0.27 (hexanes/ethyl acetate 70/30). This compound is known.[7] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49–8.47 (m, 1H), 8.17–8.16 (m, 1H), 7.92 (*br* d, *J*=8.70 Hz, 1H), 7.79–7.75 (m, 1H), 7.36–7.33 (m, 1H), 7.09–7.05 (m, 2H), 6.78–6.75

(m, 2H), 4.25–4.15 (m, 1H), 3.70 (s, 3H), 2.61 (t, *J*=8.24 Hz, 2H), 1.91–1.75 (m, 1H), 1.25 (d, *J*=6.87 Hz, 3H).

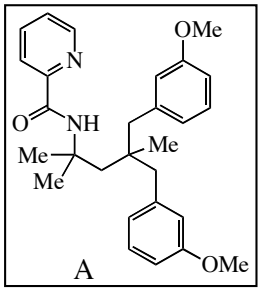


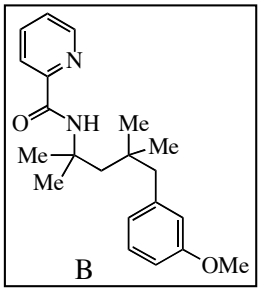
N-(4-(4-Methoxyphenyl)-2-methylbutan-2-yl)picolinamide (Table 3.5, Entry 3) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 198 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), pale yellow oil (278 mg, 91 % yield) was obtained. R_f = 0.26 (hexanes/ethyl acetate 70/30). 1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.49 (m, 1H), 8.17–8.15 (m, 1H), 8.00 (*br* s, 1H), 7.82–7.78 (m, 1H), 7.39–7.36 (m, 1H), 7.12–7.09 (m, 2H), 6.80–6.76 (m, 2H), 3.73 (s, 3H), 2.61–2.56 (m, 2H), 2.16–2.12 (m, 2H), 1.50 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 157.8, 150.7, 147.9, 137.4, 134.4, 129.4, 126.0, 121.8, 113.8, 55.3, 53.5, 42.4, 29.9, 27.2. FT-IR (neat, cm^{-1}) *v* 2963, 1675, 1510, 1464, 1247, 1178, 1033. Anal. Calcd for $C_{18}H_{22}N_2O_2$ (298.38 g/mol): C, 72.46; H, 7.43; N, 9.39; Found: C, 72.15; H, 7.31; N, 9.37.



Ethyl 4-(3-(picolinamido)cyclohexyl)benzoate (Table 3.5, Entry 4) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-cyclohexylpicolinamide (1 mmol, 194 mg), ethyl 4-iodobenzoate (4 mmol, 1.10 g), CsOAc (4 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 hr. After chromatography (hexane/ethyl acetate 70/30), light

yellow powder (269 mg, 86 % yield) was obtained. R_f=0.35 (hexanes/ethyl acetate 70/30), mp=117–118 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45–8.43 (m, 1H), 8.13–8.11 (m, 1H), 7.97 (*br* d, *J*=8.70 Hz, 1H), 7.91 (d, *J*=8.24 Hz, 2H), 7.76–7.72 (m, 1H), 7.34–7.30 (m, 1H), 7.20 (d, *J*=8.24 Hz, 2H), 4.27 (q, *J*=6.87 Hz, 2H), 4.12–4.02 (m, 1H), 2.75–2.67 (m, 1H), 2.20 (d, *J*=12.36 Hz, 1H), 2.07 (d, *J*=12.36 Hz, 1H), 1.91–1.80 (m, 2H), 1.57–1.26 (m. 7H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.7, 163.5, 151.4, 150.0, 148.1, 137.5, 129.8, 128.5, 126.9, 126.2, 122.3, 60.9, 48.7, 43.3, 40.4, 33.1, 32.7, 25.2, 14.4. FT-IR (neat, cm^{-1}) *v* 3371, 1713, 1656, 1519, 1276, 1110. Anal. Calcd for $C_{21}H_{24}N_2O$ (352.43 g/mol): C, 71.57; H, 6.86; N, 7.95; Found: C, 71.31; H, 6.69; N, 7.73.





***N*-(4-(3-methoxybenzyl)-5-(3-methoxy-phenyl)-2,4-dimethylpentan-2-yl)picolina-mide** (**A**) and ***N*-(5-(3-methoxyphenyl)-2,4,4-trimethylpentan-2-yl)picolinamide (B)** (Table 3.5, Entry 5) A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1 mmol, 245 mg), 1-iodo-4-methoxybenzene (4 mmol, 936 mg), K_2CO_3 (6 mmol, 794 mg) and *tert*-amyl alcohol (0.5 mL). The resulting suspension was stirred at 140 °C for 24 h. After chromatography (hexane/ethyl acetate 70/30), three products were obtained.

Product **A** was obtained as a light yellow oil (138 mg, 29 % yield). R_f = 0.69 (hexanes/ethyl acetate 70/30), ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49 (m, 1H), 8.17–8.15 (m, 2H), 7.82–7.79 (m, 1H), 7.38–7.35 (m, 1H), 7.17–7.14 (m, 2H), 6.76–6.72 (m, 4H), 6.68–6.67 (m, 2H), 3.76 (s, 6H), 2.83 (d, *J*=13.0 Hz, 2H), 2.60 (d, *J*=13.0, 2H), 2.10 (s, 2H), 1.56 (s, 6H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 159.1, 150.8, 147.9, 140.5, 137.5, 134.4, 128.6, 125.9, 123.7, 121.7, 116.9, 111.3, 55.2, 54.7, 48.3, 48.0, 39.0, 29.9, 24.8. FT-IR (neat, cm^{-1}) *v* 2955, 1679, 1582, 1521, 1488, 1263, 1154, 1043. Anal. Calcd for $C_{28}H_{34}N_2O$ (446.58 g/mol): C, 75.31; H, 7.67; N, 6.27; Found: C, 74.96; H, 7.67; N, 6.22.

Product **B** is was obtained as a colorless oil (46 mg, 13 %). R_f = 0.64 (hexane/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.49 (m, 1H), 8.18–8.16 (m, 1H), 8.14 (*br* s, 1H), 7.83–7.79 (m, 1H), 7.38–7.35 (m, 1H), 7.17–7.14 (m, 1H), 6.75–6.71 (m, 2H), 6.68–6.72 (m, 1H), 3.77 (s, 3H), 2.58 (s, 2H), 1.97 (s, 2H), 1.57 (s, 6H), 1.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.2, 159.0, 150.8, 147.9, 140.62, 137.4, 128.5, 125.9, 123.5, 121.7, 116.9, 111.1, 55.2, 54.7, 51.2, 51.1, 35.5, 29.6, 27.8. FT-IR (neat, cm^{-1}) *v* 2916, 1679, 1583, 1520, 1488, 1463, 1264, 1045. Anal. Calcd for $C_{21}H_{28}N_2O_2$ (340.46 g/mol): C, 74.08; H, 8.29; N, 8.23; Found: C, 73.79; H, 8.28; N, 8.11.

E. Alkylation of sp^2 and sp^3 C–H bonds

1. Optimization of the solvent

A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-phenylethyl)picolinamide. (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg) and K_3PO_4 (2mmol, 424 mg) The test solvent (0.50 mL) was added to this mixture (Table 1). The resulting suspension was stirred in an oil bath at the 140 °C. After 24 h, the reaction mixture was cooled, and diluted with 4 mL dichloromethane and analysed by GC-MS. See Table 3.6 for the results.

2. Optimization of the additive

A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-phenylethyl)picolinamide. (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg) and Na_3PO_4 (2 mmol, 326 mg). The additive (10 mol %) was added to this mixture (Table 1). The resulting suspension was stirred in an oil bath at 120 °C. After 24 h, the reaction mixture was cooled, and diluted with 4 mL dichloromethane and analysed by GC-MS. See Table 3.7 for the results.

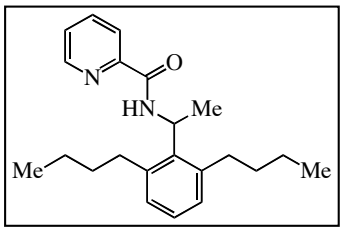
3. Optimization of the base

A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg), $CuBr_2$ (10 mol %, 11 mg) *N*-(1-phenylethyl)picolinamide. (0.5 mmol, 134 mg), iodobutane (2 mmol, 367 mg), base (2 mmol, 424 mg), and water (0.30 mL). The resulting suspension was stirred in an oil bath at the 120 °C. After 24 h, the reaction mixture was cooled, and

diluted with 4 mL dichloromethane and analysed by GC-MS. See Table 3.8 for the results.

4. General procedure for the alkylation of picolinamides

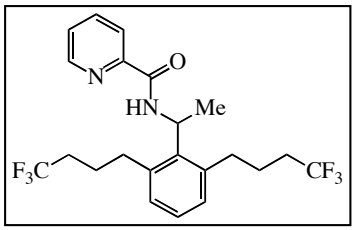
A Kontes flask or a 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol %, 22 mg), $CuBr_2$ (20 mol %, 44 mg), picolinamide (1 mmol), aryl iodide (4–6 mmol), K_2CO_3 (4 mmol, 794 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. The reaction mixture was diluted with dichloromethane (4 mL) and filtered through a pad of cotton. The residue was then washed with dichloromethane (4 mL X 2). The extract and the washings were combined, concentrated, and then loaded in a chromatography column with hexanes/ethyl acetate mixture as eluent. The solvent from the fractions containing the desired compound was evaporated to give pure product.



***N*-(1-(2,6-Dibutylphenyl)ethyl)picolinamide** (Table 3.9, Entry 1). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 11 mg), $CuBr_2$ (20 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 239 mg), *n*-butyl iodide (4 mmol, 736 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (336 mg, 99 % yield) was obtained. R_f = 0.60 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (*br* d, *J*=7.79 Hz, 1H), 8.52–8.5- (m, 1H), 8.19–8.17 (m, 1H), 7.80 (td, *J*=7.51, 1.37 Hz, 1H), 7.40–7.36 (m, 1H), 7.14–7.10 (m, 2H), 7.06–7.04 (m, 1H), 5.76 (q, *J*=7.33, 1H), 2.98–2.90 (m, 2H), 2.80–

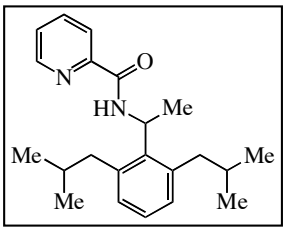
2.73 (m, 2H), 1.70–1.60 (m, 7H), 1.52–1.43 (m, 4H), 0.93 (t, J=7.33 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 150.1, 148.0, 141.0, 138.3, 137.4, 128.6, 127.1, 126.1, 122.2, 45.1, 34.5, 34.2, 23.2, 22.2, 14.1. FT-IR (neat, cm^{-1}) ν 2956, 1678, 1511, 1432, 1462,1374, 1206, 998. Anal. Calcd for $C_{22}H_{30}N_2O$ (338.49g/mol): C, 78.06; H, 8.93; N, 8.28; Found: C, 77.84; H, 8.92; N, 8.19.

When *n*-butyl bromide (4 mmol, 548 mg) was used as an alkylating agent, no product was detected in the GC-MS.

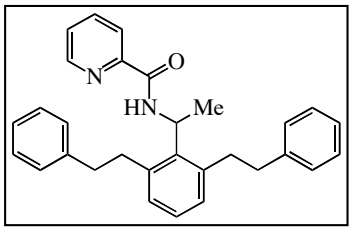


***N*-(1-(2,6-Bis(4,4,4-trifluorobutyl)phenyl)ethyl)picolinamide** (Table 3.9, Entry 2). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 229 mg), 1,1,1-trifluoro-4-iodobutane (4 mmol, 948 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (356 mg, 79 % yield) was obtained. R_f = 0.52 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.51 (m, 2H), 8.17–8.14 (m, 1H), 7.84–7.80 (m, 1H), 7.42–7.39 (m, 1H), 7.16 (t, J=7.79 Hz, 1H), 7.06 (d, J=7.79 Hz, 1H), 5.69 (q, J=7.33 Hz, 3.10–3.01 (m, 1H), 2.88–2.80 (m, 2H), 2.29–2.16 (m, 4H), 1.95–1.88 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.7, 148.1, 139.3, 138.8, 137.6, 129.1, 127.5, 127.2 (q, J=276.1 Hz), 126.4, 122.2, 45.1, 33.8 (q, J= 28.8 Hz), 33.1, 24.1, 22.1. ^{19} F NMR (376 MHz, $CDCl_3$, ppm) δ 66.1. FT-IR (neat, cm^{-1}) ν 1678, 1512, 1465, 1434, 1388, 1251, 1132, 1005. Anal. Calcd for

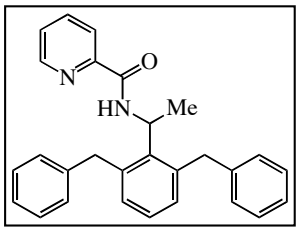
$C_{22}H_{24}F_6N_2O$ (446.43g/mol): C, 59.19; H, 5.42; N, 6.27; Found: C, 59.28; H, 5.48; N, 6.24.



***N*-(1-(2,6-Diisobutylphenyl)ethyl)picolinamide** (Table 3.9, Entry 3). A 10-mL Kontes flask was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 239 mg), 1-iodo-2-methylpropane (6 mmol, 1.10 g), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (301 mg, 84 % yield) was obtained. R_f = 0.39 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.61 (*br* d, *J*=8.02 Hz, 1H), 8.52–8.51 (m, 1H), 8.19–8.17 (m, 1H), 7.79 (td, *J*=7.45, 1.72 Hz, 1H), 7.39–7.36 (m, 1H), 7.12–7.10 (m, 1H), 7.05–7.04 (m, 2H), 5.76 (q, *J*=8.02 Hz, 1H), 2.91 (dd, *J*=13.75, 6.87 Hz, 2H), 2.62 (dd, *J*=13.75, 5.73 Hz, 2H), 2.04 (m, 2H), 1.67 (d, *J*=6.87 Hz, 3H), 1.00 (d, *J*=6.87 Hz, 6H), 0.96 (d, *J*= 6.87 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 150.1, 148.0, 139.7, 139.2, 137.4, 129.3, 126.4, 126.1, 122.2, 45.2, 43.3, 29.7, 23.0, 22.6, 22.3. FT-IR (neat, cm^{-1}) ν 2954, 1677, 1509, 1464, 1432, 1383, 998. Anal. Calcd for $C_{22}H_{30}N_2O$ (338.49 g/mol): C, 78.06; H, 8.93; N, 8.28; Found: C, 78.03; H, 9.11; N, 8.37.

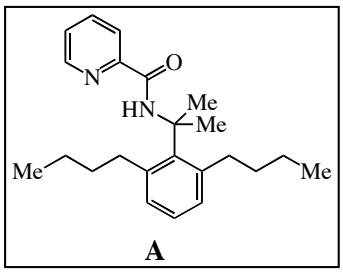


***N*-(1-(2,6-Diphenethylphenyl)ethyl)picolinamide** (Table 3.9, Entry 4). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 228 mg), (2-iodoethyl)benzene (4 mmol, 984 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (375 mg, 86 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.68 (*br* d, *J*=7.79 Hz, 1H), 8.45–8.43 (m, 1H), 8.20–8.18 (m, 1H), 7.77 (td, *J*=7.79, 1.83 Hz, 1H), 7.36–7.27 (m, 9H), 7.22–7.13 (m, 5H), 5.88 (q, *J*=7.79 Hz, 1H), 3.31–2.99 (m, 6H), 1.68 (d, *J*=6.87 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.6, 150.0, 148.2, 142.1, 140.2, 138.8, 137.6, 129.2, 128.7, 128.6, 127.5, 126.4, 126.2, 122.4, 45.4, 38.5, 36.6, 22.2. FT-IR (neat, cm^{-1}) *v* 1676, 1509, 1453, 1432, 997. Anal. Calcd for $C_{30}H_{30}N_2O$ (434.57 g/mol): C, 82.91; H, 6.96; N, 6.45; Found: C, 82.71; H, 7.22; N, 6.41.

