

Carbonylation reactions of aryl-dihalides with mixed nucleophiles

Kugler Valentin

November 21, 2024

Abstract

Transition metal catalyzed reactions display notable functional group tolerance and selectivity, allowing for the construction of complex molecules from their building blocks. Through the use of palladium catalyzed amino-, alkoxycarbonylation, and coupling of phenylene dihalides with bifunctional nucleophiles, we attempted to develop methods for the selective synthesis of 7 and 8 membered rings, namely dibenzoxazepinones and dibenzoxazocinones. The one-pot reactions conducted under carbon monoxide atmosphere resulted in the formation of various unexpected products, such as phthalimides and benzoxazole derivatives, however with optimization of reaction conditions the target compounds were formed with good to excellent conversion and selectivity.

Contents

1	List of abbreviations	3
2	Literature summary	4
2.1	Summary of homogeneous catalytic carbonylation reactions	4
2.1.1	Introduction	4
2.1.2	Transition metal catalysis	4
2.2	Carbonylative synthesis of amides	10
2.3	Carbonylative synthesis of esters	12
2.4	Homogeneous catalytic C-O & C-N coupling reactions	15
2.5	Phenylene-dihalides' homogeneous catalytic reactions	18
2.6	Applications of bifunctional nucleophiles in homogeneous catalytic reactions	21
3	Goal of research	23
4	Experimental results	24
4.1	Carbonylation reactions in the presence of 2-aminophenol	24
4.1.1	Carbonylation of 1,2-dibromobenzene	24
4.1.2	Reaction of 2-aminobenzylamine with 1,2-dibromobenzene	26
4.1.3	Carbonylation of 2-bromochlorobenzene	27
4.1.4	Carbonylation of 2-bromiodobenzene	28
4.1.5	Carbonylation of 1,2-diiodobenzene in presence of 2-(methylamino)phenol	29
4.1.6	Carbonylation of 2-bromiodobenzene in presence of 2-(methylamino)phenol	29
5	Methodology	31
5.1	Reagents	31
5.2	Analytical methods	31
5.2.1	Gas Chromatography - Mass Spectrometry	31
5.2.2	Nuclear Magnetic Resonance	31
5.3	Carbonylation reactions	31
5.4	Product characterisation	32
6	Summary	32
7	Acknowledgements	32

1 List of abbreviations

CO	Carbon monoxide
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
TPP	Triphenylphosphine
DPPP	1,3-Bis(diphenylphosphino)propane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DCPP	1,3-Bis(dicyclohexylphosphino)propane
$P(o-tolyl)_3$	Tris(<i>o</i> -tolyl)phosphine
$BuPAd_2$	Di(1-adamantyl)- <i>n</i> -butylphosphine
cod	1,5-cyclooctadiene
TBDMSOTf	Tert-butyldimethyl silyl triflate
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
MeCN	Acetonitrile
OTf	Trifluoromethanesulfonate

2 Literature summary

2.1 Summary of homogeneous catalytic carbonylation reactions

2.1.1 Introduction

"Homogenous catalysis" entails that the reactants and the catalyst are in the same phase, which during our experiments is liquid. These reactions often utilize an organometallic complex as the catalyst. Transition metal catalyzed reactions are used to produce bulk (e.g. oxo-process) and fine chemicals. The reason these metals have catalytic properties is due to their incompletely filled d orbitals, allowing them to undergo redox reactions, be coordinated by various substrates which then can interact with ease to form the desired product.

In general, the benefits of employing these reactions allows for introduction of various functional groups under relatively mild conditions, temperatures varying from RT to 120°C, and pressure in the range of 1 to 40 bars. As a result of these mild conditions, the reactions can become a viable part of a chemist's toolbox as long as they have access to high-pressure reaction vessels, and their laboratory is equipped to work with carbon monoxide in a safe manner. While in academic laboratories these reactions are conducted batch-wise, in industry often continuous-mode production is employed.

The term "carbonylation" refers to the insertion of a carbonyl group into a given substrate.¹ There is a wide array of carbonylation reactions that have been documented, however I would like to examine the carbonylations of aryl halides and alkenes in presence of nucleophiles.

In the carbonylation with nucleophiles, a palladium (II) precatalyst is reduced to Pd(0) and forms an organometallic complex with the ligand. The resulting PdL_2 complex undergoes oxidative addition with the aryl halide, and following the coordination of CO a migration occurs yielding an acyl complex. In the presence of a base and a nucleophile, a nucleophilic attack occurs at the acyl ligand, and through a reductive elimination we regain the original PdL_2 , allowing the catalytic cycle to continue. (Figure: 1)

2.1.2 Transition metal catalysis

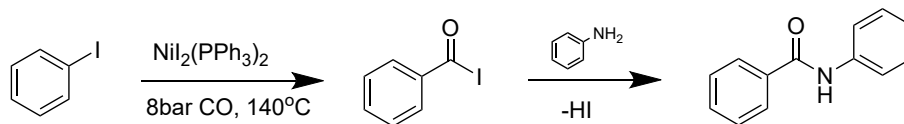


Figure 2: Nickel phosphine catalyzed carbonylation

While nickel shows widespread industrial utility as the catalyst for olefin carbonylation, its laboratory scale use is sparse due to the formation of toxic and stable byproduct $Ni(CO)_4$ formation.² Nickel carbonyl, and $Ni(CO)_2(PPh_3)_2$ complexes react unselectively with iodobenzene and aniline under nitrogen atmosphere at 100°C, functioning as the CO source, however the acyl complex undergoes reductive elim-

