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Palladium Catalyzed Non-directed Aromatic C-H Aminations

A Major Qualifying Project Report

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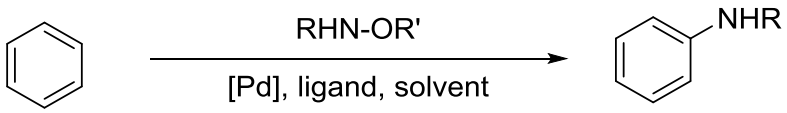
Abstract

One-step, non-directed C-H aminations of arenes has the potential to facilitate the synthesis of compounds with aromatic C-N bonds, which are important bulk and fine chemicals for the synthesis of biologically active molecules. Currently, these types of products are synthesized through sequential functional group interconversions. Our goal is to develop one-step, non-directed C-H amination reactions of arenes that are enabled by palladium catalysts and electrophilic amination reagents. The effect of palladium source, ligand, amination reagent, solvent, temperature and additives on the yield of amination reactions are investigated in detail.

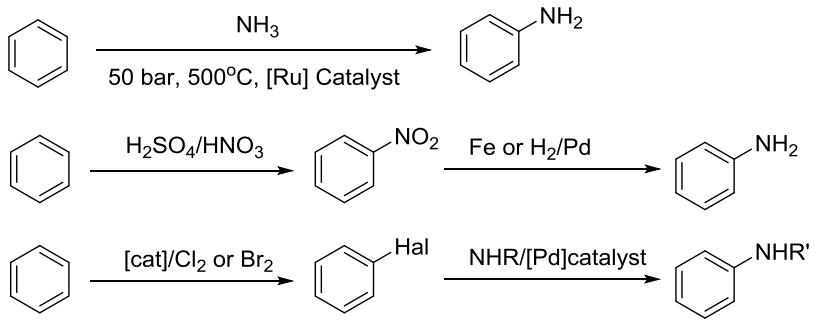


Introduction

1.1 Motivation for C-H Functionalization Protocols in Synthetic Chemistry

C-H bond functionalization is the cleavage of a C-H bond which is then followed by installation of another functional group. The original C-H bond can thus be converted into C-C or C-X (X = O, N, S, P, halogens) bonds.[1] C-H functionalization is typically performed in the presence of transition metal catalysts which allow reactions to proceed under mild conditions. Transition metal catalyzed C-H functionalizations may involve C-H bond cleavage to generate a metal-aryl intermediate (organometallic mechanism). Alternatively, C-H functionalizations can proceed through metal assisted C-H insertion.[2]

C-H functionalizations enable the transformation of abundant but unreactive hydrocarbons into industrially valuable chemicals. In this project, we focus on forming aromatic C-N bonds by C-H functionalization, as aromatic C-N bonds are present in many biologically active compounds. For example, 5 out of the 7 top-selling pharmaceuticals in the U.S. in 2010 contained an aromatic C-N bond.[3] Currently used aromatic C-N bond formation protocols require harsh reaction conditions, corrosive reagents or rely on functional group interconversions, involving multiple reaction steps (Scheme 1).[4,5]



Scheme 1. Traditional methods for C-H amination

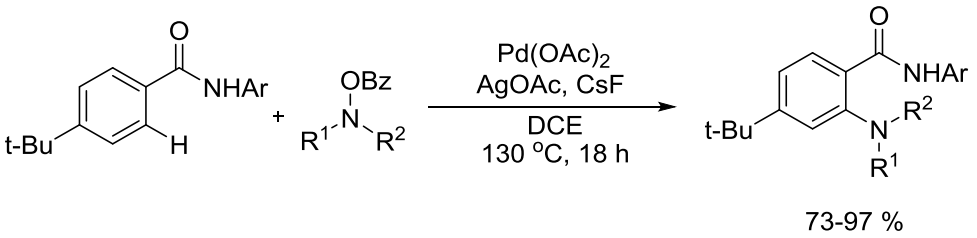
In the first reaction shown in Scheme 1, the amination proceeds only at high temperatures and under high pressure of NH_3.[5-6] This is not a useful reaction, since only few pharmaceuticals or other complex molecules are expected to be stable under such conditions. The second reaction in Scheme 1 uses strong acids and strong oxidants which is very likely to decompose the pharmaceuticals as well.[4] The third halogenation approach combined with a Buchwald-Hartwig[7] coupling is the most general approach for the synthesis of aromatic amines. However, it still requires 2 steps and therefore does not yield aromatic amines directly from the respective hydrocarbons.

In the past years, many Pd catalyzed protocols for converting C-H bonds directly into C-C and C-O bonds have been developed.[8] However, there are only a few catalytic processes for converting C-H bonds into C-N bonds in one step. Two major types of C-H amination reactions exist: chelate-directed and non-directed. Both types of C-H amination will be discussed in the next paragraphs.

1.2 Chelate-Directed C-H Amination

Directed C-H amination reactions require a catalyst directing group such as an oxime or pyridine to be present on the substrate. The directing group typically coordinates to the transition metal center, leading to the formation of a cyclometalated intermediate, which undergoes subsequent functionalization to afford the desired product.

Yu and coworkers have performed directed C-H aminations of benzoic amides catalyzed by $Pd(OAc)_2$ (Scheme 2).[9]

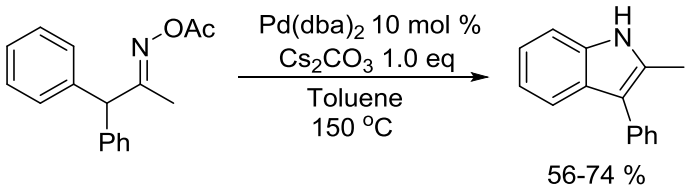


Scheme 2. Directed amination of substituted benzene

The nitrogen source and oxidant used in this protocol is an *O*-benzyl hydroxylamine derivative. A stoichiometric amount of CsF has been used as base to neutralize the H^+ formed during the reaction. A stoichiometric amount of additional oxidant AgOAc is also required for high yields (73-97%). However, the reason why two oxidants are required for this reaction has not been elucidated so far.

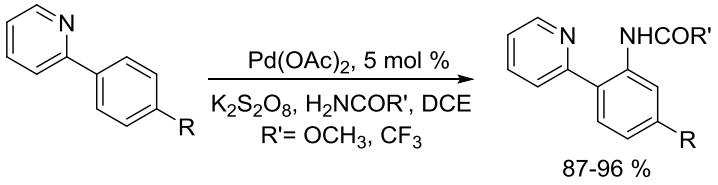
Hartwig and coworkers have reported the $Pd(dba)_2$-catalyzed, directed C-H amination in an intramolecular fashion which produces indole derivatives (Scheme 3).[10] The nitrogen source is an acetate oxime derivative which also functions as the oxidant. A

stoichiometric amount of Cs_2CO_3 is added to neutralize any acid formed during the reaction.



Scheme 3. Directed amination of substituted benzene

Furthermore, Che and coworkers have reported the Pd(II)-catalyzed *ortho*-amidation of 2-arylpyridines and aromatic oximes (Scheme 4).[11] The nitrogen on the pyridine or the oxime moiety acts as the coordinating atom directing the amination process. The reaction consumes 5 equivalents of the oxidant $K_2S_2O_8$. Various amides can be used as the nitrogen source.

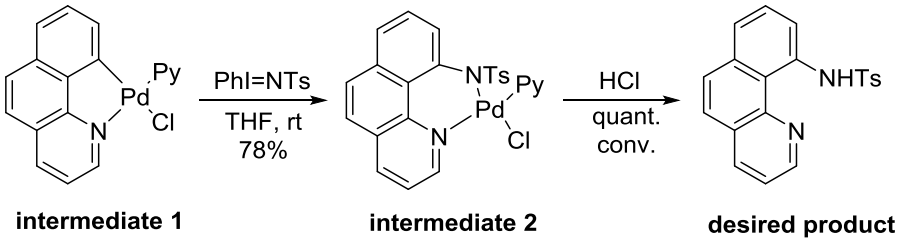


Scheme 4. Directed C-H aminationof substituted benzene

In conclusion, all the shown examples achieve relative high yields of C-H amination products through the use of catalyst directing groups. However, only the *ortho*-position of the arene in proximity to the directing group of the starting material is available for functionalization. A further drawback is the requirement for large excesses of oxidants in many of these examples.

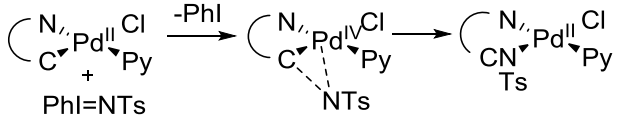
1.3 Stoichiometric Reactions with Pd Aryl Complexes

In order to elucidate if catalytic C-H aminations proceed through cyclometalated palladacycles, stoichiometric amination reactions of Pd-aryl model complexes have been investigated (Scheme 5).[12] Starting with palladium complex **1**, PhI=NTs was added as both the oxidant and amination reagent. This reaction resulted in formation of the formal nitrene product **2** which was isolated. By treating the cyclopalladated intermediate **2** with HCl, the desired product could be released.