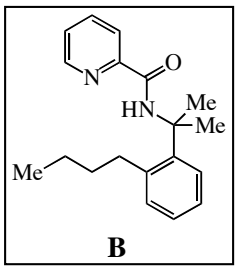


***N*-(1-(2,6-Dibenzylphenyl)ethyl)picolinamide** (Table 3.9, Entry 5). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(1-phenylethyl)picolinamide (1 mmol, 228mg), benzyl iodide (4 mmol, 872 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (349 mg, 85 % yield) was obtained. R_f = 0.43 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C, ppm) δ 8.34 (*br* d, *J*=6.87 Hz, 1H), 8.30–8.28

(m, 1H), 8.04 (d, *J*=7.45 Hz, 1H), 7.71 (td, *J*= 7.45, 1.72 Hz, 1H), 7.28–7.26 (m, 1H), 7.19–7.03 (m, 13H), 5.72 (q, *J*=7.45 Hz, 1H), 4.45 (d, *J*=16.04 Hz, 2H), 4.21 (d, *J*=16.04 Hz, 2H), 1.24 (d, *J*=7.45 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.6, 149.8, 147.9, 141.2, 139.9, 138.9 (*br*), 137.1, 130.7 (*br*), 129.0, 128.4, 127.3, 125.9, 125.8, 121.9, 45.6, 40.1 (*br*), 20.6. FT-IR (neat, cm^{-1}) *v* 3381, 1676, 1497, 1462, 1431, 998. Anal. Calcd for $C_{28}H_{26}N_2O$ (406.52 g/mol): C, 82.73; H, 6.45; N, 6.89; Found: C, 82.54; H, 6.44; N, 6.79.



A



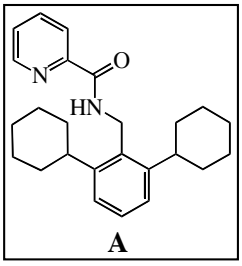
B

***N*-(2-(2,6-Dibutylphenyl)propan-2-yl)picolinamide** (**A**) and ***N*-(2-(2-Butylphenyl)-propan-2-yl)picolinamide** (**B**) (Table 3.10, Entry 1). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(2-phenylpropan-2-yl)picolinamide (1 mmol, 224 mg), iodobutane (6 mmol, 1.10 g), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), two products were obtained.

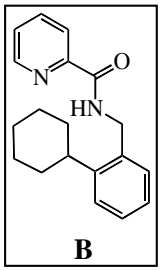
Product **A** was obtained as a light yellow oil (178 mg, 54 % yield). R_f = 0.44 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54 (*br* s, 1H), 8.51–8.49 (m, 1H), 8.15 (d, *J*=7.79 Hz, 1H), 7.80 (td, *J*=9.16, 1.37 Hz, 1H), 7.40–7.36 (m, 1H), 7.10–7.02 (m, 3H), 2.90–2.86 (m, 4H), 2.08 (s, 6H), 1.56–1.48 (m, 4H), 1.29–1.20 (m, 4H), 0.74 (t, *J*=7.33 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1, 150.9,

147.8, 141.9, 141.5, 137.4, 130.5, 126.5, 125.9, 121.8, 59.1, 36.5, 35.5, 31.0, 23.3, 14.0. FT-IR (neat, cm^{-1}) ν 2956, 1678, 1510, 1463, 998. Anal. Calcd for $C_{23}H_{32}N_2O$ (352.51 g/mol): C, 78.36; H, 9.15; N, 7.95; Found: C, 78.12; H, 9.31; N, 7.83.

Product **B** was obtained as a light yellow oil (38 mg, 14 % yield) was obtained. R_f = 0.31 (hexanes/ethyl acetate 70/30). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.47 (m, 2H), 8.14–8.12 (m, 1H), 7,82–7.79 (m, 1H), 7.50–7.48 (m, 1H), 7.41–7.37 (m, 1H), 7.23–7.15 (m, 3H), 2.82–2.78 (m, 2H), 1.92 (s, 6H), 1.47–1.40 (m, 2H), 1.18–1.12 (m, 2H), 0.61 (t, J=7.33 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.8, 150.7, 147.8, 143.2, 140.8, 137.4, 131.6, 127.4, 127.2, 126.0, 125.7, 121.8, 56.3, 34.8, 33.8, 29.0, 23.4, 13.9 (signal for one carbon is missing). FT-IR (neat, cm^{-1}) ν 2930, 1678, 1511, 1463, 1432, 998. Anal. Calcd for $C_{19}H_{24}N_2O$ (296.41 g/mol): C, 76.99; H, 8.16; N, 9.45; Found: C, 76.46; H, 8.09; N, 9.10.



A

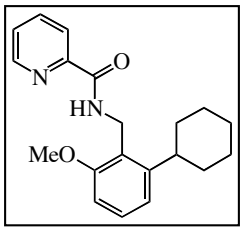


B

***N*-(2,6-Dicyclohexylbenzyl)picolinamide** (**A**) and ***N*-(2-yclohexylbenzyl)picolinamide** (**B**) (Table 3.10, Entry 2). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-benzylpicolinamide (1 mmol, 223 mg), iodocyclohexane (4 mmol, 840 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 $^{\circ}$C for 24 h. After chromatography (hexane/ethyl acetate 80/20), two products were obtained.

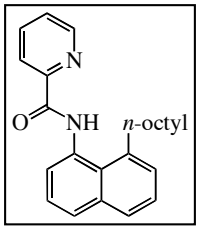
Product **A** was obtained as a light yellow oil (42 mg, 11 % yield) was obtained. R_f = 0.31 (hexanes/ethyl acetate 80/20). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.45–8.44 (m. 1H), 8.24 (d, *J*=7.8 Hz, 1H), 7.89–7.82 (m, 2H), 7.40–7.37 (m, 1H), 7.30–7.27 (m, 1H), 7.18–7.16 (m, 1H), 4.73 (d, *J*=4.6 Hz, 2H), 2.83–2.75 (m, 2H), 1.80–1.69 (m, 12H), 1.49–1.18 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 149.9, 148.7, 147.5, 137.4, 131.4, 128.3, 126.2, 124.2, 122.2, 40.5, 36.6, 35.0, 27.1, 26.3. FT-IR (neat, cm^{-1}) ν 2925, 2850, 1673, 1521, 1568, 1433, 1242, 999. Anal. Calcd for $C_{25}H_{32}N_2O$ (376.53 g/mol): C, 79.75; H, 8.57; N, 7.44; Found: C, 79.89; H, 8.21; N, 7.48.

Product **B** was obtained as a light yellow oil (62 mg, 20 % yield) was obtained. R_f = 0.50 (hexanes/ethyl acetate 80/20). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.50–8.48 (m, 1H), 8.25–8.19 (m, 2H), 7.86–7.82 (m, 1H), 7.42–7.38 (m, 1H), 7.33–7.30 (m, 1H), 7.19–7.15 (m, 1H), 4.71 (d, *J*=5.50 Hz, 2H), 2.81–2.74 (m, 1H), 1.81–1.70 (m, 5H), 1.49–1.19 (m, 5H. ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.9, 149.9, 148.2, 146.6, 137.4, 134.7, 129.3, 128.2, 126.6, 126.2, 126.0, 122.3, 41.5, 39.7, 34.5, 27.0, 26.3. FT-IR (neat, cm^{-1}) ν 2926, 2851, 1674, 1568, 1522, 1241, 999. Anal. Calcd for $C_{19}H_{22}N_2O$ (294.39 g/mol): C, 77.52; H, 7.53; N, 9.52; Found: C, 77.13; H, 7.67; N, 9.40.



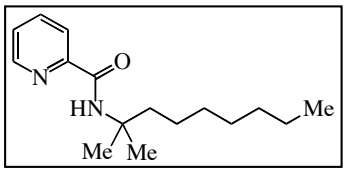
***N*-(2-Cyclohexyl-6-methoxybenzyl)picolinamide** (Table 3.11, Entry 3). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 22 mg), $CuBr_2$ (20 mol %, 44 mg), *N*-(2-methoxybenzyl)-picolinamide (1 mmol, 217 mg), iodocyclohexane (4 mmol, 840 mg), K_2CO_3 (4 mmol, 552 mg) and water (0.30 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 70/30), light yellow oil (47

mg, 14 % yield) was obtained. R_f = 0.39 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.49–8.47 (m, 1H), 8.23–8.20 (m, 1H), 7.81 (td, *J*=9.52, 2.00 Hz, 1H), 7.38–7.35 (m, 1H), 7.27–7.23 (m, 1H), 6.93–6.91 (m, 1H), 6.77–6.74 (m, 1H), 4.76 (d, *J*=5.49 Hz, 2H), 3.87 (s, 3H), 3.02–2.97 (m, 1H), 1.78–1.72 (m, 5H), 1.51–1.36 (m, 4H), 1.27–1.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 158.3, 150.4, 148.4, 148.1, 137.3, 128.7, 125.9, 123.5, 122.3, 118.8, 108.0, 55.7, 39.9, 34.6, 34.4, 27.0, 26.3. FT-IR (neat, cm^{-1}) *v* 2926, 1674, 1582, 1518, 1464, 1249, 1136, 1096, 999. Anal. Calcd for $C_{20}H_{24}N_2O_2$ (324.42 g/mol): C, 74.04; H, 7.46; N, 8.64; O, 9.86 Found: C, 73.76; H, 7.50; N, 8.49.



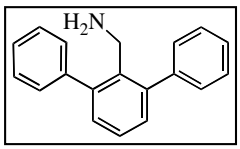
***N*-(8-Octylnaphthalen-1-yl)picolinamide** (Scheme 3.16). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol%, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-(naphthalen-1-yl)picolinamide (1 mmol, 217 mg), octyl iodide (4 mmol, 960 mg), CsOAc (3 mmol, 594 mg) and *tert*-amyl alcohol (0.50 mL). The resulting suspension was stirred at 140 °C for 24 hours. After chromatography (hexane/ethyl acetate 70/30), light yellow oil (153 mg, 49 % yield) was obtained. R_f = 0.33 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.56 (s, 1H), 8.64–8.62 (m, 1H), 8.39–8.36 (m, 1H), 8.02 (d, *J*=7.79 Hz, 1H), 7.89 (td, *J*=7.57, 1.59 Hz, 1H), 7.77–7.72 (m, 2H), 7.52–7.45 (m, 2H), 7.38–7.30 (m, 2H), 3.30–3.26 (m, 2H), 1.68–1.61 (m, 2H), 1.27–1.13 (m, 10H), 0.86 (t, *J*=7.33 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.5, 150.3, 148.1, 137.9, 137.8, 136.3, 132.7, 126.9, 128.0, 127.9, 127.5, 126.6, 125.6, 125.2, 122.8, 37.8, 32.9, 31.9, 29.8, 29.6, 29.4, 22.8, 14.3. FT-

IR (neat, cm^{-1}) *v* 2926, 1686, 1522, 1498, 1431, 1339, 999. Anal. Calcd for $C_{24}H_{28}N_2O$ (360.49 g/mol): C, 79.96; H, 7.83; N, 7.77; Found: C, 79.78; H, 7.93; N, 7.79.



***N*-(2-Methylnonan-2-yl)picolinamide** (Scheme 3.17). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (10 mol%, 11 mg), $CuBr_2$ (20 mol %, 22 mg), *N*-(2-methoxybenzyl)picolinamide (1 mmol, 217 mg), iodopentane (4 mmol, 792 mg), K_2CO_3 (4 mmol, 552 mg), pivalic acid (2 mmol, 202 mg) and *tert*-amyl alcohol (0.7 mL). The resulting suspension was stirred at 110 °C for 24 h. After chromatography (hexanes/ethyl acetate 80/20), colorless oil (67 mg, 27 % yield) was obtained. R_f = 0.31 (hexanes/ethyl acetate 80/20), ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.52 (m, 1H), 8.19–8.16 (m, 1H), 7.97 (*br* s, 1H), 7.83 (td, *J*=9.62, 1.83 Hz, 1H), 7.41–7.38 (m, 1H), 1.88–1.79 (m, 2H), 1.46 (s, 6H), 1.34–1.26 (m, 10H), 0.87 (t, *J*=6.87 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 150.9, 147.8, 137.4, 125.9, 121.7, 53.6, 40.7, 32.0, 30.1, 29.4, 26.9, 24.3, 22.7, 14.2. FT-IR (neat, cm^{-1}) *v* 2926, 1681, 1520, 1464, 1432, 1363, 1287, 998. Anal. Calcd for $C_{16}H_{26}N_2O$ (262.39 g/mol): C, 73.24; H, 9.99; N, 10.68; Found: C, 73.04; H, 10.04; N, 10.38.

F. Cleavage of the auxiliary[61]



[1,1':3',1''-Terphenyl]-2'-ylmethanamine (Scheme 3.18). *N*-([1,1':3',1''-terphe-nyl]-2'-ylmethyl)picolinamide (0.5 mmol, 182 mg), (0.5 mmol, 67 mg), *n*-butylamine (5 mmol, 0.5 mL) and toluene (1.5 mL) were added sequentially in a 2-dram vial inside glovebox. The mixture was shaken until the contents

dissolved. Anhydrous $AlCl_3$ (0.5 mmol, 67 mg) was then added to the mix. The vial was capped, taken outside the glovebox, heated and stirred at 90 ºC for 24 h. After the reaction is complete, 2 mL of water is added to the reaction mixture. The product was the extracted with ethyl acetate (5 X 3 mL). The organic layer was combined, concentrated and loaded in silica column (hexanes/ethyl acetate 60/40). The fractions containing the product was combined, concentrated and the solvent was evaporated to give white crystals (118 mg, 91 % yield). R_f = 0.12 (hexanes/ethyl acetate 60/40), mp=70–72 ºC ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.44–7.30 (m, 12 H), 7.23–7.22 (m, 1H), 3.71 (s, 2H), 1.01 (*br* s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.6, 141.8, 138.7, 129.8, 129.3, 128.4, 127.2, 126.5, 40.8. FT-IR (neat, cm^{-1}) ν 3060, 3031, 2937, 1603, 1580, 1498, 1454, 1443, 1185, 1157, 1074, 1031. Anal. Calcd for $C_{19}H_{17}N$ (259.34g/mol): C, 87.99; H, 6.61; N, 5.40; Found: C, 87.79; H, 6.70; N, 5.36.

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CHAPTER 4

Heterocycle Synthesis via Direct C-H/N-H Coupling

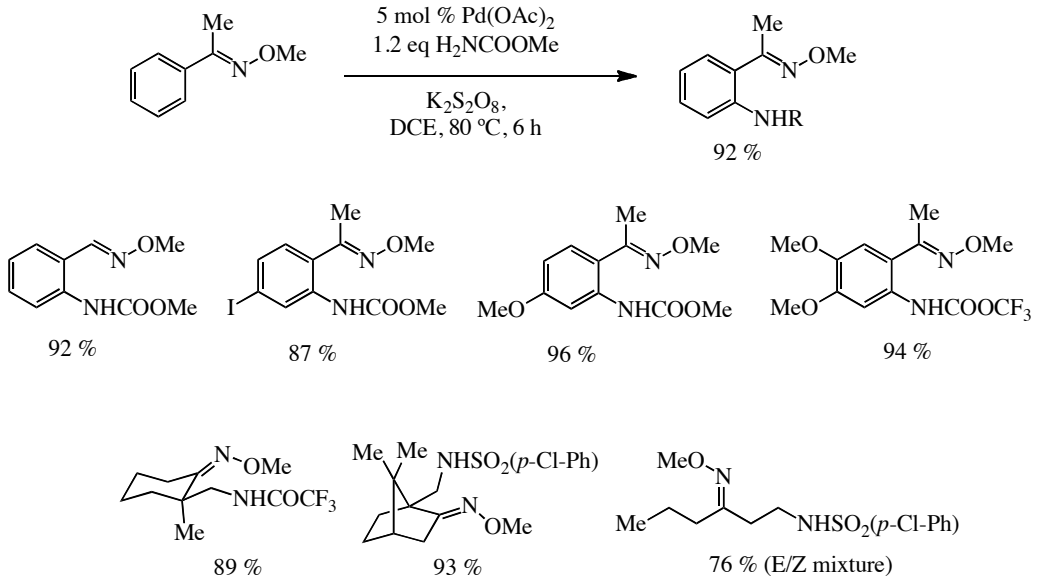
Transition-metal-catalyzed functionalization of carbon-hydrogen bonds is a topic of recent intense interest. During the last few years, significant advances have been made in conversion of C–H bonds to C–C and C–O functionalities.[1] Formation of C–N bond is also desirable since nitrogen-containing compounds are ubiquitous in drugs and agrochemicals. While there are established methods for the synthesis of amines, methods involving direct C–H/N–H coupling may provide shorter routes to target compounds.[2]

I. Mechanisms of C–H to C–N bond transformation

A. Nitrene insertion

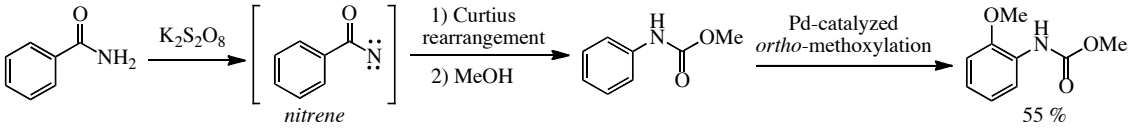
Nitrene insertion in C–H bonds was first developed in Rh catalysis.[3] Palladium complexes has been utilized as catalysts after the discovery of compatible nitrene precursors and oxidants. Methyl carbamate was used as nitrene precursor for the installation of amide on 2-arylpyridine and *O*-methyl oxime. The optimized reaction conditions use $Pd(OAc)_2$ (5 mol %), $K_2S_2O_8$ (5 eq), MgO (2 eq) in dichloroethane at 80 ºC. Sulfonamides can also be used as nitrene source. The *ortho*-amidated products were obtained in good yields (Scheme 4.1).[4] The method is also effective for sp^3 methyl C–H bond amidation.