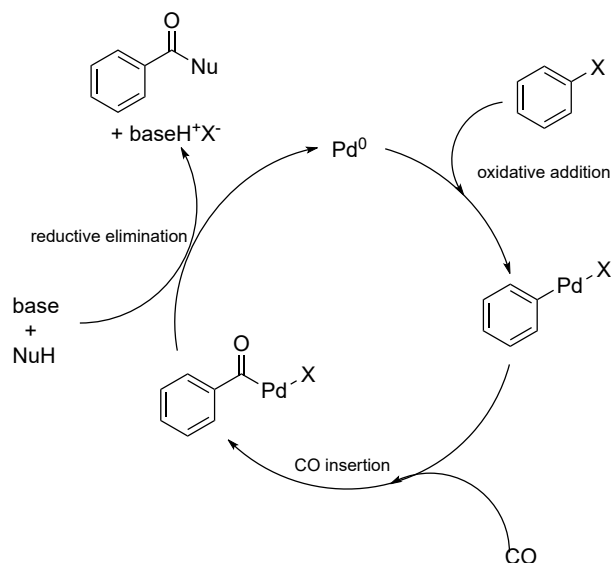


Figure 1: Proposed mechanism for palladium catalyzed carbonylation of aryl halides with nucleophiles

ination to form into the corresponding acid iodide derivative, which in turn reacts with the nucleophile.³ When the reaction is conducted under CO atmosphere, high pressures and temperatures above 140°C are required for aryl iodides to be converted into the corresponding amides, under low pressures the catalyst is rendered inactive. (Figure: 2)

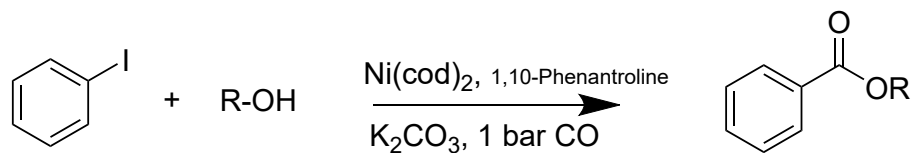


Figure 3: Nickel 1,5-cyclooctadiene catalyzed alkoxy carbonylation

Recently, 1,5-cyclooctadiene complexed nickel with 1,10-phenanthroline ligands has been shown to allow for the alkoxy carbonylation of various aryl iodides under 1 atmosphere of CO pressure in DMF with K_2CO_3 as a base.⁴ Interestingly, reactions conducted under these conditions are assumed to follow a mechanism similar to palladium catalyzed alkoxy carbonylations, with the reductive elimination being the product yielding step. (Figure: 3)

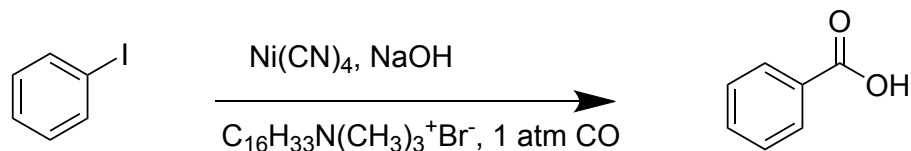


Figure 4: Nickel cyanide catalyzed carbonylation

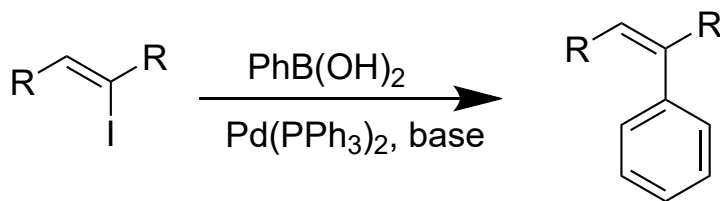


Figure 6: Suzuki coupling

Alper has demonstrated the ability of Ni(CN)_4 to catalyze the carbonylation of allyl and aryl halides under phase transfer conditions.⁵ (Figure: 4) The reaction of various aryl iodides with aqueous sodium hydroxide using cetyltrimethylammonium bromide as a phase transfer catalyst under 1 atmosphere of CO at 90°C produces good yields of the corresponding benzoic acid. The activity of the catalyst is sensitive to the concentration of hydroxide along with the polarity of the solvent, with 5N NaOH using nonpolar solvents such as toluene leading to the optimal reaction conditions. Previously a similar photocatalyzed hydroxycarbonylation catalyzed by cobalt cyanide has been reported, conducted under similar phase transfer conditions.

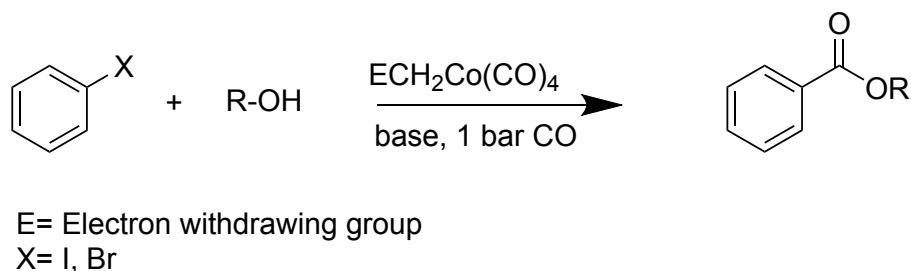


Figure 5: Alkylcobalt carbonyl catalyzed carbonylation

Using electron deficient alkylcobalt carbonyl complexes in catalytic amounts, the carbonylation of a (hetero) aryl halides in neat alcoholic solutions can be performed under 1 atmosphere of CO allows for the production of the corresponding esters in good yields.⁶ (Figure: 5) The electron withdrawing substituent on the catalyst increases its stability, along with its activity. Use of electron deficient aryl halides allows for greater rates. The reaction proceeds faster when short chain alcohols are used as the solvent. The 'in situ' generation of the catalyst is possible through the use of cobalt carbonyl complex in the presence of alkyl halides. This reaction allows for the intramolecular carbonylation of aryl bromides with N/O terminal alkyl side chains to produce the corresponding benzolactams and benzolactones.