Scheme 5. Stoichiometric C-H Amination

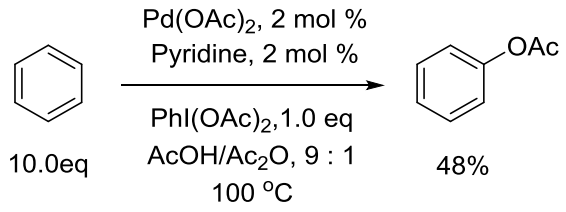
The mechanism was purposed to prefer concerted or dissociative imido transfer Pd^{IV}-imido intermediate (Scheme 6).[13]



Scheme 6. Proposed imido transfer mechanism

1.4 Non-directed C-H Activation

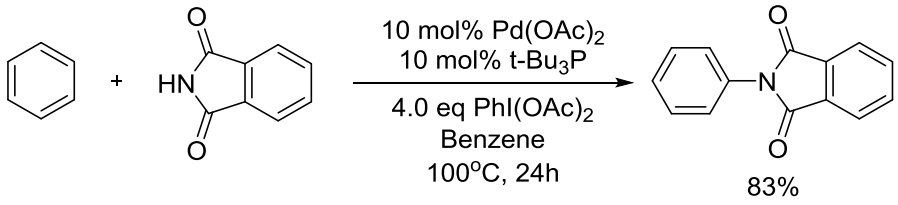
Non-directed catalytic C-H activations which involve arenes without coordinating side chains have been well studied in the past few years. However, most of the known examples focus on C-H oxygenation and C-C bond formations[7, 14]. One representative research of C-H oxygenation was conducted by Sanford, Emmert, and coworkers, using a Pd/pyridine catalyst to successfully catalyze C-H oxygenations of simple arenes (Scheme 7).[8]



Scheme 7. Pd catalyzed C-H oxygenation

The $PhI(OAc)_2$ was added as oxidantin these reactions;benzene served as starting material and $AcOH/Ac_2O$ was used as the solvent system. The turnover number (TON) of the catalytic reaction reached as high as 4756, implying the high efficiency of the palladium/pyridine catalytic system in C-H activation.

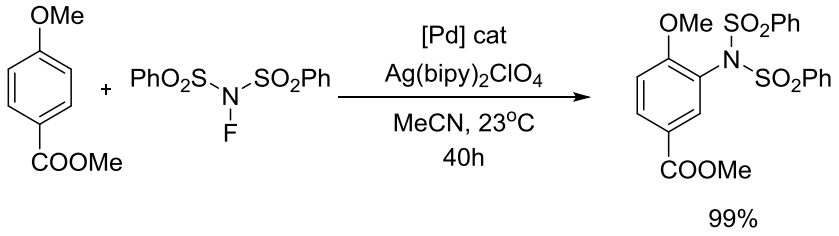
Non-directed catalytic C-H amination reactions have become a popular topic very recently. Hartwig and coworkers have reported the non-directed C-H amination of benzene catalyzed by $Pd(OAc)_2$/phosphine catalysts (Scheme 8).[15]



Scheme 8. Non-directed C-H amination of benzene

In this reaction, benzene is used as both substrate and solvent and phthalimide (1.0 eq) is used as the nitrogen source. Excess $PhI(OAc)_2$ (4.0 eq) is added as an oxidant to regenerate the palladium catalyst. Although non-directed C-H amination was achieved in this reaction, it requires a large excess of 4.0 eq of the expensive oxidant $PhI(OAc)_2$ and generates about 60 % of PhOAc as a byproduct, which causes unnecessary waste formation and potential separation problems.

Ritter and coworkers have also demonstrated in 2013 that non-directed selective C-H aminations of substituted benzene derivatives can be catalyzed by palladium complexes with a Ag cocatalyst (Scheme 9).[16] N-fluorobenzenesulfonimide (NFSI) functions both as the nitrogen source and oxidant. However, the introduced protected amino group, as the only installable group, is not a common pharmaceutical precursor which means that further functional group conversions are required.



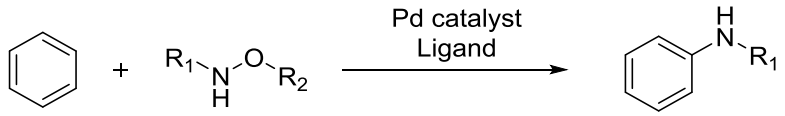
Scheme 9. Non-directed C-H amination of subsituted benzene

In conclusion, current non-directed aminations of arenes still have considerable room for improvements: they ether requires excess amounts of expensive oxidants or is limited to few commercially available amination reagents.

Approach and Objectives

2.1 Hypothesis

Based on the literatures reports discussed in the sections above, we hypothesize that a suitable combination of electrophilic amination reagents and palladium catalysts will enable the one-step, non-directed C-H amination of simple arenes in the presence of pyridine-type ligands (Scheme 10).



Scheme 10. Pd catalyzed C-H amination

2.2 Amination Reagent Design

Several factors were taken into consideration for the design of the used electrophilic amination reagents:

1. The electrophilic amination reagents should be readily accessible through one or two synthetic steps.
2. The protecting group on the nitrogen should be varied easily to modify the amination reagent and adjust its selectivity and reactivity.
3. A protecting group (PG) on the N atom will be needed to prevent secondary reactions.
4. The protecting group (R) on the O atom needs to result in a good leaving group OR in order to prevent to re-coordination to the palladium center.

Figure 1 below shows the electrophilic amination reagents that will be used in our investigations. Different combinations of protecting groups (PG) and leaving group (OR) will be tested to determine the optimal electrophilic amination reagent for the Pd catalyzed amination of arenes.

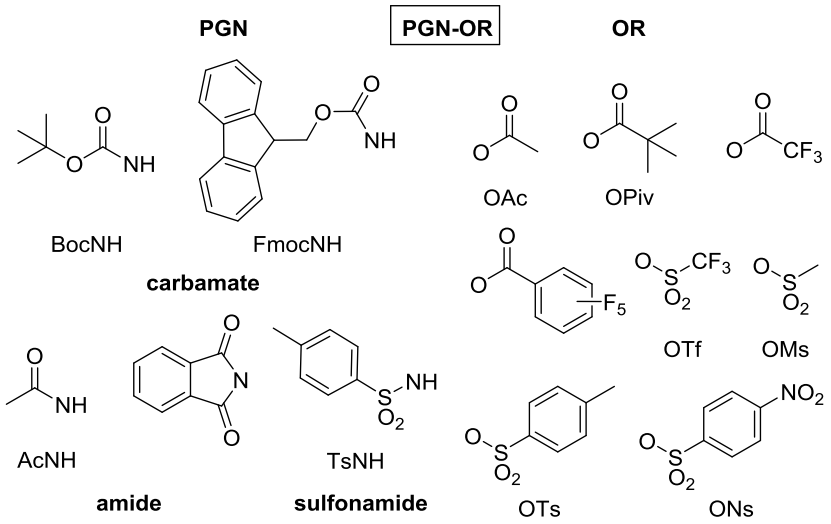
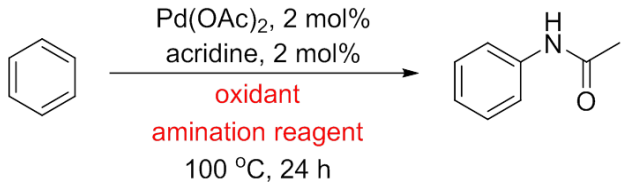


Figure 1. Electrophilic Amination Reagents.

Results and Discussion

3.1 Previous Work

To execute a catalytic reaction, starting material, amination reagent, oxidant, palladium source and ligand is required. According to previous research, we developed a brand new type of amination reagent, **1**(AcNHOAc), which combines the nitrogen source and oxidant into one molecule which provided a much higher yield than using separate nitrogen source and oxidant.



Amination Reagent	Oxidant	Yield
Acetamide	$K_2S_2O_8$	2.9 %
AcNHOAc	-	7.6 %

We did the palladium source screen of a broad range of palladium salts and concluded that palladium (II) acetate always provided higher yield than other salts.

Then after series of ligand screen, we discovered that pyridine type ligands had the tendency to produce higher yield which corresponding to the presenting literature.[8] And one pyridine derivative, the acridine provides the highest yield among pyridine type ligands. Then we tested the electron effect of the ligand, we installed strong electron donating group, -NMe_2 and the yield of the reaction slightly increased. We also discovered than the addition of additives, with optimized amount of AcOH(1.0 eq)

and AgOAc (5 mol %) could greatly increase the yield of the catalytic reaction.

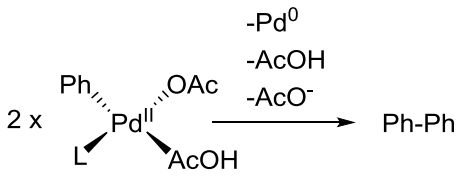
We also detected the problem that responding to the low yield, the formation of palladium black was constantly observed in catalytic reactions which indicated that the catalyst was deactivated during the reaction.

3.2 Experimental Results

3.2.1 Catalytic Reaction Optimization

Ligand Development

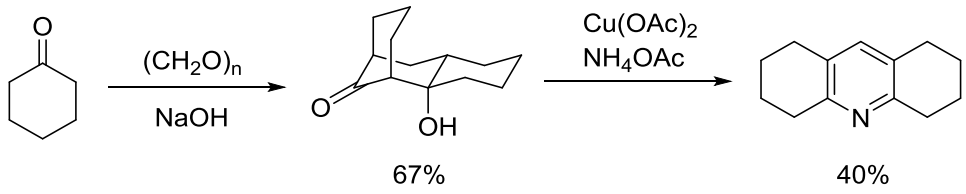
Palladium black was observed in all reactions after various times (1 h to 4 h), which indicates that the active catalyst is lost in the reaction. As biphenyl is often observed as a byproduct, we hypothesized that two Pd-aryl intermediates are able to react with each other, generating biphenyl and palladium black. (Scheme 11).