Scheme 4.1. Pd-catalyzed amidation of *O*-methyloximes



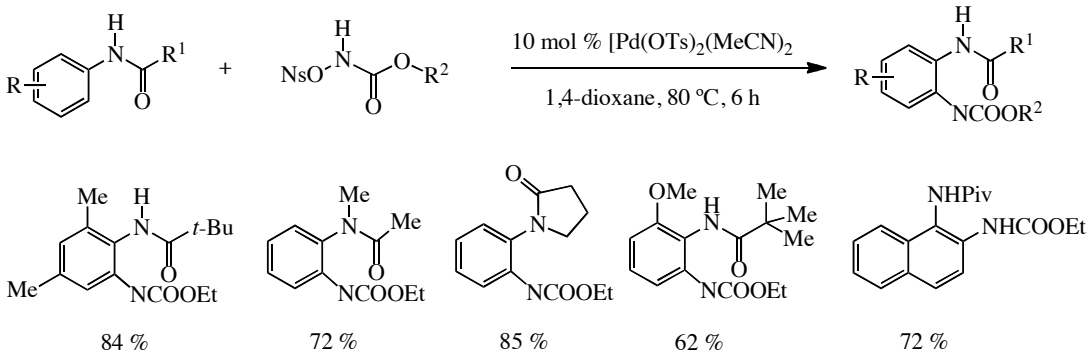
The involvement of nitrene in the reaction was established by subjecting benzamide to the optimized amidation condition in methanol (Scheme 4.2).[4] The only product obtained was methyl *N*-(2-methoxyphenyl)carbamate in 55 % yield. The carbamate formation was explained by formation of nitrene intermediate which underwent Curtius rearrangement to isocyanate. This is followed by nucleophilic attack of methanol resulting to methyl *N*-phenylcarbamate. Subsequent C–H activation and *ortho*-methoxylation affords methoxylated *N*-phenylcarbamate.

Scheme 4.2. Conversion of benzamide to methyl N-(2-methoxyphenyl)carbamate



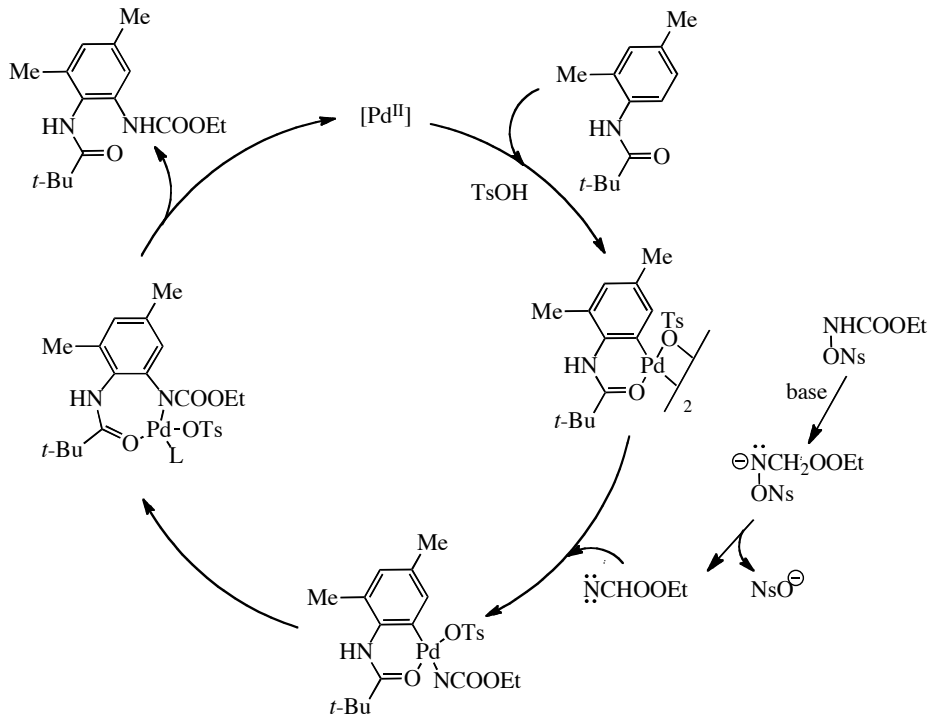
Method for catalytic C–H amidation of anilides by *N*-nosyloxycarbamates was developed for the synthesis of 2-aminoanilines (Scheme 4.3). Acetanilides, benzamides and pivalanilides are reactive. Electron-donating and electron-withdrawing groups are tolerated under the amidation conditions.

Scheme 4.3. Intermolecular *ortho*-C–H amidation of anilides by *N*-nosyloxycarbamate



The proposed mechanism of the reaction involves cyclopalladation of the substrate in the initial step (Scheme 4.4). Competition experiment between acetanilide and *ortho*-deuterated acetanilide exhibited primary kinetic isotope effect (k_H/k_D)=3.7, suggesting that cyclopalladation is the rate-limiting step. Arylsulfonyloxycarbamates are converted to nitrenes in the presence of base.[5] The cyclopalladated species undergo nitrene insertion to form the C–N bond, followed by dissociation of the Pd catalyst.

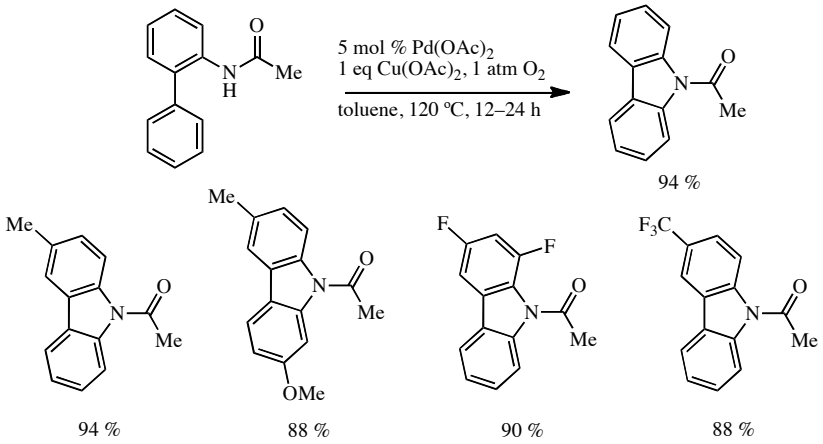
Scheme 4.4. Mechanism of amination of anilides via nitrene insertion



B. Direct amination

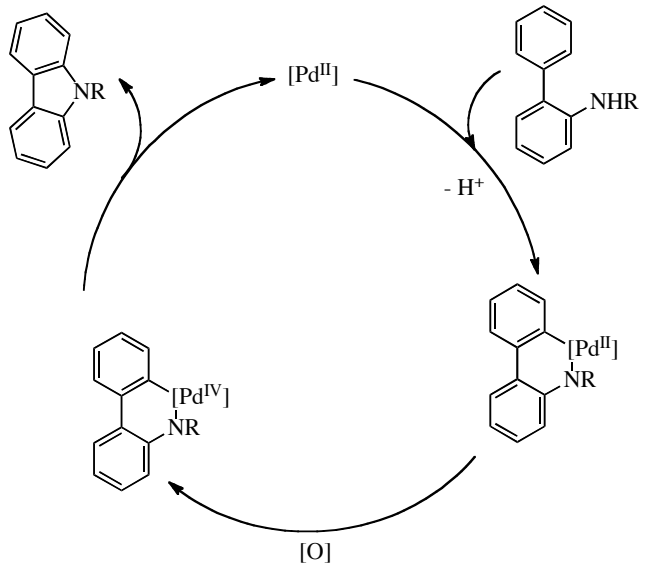
Direct coupling of C–H and N–H bonds to form C–N bond is an attractive synthethic transformation due to atom economy and simplicity. Early methods that were developed involve cyclization via sp^2 C–H/N–H coupling.[6] Carbazoles has been prepared via cyclization of 2-phenylacetanilides under Pd-catalyst and $O_2/Cu(OAc)_2$ oxidation system (Scheme 4.5).[7] Milder reaction conditions that employ oxone[8] and iodosobenzene diacetate[9] as oxidants have also been developed. Copper-catalyzed and transition-metal-free synthesis of carbazoles has been reported.[10]

Scheme 4.5. Cyclization of 2-phenylacetanilides



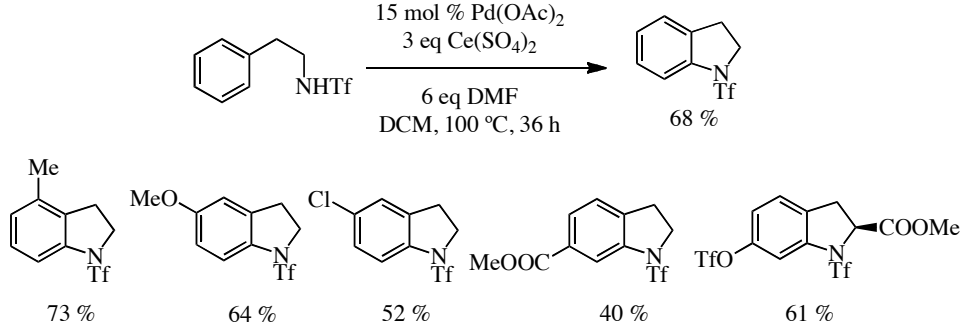
The proposed mechanism for the reaction involves a Pd(II)/(IV) catalytic cycle (Scheme 4.6).[9, 11] The nitrogen coordinates with the Pd(II) catalyst, followed by formation of six-membered palladacycle. This is followed by oxidation of the Pd(II) to Pd(IV). Reductive elimination affords the carbazole and regenerates catalyst.

Scheme 4.6. Mechanism for the formation of carbazole

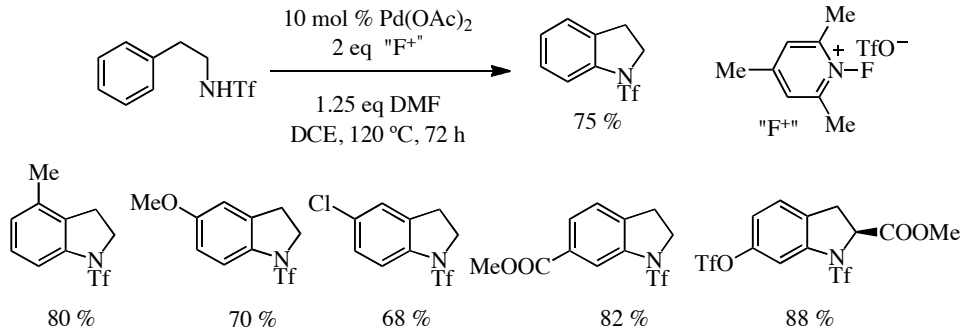


Cyclization of *N*-triflated phenethylamines to indolines were performed under palladium catalysis.[12] Single-electron oxidant $Ce(SO_4)_2$ was effective for the transformation (Scheme 4.7). Two-electron oxidants are also effective (Scheme 4.8).

Scheme 4.7. Palladium-catalyzed sp^2 C–H/N–H coupling using a single-electron oxidant

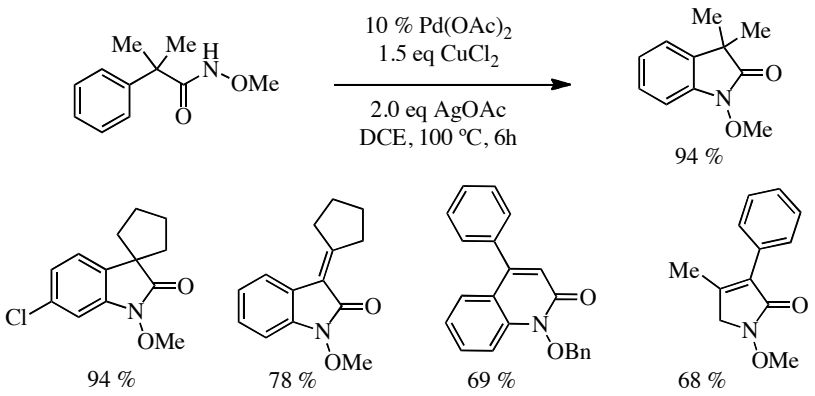


Scheme 4.8. Palladium-catalyzed sp^2 C–H/N–H coupling using a two-electron oxidant



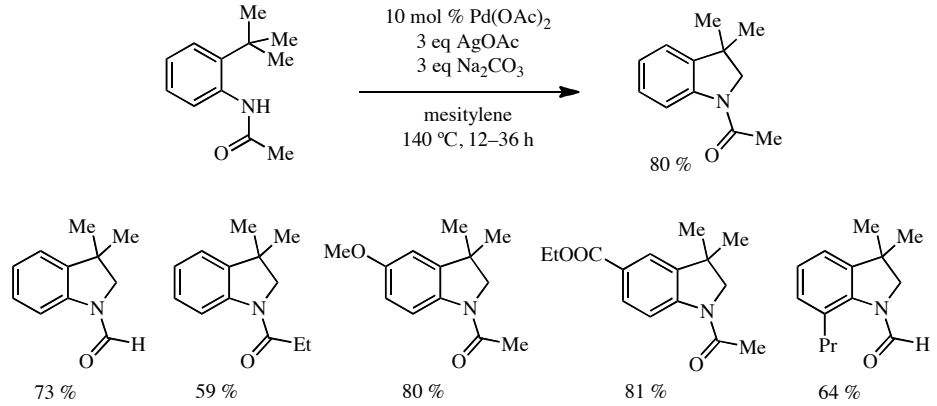
Only a few papers describe palladium-catalyzed amination of alkane C–H bonds. Most of the reports demonstrate functionalization of either sp^2 or activated (benzylic or allylic) sp^3 C–H bonds.[10, 13] For example, a method that is effective for both sp^2 and allylic sp^3 C–H bond functionalization was developed for lactam synthesis from *N*-methoxyhydroxamic acids (Scheme 4.9).[13f]

Scheme 4.9. Synthesis of lactams from *N*-methoxyhydroxamic acids



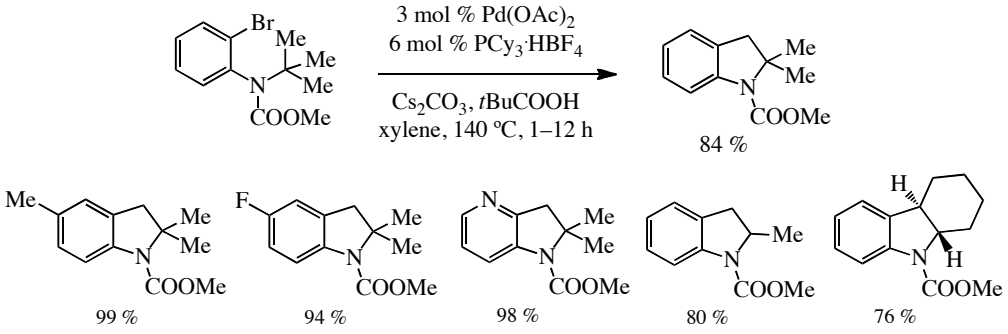
Functionalization of sp^3 C–H bonds of methyl groups adjacent to quartenary centers is described in most cases. A method was developed for intramolecular, palladium-catalyzed amination of unactivated sp^3 C–H bonds that results in the formation of indolines (Scheme 4.10).[14] A stoichiometric Ag(I) oxidant was employed and no examples of pyrrolidine formation were presented.