Palladium The Suzuki coupling allows for the coupling of vinyl halides with aryl-, alkenyl boronic acids using a palladium catalyst in presence of a base.⁷ (Figure: 6)

The carbonylation of olefins is facilitated by the presence of electrophilic Pd^{II} , allowing the simultaneous coordination of the π system and carbon monoxide.⁸ (Figure: 7) These reactions allow for the

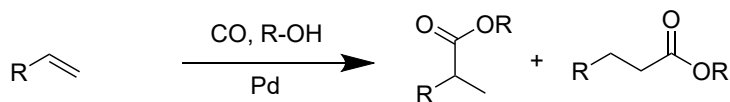


Figure 7: Alkene alkoxy carbonylation

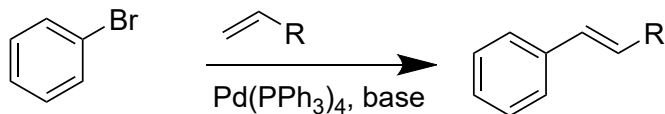


Figure 8: Heck coupling, C-H activation

formation branched and terminal carboxylic acid derivatives, and with utilization of appropriate catalytic systems allows for high degrees of selectivity between these products.

In 1986 Kobayashi and Tanaka reported the carbonylation of organic halides with activated methylene compounds under CO atmosphere in presence of Et_3N , resulting in the formation of ketones. These reactions require the presence of strong electron withdrawing groups to allow for the activation of the C-H bond, which in turn will provide the nucleophile for the reaction.

In 1972 Heck described the palladium catalyzed coupling of iodobenzene with styrene, which has been coined as the "Heck" reaction.¹ (Figure: 8)

Catalyst The formation of the active catalyst complex requires the addition of a Pd(0) or a Pd(II) precatalyst. Pd(0) have the advantage of not requiring reduction to form the active species, however they are generally not considered shelf-stable. When Pd(II) precursors are used, its reduction to Pd(0) is affected by choice of base and concentration of added ligand. Pd^{II} can also be reduced through β -hydride elimination, or by carbon monoxide in the presence of acetate ions, resulting in the formation acetic anhydride and carbon-dioxide.⁹

Nucleophile When examining nucleophiles in amino/alkoxy carbonylation, basicity-acidity is the most influential factor in determining reactivity, followed by steric hindrance and electronic properties.¹⁰ Interestingly, reactivity trends with regards to basicity-acidity are opposing when amines and alcohols are compared. Amine with higher degrees of substitution are able to stabilize the positive charge on nitrogen created upon coordination to the catalytic metal center, leading to increased binding affinity, and by extension the more time the reagent spends near the catalytic center the more likely is it to react with the acyl ligand of the intermediate. As a consequence, aliphatic amines display higher reactivity, while aromatic amines are less reactive, since they have difficulty in stabilizing the positive charge after coordination. N-Phenylaniline has shown low reactivity in previous studies,¹¹ presumably due to the notable lack of basicity - in fact, N,N-diaryl amines exhibit acidity, due to the extensive stabilization of the anionic form.

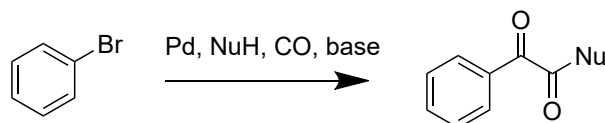


Figure 9: Ketocarboxamide formation

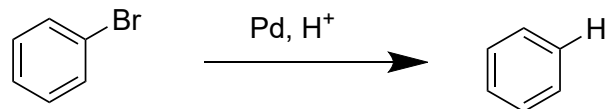


Figure 10: Reductive dehalogenation

Pd carbonyl complex The carbonyl ligand reduces electron density at the metal center by back-donation, making it less likely to undergo oxidative addition.

Nucleophilic attack, reductive elimination Ligands that are otherwise electron rich such as CO and acyl anion equivalent become activated towards nucleophilic attack upon coordination to electron deficient PdL_2 complexes.

When the catalyst operates on aliphatic substrates, such as alkyl halides, amines, alcohols, the active catalyst can be generated through β -hydride elimination.

When examining the makeup of the reaction mixture, there are various unexpected products present, and it's good to know how they affect the reaction. (Figure: 9, 10, 11, 12) Since one of the methods of producing the active Pd^0 species is through a redox reaction with the phosphine ligands, leading to the formation of phosphine oxides. The different complexes composed of palladium, carbon monoxide, ligand, halide ions are in constant equilibrium, with each of them offering different activities as catalysts, and some of them being completely inactive. The palladium catalyst's stability depends greatly on ligand identity and concentration, and in conditions offering low stability the production of palladium nanoparticles occurs readily.