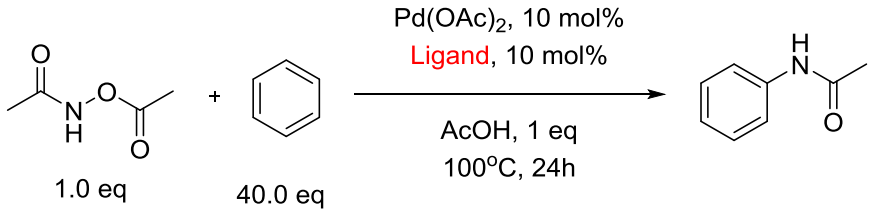
Scheme 11. Formation of palladium black by biaryl coupling process

This has been observed before by Suzuki[14] and Heck[17] and is a typical reaction in Pd catalysis, when the stabilizing ability of the used ligand is not sufficient, or in PdII/IV catalyzed reactions when the oxidant has been used up.

In order to slow down biaryl coupling, we decided to synthesis octahydroacridine (**L2**) to be applied as ligand (Scheme 12).[18] Octahydroacridne is not only an electron-richer derivative of acridine (as we known the electron richer the ligand is, the higher yield we intended to get), but also has a much bulkier structure. We proposed that Pd aryl intermediates with a bulkier ligand would have difficulties approaching each other and therefore slow down the coupling process. As a result of a slower coupling, less catalyst would precipitate as palladium black and the yield and turnover number (TON) of the catalytic reaction could be boosted.



Scheme 12. Synthesis of Octahydroacridine.



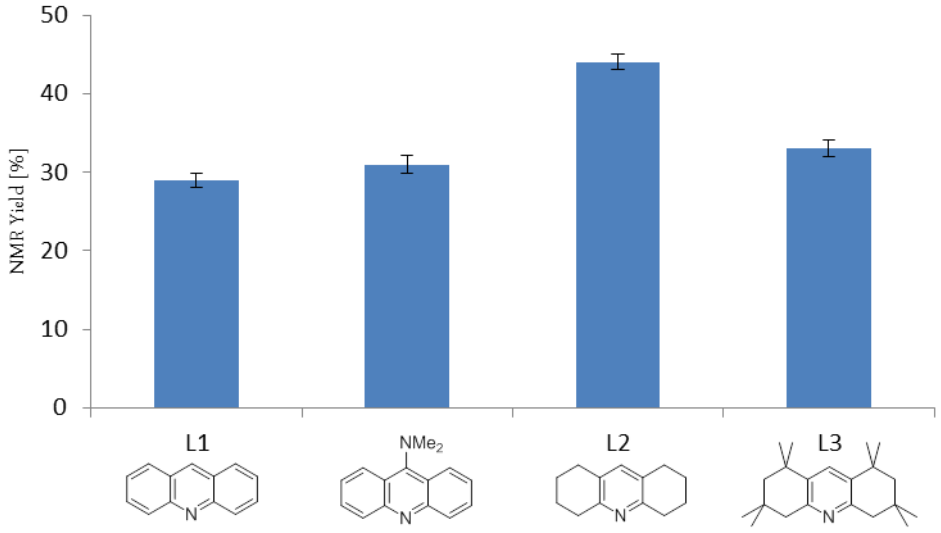
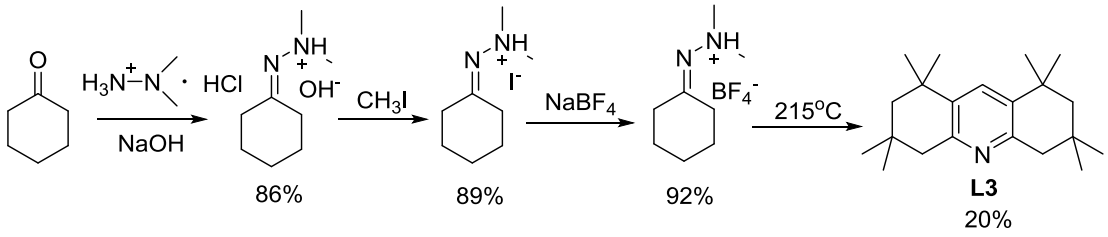


Figure 2. Yields of Ligand Studies

According to Figure 2, employing **L2** increased the 24 h yield of aminated product from 29% with acridine to 44%.

However, GC-MS analysis indicated that octahydroacridine was oxidized during the catalytic reaction to generate acridine as well as partially dehydrogenated products, which decreases the steric effect of using octahydroacridine as ligand.

To overcome the problem of ligand oxidation, octamethylacridine (**L3**) was synthesized according to a literature procedure (Scheme 13).[18] With eight methyl groups, the new ligand **3** is resistant to oxidation by dehydrogenation; moreover it contains an even bulkier structure and more electron rich properties than octahydroacridine.



Scheme 13. Synthesis of octamethylacridine

However, according to Figure 2, the yields of the reaction with octamethylacridine actually decreased to 33% from the octahydroacridine providing 44% yield. We hypothesized that the four methyl groups on carbon 3 and carbon 8 block the active sites on the planar palladium intermediate from reacting with the amination reagent,

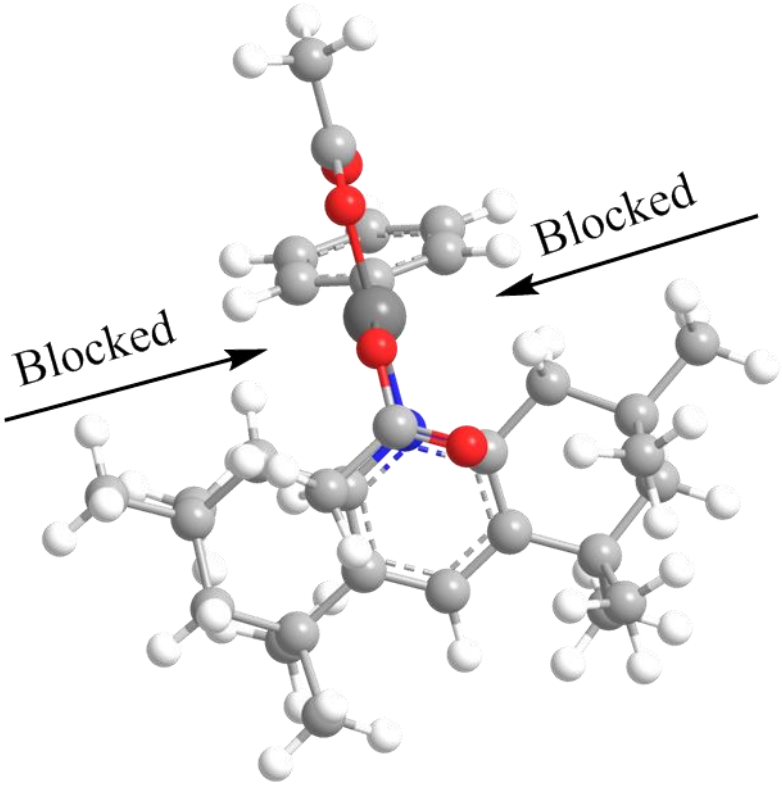


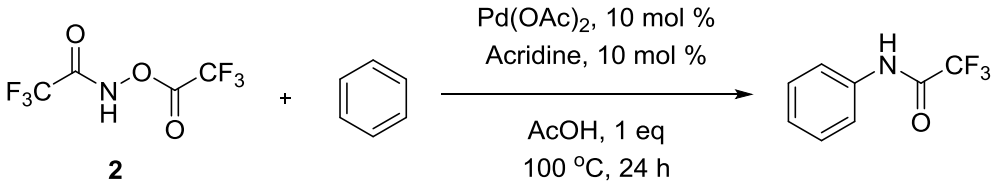
Figure 3. Steric Effect of L3

resulting in the slow formation of the octahedral Pd^{IV} intermediate. Then with the accumulation of the square planar Pd^{II} intermediate, coupling process was driven by equilibrium and the deactivation of the palladium catalyst was faster.

In conclusion, the change of ligand had a great impact on the yield of catalytic reactions. Steric bulkier and electron richer ligand is, the higher yield will be more likely to be obtained.