Scheme 4.10. Synthesis of indolines by activation of sp^3 C–H bond



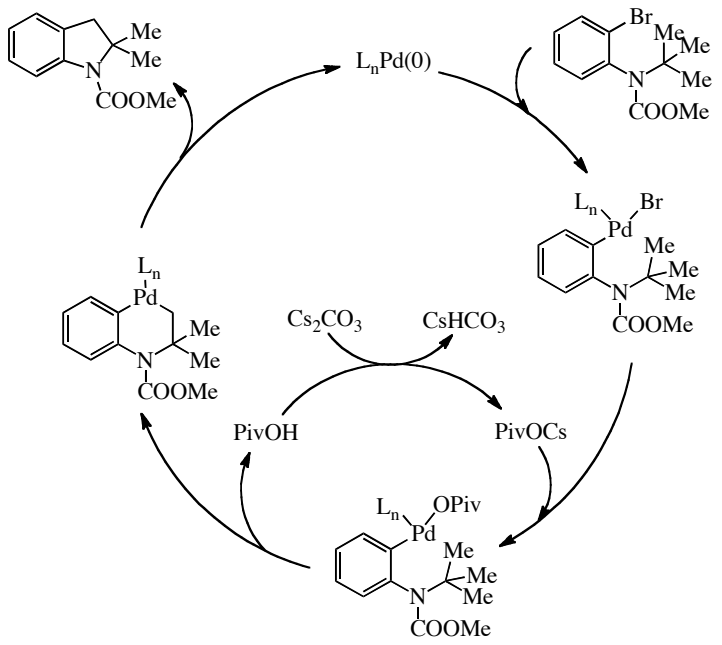
Palladium-catalyzed formation of indolines has been accomplished by C–Br/sp^3 C–H coupling.[15] In these cases, functionalization of C–H bonds that are not part of *t*-butyl groups is also possible (Scheme 4.11). The *ortho*-C(sp^2)–Br bond is used as an internal oxidant.

Scheme 4.11. Pd-catalyzed cyclization of *N*-alkylaniline derivatives



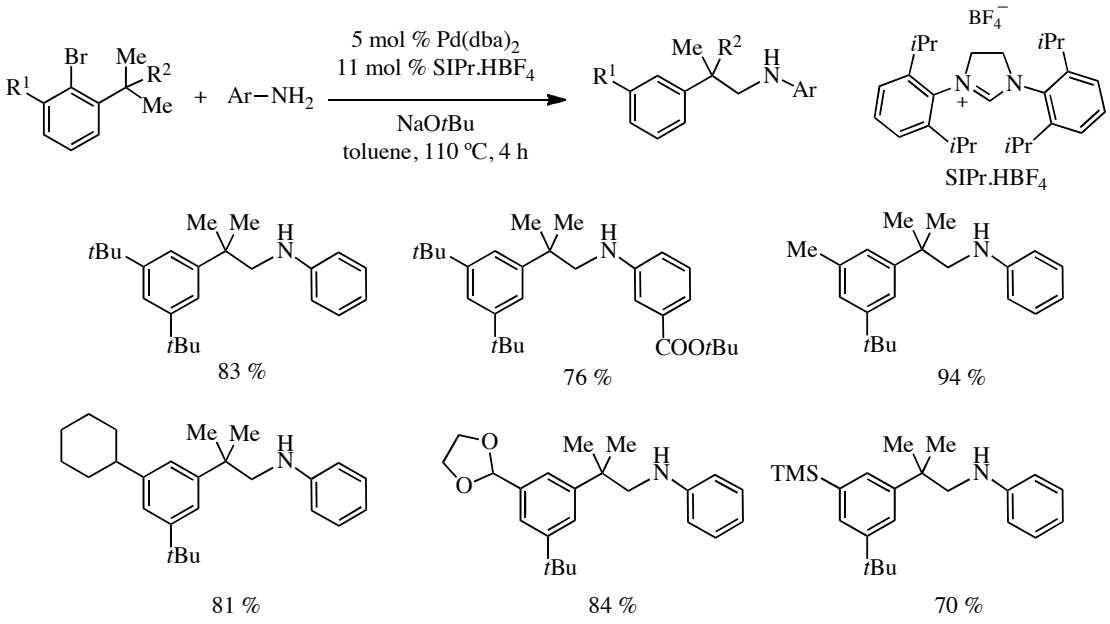
The reaction proceeds through Pd(0)/(II) cycle (Scheme 4.12).[15a] The first step is oxidative addition of aryl bromide to the Pd(0) species, followed by ligand exchange to give a cyclometallated Pd(II) species. The activation of sp^3 C–H bond involves pivalate, acting as a proton shuttle. Finally, reductive elimination affords the indoline product and regenerates the reactive Pd(0) species.

Scheme 4.12. Mechanism for Pd-catalyzed cyclization of *N*-alkylaniline derivatives



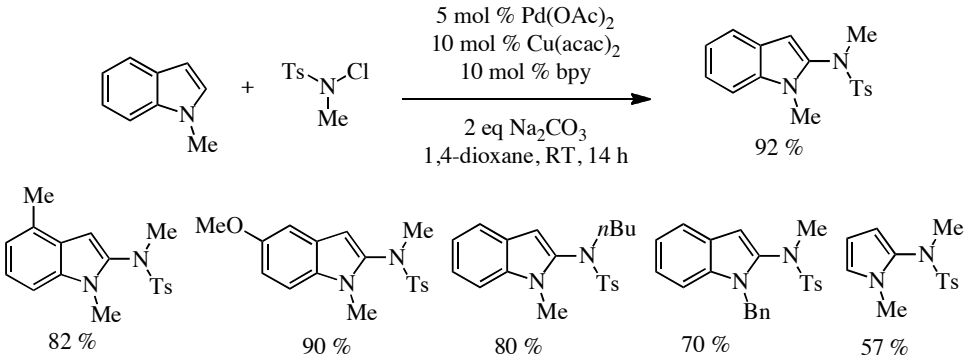
Palladium-catalyzed amination of 2-bromo-*t*-butylbenzenes by aryl amines was also performed (Scheme 4.13).[16] This is the earliest example of intermolecular sp^3 C–H bond activation leading to C–N bond formation.

Scheme 4.13. Amination of unactivated sp^3 C–H bonds with anilines



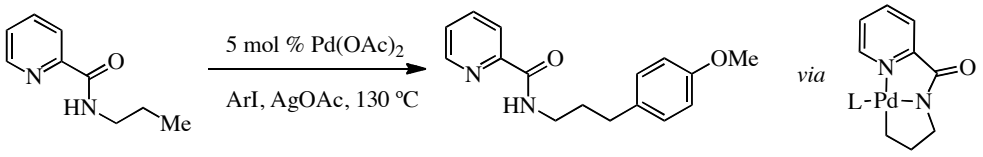
Intermolecular amination of indoles and pyrroles has been developed (Scheme 4.14).[17] The method allows regioselective C–H amination at the C–2 position.

Scheme 4.14. Intermolecular amination of indoles and pyrrole



Our group has developed a strategy to functionalize sp^3 C–H bonds of amines. Picolinamide was shown to be a good directing group for the arylation of amine derivatives when used in combination with catalytic $Pd(OAc)_2$, stoichiometric AgOAc base, and an aryl iodide coupling partner (Scheme 4.15).[18] The arylation proceeds via five membered double chelate that imparts reaction regioselectivity. Several other groups have used this strategy for synthetic purposes.[19] Subsequently, a number of conditions were investigated for arylation and alkylation and it was shown that simple inorganic bases could replace silver salts as shown in Chapter 3.

Scheme 4.15. Picolinic acid directing group



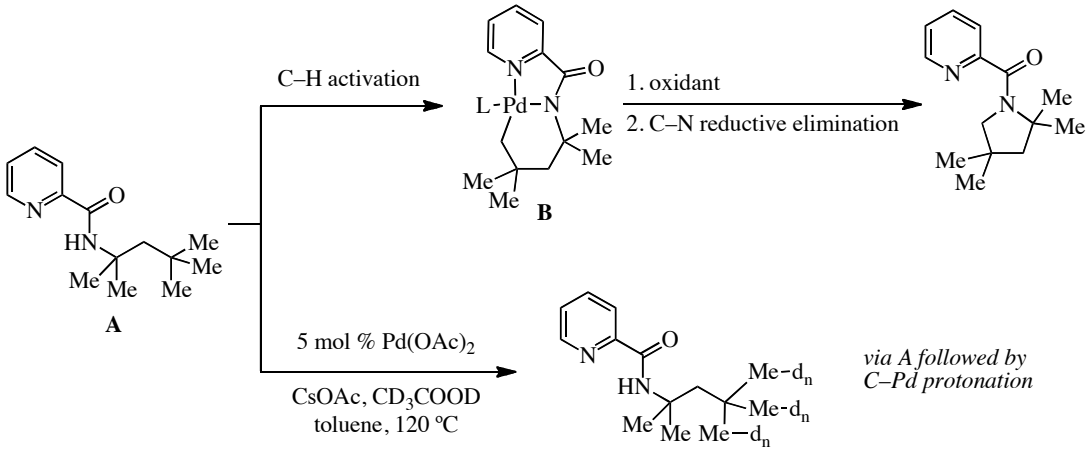
Picolinamide directing group has also been employed for the formation of C–O bonds by acetoxylation of sp^2 C–H bonds.[20] A corresponding method for the formation of C–N bond is also needed. Direct conversion of C–H bonds into C–N bonds would be a useful method and would provide a new disconnection for synthesis of nitrogen-containing compounds.

A general method for C–H/N–H bond coupling that could utilize both sp^2 and sp^3 C–H bonds has not yet been disclosed. A method for picolinamide auxiliary assisted, palladium-catalyzed pyrrolidine, indoline, and isoindoline synthesis by a C–H/N–H coupling is presented.

II. Results and discussions

Direct C–H/N–H coupling provides a shortcut for C–N bond formation. The C–H bond functionalization reactions proceeds via a double five-membered ring chelate (Scheme 4.16). If C–H activation in δ-positions would be possible, oxidation of the palladacycle **B** would form a high-valent palladium species, followed by C–N reductive elimination affording a pyrroline derivative. Treatment of **A** with 5% $Pd(OAc)_2$ in toluene/CD_3CO_2D at 120 °C showed 33% deuterium incorporation at the terminal methyl groups. No other C–H bonds were deuterated. Hence, C–H δ-activation is possible by employing a picolinic acid directing group.[14, 21]

Scheme 4.16. Activation of C–H bonds in δ-Positions



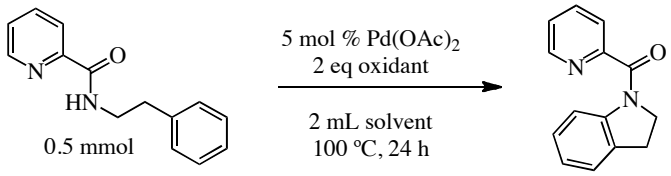
Subsequent reaction steps require oxidant capable of converting palladium to a higher oxidation state followed by reductive elimination that would afford cyclized product and regenerate the Pd(II) catalyst. In general, amination is preferable to acetoxylation which is observed if a six-membered chelate such as **B** cannot be formed. Choice of oxidant is crucial in this reaction.

A. Cyclization via direct C–N bond formation from sp^2 C–H/N–H bonds

1. Optimization of the solvent and oxidants

Several combinations of oxidants and solvents were investigated for the cyclization of *N*-phenylethylamine picolinamide. The best results were obtained by employing $PhI(OAc)_2$ in toluene (Table 4.1, entry 2).

Table 4.1. Optimization of the solvent and oxidant combination

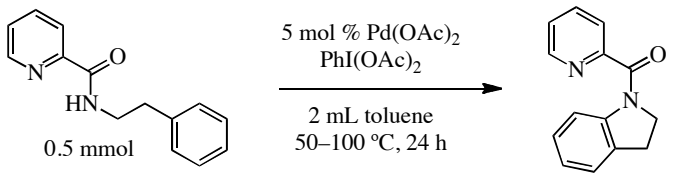


Entry	Oxidant	Solvent	% Yield (GC)
1	$PhI(OAc)_2$	dichloromethane	57
2	**$PhI(OAc)_2$**	**toluene**	**73**
3	$PhI(OAc)_2$	*t*-amyl alcohol	58
4	$PhI(OAc)_2$	*m*-xylene	67
5	$PhI(OAc)_2$	CH_3COOH	44
6	$PhI(OAc)_2$	CF_3COOH	3
7	$PhI(OAc)_2$	toluene/MeCN (9/1)	65
8	1,2-dichloroethane	dichloromethane	0
9	1,2-dichloroethane	toluene	0
10	1,2-dichloroethane	*t*-amyl alcohol	0
11	1,2-dichloroethane	*m*-xylene	0
12	1,2-dichloroethane	CH_3COOH	0
13	1,2-dichloroethane	CF_3COOH	trace
14	AgOAc	dichloromethane	0
15	AgOAc	toluene	0
16	AgOAc	*t*-amyl alcohol	0
17	AgOAc	*m*-xylene	0
18	AgOAc	CH_3COOH	0
19	AgOAc	CF_3COOH	0
20	$PhI(CF_3COO)_2$	toluene	0
21	$PhI(p\text{-nitrobenzoate})_2$	toluene	38

2. Optimization of the amount of oxidant and the temperature of the reaction

Different amounts of the $PhI(OAc)_2$ and reaction temperature were tested. The optimal conditions involve the use of 2.0 eq of the iodobenzene diacetate at 80 ºC (Table 4.2, entry 10).

Table 4.2. Optimization of the amount of oxidant and the temperature

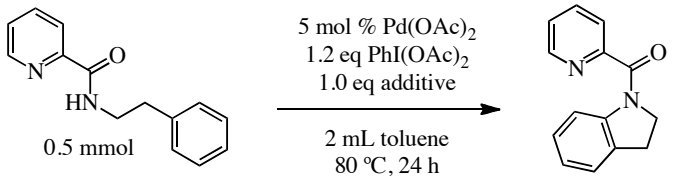


Entry	$PhI(OAc)_2$ (eq)	Temp (°C)	% Yield
01	1.2	50	68
02	1.2	60	74
03	1.2	70	77
04	1.2	80	78
05	1.2	90	64
06	1.2	100	66
07	1.6	100	63
08	2.0	100	72
09	2.0	90	68
10	**2.0**	**80**	**82**
11	2.0	70	77
12	2.0	60	73
13	3.0	80	65
14	1.5	80	74
15	1.1	80	54

3. Attempted yield enhancement using different additives

Different additives were tested for the possible enhancement of yield for the cyclization. Among the additives tested, nothing was found to increase the yield of the products (Table 4.3).

Table 4.3. Additives tested for the attempted enhancement of yields

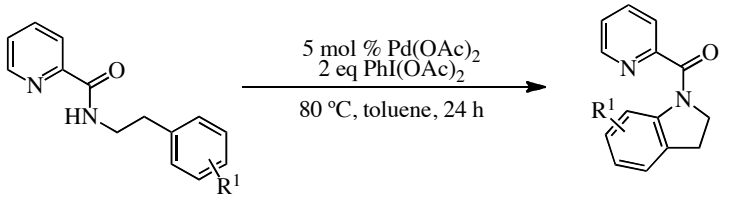


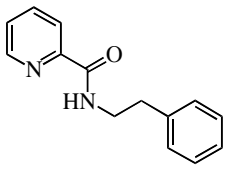
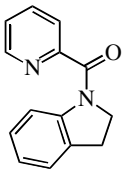
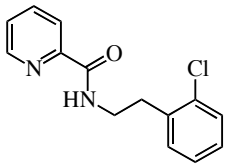
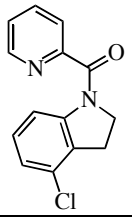
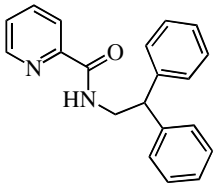
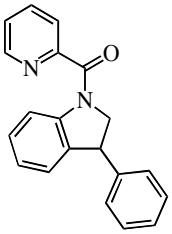
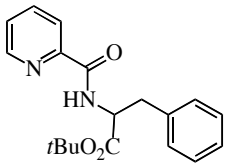
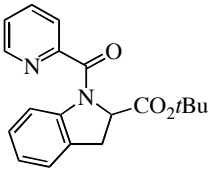
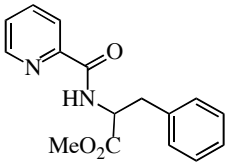
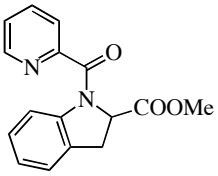
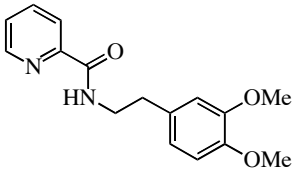
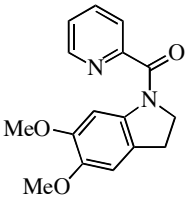
Entry	Additive	% Yield (GC)
01	NaOAc	63
02	K_2CO_3	20
03	CsOAc	31
04	K_3PO_4	46
05	KPivalate	28
06	Pivalic acid	65
07	DMF	53
08	CH_3COOH	58
09	CF_3COOH	4
10	$CuBr_2$	trace
11	$Cu(OAc)_2$	4
12	LiOTf	6
13	**No additive**	**78**

4. Coupling of sp^2 C–H/N–H bonds

Cyclization results are presented in Table 4.4. Direct sp^2 C–H/N–H coupling is possible, generating indolines in fair to good yields (entries 1-5). Chloro substitution on aromatic ring is tolerated (entry 2), as is ester on indoline (entry 3). 2,2-Diphenylethylamine picolinamide is cyclized in a good yield affording 3-phenylindoline (entry 3). *Tert*-Butyl and methyl esters functional groups are tolerated (entries 4 and 5) Low yield is observed for cyclization of 3,4-dimethoxyphenetylamine picolinamide (entry 5). In addition to the cyclized product, the corresponding indole and sp^2 C–H bond acetoxylation products are obtained.