The reaction doesn't always pan out as imagined, some conditions lead to ketoamide formation, while dihalides can produce double carbonylation products such as phthalimides with amines, and phthalic anhydride with water. Presence of water in the reaction suppresses the desired carbonylation reaction with the nucleophile, since water can act as a nucleophile as well, resulting in formation of carboxylic

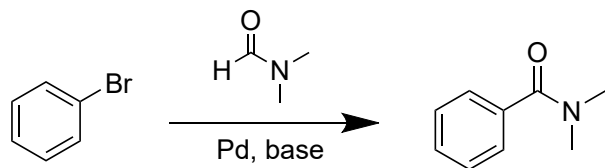


Figure 11: Side reaction with dimethylformamide

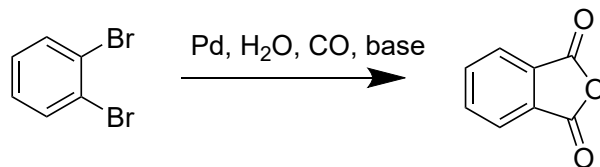


Figure 12: Phthalic anhydride formation with water

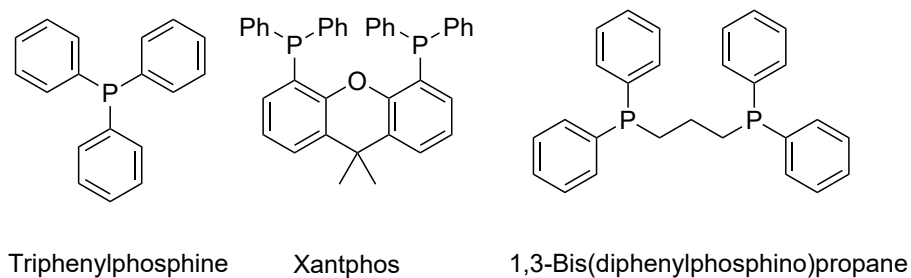


Figure 13: Different ligands used for transition metal catalyzed carbonylation

acids. Reductive dehalogenation can occur when proton sources are present in the solution, and this side reaction is greatly depended on the identity of the ligand as well. To decrease these unwanted side products, care has to be taken to use dry glassware and anhydrous solvents when conducting the reaction, along with ensuring that all air is removed from the system, the oxygen content of which can also poison the catalyst.

Ligand The choice of ligand is one of the key factors in deciding whether transition metal catalyzed reactions will succeed according to our expectations. The type of reaction, nature of the nucleophile and aryl halide has to be taken into account when deciding which ligand to utilize. These variables affect key mechanistic steps such as oxidative addition, reductive elimination, migration - which can be modulated with the right ligand to our benefit.

When the catalytic activity of palladium for the carbonylation of vinyl halides was demonstrated, the absence of a ligand in all 3 products forming in equal amounts, however the reaction was conducted with added TPP the reaction displayed notable stereoselectivity.⁹

During migration step, organopalladium complexes facilitating the formation of the transition state increase rates.¹² Larger bite angles allow for greater level of interaction between the substrates, and rigid backbones geometrically restrict possible coordination modes.

For aryl chlorides to undergo oxidative addition, the ligand needs to be sufficiently basic, preferably form a 6 membered chelate ring, have chelating properties and steric bulk.¹³

One of the factors influencing catalytic activity is the cone angle of the ligand, the optimum range being in the range of 160-180. Electron donating ligands increase rate of oxidative addition, however when it is not rate determining less electron donating ligands increase rate of carbonylation step. Using

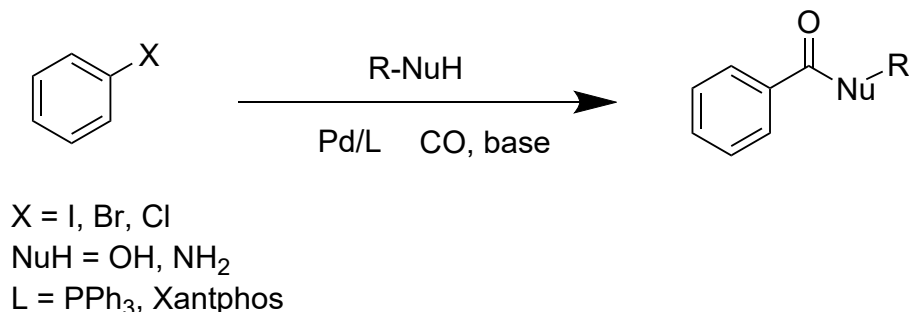


Figure 14: Palladium catalyzed carbonylation of aryl halides in presence of nucleophiles

bidentate aromatic phosphine ligands inhibits competing beta elimination reaction.¹⁴ Sterically hindered alkyl monophosphines allow the activation of less reactive alkyl halides in coupling with weaker oxygen nucleophiles.

These reactions can be carried out without the use of a CO atmosphere by using formic acid, transition metal carbonyls as CO sources, or by using formates or formamides as substrates.¹ Utilizing these methods allows for the mitigation of risks posed by CO use, such as CO poisoning or negate the use of pressurised vessels.

During the course of the reaction, the catalyst slowly loses its activity, either through the formation of palladium nanoparticles or inactive complexes.¹⁵ The former shows activity towards certain carbonylation reactions, and can be recycled by filtering of reaction mixture. There have been methods devised to improve the recyclability of the catalyst, such as supporting the catalyst on a fixed bed, or through the use of ionic liquids in which products have poor solubility.

In recent years reactions utilizing palladium catalysts have become a staple in organic chemistry, enjoying widespread use during the synthesis of pharmaceuticals and fine chemicals.

As we've observed, the reason these reactions are of interest is due to their ability to proceed under mild conditions, with notable selectivity and atom efficiency, allowing the parallel functionalisation of molecules in a versatile manner, while using less harsh reagents than alternative reactions.