Study of Amination Reagent Derivatives

In order to facilitate the oxidation to form the Pd^{IV} intermediate, we hypothesized that by the introduction of electron-withdrawing fluorine atoms in amination reagent would render the oxidative N-O bond more labile and thus could accelerate oxidation of the Pd-aryl intermediate. Same strategies that improve the yield of the catalytic reactions that using **1** were applied to the **2**. Different ligands including acridine, octahydroacridine, and octamethylacridine; additives including AgOAc, AcOH; the two amination reagent reacted very different to the additives AcOH and AgOAc:



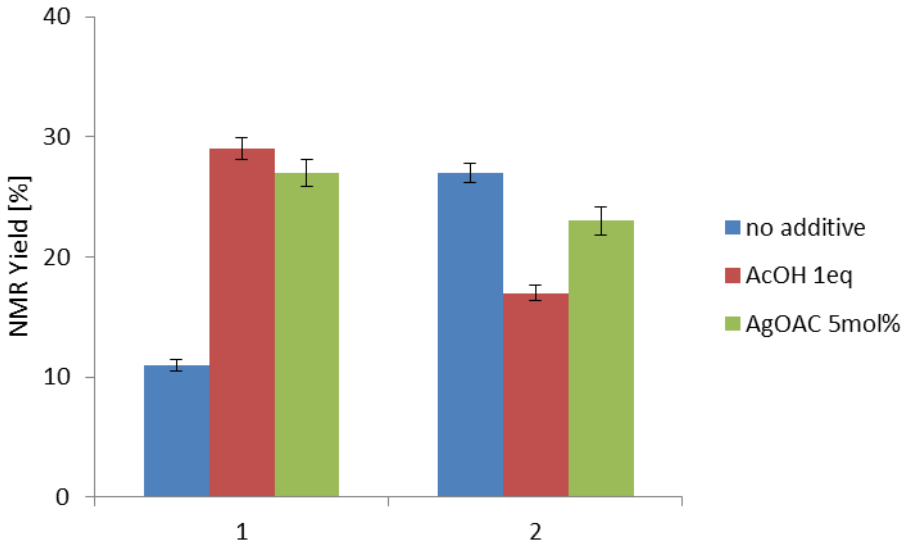


Figure 4. Yields of Amination Reagent Study with Acridine as Ligand

As shown in Figure 3, two amination reagents have very similar peak yields. However, they respond very differently to the addition of additives. The addition of AcOH and

AgoAc increase the yields that using **1** as amination reagent while significantly decrease the yields of the reactions that using **2** as amination reagent.

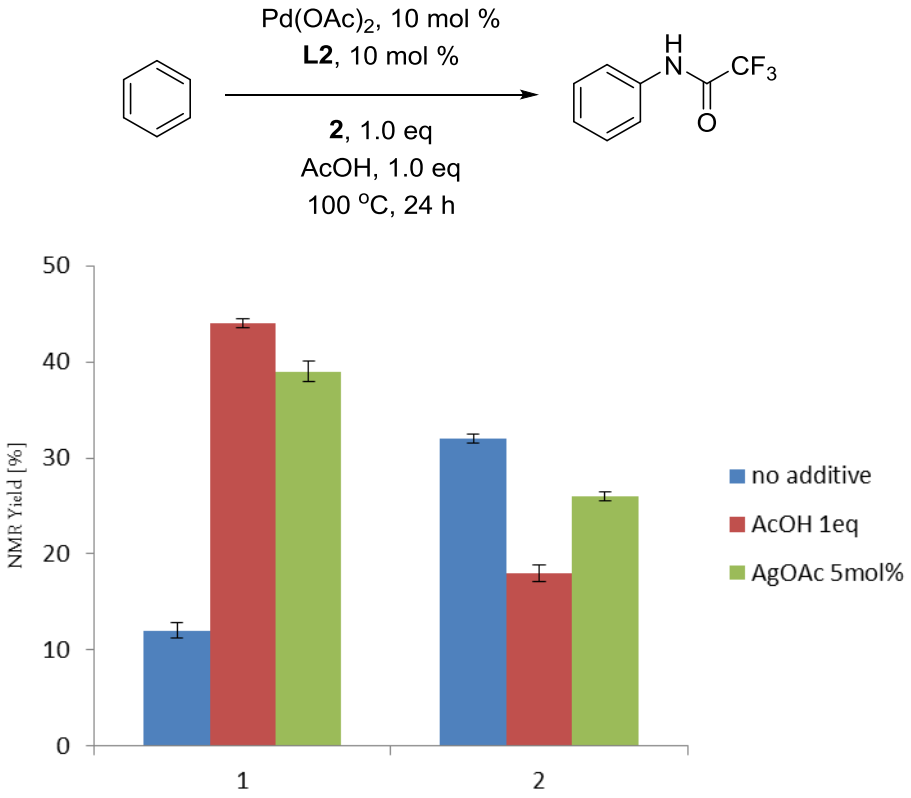


Figure 5. Yields of Amination Reagent Study with Octahydroacridine as Ligand

According to Figure 4 and Figure 5, the change of the ligand from acridine to octahydroacridine also increases the yields of those reactions using **2** while the respond to additives still kept the same.

Additive Studies

Since octahydroacridine and octamethylacridine were applied as the new ligands, the amounts of the additives (AcOH and AgOAc) need to be re-optimized. 5 mol %, 10 mol %, 20 mol % and 30 mol % of silver acetate were tested in Figure 6;

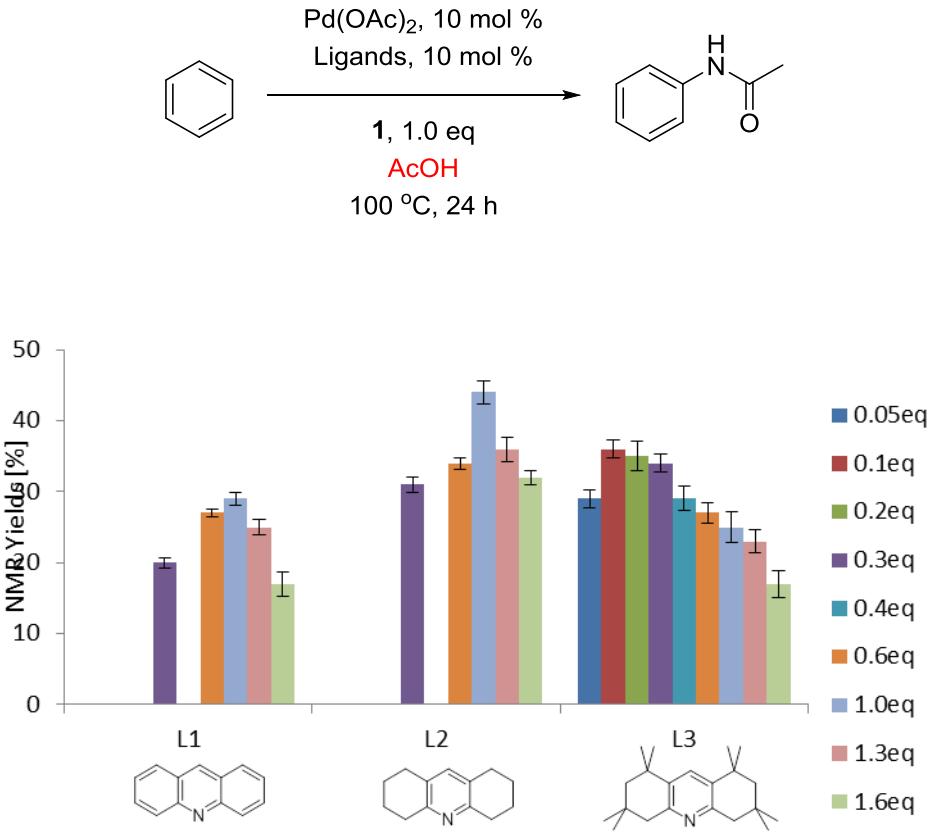


Figure 6. Yields of Acetic Acid Study

0.05 eq, 0.1 eq, 0.2 eq, 0.3 eq, 0.6 eq, 1.0 eq, 1.3 eq and 1.6 eq of AcOH were tested in Figure 7.

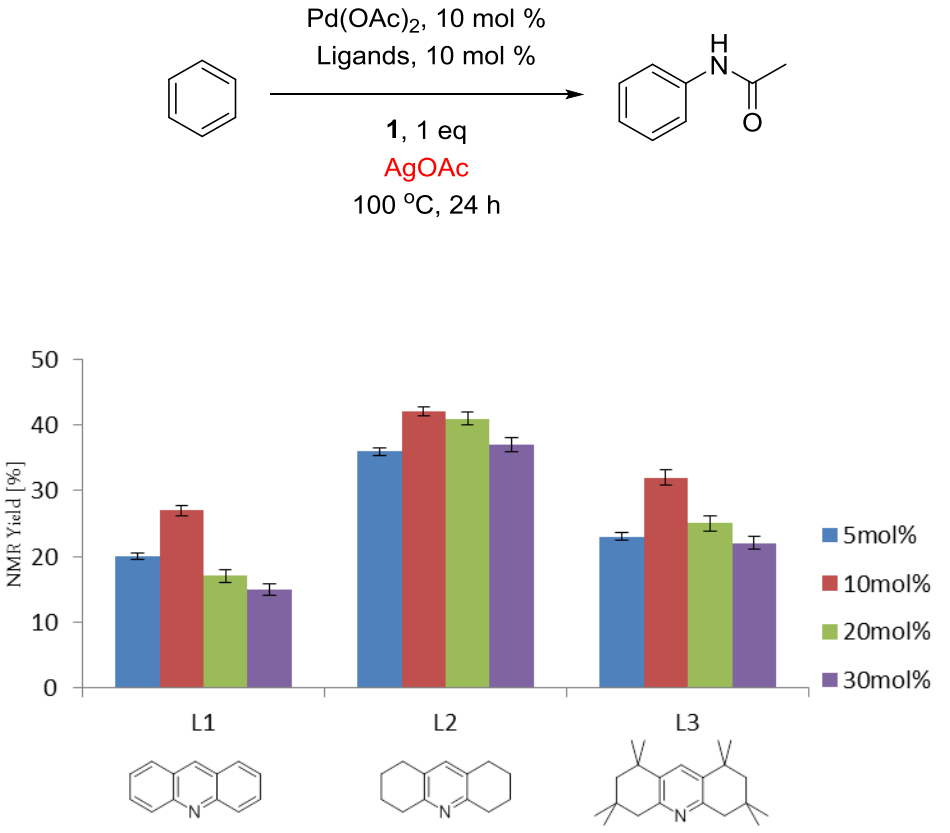
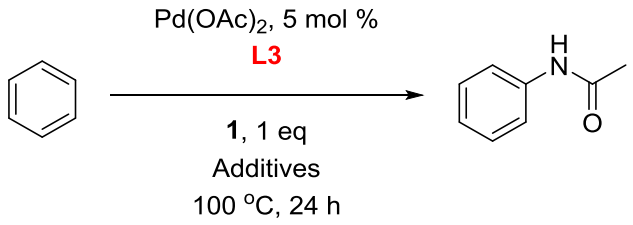


Figure 7. Yields of Silver Acetate Study

According to Figure 6 and 7, octahydroacridine and acridine both have the same peak yield at 5 mol % of AgOAc and 1.0 eq of AcOH. However, octamethylacridine exhibits a different behavior, with 10 mol % of AgOAc and 0.02 eq of AcOH resulting in maximum yields. As mentioned previously, this might be due the ligands affecting different step of the catalytic cycle.