Table 4.4. Cyclization of picolinamides via direct sp^2 C–H/N–H coupling

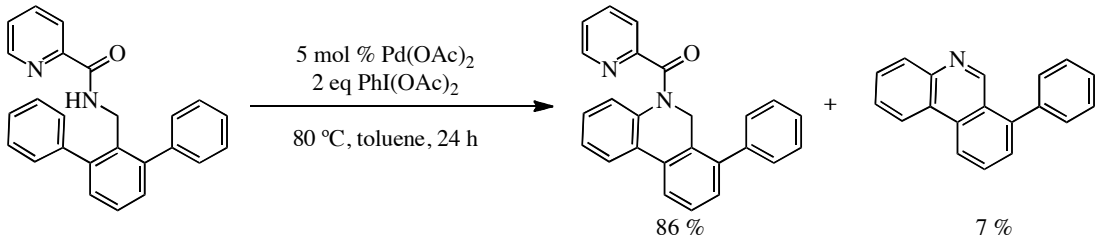


Entry	Starting Compound	Cyclized Product	Yield, %
1			80
2[b]			80
3			76
4			77
5			67
6			16

[a]Yields are isolated yields. [b]100 °C.

Formation of a six-membered ring structure is also possible in a good yield (Scheme 4.17), showing that cyclopalladation via a seven-membered ring is feasible. In addition to dihydrophenanthridine derivative, a minor amount of 7-phenylphenanthridine was also isolated.

Scheme 4.17. Formation of six-membered *N*-containing heterocycles

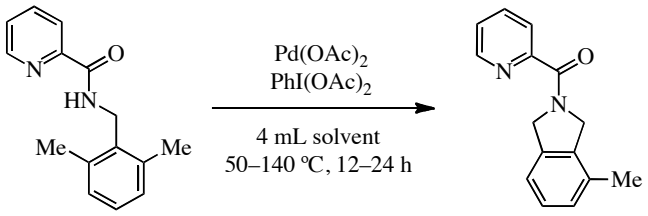


B. Cyclization via direct C–N bond formation from sp^3 C–H/N–H bonds

1. Optimization of the solvent and oxidant

The highest yields were obtained by using 2.0 equivalents of the iodobenzene diacetate in toluene/MeCN (9:1) at 120 °C. (Table 4.5, entry 9). Increasing the temperature promotes degradation. The acetonitrile co-solvent might serve as ligand that promotes the reaction.[22]

Table 4.5. Optimization of the conditions for sp^3 C-H bond functionalization

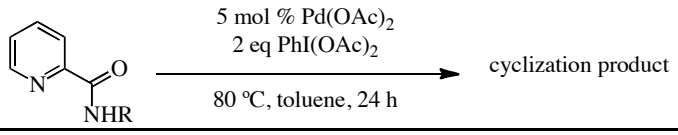


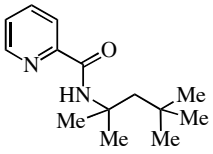
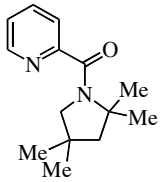
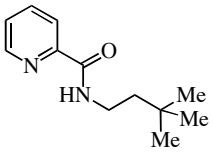
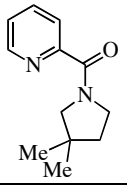
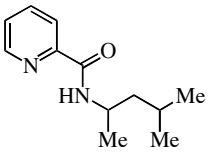
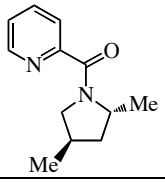
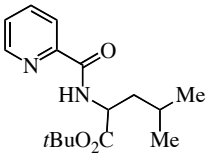
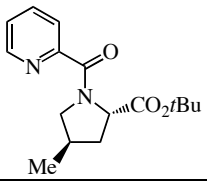
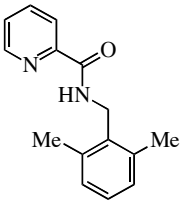
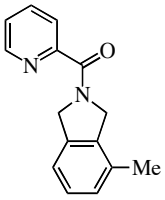
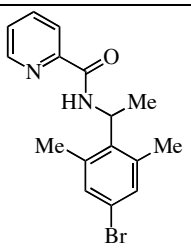
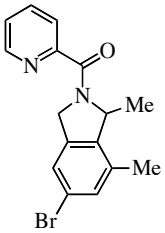
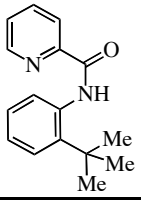
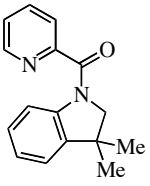
Entry	$Pd(OAc)_2$ (mol %)	$PhI(OAc)_2$ (eq)	Solvent	Temp (°C)	Time (h)	% Yield (GC)
01	5	2.0	toluene	80	24	34
02	10	2.0	toluene	80	24	38
03	5	1.2	toluene	80	24	35
04	5	2.0	toluene	50	48	14
05	5	2.0	toluene	80	12	36
06	5	2.0	toluene	100	24	41
07	5	2.0	Toluene/MeCN	80	24	51
08	5	2.0	Toluene/MeCN	100	24	55
09	**5**	**2.0**	**Toluene/MeCN**	**120**	**24**	**70**
10	5	2.0	Toluene/MeCN	140	24	16

2. Coupling of sp^3 C–H/N–H bonds

More challenging sp^3 C–H/N–H cyclizations also proceed smoothly (Table 4.6). *t*-Octylamine picolinamide is cyclized in a good yield (entry 1), and 3,3-dimethylbutylamine derivative affords the product in moderate yield (entry 2). 4-Methyl-2-aminopentane picolinamide cyclizes in 59% yield (entry 3). Leucine picolinamide gives cyclized product in fair yield (entry 4). Benzylic sp^3 C–H bonds are also reactive. 2,6-Dimethylbenzylamine picolinamide affords a 4-methylisoindoline derivative (entry 5). A 2,4,6-trisubstituted isoindoline can be obtained if 2,6-dimethyl-4-bromo-α-methylbenzylamine picolinamide is cyclized (entry 6). 2-*t*-Butylaniline derivative is cyclized in a modest yield (entry 7). For sp^3 C–H bond amination, addition of acetonitrile or DMF solvent is sometimes beneficial (entries 2, 3, 5, 7). Ester (entry 4) as well as aromatic bromide substituents (entry 6) were tolerated.

Table 4.6. Cyclization by direct coupling of sp^3 C–H/N–H bonds of picolinamides

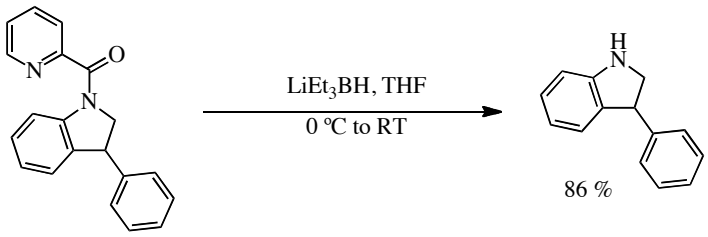


Entry	Starting Compound	Cyclized Product	Yield, %
1			88
2			40
3			59
4			36
5			68
6			42
7			36

C. Auxiliary removal

The picolinyl group auxiliary can be removed by $LiEt_3BH$ (Scheme 4.18). The arylated picolinamide was treated with lithium triethylborohydride (Superhydride) in THF at 0 ºC.

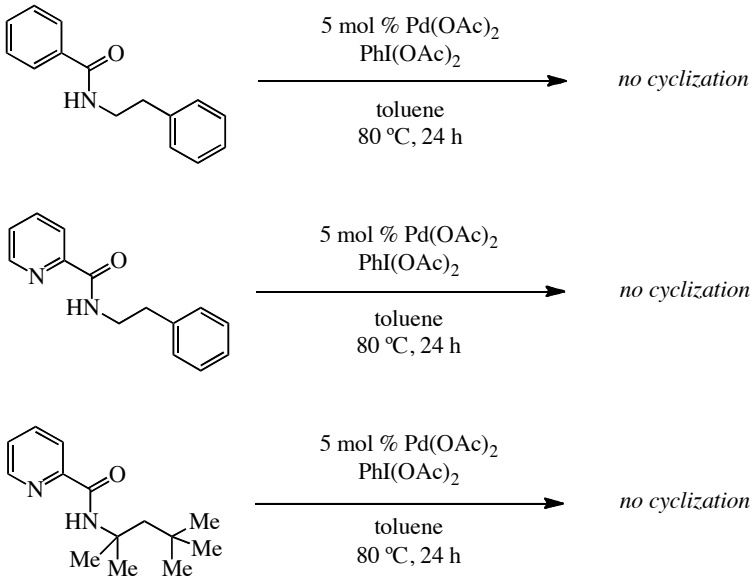
Scheme 4.18. Removal of auxiliary



D. Control experiments

Several control experiments were run to exclude the possibility of other reaction pathways. First, subjecting 2-phenylethylamine benzamide to the cyclization conditions afforded no product. Consequently, picolinamide directing group is essential for achieving cyclization. (Scheme 4.19). Second, the reaction of phenylethylamine picolinamide and *N*-(2,4,4-trimethylpentan-2-yl)picolinamide with $PhI(OAc)_2$ in toluene at 80 °C did not afford cyclization product, showing that palladium catalyst is required.

Scheme 4.19. Control experiments



III. Conclusions

In conclusion, we have developed a palladium-catalyzed method for pyrrolidine, indoline, and isoindoline formation by a C–H/N–H coupling. The method employs a picolinamide directing group, $PhI(OAc)_2$ oxidant, and toluene solvent at 80–120 °C. Cyclization is effective for sp^2 as well as aliphatic and benzylic sp^3 C–H bonds.

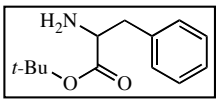
IV. Experimental details

A. General considerations

Flash chromatography was performed on 60 Å silica gel. Preparative TLC was performed on TLC plates, 20 x 20 cm, 2000 μm thick, with fluorescent indicator. Residual solvent peak was used as a reference in ^{1}H NMR and ^{13}C NMR spectra. Melting points are uncorrected.

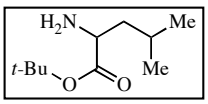
B. Materials

The following starting materials were obtained from commercial sources and were used without further purification: phenylalanine, *tert*-butyl acetate, concentrated $HClO_4$, concentrated HCl, K_2CO_3, $MgSO_4$, silica, hexanes, ethyl acetate, leucine, picolinic acid, triethylamine, dichloromethane, ethyl chloroformate, phenethylamine, 2-(2-chlorophenyl)ethylamine, 2,2-diphenylethylamine, 3,4-dimethoxyphenethylamine, *tert*-octylamine, 4-methyl-2-pentanamine, (2,6-dimethylphenyl)methanamine, *tert*-butyl 2-amino-4-methylpentanoate, 3,3-dimethylbutan-1-amine, 1-(4-bromophenylethanamine, 2-methoxybenzylamine, *N*-benzylpicolinamide, $CuBr_2$, iodomethane, dodecane, iodobenzene diacetate, toluene and acetonitrile.



***tert*-Butyl 2-amino-3-phenylpropanoate** (S1). The procedure of Chen was used.[23] Phenylalanine (35 mmol, 5.78 g) was dissolved in *tert*-butyl acetate (85 mL). The solution was cooled to 0 °C and concentrated $HClO_4$ (55 mmol, 4.80 mL) was added dropwise. The mixture was warmed to room temperature and

stirred for 24 h. After that, reaction mixture was extracted with water (200 mL). Then, the organic layer was extracted with 5 % HCl (100 mL). The aqueous layers were combined and solid K_2CO_3 was added with stirring until no more gas evolution was observed. The mixture was extracted with diethyl ether (2 X 200 mL). The ether layers were combined, dried with $MgSO_4$, concentrated, and loaded on silica column. After chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained (3.96 g, 51 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30). This compound is known.[1] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28–7.25 (m, 2H), 7.21–7.17 (m, 3H), 3.60–3.56 (m, 1H), 3.00 (dd, *J*=13.7, 5.5 Hz, 1H), 2.83 (dd, *J*=13.7, 6.9 Hz, 1H), 1.91 (s, 2H), 1.40 (s, 9H).

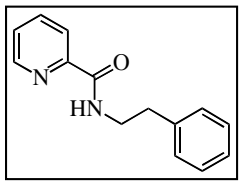


***tert*-Butyl 2-amino-4-methylpentanoate** (S2). The procedure of Chen was used.[23] Leucine (35 mmol, 4.60 g) was dissolved in *tert*-butyl acetate (85 mL). The solution was cooled to 0 °C and concentrated $HClO_4$ (55 mmol, 4.80 mL) was added dropwise. The mixture was warmed to room temperature and stirred for 24 h. The reaction mixture was extracted with water (200 mL). Then, the organic layer was extracted with 5 % HCl (100 mL). The aqueous layers were combined and solid K_2CO_3 was added with stirring until no more gas evolution was observed. The mixture was extracted with diethyl ether (2 X 200 mL). The ether layers were combined, dried with $MgSO_4$, concentrated, and the residue was loaded on silica column. After chromatography (hexanes/ethyl acetate 40/60), colorless oil was obtained (2.58 g, 65.5 % yield). R_f = 0.25 (hexanes/ethyl acetate 40/60). This compound is known.[24] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.87 (*br* s, 2H), 3.86 (m, 1H), 1.83–1.64 (m, 3H), 1.48 (s, 9H), 0.95 (d, *J*=6.9 Hz, 6H).

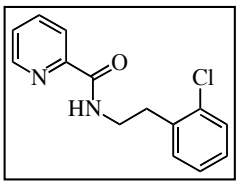
C. Preparation of the picolinamides

1. Method A: Amidation[25]

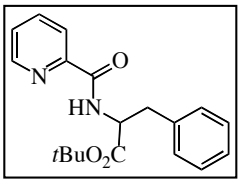
Picolinic acid (35 mmol, 4.3 g) and triethylamine (70 mmol, 9.70 mL) were dissolved in dry dichloromethane (80 mL). The solution was cooled to 0 °C followed by addition of ethyl chloroformate (35 mmol, 3.30 mL). The mixture was subsequently stirred for 30 minutes in ice bath. Amine (20 mmol) was added dropwise via a syringe and the suspension was stirred for one hour. The solution was warmed to room temperature and stirred for another 24 h. Water (100 mL) was then added to the reaction mixture and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried with $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography using hexanes/ethyl acetate as eluent.



***N*-Phenethylpicolinamide** (S3). Picolinic acid (70 mmol, 8.60 g), triethylamine (140 mmol, 19.6 mL), dichloromethane (160 mL), ethyl chloroformate (70 mmol, 5.65 mL), and phenethylamine (40 mmol, 5.03 mL). After column chromatography (hexanes/ethyl acetate 70/30), yellowish crystals were obtained (9.04 g, 89 % yield). R_f = 0.28 (hexanes/ethyl acetate 70/30). This compound is known.[26] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.47 (d, J=4.6 Hz, 1H), 8.19 (d, J=7.8 Hz, 2H), 7.80–7.76 (m, 1H), 7.37–7.34 (m, 1H), 7.32–7.28 (m, 2H), 7.24–7.19 (m, 3H), 3.75–3.70 (m, 2H), 2.93 (t, J=7.3 Hz, 2H).

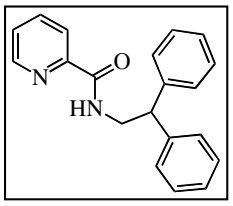


***N*-(2-Chlorophenethyl)picolinamide** (S4). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-(2-chlorophenyl)ethylamine (20 mmol, 3.1 g). After column chromatography (hexanes/ethyl acetate 60/40), colorless liquid was obtained (3.4 g, 65 % yield). R_f = 0.44 (hexanes/ethyl acetate 60/40). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.52–8.50 (m, 1H), 8.23–8.19 (m, 2H), 7.85–7.81 (m, 1H), 7.41–7.33 (m, 2H), 7.28–7.24 (m, 1H), 7.21–7.14 (m, 2H), 3.77–3.72 (m, 2H), 3.08 (t, *J*=6.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 164.5, 149.9, 148.1, 137.4, 136.6, 134.2, 131.0, 129.7, 128.1, 127.0, 126.2, 122.2, 39.2, 33.7. FT-IR (neat, cm^{-1}) *v* 1673, 1524, 1475, 1434, 1288, 1053. Anal. Calcd. for $C_{14}H_{13}ClN_2O$ (260.72 g/mol): C, 64.49; H, 5.03; N, 10.74; Found: C, 64.11; H, 4.85; N, 10.53.