2.2 Carbonylative synthesis of amides

Using $\text{PdX}_2(\text{PPh}_3)_2$, various aryl, heterocyclic bromides and iodides were aminocarbonylated by Heck at atmospheric pressure. 2-Chloropropene's aminocarbonylation required 40 bars of CO pressure.⁹ It was found that the reaction proceeded more rapidly than the ester synthesis under these conditions, and that if the nucleophile was sufficiently basic, it didn't require additional base. Complementary to their findings, a mechanistic study by Lin Yamamoto proposed that alkoxy and aminocarbonylation proceed through different mechanism to rationalize their findings.¹⁰ Higher L/Pd ratios, and employment of a bulky strong base both suppressed the alkoxy carbonylation reaction considerably, implying that it wasn't sufficient

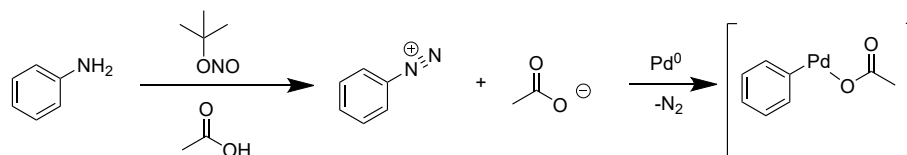


Figure 15: Diazotation of aniline, and the following oxidative addition

to utilize a strong base, but that the base has to be able to deprotonate the ethanol coordinated to the sterically hindered complex. Reactivity of amines were found to correlate with their basicity, inconsistent with mechanisms that assume direct deprotonation of the amine coordinated to the metal center, therefore it's presumed that deprotonation happens after the migration of the amine to the acyl ligand.

Buchwald labs has developed a general method for synthesis of Weinreb amides at atmospheric pressure using Pd/Xantphos, which proved to be successful for the aminocarbonylation of aryl bromides.¹⁶ The catalytic system proved to have great tolerance for a wide variety of substrates, however aryl bromides with ortho methyl ester functionalities yielded phthalimides upon reaction with primary amines. During a study of mild condition aminocarbonylation of aryl-chlorides, DCPD proved to be a suitable ligand, believed to be due to its 3 carbon linker between the phosphorous atoms, along with its properties of being electron-rich and bulky. While screening for solvents, the peculiar effect of sodium phenoxide acting as an acyl transfer catalyst was observed. Using 'in situ' IR spectroscopy, the reaction was monitored and an intermediate phenyl ester species was found to be present for the duration of the transformation. Kinetic study of a phenyl ester in presence of the amine resulted in very slow formation of the product amide, however upon addition of sodium phenoxide rapid conversion to amide was observed. These observations suggest that phenoxide intercept the acyl palladium species, and in a following step acts a base catalyst for the reaction of amine with the intermediate phenyl ester.

DBU has frequently been applied as a base in aminocarbonylation, however recently its ability to function as a cocatalyst has been demonstrated.¹⁷ During the base screening of a Pd-Xantphos catalyzed aminocarbonylation, DBU led to a faster reaction with good selectivity, while K_2CO_3 exhibited slower conversion, but excellent selectivity. Experiments conducted without the presence of phosphine ligands resulted in the formation of the product amide, and an optimized catalytic system consisting of $Pd(dba)_2$, DBU, and K_2CO_3 was found. K_2CO_3 was applied as a base to regenerate the DBU from the HI salt. They found that highly electron poor anilines didn't allow for the formation of the amide, and noted the absence of ketoamide formation when aniline was used as a nucleophile, in contrast to similar studies conducted previously, where a significant formation of ketoamides was observed when alkyl-amines were used as a nucleophile.

A variety of alkenyl and aryl iodides were carbonylated in presence of $tBuNH_2$, yielding secondary amides and α -ketoamides.¹⁸ Upon isolation of the compounds, treatment with TBDMSOTf in toluene at modest temperatures to induce cleavage of the N-tBu group, resulting in primary amides. (Figure: 16)

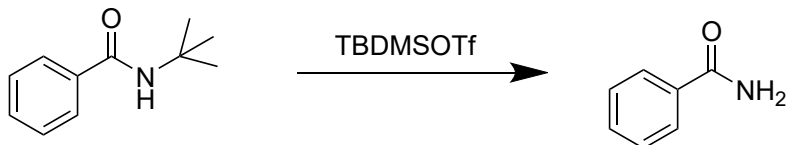


Figure 16: Amide deprotection to yield primary amides

The 'in situ' diazotization of aniline in presence of acetic acid and *tert*-Butyl nitrite has proven to be a feasible way of generating N-arylbzamidates.¹⁹ The reaction proceeds well in polar solvents with monodentate phosphine ligands at higher CO pressures. It's assumed that the 'in situ' generated PhN_2OAc undergoes oxidative addition with the complex, releasing N_2 in the process, and ligand exchange of the acetate ion for aniline allows migratory insertion to take place, forming the product. (Figure: 15)

Perry performed a series of carbonylations of 4-chloro-N-phenylphthalimide with aniline using various halide salts to study their effect on the reaction.²⁰ The catalytic system was comprised of $PdCl_2(PPh_3)_2$, using DBU in DMAc, and while aryl-chlorides are generally unreactive under these conditions, the substrate was sufficiently activated due the presence of electron-withdrawing groups. The degree of rate enhancement increased with NaI concentration, with rate improvement diminishing above the use of 1 equivalent. Out of the various halide salts, iodide provided the greatest enhancement. Upon optimization of conditions using 4-chlorophenyl phenyl sulphone as a model substrate, the scope of the reaction was expanded to substituted aryl chlorides, it became evident that strong electron withdrawing groups were required for the reaction to succeed. It is postulated that an anionic zerovalent iodide palladium complex is responsible for the rate enhancement.²¹ Catalyst stability is a key factor in Pd catalyzed reactions, since the reactions were conducted with DBU, it is possible that increased catalyst availability was ensured by DBU through prevention of Pd_nL_m formation.²²