Ligand Loading Studies

We hypothesized that excess of ligand is very likely to occupy the vacant site on the activate palladium catalyst and deactivate its reactivity resulting in lower yield and TON. Then different loading of octamethylacridine (5 mol % and 10 mol %) were tested below;



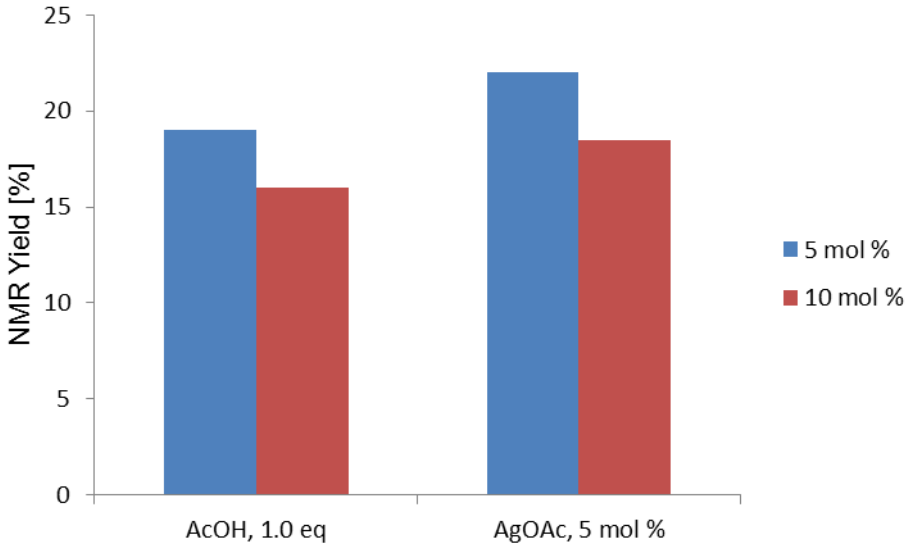


Figure 8. Yields of Octamethylacridine Loading Study

Figure 8 indicates that the yield of the product is higher when the ratio of palladium/ligand equal to 1 than 0.5. This fact implies that extra ligand (over 1:1 ratio) will deactivate the catalyst as predicted.

Temperature Studies

Temperature was also considered to be a crucial factor affecting the yields of the catalytic reactions. To slow down the decomposition of the amination reagent, decreasing temperature is a very considerable approach. However, lower temperature might not provide enough kinetic energy for the C-H bond of the arenes to be activated. To test the effect of temperature, 100 ^{o}C, 90 ^{o}C and 80 ^{o}C were selected and the yields of the reactions were determined (Figure 9).

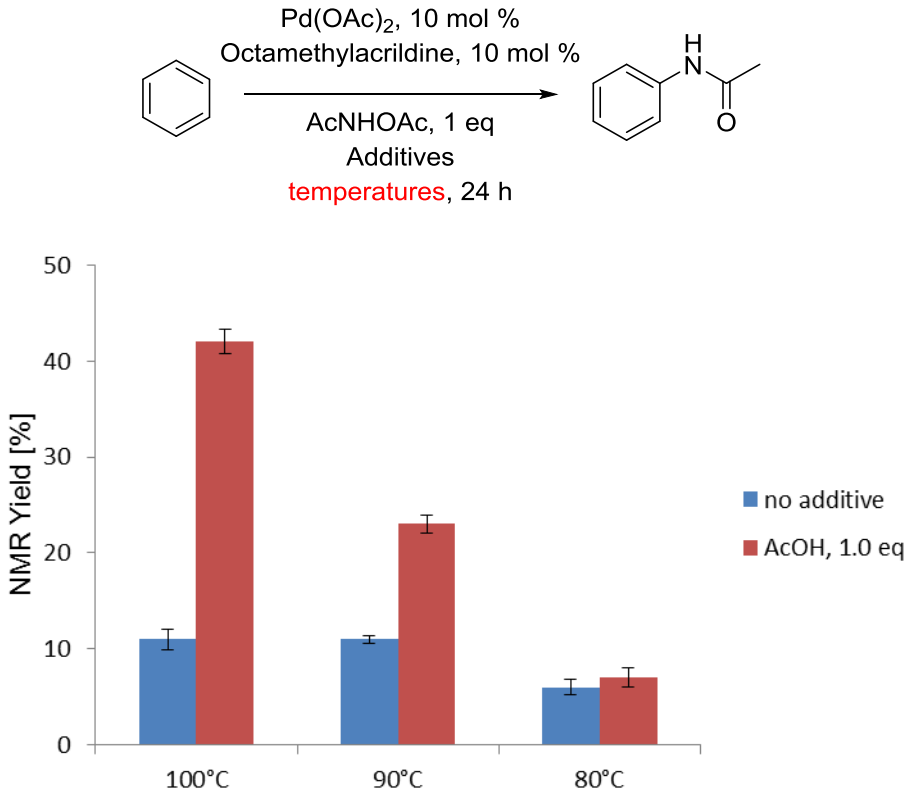


Figure 9. Yields of Temperature Study.

The result implies a tendency that the yield significantly decreases as the temperature decreases from 100 oC; which means the decrease of temperature greatly slows down the rate of the C-H activation.

Solvent Studies

Since benzene has been acting as both substrate and solvent which is a rare situation in the synthesis of complex molecules, also the large application of such volatile and toxic liquid does not fit the concept of green chemistry, we decided to examine several solvents (dichloromethane, acetonitrile, mesitylene, dibutyl ether, benzonitrile, trifluorotoluene, tert-amyl alcohol, and hexafluorobenzene) while decrease the loading of benzene to 1.0 eq in order to simulate the situations of C-H amination in complex molecules. We predict that the C-H activation will be slower at lower benzene concentrations which will lead to the decrease of the yield.

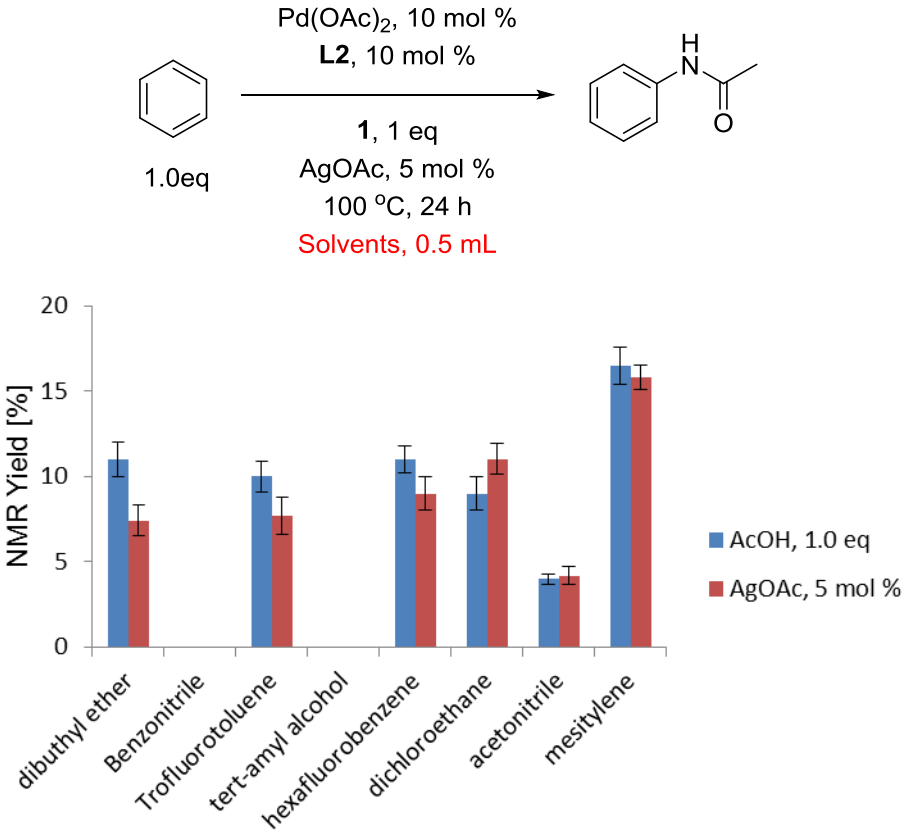
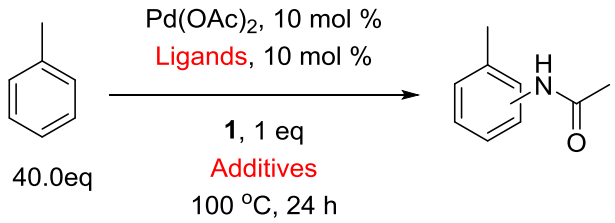


Figure 10. Yields of Solvent Study.