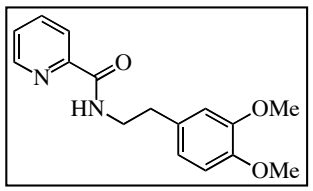


***tert*-Butyl 3-phenyl-2-(picolinamido)propanoate** (S5). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-butyl 2-amino-3-phenylpropanoate (15 mmol, 3.35 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (4.40 g, 90 % yield). R_f = 0.21 (hexanes/ethyl acetate 60/40), mp=96–97 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.52 (m, 2H), 8.16 (d, *J*=8.2 Hz, 1H), 7.84–7.80 (m, 1H), 7.42–7.39 (m, 1H), 7.28–7.21 (m, 5H), 4.97–4.92 (m, 1H), 3.20 (d, *J*=6.4 Hz, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 163.9, 149.6, 148.4, 137.3, 136.5, 129.6, 128.4, 127.0, 126.3, 122.2, 82.3, 53.9, 38.6, 28.0. FT-IR (neat, cm^{-1}) *v* 3345, 1706,

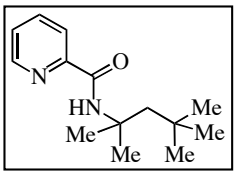
1662, 1530, 1470, 1365, 1295, 1255, 1155. Anal. Calcd for $C_{19}H_{22}N_2O_3$ (326.39 g/mol): C, 69.92; H, 6.79; N, 8.58; Found: C, 69.79; H, 6.72; N, 8.54.



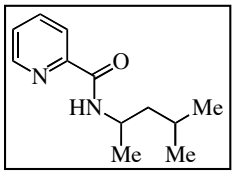
***N*-(2,2-Diphenylethyl)picolinamide** (S6). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2,2-diphenyl-ethylamine (20 mmol, 3.94 g). After column chromatography (dichloromethane), colorless oil was obtained (4.30 g, 71 % yield). R_f = 0.31 (dichloromethane), mp=152.5–153.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.41 (m, 1H), 8.18–8.15 (m, 1H), 8.1 (*br* s, 1H), 7.81–7.77 (m, 1H), 7.36–7.28 (m, 8H), 7.25–7.20 (m, 2H), 4.34 (t, *J*=7.8 Hz, 1H), 4.12 (dd, *J*=7.8, 5.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.4, 149.8, 148.2, 142.1, 137.3, 128.8, 128.2, 126.9, 126.2, 122.2, 50.9, 43.9. FT-IR (neat, cm^{-1}) ν 1665, 1522, 1440, 1250. Anal. Calcd for $C_{20}H_{18}N_2O$ (302.37 g/mol): C, 79.44; H, 6.00; N, 9.26; Found: C, 79.35; H, 6.11; N, 9.25.



***N*-(3,4-Dimethoxyphenethyl)picolinamide** (S7). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 3,4-dimethoxyphenethylamine (20 mmol, 3.37 mL). After chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (5.56 g, 97 % yield). R_f = 0.30 (hexanes/ethyl acetate 60/40). This compound is known.[27] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52–8.51 (m, 1H), 8.21–8.16 (m, 2H), 7.87–7.82 (m, 1H), 7.43–7.39 (m, 1H), 6.84–6.78 (m, 3H), 3.87–3.85 (m, 6H), 3.74–3.69 (m, 2H), 2.91–2.87 (m, 2H).

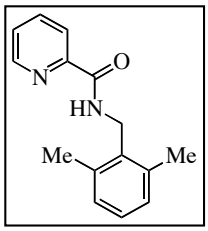


***N*-(2,4,4-Trimethylpentan-2-yl)picolinamide** (S8). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-octylamine (20 mmol, 3.20 mL). After column chromatography (hexanes/ethyl acetate 70/30), colorless oil was obtained (3.20 g, 62 % yield). R_f = 0.56 (hexanes/ethyl acetate 70/30). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, J=4.0 Hz, 1H), 8.18 (d, J=8.0 Hz, 1H), 8.1 (*br* s, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.1, 151.0, 148.9, 137.4, 125.8, 121.7, 54.7, 52.0, 31.8, 31.6, 29.2. FT-IR (neat, cm^{-1}) ν 2956, 1681, 1522, 1464, 1432, 1365, 1228. Anal. Calcd for $C_{14}H_{22}N_2O$ (234.34 g/mol): C, 71.76; H, 9.46; N, 11.95; Found: C, 71.46; H, 9.29; N, 11.86.

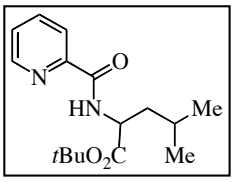


***N*-(4-Methylpentan-2-yl)picolinamide** (S9). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 4-methyl-2-pentanamine (20 mmol, 2.02 g). After column chromatography (hexanes/ethyl acetate 60/40), light orange solid was obtained (3.81 g, 93 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.53 (m, 1H), 8.22–8.20 (m, 1H), 7.88–7.81 (m, 2H), 7.42–7.39 (m, 1H), 4.30–4.26 (m, 1H), 1.71–1.66 (m, 1H), 1.56–1.50 (m, 1H), 1.39–1.33 (m, 1H), 1.25 (d, J=6.9 Hz, 2H), 0.94 (t, J=6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.5, 150.2, 148.0, 137.3, 126.0, 122.2, 46.4, 43.4, 25.1, 22.9, 22.5, 21.6. FT-IR (neat, cm^{-1}) ν 3359, 2955, 1655, 1591, 1526, 1462, 1433,

1172. Anal. Calcd for $C_{12}H_{18}N_2O$ (206.28 g/mol): C, 69.87; H, 8.80; N, 13.58; Found: C, 69.81; H, 8.59; N, 13.50.

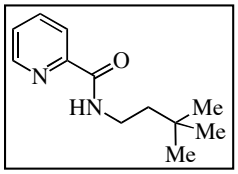


***N*-(2,6-Dimethylbenzyl)picolinamide** (S10). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and (2,6-dimethylphenyl)methanamine (12 mmol, 1.80 g). After column chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (2.75 g, 95 % yield). R_f = 0.40 (hexanes/ethyl acetate 70/30), mp=142–142.5 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.47–8.45 (m, 1H), 8.23–8.21 (m, 1H), 7.91 (*br* s, 1H), 7.85–7.81 (m, 2H), 7.40–7.37 (m, 1H), 7.15–7.06 (m, 2H), 4.69 (d, *J*=4.9 Hz, 2H), 2.41 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 164.2, 149.9, 148.1, 137.8, 137.4, 134.0, 128.5, 127.9, 126.2, 122.3, 38.3. 20.0. FT-IR (neat, cm^{-1}) *v* 3387, 1671, 1521, 1463, 1434, 1241. Anal. Calcd for $C_{15}H_{16}N_2O$ (240.30 g/mol): C, 74.97; H, 6.71; N, 11.66; Found: C, 74.98; H, 6.82; N, 11.60.

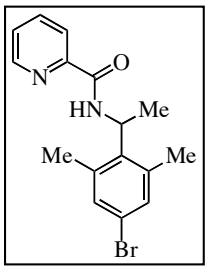


***tert*-Butyl 4-methyl-2-(picolinamido)pentanoate** (S11). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and *tert*-butyl 2-amino-4-methylpentanoate (10 mmol, 1.87 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (1.64 g, 56 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.58–8.57 (m, 1H), 8.41 (d, *J*=8.2 Hz, 1H), 8.19–8.17 (m, 1H), 7.87–7.82 (m, 1H), 7.45–7.41 (m, 1H), 4.74–4.72 (m, 1H), 1.77–1.70 (m, 3H), 1.48 (s, 9H), 1.02–0.98 (m, 6H). ^{13}C

NMR (125 MHz, $CDCl_3$, ppm) δ 172.1, 164.0, 149.7, 148.3, 137.3, 126.3, 122.3, 81.9, 51.4, 42.1, 28.1, 25.1, 23.0, 22.1. FT-IR (neat, cm^{-1}) v 3376, 1734, 1667, 1507, 1366, 1149, 1232, 1046. Anal. Calcd for $C_{16}H_{24}N_2O_3$ (292.37 g/mol): C, 65.73; H, 8,27; N, 9.58; Found: C, 65.84; H, 8.25; N, 9.56.

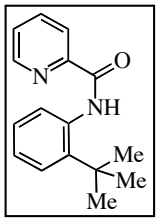


***N*-(3,3-Dimethylbutyl)picolinamide** (S12). Picolinic acid (35 mmol, 4.30 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.30 mL), and 3,3-dimethylbutan-1-amine (12 mmol, 1.23 g). After column chromatography (hexanes/ethyl acetate 60/40), colorless oil was obtained (2.19 g, 88 % yield). R_f = 0.59 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.42 (m, 1H), 8.09 (d, J=7.8 Hz, 1H), 7.94 (*br* s, 1H), 7.74–7.70 (m, 1H), 7.31–7.28 (m, 1H), 3.41–3.35 (m, 2H), 1.47–1.43 (m, 2H), 0.85 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.1, 150.1, 148.0, 137.3, 126.0, 122.1, 43.3, 36.1, 30.0, 29.4. FT-IR (neat, cm^{-1}) v 2956, 1671, 1527, 1465, 1433, 1367, 1287. Anal. Calcd for $C_{12}H_{18}N_2O_2$ (206.28 g/mol): C, 69.87; H, 8.80; N, 13.58; Found: C, 69.09; H, 8.51; N, 13.42.



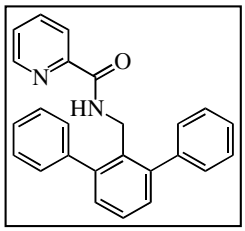
***N*-(1-(4-Bromophenyl)ethyl)picolinamide** (S13). Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 1-(4-bromophenyl)ethanamine (16.5 mmol, 3.30 g). After column chromatography (hexanes/ethyl acetate 60/40), white powder was obtained (4.19 g, 83 % yield). R_f = 0.42 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.53 (m, 2H), 8.13–8.11 (m, 1H), 7.81–7.78 (m, 1H), 7.40–7.38 (m, 1H), 7.12 (s, 2H),

5.65–5.58 (m, 1H), 2.49 (s, 6H), 1.59 (d, *J*=7.45 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.8, 148.2, 138.4, 137.9 137.5, 132.1, 126.3, 122.2, 120.3, 45.5, 20.9, 19.5. FT-IR (neat, cm^{-1}) *v* 3354, 1652, 1517, 1431, 1010, 997, 824, 756. Anal. Calcd for $C_{14}H_{13}BrN_2O$ (305.17 g/mol): C, 55.10; H, 4.29; N, 9.18; Found: C, 55.18; H, 4.49; N, 9.06.



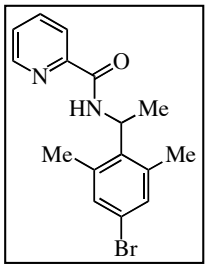
***N*-(2-(*tert*-Butyl)phenyl)picolinamide** (S14) Picolinic acid (35 mmol, 4.3 g), triethylamine (70 mmol, 9.70 mL), dichloromethane (80 mL), ethyl chloroformate (35 mmol, 3.3 mL), and 2-*tert*-butylaniline (20 mmol, 2.58 g). After column chromatography (hexanes/ethyl acetate 80/20), yellow oil was obtained (1.12 g, 22 % yield). R_f = 0.23 (hexanes/ethyl acetate 80/20). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.33 (*br* s, 1H), 8.65–8.62 (m, 1H), 8.33–8.32 (m, 1H), 8.15 (dd, *J*=9.6, 1.4 Hz, 1H), 7.92–7.87 (m, 1H), 7.49–7.43 (m, 2H), 7.32–7.28 (m, 1H), 7.18–7.14 (m, 1H), 1.51 (s, 9H).

2. Method B: Arylation and alkylation



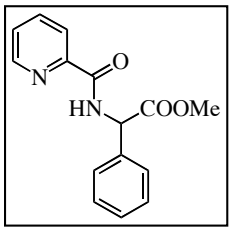
***N*-([1,1':3',1''-Terphenyl]-2'-ylmethyl)picolinamide** (S15). A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), $CuBr_2$ (10 mol %, 22 mg), *N*-benzylpicolinamide (1.0 mmol, 212 mg), iodobenzene (4.0 mmol, 816 mg), CsOAc (4.0 mmol, 794 mg), and *tert*- amyl alcohol (1.0 mL). The resulting suspension was stirred at 140 °C for 24 $_h$. After chromatography (hexane/ethyl acetate 70/30), white needles (360 mg, 99 % yield) were obtained. R_f = 0.34 (hexanes/ethyl acetate 70/30), mp=119–120 °C (hexanes). ^{1}H

NMR (400 MHz, $CDCl_3$, ppm) δ 8.44–8.43 (m, 1H), 7.98–7.96 (m, 1H), 7.78–7.72 (m, 2H), 7.43–7.29 (m, 14H), 4.49 (d, J=5.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.9, 149.8, 147.9, 143.9, 141.2, 137.1, 132.7, 129.8, 129.1, 128.3, 127.5, 127.4, 125.9, 122.0, 39.4. FT-IR (neat, cm^{-1}) δ 3378, 1678, 1510, 1464, 1435, 1000. Anal. Calcd for $C_{25}H_{20}N_2O$ (364.44 g/mol): C, 82.39; H, 5.53; N, 7.69; Found: C, 82.50; H, 5.45; N, 7.68.



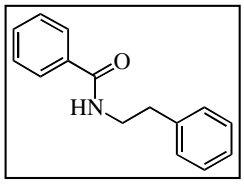
***N*-(1-(4-bromo-2,6-dimethylphenyl)ethyl)picolinamide** (S16). A 100 mL Kontes flask was charged with $Pd(OAc)_2$ (10 mol %, 224 mg), $CuBr_2$ (20 mol %, 446 mg), *N*-(1-(4-bromophenyl)ethyl)-picolinamide (10 mmol, 3.04 g), iodomethane (50 mmol, 7.10 g), K_2CO_3 (40 mmol, 552 mg), and water (3.0 mL). The resulting suspension was stirred at 120 °C for 24 h. After chromatography (hexanes/ethyl acetate 50/50), yellowish oil (175 mg, 5 % yield) was obtained. R_f = 0.41 (hexanes/ethyl acetate 50/50). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.53 (m, 2H), 8.13–8.11 (m, 1H), 7.81–7.78 (m, 1H), 7.40–7.38 (m, 1H), 7.12 (s, 2H), 5.65–5.58 (m, 1H), 2.49 (s, 6H), 1.59 (d, J=7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 149.8, 148.2, 138.4, 137.8, 137.5, 132.1, 126.3, 122.2, 120.3, 45.4, 20.9, 19.5. FT-IR (neat, cm^{-1}) ν 1676, 1572, 1512, 1464, 1433, 1245, 1144, 1040. Anal. Calcd for $C_{16}H_{17}BrN_2O$ (333.22 g/mol): C, 57.67; H, 5.14; N, 8.41; Found: C, 57.40; H, 5.24; N, 8.17.

3. Method C: Transesterification



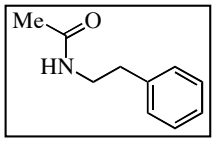
Methyl 3-phenyl-2-(picolinamido)propanoate (S17) This compound was synthesized via transesterification of the *tert*-butyl ester with methanol.[29] A 6-dram vial with septum cap was charged with *tert*-butyl 1-picolinoylindoline-2-carboxylate (3.0 mmol, 978 mg) and anhydrous methanol (20 mL). The vial was cooled to 0 °C followed by dropwise addition of acetyl chloride (1.0 mL). The mixture was stirred at 50 °C. After 16 h, the solvent was evaporated and the resulting oil was dissolved in dichloromethane and loaded in chromatography column (50/50 hexanes/ethyl acetate). The fractions containing the compound were combined and the solvent was evaporated leaving a colorless oil (792 mg, 93 % yield). R_f = 0.54 (hexanes/ethyl acetate 50/50). This compound is known.[30] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.54–8.49 (m, 2H), 8.15 (dd, *J*=7.8, 0.9 Hz, 1H), 7.84–7.80 (m, 1H), 7.43–7.39 (m, 1H), 7.30–7.17 (m, 5H), 5.09–5.05 (m, 1H), 3.72 (s, 3H), 3.16–3.27 (m, 2H).