Palladium catalyzed carbonylation reactions of aryl halides and triflates under 2 bar $CO - NH_3$ atmosphere presented a new method of generating primary amides.²³ A wide selection of bidentate ligands were activate for aryl bromides, however for chlorides $n - BuPAd_2$ was necessitated. Electron poor substrates were reluctant to undergo the transformation, but still produced the primary amide in moderate yield. Ammonia plays a dual role in this reaction, it not only function as a nucleophile, but also fulfills the role of base in reductive elimination to regenerate the catalyst.

2.3 Carbonylative synthesis of esters

The initial chemical trials on the catalytic activity of palladium with regards to alkoxycarbonylation by Heck have demonstrated that the alkoxycarbonylation of aryl iodides is feasible using Pd^0 , even if no ligand is present.²⁴ It has been noted that the presence of a base (in the form of a tertiary amine) is required for the reaction to proceed. Aryl bromides required activation in the form of strong electron withdrawing groups to undergo carbonylation, however addition of TPP allowed for the formation of

an organometallic complex which is able to undergo oxidative addition with unactivated aryl bromides. Electron withdrawing substituents on the aryl-halide were shown to increase, while electron donating substituents decrease the rate of the reaction. When the carbonylation of aryl-iodides and aryl-bromides was attempted in the same reaction mixture, the conversion of aryl-iodide proceeded to completion, while the conversion of aryl-bromide was negligible, this is explained by the inhibitory effect of the iodide ions present in solution - generated during the reductive elimination step.

Along with the carbonylation of aryl halides, the system's capability extended to vinylic iodides and bromides. When the reactions were performed with palladium acetate as the sole catalyst, mixtures of E and Z isomers were produced, however when TPP is utilized the major product retains the original stereochemistry.

During the optimization of 4-bromoacetophenone's carbonylation in neat butanol as solvent/nucleophile, factors such as solvent choice, nucleophile concentration, base, CO pressure, catalyst choice and concentration have been investigated.²⁵ Increase in CO pressure resulted in significantly decreased ester formation, with the rationale that at higher CO concentrations, more coordination sites are occupied by the carbonyl ligand, therefore through π backdonation electron density is reduced at the Pd center, resulting in lower activity towards oxidative addition with aryl halides. Furthermore, the stability of the catalyst is affected by the ligand to palladium ratio, with its increase allowing for the stabilization of the catalyst even at high CO concentrations, preventing catalyst deactivation - Pd precipitation at the expense of decreased activity. Performing the reaction in different solvents, no trend in relation to solvent polarity could be deciphered, however it has been noted that decreased nucleophile concentration and increased reaction volume significantly decreased ester yield, arriving at the assumption that at low nucleophile concentrations the nucleophilic attack on the acyl complex becomes the rate-determining step. Slight excess of base allowed for the greatest degree of conversion. During the investigation of $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ as catalysts, two trends have been identified in correlation with catalyst concentration, lowered concentrations have slightly decreased yield, however the TON of the catalyst increased.

In a study of the carbonylation reaction of substituted phenols with p-iodotoluene conducted in DMF in presence of nBu_3N , both electron withdrawing and electron donating groups on the phenol, along with the presence of a CuI cocatalyst were demonstrated to increase the rate of the reaction.²⁶ Electron withdrawing groups significantly increased the rate, which can be attributed to the higher degree of deprotonation of phenol, while the increase of rate from electron-donating groups may be due to increased electron density on the phenolic oxygen. Since ionization was deemed more influential in enhancing reactivity, substituted sodium phenoxides' carbonylations were further studied, resulting in the finding that electron withdrawing groups decreased reactivity.

Phenoxycarbonylations of various aryl halides have been reported.^{27,28} (Figure: 17) In the carbonylation of 2-chloropyridine using Pd with DPPP as a ligand, 7 out of 12 phenols were isolated, with two of them being sterically hindered nucleophiles, however aromatic aldehydes, nitro groups, and nitriles were

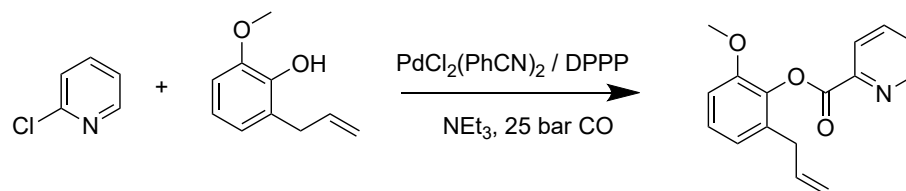


Figure 17: Phenoxycarbonylation of 2-chloropyridine

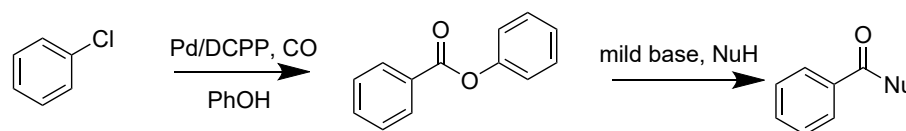


Figure 18: Buchwald phenoxycarbonylation

not tolerated. The phenoxycarbonylation of bromobenzene in dioxane was screened using various ligands, with the use of *BuPAd*₂ and DPPF resulting in the best yield. Using the optimized reaction conditions, excellent yield was achieved with a variety of phenols, displaying good functional group tolerance for phenols with aldehyde, ketone, aminocarbonyl, chloride, and cyano functionalities. The carbonylation of 4-methoxyphenol with a variety of bromoarenes was examined, aryl bromides of different electronic properties displayed high reactivity and selectivity, with the exception of 4-nitrobenzene.