As shown in Figure 10, mesitylene as solvent gave the highest yield ~16%; overall, the yields are much lower than when the reaction is performed in neat benzene. Because the decrease concentration of benzene cause the C-H activation step lost its equilibrium driving force by concentration.

3.2.2 Amination of Toluene

To study the behavior of the catalyst on the substituted arenes, toluene was selected to examine the yield of the product and the *ortho : meta : para* product ratio (Figure 11). Due to the methyl group on toluene, the electron density on the benzene ring is higher. As shown in Figure 11, the yield of the sum of o/m/p product is about 10% lower than the yield obtained with benzene as substrate. The amount of *meta*- and *para*-product is similar while much less *ortho*-product is formed. This impliesthat a steric effect might play a role in the mechanism.



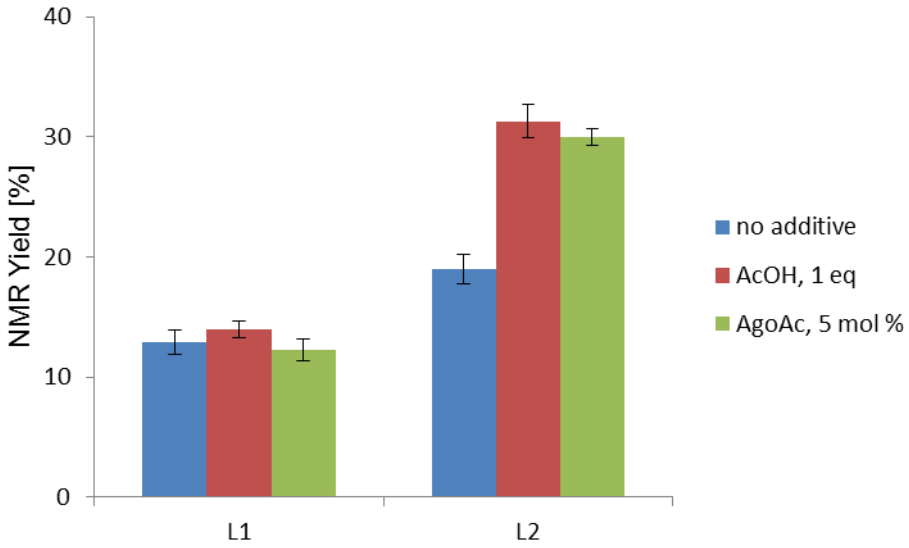
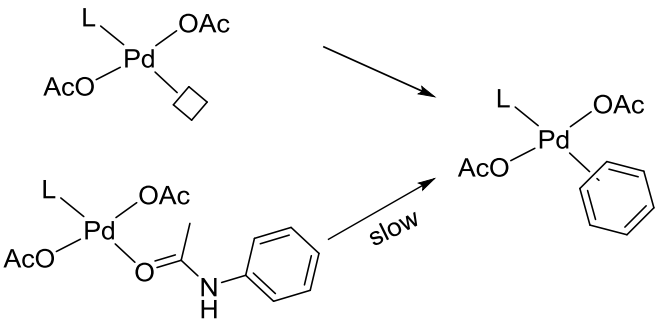


Figure 11. Yields of Toluene Study

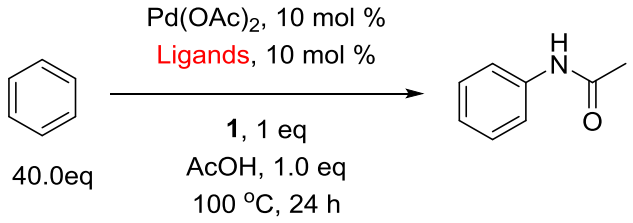
3.2.3 Product Inhibition Study

Product inhibition is the inhibition of a catalytic reaction by product binding to the active site of a catalyst. We hypothesize that the palladium center in the active C-H amination catalyst has a vacant coordination site through which benzene coordination and subsequent C-H activation of benzene occurs (Scheme 14).



Scheme 14. Product inhibition prevents coordination of benzene

When the product concentration is high, a product molecule could occupy the vacant site on palladium, preventing coordination and C-H activation of benzene. To test our hypothesis, we carried out the reaction between benzene and **1**(AcNHOAc) in the presence of 0.50 eq of the aminated product acetanilide (Figure 12).



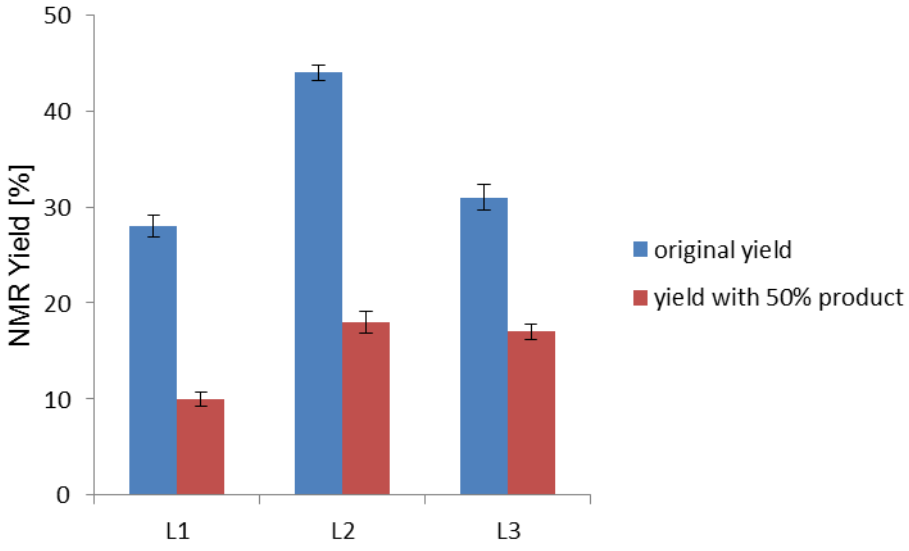


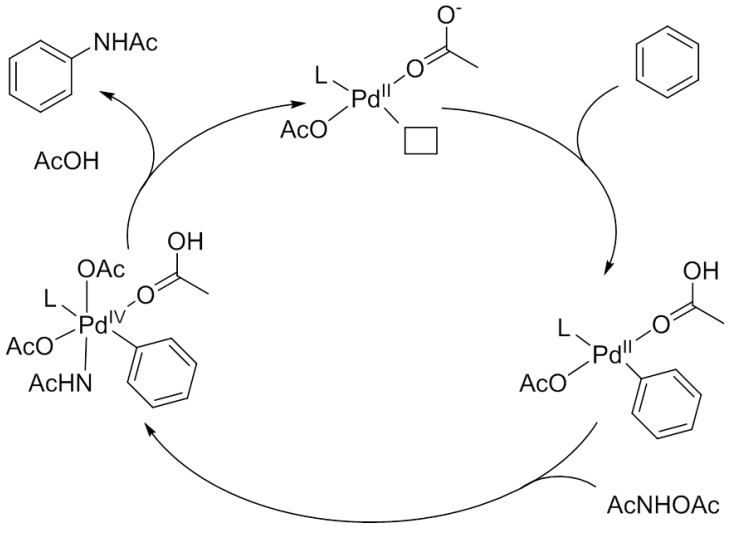
Figure 4. Yields of Product Inhibition Study

In the absence of acetanilide, the reaction yield is 44% with octahydroacridine as

ligand. If there is no product inhibition, we would expect a total yield of 94% (= 50 + 44) from this reaction. However, the observed yield was only 62%, indicating significant product inhibition. As shown in Figure 11, product inhibition occurs with all three ligands tested (**L1, L2, L3**).

3.3 Mechanistic Study

Based on our experimental results and a literature study of the mechanism of directed C-H amination[13], we propose that the mechanism for our C-H amination reaction follows a Pd^{II}/Pd^{IV} cycle (Scheme 15).



Scheme 15. Proposed Mechanism

After the palladium acetate trimer and the ligand dissolve, the ligand coordinates to palladium to yield monomers **1** with a vacant coordination site.Benzene then

coordinates to the vacant site to afford a π-complex, which then rearranges into a σ-complex, followed by acetate-assisted C-H activation to give the Pd-aryl complex **2**. In a next step, the amination reagent reacts with **1**, forming Pd^{IV} complex **3**. Afterwards, acetanilide is formed through reductive elimination from intermediate **3** and acetic acid can dissociate to regenerate the catalyst **3**.

3.4 Supporting Facts for Mechanistic Study

The presence of intermediate **1** with a vacant site is supported by the product inhibition study. Since the product acetanilide could coordinate to the vacant site of the intermediate, slowing down the C-H activation step. After the increase of the concentration of acetanilide, more acetanilide will coordinate to the vacant site and deactivate the catalyst. Our experimental results discussed above support this thesis..