4. Synthesis of other amides



***N*-Phenethylbenzamide** (S18). Procedure same as that for the synthesis of picolinamides. Benzoic acid (18 mmol, 2.19 g), triethylamine (18 mmol, 5.0 mL), dichloromethane (50 mL), ethyl chloroformate (18 mmol, 1.70 mL), phenethylamine (10 mmol, 1.21 g). After column chromatography (hexanes/ethyl acetate 70/30), white powder was obtained (1.58 g, 70 % yield). R_f = 0.68 (hexanes/ethyl acetate 70/30). This compound is known.[31] ^{1}H NMR (400

MHz, $CDCl_3$, ppm) δ 7.74–7.25 (m, 10H), 6.29 (s, 1H), 3.74 (m, 2H), 2.56 (m, 2H).



***N*-Phenethylacetamide** (S19). Acetic anhydride (12 mmol, 1.13 mL) was mixed with phenethylamine (10 mmol, 1.21 g) and the solution was stirred at room temperature. After one hour, the reaction mixture was added dropwise to saturated aqueous $NaHCO_3$ (100 mL). The mixture was then extracted with diethyl ether (2 X 100 mL). The organic extracts were combined, dried with $MgSO_4$ and the solvent was evaporated to give white powder (1.30 g, 80 % yield). This compound is known.[32] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.15–7.37 (m, 5H), 5.57 (*br* s, 1H), 3.51 (m, 2H), 2.81 (t, *J*= 7.1 Hz, 2H), 1.93 (s, 3H).

D. Determination of the GC conversion using internal standard

The GC conversion for the arylation (for optimization experiments) was calculated based on an internal standard (dodecane) as described here. First, a 1:1 molar mixture of dodecane and the pure target compound was dissolved in ethyl acetate and injected into GC to determine detector response ratio $F=A_{tc}/A_{do}$ (A_{tc}: area of target compound peak, A_{do}: area of dodecane peak). Second, the investigating reaction is set up as usual on a 1.0 mmol scale with the addition of dodecane as internal standard (0.3 mmol). After the completion of reaction, 1 drop of reaction mixture is diluted with CH_2Cl_2 and injected into GC to determine area of dodecane (A_{dor}) and the target compound (A_{tcr}). The amount of target compound in reaction mixture can be calculated by the following equation: $n_{tcr}=0.3\cdot A_{tcr}/(A_{dor}*F)$ (mmol). The conversion is derived based on the amount of starting material added (n_{sm}): $C=(n_{tcr}/n_{sm})*100\%$.

E. Cyclization via direct C–N bond formation from sp^2 C–H/N–H bonds

1. Optimization of the reaction conditions for sp^2 C–H/N–H cyclization

General procedure. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant and solvent were added to this mixture. The resulting suspension was stirred in an oil bath at the specified temperature. After the designated time, the reaction mixture was cooled. A drop of sample was then diluted with about one mL ethyl acetate and the resulting mixture was passed through silica plug. The filtrate was analyzed by GC-MS.

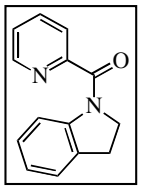
a. Solvent and oxidants. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (2 equiv, 1.0 mmol) and the solvent (2.0 mL, Table 1) was added to this mixture. The resulting suspension was stirred in an oil bath at 100 °C. After 24 h, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. Results are shown in Table 1.

b. Amount of oxidant and the temperature of the reaction. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (1.01–3.0 eq) and toluene (2.0 mL) was added to this mixture. The resulting suspension was stirred in an oil bath at 50–100 °C. After 24 h, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. Results are shown in Table 2.

c. Attempted yield enhancement using different additives. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-phenethylpicolinamide (0.5 mmol, 113 mg). The oxidant (1.2 eq, 0.6 mmol), additive (1 eq, 0.5 mmol) and toluene (2.0 mL) was added to this mixture. The resulting suspension was stirred in an oil bath at 80 °C. After 24 h, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. Results are shown in Table 3.

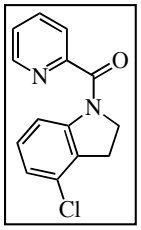
2. Coupling of sp^2 C–H/N–H bonds

General procedure. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), picolinamide (1.0 mmol), iodobenzene diacetate (2.0 eq, 2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in an oil bath at 80–120 °C. After 24 h, the reaction mixture was cooled and then loaded on silica chromatography column with hexanes/ethyl acetate mixture as eluent.

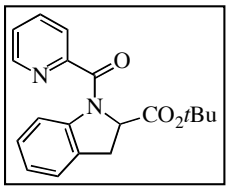


Indolin-1-yl(pyridin-2-yl)methanone (Table 1, entry 1). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-phenethylpicolinamide (1.0 mmol, 229 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 80/20), white crystals were obtained (182 mg, 80 % yield). R_f = 0.19 (hexanes/ethyl acetate 80/20), mp 103–103.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (d, *J*=5.0 Hz, 1H), 8.31 (d, *J*=7.8 Hz, 1H), 7.88–7.81 (m, 2H), 7.38–7.36 (m, 1H), 7.27–7.21 (m, 2H), 7.08–7.05 (m, 1H), 4.34 (t, *J*=8.2 Hz, 2H), 3.14 (t, *J*= 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.2, 154.7, 148.1, 143.4, 137.1, 132.2, 127.5, 125.1, 124.7, 124.4, 124.2, 118.0, 50.6, 28.8. FT-IR

(neat, cm^{-1}) ν 1632, 1592, 1482, 1436, 1397. Anal. Calcd for $C_{14}H_{12}N_2O$ (224.26 g/mol): C, 74.98; H, 5.39; N, 12.49; Found: C, 74.47; H, 5.54; N, 12.31.

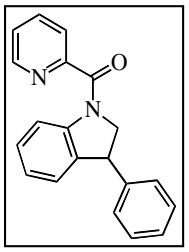


(4-Chloroindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 2). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-chlorophenethyl)picolinamide (1.0 mmol, 257 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 80/20), white crystals were obtained (204 mg, 80 % yield). R_f = 0.26 (hexanes/ethyl acetate 80/20), mp=129.5-130 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.63–8.61 (m, 1H), 8.20 (d, *J*=7.3 Hz, 1H), 7.89–7.82 (m, 2H), 7.41–7.38 (m, 1H), 7.22–7.19 (m, 1H), 7.05 (d, *J*=7.3 Hz, 1H), 4.41 (t, *J*=8.2 Hz, 2H), 3.15 (t, *J*=8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.4, 154.2, 148.1, 144.7, 137.2, 130.7, 130.5, 129.1, 125.3, 124.4, 124.3, 116.2, 50.4, 28.2. FT-IR (neat, cm^{-1}) ν 1652, 1590, 1450, 1387, 1252. Anal. Calcd. for $C_{14}H_{11}ClN_2O$ (258.70 g/mol): C, 65.00; H, 4.29; Cl, 13.70; N, 10.83; Found: C, 64.41; H, 4.34; N, 10.67.

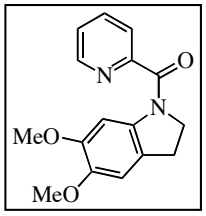


***tert*-Butyl 1-picolinoylindoline-2-carboxylate** (Table 1, entry 3). $Pd(OAc)_2$ (5 mol %, 11 mg), *tert*-butyl 3-phenyl-2-(picolinamido)propanoate (1.0 mmol, 332 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 70/30), colorless solid was obtained (254 mg, 77 % yield). R_f = 0.36 (hexanes/ethyl acetate 70/30), mp=108.6–109.1 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 (d, *J*=4.1 Hz, 1H), 8.41 (d, *J*=8.2 Hz, 1H), 8.08 (d, *J*=7.8 Hz, 1H), 7.86–7.82 (m, 1H), 7.38–7.36 (m, 1H), 7.30–7.26 (m, 1H), 7.20 (d, *J*=7.3

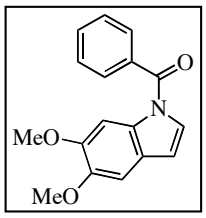
Hz, 1H), 7.09–7.06 (m, 1H), 5.77 (m, 1H), 3.61 (dd, *J*=16.5, 5.0 Hz, 1H), 3.20 (dd, *J*=16.5, 2.7 Hz, 1H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 165.7, 153.7, 147.3, 143.9, 137.2, 129.3, 127.8, 125.3, 124.4, 124.3, 118.1, 81.6, 62.9, 34.0, 27.8 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) *v* 1737, 1641, 1568, 1481, 1395, 1161, 1105. Anal. Calcd for $C_{19}H_{20}N_2O_3$ (324.37 g/mol): C, 70.35; H, 6.21; N, 8.64; Found: C, 70.14; H, 6.20; N, 8.47.



(3-Phenylindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 4). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,2-diphenylethyl)picolinamide (1.0 mmol, 308 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 90/10), white powder was obtained (234 mg, 76 % yield). R_f = 0.22 (dichloromethane/ethyl acetate 90/10), mp=141–142 °C (acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.57 (d, *J*=4.6 Hz, 1H), 8.38 (d, *J*=7.8 Hz, 1H), 7.92–7.77 (m, 2H), 7.42–7.19 (m, 7H), 7.09–6.94 (m, 2H), 4.77 (dd, *J*=11.4, 10.1 Hz, 1H), 4.60 (dd, *J*=10.1, 7.8 Hz, 1H), 4.29 (dd, *J*=11.4, 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 154.3, 154.2, 148.1, 143.5, 142.9, 137.2, 135.6, 128.9, 128.2, 127.3, 125.2, 125.1, 124.9, 124.4, 118.0, 59.8, 47.4. FT-IR (neat, cm^{-1}) *v* 1648, 1594, 1480, 1453, 1440, 1395, 1327, 1296, 1248, 1155, 1087, 1048, 1032. Anal. Calcd for $C_{20}H_{16}N_2O$ (300.35 g/mol): C, 79.98; H, 5.37; N, 9.33; Found: C, 79.17; H, 6.04; N, 9.27.

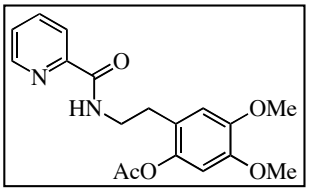


(5,6-Dimethoxyindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 5). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(3,4-dimethoxyphenethyl)-picolinamide (1.0 mmol, 284 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 40/60), colorless oil was obtained (44 mg, 16 % yield). R_f = 0.41 (hexanes/ethyl acetate 40/60). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.53–8.52 (m, 1H), 8.21–8.18 (m, 2H), 7.88–7.84 (m, 1H), 7.44–7.41 (m, 1H), 7.23 (s, 1H), 6.78 (s, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.72–3.67 (m, 2H), 3.01 (t, *J*=7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 149.9, 149.4, 148.2, 148.1, 137.5, 134.0, 126.3, 122.3, 121.7, 112.8, 88.1, 56.2, 55.9, 40.2, 39.5. FT-IR (neat, cm^{-1}) ν 2929, 1671, 1569, 1591, 1525, 1505, 1463, 1436, 1254, 1217, 1162, 1377, 1254, 1218, 1031. Anal. Calcd for $C_{16}H_{16}N_2O_3$ (284.31 g/mol): C, 67.59; H, 5.67; N, 9.85; Found: C, 66.68; H, 6.24; N, 9.82.

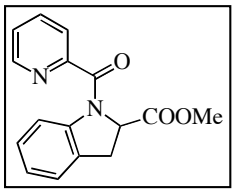


(5,6-Dimethoxy-1*H*-indol-1-yl)(pyridin-2-yl)methanone (Table 1, entry 5). In addition to the indoline above, dehydrogenation product was also isolated from the reaction mixture as yellowish crystals (53 mg, 18 % yield). R_f = 0.56 (hexanes/ethyl acetate 40/60), mp=128–129 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.74–8.73 (m, 1H), 8.20 (s, 1H), 8.07–8.06 (m, 1H), 7.94–7.90 (m, 1H), 7.84 (d, *J*=4.1 Hz, 1H), 7.52–7.48 (m, 1H), 7.04 (s, 1H), 6.54 (d, *J*=3.7 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 152.5, 148.6, 147.9, 147.3, 137.4, 130.6, 127.1, 126.1, 125.7, 123.5, 109.2, 102.4, 100.7, 56.3, 56.2. FT-IR (neat, cm^{-1}) ν 2928, 1673, 1583, 1540, 1480, 1470, 1438, 1382, 1344,

1301, 1251, 1151, 1194. Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.29 g/mol): C, 68.07; H, 5.00; N, 9.92; Found: C, 68.88; H, 6.20; N, 9.85.

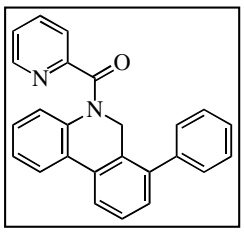


4,5-Dimethoxy-2-(2-(picolinamido)ethyl)phenyl acetate (Table 1, entry 5). In addition to indole and indoline products described above, acetoxylation product was also observed. The product was isolated as yellowish oil (206 mg, 59 % yield). R_f = 0.24 (hexanes/ethyl acetate 40/60). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51–8.50 (m, 1H), 8.24–8.18 (m, 1H), 7.86–7.82 (m, 1H), 7.43–7.40 (m, 1H), 6.77 (s, 1H), 6.61 (s, 1H), 3.83 (s, 3H), 3.81 (s, 1H), 3.68–3.63 (m, 2H), 2.80 (t, *J*=7.3 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.1, 164.5, 149.9, 148.1, 148.0, 147.0, 142.3, 137.4, 126.3, 122.2, 112.7, 106.4, 56.2, 56.1, 39.8, 30.2, 20.9 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) ν 2938, 1756, 1669,1515, 1465, 1402, 1368, 1208, 1179, 1104, 1015. Anal. Calcd for $C_{18}H_{20}N_2O_5$ (344.36 g/mol): C, 62.78; H, 5.85; N, 8.13; Found: C, 62.22; H, 5.90; N, 7.94.

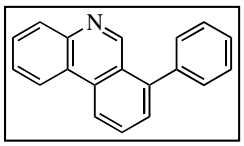


Methyl 1-picolinoylindoline-2-carboxylate (Table 1, entry 13). $Pd(OAc)_2$ (5 mol %, 11 mg), methyl 3-phenyl-2-(picolinamido)-propanoate (1.0 mmol, 289 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL) at 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 60/40), colorless oil was obtained (287 mg, 67 % yield). R_f = 0.38 (hexanes/ethyl acetate 60/40). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, *J*=4.0 Hz, 1H), 8.41 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.2 Hz, 1H), 7.85–7.83 (m, 1H), 7.38 (dd, *J*=6.9, 5.2 Hz, 1H), 7.31–7.26 (m, 1H), 7.21 (d, *J*=6.9 Hz, 1H), 7.09 (m, 1H), 5.79 (dd, *J*=10.9,

2.3 Hz, 1H), 3.65–3.60 (m, 4H), 3.26–3.23 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.9, 165.4, 153.2, 147.2, 143.7, 137.3, 129.3, 127.9, 125.5, 125.2, 124.7, 124.4, 118.2, 62.7, 52.5, 33.9. FT-IR (neat, cm^{-1}) *v* 1747, 1650, 1585, 1481, 1389, 1279, 1203, 1099. . Anal. Calcd for $C_{13}H_{16}N_2O_3$ (248.28 g/mol): C, 62.89; H, 6.50; N, 11.28; Found: C, 62.57; 6.10; N, 11.28.



(7-Phenylphenanthridin-5(6*H*)-yl)(pyridin-2-yl)methanone (Table 1, entry 6). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-([1,1':3',1"-terphenyl]-2'-ylmethyl)picolinamide (1.0 mmol, 369 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 60/40), white solid was obtained (315 g, 86 % yield). R_f = 0.23 (hexanes/ethyl acetate 60/40), 165–166 °C (hexanes). ^{1}H NMR (400 MHz, acetonitrile-d_3, ppm, 80 °C) δ 8.27–8.25 (m, 1H), 7.93–7.89 (m, 2H), 7.22–7.68 (m, 1H), 7.50–7.47 (m, 1H), 7.42–7.37 (m, 4H), 7.32–7.23 (m, 7H), 4.82 (s, 2H). ^{13}C NMR (125 MHz, acetonitrile-d_3, ppm, 80 °C) δ 167.2, 154.1, 148.4, 139.9, 139.8, 138.1, 136.8, 132.6, 132.0, 129.4, 129.3, 129.0, 128.3, 127.9, 127.6, 127.4, 125.8, 124.9, 124.6, 124.5, 123.4, 123.0, 116.9. FT-IR (neat, cm^{-1}) *v* 1648, 1594, 1480, 1453, 1440, 1395, 1327, 1296, 1248, 1155, 1087, 1048, 1032. Anal. Calcd for $C_{25}H_{18}N_2O$ (362.42 g/mol): C, 82.85; H, 5.01; N, 7.73; Found: C, 82.80; H, 4.98; N, 7.77.