Buchwald labs reported a mild method of phenoxycarbonylation of aryl-chlorides using shelf-stable *dcpp* · 2*HBF*₄.²⁹ (Figure: 18) Upon examination of the reactivity of aryl chlorides, they noted that electron-poor substrates preferred highly polar DMF instead of DMSO as a solvent, and that the system wasn't tolerant of ortho substituted aryl chlorides.

Under carbon monoxide free conditions, the palladium catalyzed phenoxycarbonylation of a wide array of aryl halides was conducted with phenyl formate as the reaction partner.³⁰ (Figure: 19) Initially the reaction was carried out utilizing a *Pd*–*PPh*₃/*Ru* bimetallic catalytic system, however upon investigation of the necessity of the ruthenium cocatalyst via a control reaction without *Ru* still resulted in product formation. Most phosphine-based ligands were suitable for the reaction, with the exception of bidentate ligands possessing short bridges, and monodentate ligands containing cycloalkyl substituents. During solvent screening, halogenated solvents performed poorly. The system tolerated most substituents on the aryl halides, with the presence of a nitro group still resulting in good yield, in addition vinylic and

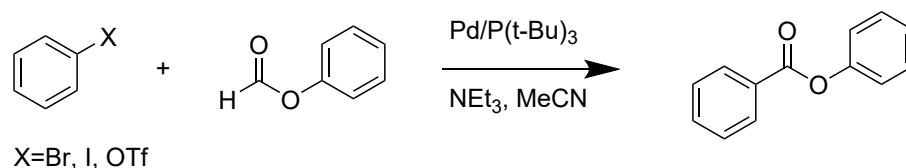


Figure 19: Carbonylation with Phenyl formate

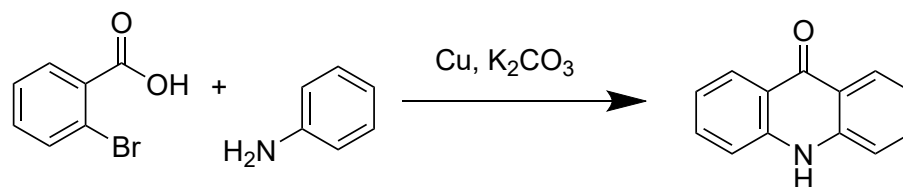


Figure 20: Copper catalyzed Ullmann coupling of aniline and 2-bromobenzoic acid

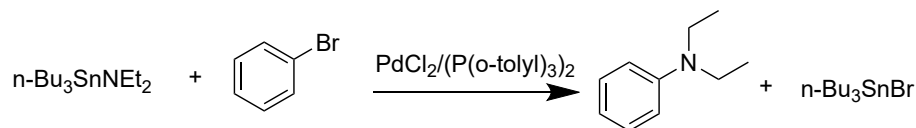


Figure 21: Migita's amination

allylic bromides also successfully underwent the reaction. Through the monitoring of reaction profile, in addition to performing a control reaction with only formate and Et_3N , it was demonstrated that the base catalyzed decarbonylation of phenyl formate is indicated to be the rate-limiting step.

2.4 Homogeneous catalytic C-O & C-N coupling reactions

Copper assisted nucleophilic displacement of aryl halides allows for the coupling of nucleophiles to the C-X bond. In contrast to nucleophilic aromatic substitution reactions, the reactivity of the halide increases in correlation to its size.³¹ (Figure: 20) The rate of the reaction is only slightly influenced by the presence of substituents para or meta to the halogen, while the presence of potential chelating groups in the ortho position have an activating effect. Unsubstituted aryl halides can be aminated in aqueous solutions of ammonia using copper catalysts of various oxidation states (0, +1, +2) at temperatures above of 150°C, while activated aryl halides can be aminated using milder conditions. Reductive dehalogenation and phenol formation compete with the amination. Amination of aryl halides sensitive to hydrolysis can be carried out in non-aqueous systems utilizing excess KF and $CuCl_2$. The Ullmann coupling of aryl halides with amines is traditionally carried out by heating with copper powder in aqueous solutions in presence of carbonate or hydroxide bases. Kinetic and ESR studies indicate that Cu^I is the active catalyst in the system. The presence of reducing agents such as Sn^{II} , Fe^{II} , Ti^{III} promote the reaction, while molecular oxygen inhibits it. The coupling of aryl halides with phthalimides yields N-arylphthalimides, from which anilines can be generated following hydrolysis. Solvent-free couplings performed with copper powder at high temperatures have been reported to give good yields of N-arylamides. Heating unfunctionalized aryl-halides and phenoxide salts in the presence of copper powder is reported to produce the corresponding phenyl ether at good yield. In a study of the coupling reaction of alkoxides with aryl halides in presence of CuI , it was noted that increasing the number of ortho methoxy substituents on the aryl halides increased the degree to which reductive dehalogenation occurred.³¹