The presence of intermediate **2** is supported by the study using toluene as substrate. Since the methyl group hinders the approach of the palladium catalyst to the *ortho*-C-H bond, while *meta* and *para* position are not affected by the presence of methyl group, significant lower yields of the *ortho*-product are observed. This supports that C-H activation occurs in the mechanism, as similar observations have been made in other C-H functionalizations.[10]

The formation of the octahedral Pd^{IV} intermediate was supported by the ligand test,

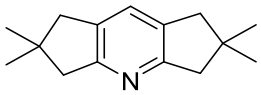
the octamethylacridine. After the formation of the square planar Pd^{II} intermediate, the methyl groups on the octamethylacridine partially block the z axis for the amination reagent to approach to the palladium center. According to Figure 1, decrease of reactivity occurred when switching the octahydroacridine to octamethylacridine which means the z axis is essential for the oxidative addition to form the octahedral Pd^{IV} intermediate.

According to a detailed Density Functional Theory study executed by the Cundari group on palladium catalyzed, chelate-directed C-H aminations,[13] we hypothesize that the oxidative addition of the amination reagent proceeds through a dissociative imido transfer mechanism which is corresponding to the literature.

Future Directions

4.1 New Ligand Syntheses

To further develop the ligand, two adjacent six membered rings could be changed to five membered rings with four methyl groups on both edges. The new molecule will maintain a similar steric effects and oxidation resistance while its more tied-back structure will not interfere with the coordination of the amination reagent to the palladium center to process the oxidative addition.



L4

Figure 5. New Ligand Structure

4.2 Substrate Scope

After successfully performing C-H aminations of simple arenes with solvents, we plan to not only use benzene as the only substrate: indole, furan, other substituted benzene derivatives will be investigated. Since the benzene aromatic C-H was successfully activated, it is very possible for other arene C-H bond to be activated under the same condition. The expansion of the substrate scope could give this C-H amination a much broader application.

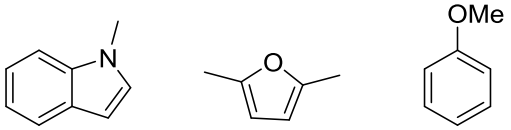


Figure 6. Substrate Scope

4.3 Solvent Evaluation

Although mesitylene was determined to provide the highest yield for benzene C-H amination so far, the yield itself (~16 %) is still much lower than the usage of neat benzene (~44 %). Therefore, plenty of other inert solvents can be tested and the yield of the catalytic reactions with solvent still has potential to increase further. (e.g. hexafluoroisopropanol, pentafluorobenzene, trifluoroethanol).

Experimental Part

5.1 General Procedures

All reactions were conducted without rigorous exclusion of air and moisture unless noted otherwise. [D_6]acetone and [D_1]chloroform were purchased from Cambridge Isotopes Lab and used as received. Ethyl acetate (EtOAc), hexane, dichloromethane (CH_2Cl_2) and toluene were obtained from Pharmco and used as purchased. Benzene, chlorobenzene, acridine, pyridine, 2-pyridone, 2-fluoropyridine, 2-aminopyridine, 4-hydroxypyridine, quinoline, triethylanime and trifluoroacetic acid (TFA) were purchased from VWR and used as purchased. Palladium(II) acetate trimer ($Pd(OAc)_2$) was purchased from Alfa Aesar and used as purchased.

Stock solutions of ligands and co-ligands were prepared using volumetric glassware and all liquid reagents were dispensed by difference using syringes. Gas chromatography (GC) was carried out on an Agilent 7890A instrument using a 19091J-413 (HP-5; 30 m, 0.32 mm i.d., 0.25 μm df) column. GC-MS investigations were carried out on an Agilent 5975C instrument using a 19091S-433 (HP-5MS; 30 m, S4 0.25 mm i.d., 0.25 μm df) column. Retention times were verified using samples prepared according to literature methods. NMR spectra were recorded on Brucker Ultrashield 300 MHz NMR spectrometers with the residual solvent peak ([D_6]acetone: ^{1}H: δ = 2.05 ppm, [D_1]chloroform: ^{1}H: δ = 7.26 ppm) as the internal reference unless otherwise noted. Yields were calculated by calibrating prepared samples and standard to the response of the instrument.

Amination reagents **1**[19] and **2**[20] (Figure 2) were synthesized according to literature

procedures. The ligands octahydroacridine[18] and 2,2-4,4-6,6-8,8-octamethylhydroacridine (Figure 3) were synthesized according to literature procedures.

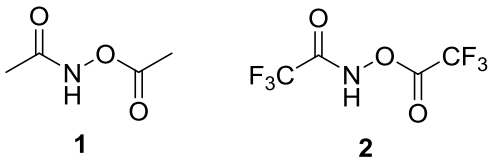


Figure 7. Electrophilic Amination Reagents.

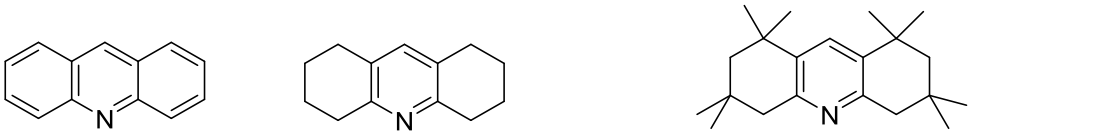


Figure 8. Ligand Structure.

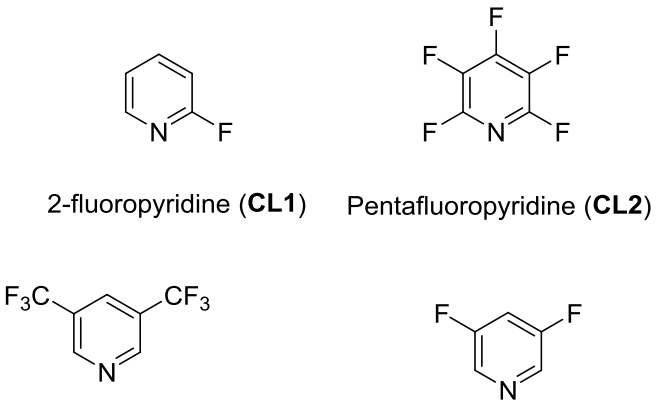


Figure 9. Co-ligand Structure.

5.2 Optimization of Catalytic Reaction

General Procedure for Determining Effect of Ligand at 10 mol % of Catalyst Loading

To a scintillation vial (5 mL) the amination reagent, **1** (140 μmol, 1.0 equiv), benzene (0.50 mL, 5.6 mmol, 40 equiv), palladium acetate trimer (14 μmol, 10 mol %) and corresponding ligands (14 μmol, 10 mol %) were added. The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 h. The reaction was allowed to cool to room temperature and 0.5 mL of a standard solution of 10.0 mg of 1,3-dinitrobenzene (0.6mmol) in 10 mL of $CDCl_3$ was added to the mixture. The resulting solution was filtered through celite. The amount of product was determined by quantitative NMR analysis (relaxation time = 15 s), using the signals at 8.99 ppm (1,3-dintirobenzene) and 2.12 ppm (acetylaniline).

Table 1. Yields for reaction in benzene in the presence of monodentate acridine derivatives at 100 °C after 24 h. Conditions: Benzene (0.50 mL, 5.6 mmol, 40 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligand (14 μmol, 10 mol %).

Amination Reagents (1eq)	Ligand (10 mol %)	Additive	Yield %
1	**L1**	-	11.3 ± 0.5
1	**L1**	AcOH (1.0 eq)	29.3 ± 0.9
1	**L1**	AgOAc (5 mol %)	27.1 ± 0.8
1	**L2**	-	12.3 ± 0.7
1	**L2**	AcOH (1.0 eq)	44.6 ± 1.0
1	**L2**	AgOAc (5 mol %)	29.1 ± 0.6
1	**L3**	-	12.1 ± 0.4
1	**L3**	AcOH (1.0 eq)	33.2 ± 1.1
1	**L3**	AgOAc (5 mol %)	32.3 ± 0.3

General Procedure for Determining Effect of Amination Reagents at 10mol% of Catalyst Loading

To a scintillation vial (5 mL) was added the benzene (0.50 mL, 5.6 mmol, 40 equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μmol, 10 mol %) and corresponding amination reagents (140 μmol, 1.0 equiv). The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p.16.

Table 2. Yields for reaction in benzene under the presence of different amination reagents at 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), amination reagents (140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %).

Amination Reagents (1eq)	Ligand (10 mol %)	Yield %
1	**L1**	11.3 ± 0.5
2	**L1**	27.3 ± 0.5
1	**L2**	12.3 ± 0.7
2	**L2**	32.1± 1.0

General Procedure for Determining Effect of Additives at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagents (1.0 equiv), benzene (0.50 mL, 5.6 mmol, 40 equiv), palladium acetate trimer (14 μmol, 10 mol %) and corresponding ligands (14 μmol, 10 mol %). The vessel was sealed with a Teflon cap,

placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 3. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), amination reagents (140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), additives.