7-Phenylphenanthridine (Table 1, entry 6)**.** In addition to the major product in previous entry, phenanthridine byproduct was also isolated (19 mg, 7 % yield). R_f = 0.65 (hexanes/ethyl acetate 60/40), mp=114–114.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.36 (s, 1H), 8.66–8.63 (m, 2H), 8.18 (dd,

J=8.2, 1.4 Hz, 1H), 7.89 (dd, *J*=8.7, 7.3 Hz, 1H), 7.78–7.70 (m, 2H), 7.63 (dd, *J*=7.3, 0.9 Hz, 1H), 7.55–7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.0, 144.2, 142.4, 138.9, 133.1, 130.5, 130.4, 130.1, 128.9, 128.6, 128.1, 127.2, 124.1, 124.0, 122.5, 121.3 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) ν 1600, 1451, 1032.

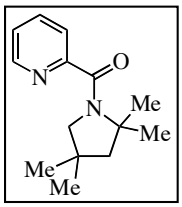
F. Cyclization via direct C–N bond formation from sp^3 C–H/N–H bonds

1. Optimization of the solvent and oxidant

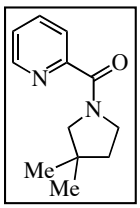
A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 6 mg) and *N*-(2,6-Dimethylbenzyl)picolinamide (1.0 mmol, 224 mg). The iodobenzene diacetate (2.0 eq, 2.0 mmol, 644 mg) and the solvent (4.0 mL, Table 2) was added to this mixture. The resulting suspension was stirred in an oil bath. After the designated reaction time, the reaction mixture was cooled, followed by analysis with GC-MS using dodecane as an internal standard as described earlier. Results are shown in Table 4.

2. Coupling of sp^3 C–H/N–H bonds

General procedure. A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), picolinamide (1.0 mmol), iodobenzene diacetate (2.0 eq, 2.0 mmol, 644 mg), and toluene/DMF or acetonitrile (4.0 mL). The resulting suspension was stirred in an oil bath at 80–120 °C. After 24 h, the reaction mixture was cooled and then loaded on silica chromatography column with hexanes/ethyl acetate mixture as eluent.

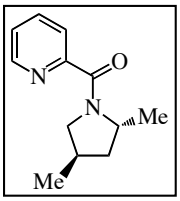


Pyridin-2-yl(2,2,4,4-tetramethylpyrrolidin-1-yl)methanone (Table 1, entry 7). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 80 °C for 24 h. After column chromatography (hexanes/ethyl acetate 50/50), white powder was obtained (204 g, 88 % yield). R_f = 0.38 (hexanes/ethyl acetate 50/50), mp=90–90.5 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.56–8.55 (m, 1H), 7.78–7.74 (m, 1H), 7.62–7.60 (m, 1H), 7.31–7.28 (m, 1H), 3.39 (s, 2H), 1.79 (s, 2H), 1.68 (s, 6H), 1.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.8, 156.4, 148.1, 136.9, 124.1, 122.8, 63.5, 63.0, 56.0, 36.8, 27.8, 27.6. FT-IR (neat, cm^{-1}) ν 2963, 1626, 1444, 1407, 1152, 1033. Anal. Calcd for $C_{14}H_{20}N_2O$ (232.32 g/mol): C, 72.38; H, 8.68; N, 12.06; Found: C, 72.40; H, 8.82; N, 11.98.

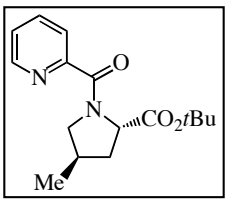


(3,3-Dimethylpyrrolidin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 8) $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(3,3-dimethylbutyl)picolinamide (1.0 mmol, 206 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.6 mL), 120 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 30/70), yellow oil was obtained (80 mg, 40 % yield). R_f = 0.36 (dichloromethane/ethyl acetate 30/70). ^{1}H NMR (500 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.35–8.49 (m, 1H), 7.85–7.77 (m, 2H), 7.36–7.32 (m, 1H), 3.82–3.79 and 3.72–3.69 (m, 2H), 3.48 and 3.46 (s, 2H), 1.73 (t, *J*=6.9 Hz, 2H), 1.16 and 1.07 (s, 6H,). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 166.7, 166.6, 154.5, 154.4, 148.0, 136.9, 136.8, 124.8, 124.7, 124.0, 61.8, 59.5, 48.3, 46.1, 40.1, 39.1, 37.5, 36.5, 26.4, 25.9 (signal for two carbons could not be located). FT-IR (neat,

cm^{-1}) ν 1625, 1586, 1476, 1446, 1414, 1144. Anal. Calcd for $C_{12}H_{16}N_2$ (204.27 g/mol): C, 70.56; H, 7.90; N, 13.71; Found: C, 69.27; H, 8.87; N, 13.42.

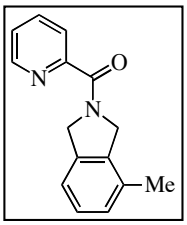


***trans*-(2,4-Dimethylpyrrolidin-1-yl)(pyridin-2-yl)methanone** (Table 1, entry 10). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(4-methylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL), 120 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 50/50), yellowish oil was obtained (127 mg, 59 % yield). R_f = 0.30 (dichloromethane/ethyl acetate 50/50). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, mixture of 2 amide rotamers) δ 8.59–8.57 (m, 1H), 7.81–7.73 (m, 2H), 7.40–7.29 (m, 1H), 4.78–4.74 and 4.50–4.42 (m, 1H), 4.02–3.90 (m, 1H), 3.25–3.13 (m, 1H), 2.49–2.40 (m, 1H), 1.83–1.67 (m, 1H), 1.36 (d, J=6.4 Hz) and 1.13 (d, J=6.2 Hz; 3H), 1.00 and 0.97 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 166.5, 155.1, 154.9, 148.1, 148.0, 136.9, 124.6, 124.5, 123.8, 123.7, 56.1, 54.6, 54.0, 53.8, 41.8, 39.9, 32.1, 29.4, 21.7, 19.8, 18.1, 17.8 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) ν 1739, 1674, 1631, 1567, 1521, 1409, 1229, 1050, 1032. Anal. Calcd for $C_{12}H_{16}N_2O$ (204.27 g/mol): C, 70.56; H, 7.90; N, 13.71; Found: C, 69.93; H, 8.05; N, 13.13.



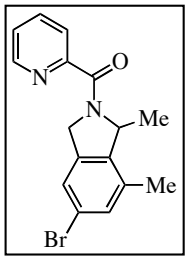
***trans tert*-Butyl 4-methyl-1-picolinoylpyrrolidine-2-carboxylate** (Table 1, entry 9) $Pd(OAc)_2$ (5 mol %, 11 mg), *tert*-butyl 2-amino-4-methylpentanoate (1.0 mmol, 292 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.60 mL), 100 °C for 24 h. After column chromatography (hexanes/ethyl acetate 50/50), yellow oil was obtained (105 mg, 36 % yield, *trans-cis* mixture). R_f = 0.39 (hexanes/ethyl acetate 50/50. ^{1}H NMR (500

MHz, $CDCl_3$, ppm, 1.8/1 mixture of rotamers) δ 8.60–8.59 and 8.50–8.49 (m, 1H), 8.04–8.01 and 7.89–7.87 (m, 1H), 7.81–7.76 (m, 1H), 7.36–7.30 (m, 1H), 5.11 (dd, *J*=10.9, 8.5 Hz) and 4.61 (dd, *J*=9.2 Hz, 2.9 Hz; 1H), 4.07–4.03 (m, 1H), 3.49 (dd, *J*=10.9, 8.6 Hz) and 3.31 (dd, *J*=12.0, 9.2 Hz; 1H), 2.53–2.38 (m, 1H), 2.22–1.83 (m, 2H), 1.49 (s) and 1.34 (s; 9H), 1.13 (d, *J*=6.9 Hz) and 1.05 (d, *J*= 6.3 Hz; 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of rotamers) δ 172.0, 171.4, 162.2, 165.7, 153.8, 153.1, 148.0, 147.3, 136.9, 124.9, 124.7, 124.3, 81.3, 80.9, 62.7, 61.0, 56.5, 55.1, 39.7, 36.6, 32.8, 29.7, 28.1, 27.9, 27.7, 17.6, 17.3 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) *v* 2968, 1737, 1633, 1567, 1445, 1409, 1367, 1219, 1154. Minor amounts of cis-isomer and its rotamer were also observed but are not reported. Anal. Calcd for $C_{16}H_{22}N_2O$ (290.36 g/mol): C, 66.18; H, 7.64; N, 9.65; Found: C, 65.68; H, 8.21; N, 9.52.

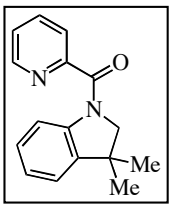


(4-Methylisoindolin-2-yl)(pyridin-2-yl)methanone (Table 1, entry 11). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,6-dimethylbenzyl)picolinamide (1.0 mmol, 238 mg), iodobenzene diacetate (2.0 mmol, 644 mg), acetonitrile (0.40 mL), and toluene (3.6 mL), 120 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 50/50), white powder was obtained (159 mg, 68 % yield). R_f = 0.35 (dichloromethane /ethyl acetate 50/50), mp=87–88 °C (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.67–8.63 (m, 1H), 7.97–7.95 (m, 1H), 7.85–7.80 (m, 1H), 7.40–7.36 (m, 1H), 7.21–7.13 and 7.08–7.01 (m, 3H), 5.22 and 5.13 (s, 2H), 5.05 and 4.98 (s, 2H), 2.30 and 2.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 170.5, 166.5, 153.9, 153.8, 148.1, 148.0, 147.9, 137.3, 137.1, 136.9, 136.6, 135.4, 134.8, 133.0, 132.6, 131.6,

128.3, 128.2, 127.9, 127.8 125.1, 124.4, 120.1, 119.8, 55.5, 54.3, 54.0, 53.0, 18.9, 18.1 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) *v* 2962, 1626, 1586, 1565, 1468, 1444, 1407, 1289, 1224, 1152, 1033. Anal. Calcd for $C_{15}H_{14}N_2O$ (238.28 g/mol): C, 75.61; H, 5.92; N, 11.76; Found: C, 74.70; H, 6.76; N, 11.61.

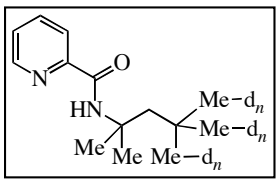


(5-Bromo-1,7-dimethylisoindolin-2-yl)(pyridin-2-yl)methanone (Table 1, entry 12) $Pd(OAc)_2$ (5 mol %, 6 mg), *N*-(1-(4-bromophenyl)-ethyl)picolinamide (0.5 mmol, 142 mg), iodobenzene diacetate (1.0 mmol, 322 mg), acetonitrile (0.20 mL), and toluene (1.8 mL), 120 °C for 24 h. After column chromatography (hexanes/ethyl acetate 50/50), yellowish oil was obtained (59 mg, 42 % yield). R_f = 0.46 (hexanes/ethyl acetate 50/50). ^1H NMR (500 MHz, $CDCl_3$, ppm, mixture of two amide rotamers) δ 8.62–8.61 (m, 1H), 7.91–7.84 (m, 1H), 7.83–7.78 (m, 1H), 7.37–7.35 (m, 1H), 7.26 and 7.13 (s, 1H), 7.18 (m, 1H), 6.08–6.59 and 5.46–5.59 (m, 1H), 5.27 (d, *J*=15.5 Hz) and 5.03 (d, *J*=17.2 Hz; 1H), 4.89–4.84 (m, 1H), 2.30 and 2.23 (s, 3H), 1.55 (d, *J*=6.3 Hz) and 1.18 (d, *J*=6.3 Hz; 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.2, 165.9, 153.8, 153.7, 148.2, 148.0, 140.7, 139.2, 138.9, 137.2, 137.1, 137.0, 134.5 134.0, 131.9, 125.2, 125.1, 124.5, 124.4, 123.4, 123.0, 121.3, 121.2, 59.2, 59.1, 53.8, 51.9, 21,3, 18.8, 18.6, 18.6 (signal for one carbon could not be located). FT-IR (neat, cm^{-1}) *v* 1631, 1566, 1445, 1407, 1333, 1155, 1051. Anal. Calcd for $C_{16}H_{15}BrN_2O$ (331.21 g/mol): C, 58.02; H, 4.56; N, 8.46; Found: C, 57.48; H, 5.20; N, 8.24.



(3,3-Dimethylindolin-1-yl)(pyridin-2-yl)methanone (Table 1, entry 14). $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2-(*tert*-butyl)phenyl)picolinamide (1.0 mmol, 275 mg), iodobenzene diacetate (2.0 mmol, 644 mg), toluene (3.6 mL) and dimethylformamide (0.40 mL) at 120 °C for 24 h. After column chromatography (dichloromethane/ethyl acetate 90/10), yellow oil was obtained (99 mg, 36 % yield). R_f = 0.46 (dichloromethane/ethyl acetate 90/10). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.63 (d, *J*=4.6 Hz, 1H), 8.28 (d, *J*=8.2 Hz, 1H), 7.91–7.80 (m, 2H), 7.41–7.38 (m, 1H), 7.29–7.26 (m, 1H), 7.19–7.10 (m, 2H), 4.09 (s, 2H), 1.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 154.5, 148.1, 142.0, 141.5, 137.2, 127.7, 125.1, 124.8, 124.4, 121.9, 118.0, 65.1, 40.7, 28.3. FT-IR (neat, cm^{-1}) ν 2925, 1645, 1596, 1481, 1397, 1289, 1095, 1022. Anal. Calcd for $C_{16}H_{16}N_2O$ (252.31 g/mol): C, C, 76.16; H, 6.39; N, 11.10; Found: C, 75.34; H, 6.23; N, 10.95.

G. Deuterium exchange experiment



A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), cesium acetate (2.0 mmol, 392 mg), CH_3COOH-d_4 (30 mmol, 1.70 mL) and toluene (2.0 mL). The resulting suspension was stirred in an oil bath at 120 °C. After 6 hours, the reaction mixture was cooled and an aliquot was purified by preparative TLC (hexane/ethyl acetate 70/30) followed by NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, *J*=4.0 Hz, 1H), 8.18 (d, *J*=8.0, Hz, 1H), 8.1 (br s, 1H), 7.84–7.81 (m, 1H), 7.40–7.38 (m, H), 1.87 (s, 2H), 1.56 (s, 6H), 1.03 (m, 6H).

H. Control experiments

1. Reaction of *N*-phenethylbenzamide

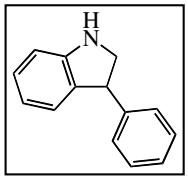
A 2-dram screw-cap vial was charged with $Pd(OAc)_2$ (5 mol %, 11 mg), *N*-phenethylbenzamide (1.0 mmol, 225 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in oil bath at 80 °C. After 24 h, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

2. Exclusion of $Pd(OAc)_2$ catalyst from the reaction mixture

A 2-dram screw-cap vial was charged with *N*-phenethylpicolinamide (1.0 mmol, 227 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in oil bath at 80 °C. After 24 h, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

A 2-dram screw-cap vial was charged with *N*-(2,4,4-trimethylpentan-2-yl)picolinamide (1.0 mmol, 234 mg), iodobenzene diacetate (2.0 mmol, 644 mg), and toluene (4.0 mL). The resulting suspension was stirred in an oil bath at 80 °C. After 24 h, the reaction mixture was cooled and analyzed by TLC and GC-MS. No cyclization product was detected.

I. Auxiliary removal



3-Phenylindoline. Method by Tanaka et al.[33] was followed with a minor modification. In a 50 mL Schlenk flask, (3-phenylindolin-1-yl)(pyridin-2-yl)methanone (1.0 mmol, 300 mg) was dissolved in anhydrous THF (10 mL). The mixture was cooled in an ice bath and then Super-Hydride (4.0 mL, 1.0 M solution in THF) was added dropwise. The mixture was warmed to room temperature and stirred for an hour. After that, THF was evaporated. The residue was suspended in dichloromethane and loaded onto chromatography column (hexane/ethyl acetate). Evaporation of the solvent gave yellow crystals (168 mg, 86 %). R_f = 0.63 (hexane/ethyl acetate 80/20) This compound is known.[34] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32–7.20 (m, 5H), 7.08–7.05 (m, 1H), 6.92–6.80 (m, 1H), 6.72–6.86 (m, 2H), 4.47 (dd, *J*=9.2 Hz, 8.7 Hz, 1H), 3.91 (dd, *J*=9.2, 9.2 Hz, 1H), 3.59 (br s. 1H), 3.48 (dd, *J*=9.2, 8.7 Hz, 1H).

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