Amination Reagents (1eq)	Ligand (10 mol %)	Additive	Yield %
1	**L1**	-	11.3 ± 0.5
1	**L1**	AcOH (1.0 eq)	29.3 ± 0.9
1	**L1**	AgOAc(5 mol %)	27.1 ± 0.8
2	**L1**	-	27.3 ± 0.5
2	**L1**	AcOH (1.0 eq)	17.3 ± 1.1
2	**L1**	AgOAc(5 mol %)	23.1 ± 0.8
1	**L2**	-	12.3 ± 0.8
1	**L2**	AcOH (1.0 eq)	44.6 ± 0.9
1	**L2**	AgOAc(5 mol %)	39.1 ± 1.0
2	**L2**	-	32.1 ± 1.0
2	**L2**	AcOH (1.0 eq)	18.3 ± 0.8
2	**L2**	AgOAc(5 mol %)	26.3 ± 1.0

General Procedure for Determining Effect of the Solvent at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagent (140 μmol, 1.0 equiv), benzene (12.5 μL, 140 μmol, 1.0 equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), additive and corresponding solvent (0.5 mL). The

vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 4. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (140 μmol, 1.00 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), dichloroethane (0.5 mL) additives.

Ligand (10 mol %)	Additive	Yield %
L1	-	3.6 ± 1.0
L1	AcOH (1.0 eq)	8.0 ± 1.0
L1	AgOAc (5 mol %)	10.6 ± 2.0
L2	-	3.1 ± 0.9
L2	AcOH (1.0 eq)	9.2 ± 1.0
L2	AgOAc (5 mol %)	10.3 ± 2.0

Table 5. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (140 μmol, 1.00 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), Acetonitrile (0.5 mL) additives.

Ligand (10 mol %)	Additive	Yield %
L1	-	0
L1	AcOH (1.0 eq)	4.6 ± 2.0
L1	AgOAc (5 mol %)	4.0 ± 1.0
L2	-	3.6 ± 2.0
L2	AcOH (1.0 eq)	4.0 ± 1.0
L2	AgOAc (5 mol %)	4.2 ± 2.0

Table 6. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (140 μmol, 1.00 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), Mesitylene (0.5 mL) additives.

Ligand (10 mol %)	Additive	Yield %
L1	-	11.1 ± 0.9
L1	AcOH (1.0 eq)	13.1 ± 0.4
L1	AgOAc (5 mol %)	14.4 ± 0.7
L2	-	14.3 ± 0.2
L2	AcOH (1.0 eq)	16.4 ± 0.3
L2	AgOAc (5 mol %)	15.1 ± 0.7

Table 7. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (140 μmol, 1.00 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), **L2** (2.6mg, 14 μmol, 10 mol %), Solvents (0.5 mL) additives.

Solvent (0.5 mL)	Additive	Yield %
Dibuthyl Ether	AcOH (1.0 eq)	10.9 ± 0.8
Dibuthyl Ether	AgOAc (5 mol %)	7.4 ± 0.8
Benzonitrile	AcOH (1.0 eq)	0
Benzonitrile	AgOAc (5 mol %)	0
Trifluorotoluene	AcOH (1.0 eq)	10.0 ± 0.9
Trifluorotoluene	AgOAc (5 mol %)	7.7 ± 1.1
Tert-amyl alcohol	AcOH (1.0 eq)	0
Tert-amyl alcohol	AgOAc (5 mol %)	0
Hexafluorobenzene	AcOH (1.0 eq)	11.0 ± 0.8
Hexafluorobenzene	AgOAc (5 mol %)	9.1 ± 1.1

General Procedure for Determining Behavior of Toluene at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagent (140 μmol, 1.0 equiv), Toluene (5.6 mmol, 40.0 equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μmol, 10mol%), additive and corresponding solvent (0.5 mL). The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 8. Yields for reaction in toluene under the presence of different additives at 100 °C after 24 hr. Conditions: Toluene (5.6 mmol, 40.0 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), additives.

Ligand (10 mol %)	Additive	Yield %	o/m/p
L1	-	12.9 ± 1.0	1:12:10
L1	AcOH (1.0 eq)	14.1 ± 0.9	1:7:7
L1	AgOAc (5 mol %)	12.3 ± 0.8	1:10:9
L2	-	18.9 ± 2.0	1:11:9
L2	AcOH (1.0eq)	31.3 ± 4.0	1:5:3
L2	AgOAc (5 mol %)	29.9 ± 2.0	1:4:3

General Procedure for Determining Effect of Loading of Additives at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagent (140 μmol, 1.0 equiv), Benzene (0.5 mL, 5.6 mmol, 40.0 equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μmol, 10 mol %) and corresponding additive with different amount. The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 9. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), additives.

Ligand (10 mol %)	AgOAc (mol%)	Yield %
L1	5 %	20.1 ± 0.9
L1	10 %	27.3 ± 1.5
L1	20 %	17.0 ± 1.1
L1	30 %	15.3 ± 0.9
L2	5 %	36.3 ± 0.9
L2	10 %	42.5 ± 1.8
L2	20 %	41.3 ± 1.6
L2	30 %	37.3 ± 1.4
L3	5 %	27.3 ± 0.9
L3	10 %	33.5 ± 1.8
L3	20 %	25.3 ± 1.6
L3	30 %	21.3 ± 1.4

Table 10. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), additives.

Ligand (10 mol %)	AcOH (equiv)	Yield %
L1	0.3 eq	20.2 ± 2.1
L1	0.6 eq	27.3 ± 1.7
L1	1.0 eq	29.3 ± 1.6
L1	1.3 eq	25.3 ± 2.0
L1	1.6 eq	17.3 ± 0.9
L2	0.3 eq	27.4 ± 2.6
L2	0.6 eq	32.3 ± 1.6
L2	1.0 eq	46.3 ± 1.8
L2	1.3 eq	37.3 ± 1.7
L2	1.6 eq	31.0 ± 2.0
L3	0.05 eq	21.1 ± 1.3
L3	0.1 eq	29.2 ± 1.0
L3	0.2 eq	36.3 ± 1.5
L3	0.3 eq	35.2 ± 2.5
L3	0.4 eq	33.5 ± 2.0
L3	0.6 eq	27.3 ± 1.7
L3	1.0 eq	29.3 ± 1.6
L3	1.3 eq	25.3 ± 2.0
L3	1.6 eq	17.3 ± 0.9

General Procedure for Determining Effect of Ligand Loading

To a scintillation vial (5 mL) was added the amination reagent (140 μmol, 1.0 equiv), Benzene (0.5mL, 5.6mmol, 40.0equiv), palladium acetate trimer(1.6mg, 7μmol, 5 mol %) , ligands and corresponding additive. The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 11. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (0.5mL, 5.6mmol, 40equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$,(1.6mg, 7μmol, 5 mol %) , **L3** and additives.

L3 (mol %)	Additive	Yield %
5%	AgOAc (5 mol %)	23.4 ± 2.0
5%	AcOH (1eq)	19.3 ± 1.6
10%	AgOAc (5 mol %)	19.3 ± 1.9
10%	AcOH (1eq)	16.3 ± 1.2

General Procedure for Determining Effect of Temperature at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagent (560 μmol, 4.0 equiv), Benzene (0.5 mL, 5.6 mmol, 40.0 equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μmol, 10 mol %) and corresponding additive with different amount. The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and

stirred at 80, 90, 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16.

Table 12. Yields for reaction in benzene under the presence of different additives at 80, 90, 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), **L3** (3.6 mg, 14 μmol, 10 mol %), additives.

Additive (equiv)	Temp ^oC	Yield %
-	100	11.1 ± 1.1
AcOH (1.0 eq)	100	31.2 ± 2.1
AgOAc (5 mol %)	100	42.5 ± 1.8
-	90	11.7 ± 0.9
AcOH (1.0 eq)	90	23.2 ± 1.5
-	80	6.1 ± 1.3
AcOH (1.0 eq)	80	7.2 ± 1.6

General Procedure for Determining Effect of 50 % of Product at 10 mol % of Catalytic Loading

To a scintillation vial (5 mL) was added the amination reagent1 (140 μmol, 4.0 equiv), Benzene (0.5 mL, 5.6 mmol, 40.0equiv), palladium acetate trimer (14 μmol, 10 mol %), ligands (14 μ mol, 10 mol %) , acetanilide (0.5 eq) and corresponding additive with different amount. The vessel was sealed with a Teflon cap, placed on a pre-heated heating block and stirred at 100 °C for 24 hr. Workup and analysis was performed in analysis to the procedure on p. 16. The yield of reactions with product was calculated by adding the percentage amount of aminated acetanilide to the detected percentage amount of acetanilide then subtracted by 50 %.

Table 13. Yields for reaction in benzene under the presence of different additives at 100 °C after 24 hr. Conditions: Benzene (0.5 mL, 5.6 mmol, 40 equiv), **1** (16.0 mg, 140 μmol, 1.00 equiv), $Pd(OAc)_2$ (3.1 mg, 14 μmol, 10 mol %), ligands (14 μmol, 10 mol %), acetanilide (0.5 eq) and additives.

Ligand (10 mol %)	Additive	Acetanilide (mol%)	Calculated Yield %
L3	AgOAc (10 mol %)	0%	42.5
L3	AgOAc (10 mol %)	50%	22.1
L3	AcOH (1.0 eq)	0%	31.2
L3	AcOH (1.0 eq)	50%	16.9
L2	AcOH (1.0 eq)	0%	44.1
L2	AcOH (1.0 eq)	50%	18.2
L1	AcOH (1.0 eq)	0%	27.6
L1	AcOH (1.0 eq)	50%	10.2

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Secondary Sources

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