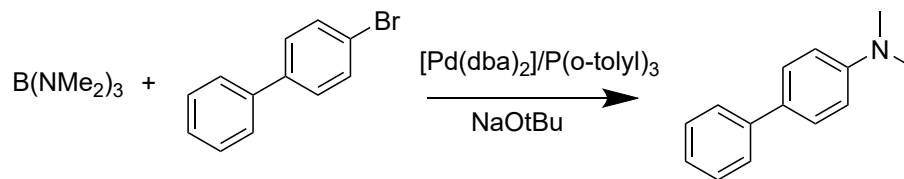


Figure 22: Buchwald's amination

In 1983, Migata reported the aromatic amination of bromobenzene with N,N-diethylamino-tributyltin using a $PdCl_2(P(O-tolyl)_3)_2$ catalyst.³² (Figure: 21) According to their report, iodobenzene and chlorobenzene weren't suitable substrates for the reaction. This amination proceeds through a mechanism different from benzyne or $S_{RN}1$ mechanisms.

The aryne mechanism proceeds through a benzyne intermediate, which possesses two electrophilic carbon atoms that can interact with nucleophiles, resulting in the formation of mixtures containing both amination products. In contrast, the product of the reaction conducted by Migata was isomerically pure. Use of the best substrate for $S_{RN}1$, iodobenzene, did not result in product formation. A control reaction was performed using p-chlorobromobenzene and potassium N,N-diethylamide in diethylamine - conditions preferential for $S_{RN}1$ -, in which the major product was N,N-diethylaminobenzene, indicating the intermediacy of p-N,N-diethylaminophenyl radical. The reaction is thought to proceed through a mechanism composed of oxidative addition, transmetalation, and reductive elimination.

Initially, Buchwald developed a method of generating aminostannanes 'in situ' for the palladium catalyzed coupling of aryl halides with amines.³³ (Figure: 22) In an attempt to abstain from the use of tin reagents, they devised a method of transaminating $B(NMe_2)_3$, which would further react with aryl halides in presence of $Pd(dba)_2/2P(o-tolyl)_3$ and $NaOtBu$ to yield arylamine. After some experimentation they found that aryl bromides react with amines efficiently in presence of the $PdCl_2(P(o-tolyl)_3)_2$ catalyst in presence of $NaOtBu$ in toluene. Aryl bromides with both electron donating and withdrawing substituents reacted efficiently, however base sensitive functional groups weren't tolerated well.

During the course of the reaction, a side product resulting from the reduction of the aryl halide forms, the process of which can be inhibited by the presence of para electron withdrawing substituents on the aryl halide and through the use of secondary amines. Following oxidative addition, a ligand exchange of halide with the anionic amine is presumed to occur, which can undergo subsequent β -hydride elimination yielding $Ar-Pd^{II}-H$, which upon reductively elimination results in the formation of the dehalogenated side product. The choice of the ligand was demonstrated to be critical for the success of the reaction, use of TPP resulted in excessive reductive dehalogenation, while DPPP left the aryl halide unreacted. For intramolecular coupling reactions, aryl iodides proved to be superior substrates and use of TPP facilitated the reaction.

Following mechanistic investigations of the palladium catalyzed coupling of tin amides with aryl halides, Hartwig arrived at a similar method of C-N coupling with the use of $LiN(SiMe_3)_2$ as base.³⁴

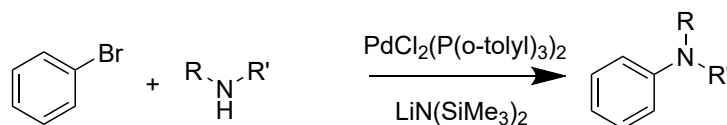


Figure 23: Hartwig's amination

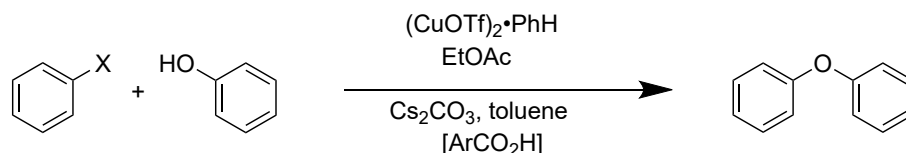


Figure 24: Buchwald C-O coupling

(Figure: 23) Oxidative addition of aryl halide to $Pd^0(P(o-tolyl)_3)_2$ results in the formation of a dimeric complex, which are cleaved by the presence of amine to form monometallic aryl halide complexes with one phosphine and one amine ligand. Upon deprotonation of the monoamine ligand, the complex can undergo reductive elimination to form the product. Since palladium, but not lithium dialkylamides provide clean reaction chemistry in presence of aryl halides, it is important that deprotonation of the amine occurs at the metal center. For reactions with $p-(nBu)C_6H_4Br$, amine, silylamide base, the resting state of the catalyst was Pd^0L_2 , leading to the conclusion that oxidative addition is the rate limiting step in this system. Reactions conducted with LiOtBu as a base had aryl bromide palladium complex as the resting state of the catalyst, meaning that this system was limited by the generation and reductive elimination of the palladium amide intermediate.

An Ullmann coupling of aryl halides and phenols utilizing catalytic amounts of copper in nonpolar solvent has been reported.³⁵ (Figure: 24) The reaction uses $(CuOTf)_2 \cdot benzene$ for improved solubility in toluene, and in the case of less reactive phenols 1-naphthanoic acid is employed as an additive to solubilize the cesium phenoxide and the intermediate. Survey of conditions indicated that Cs_2CO_3 is crucial for this reaction. The reaction tolerates a wide array of functional groups, with the exception of substrates containing amide functionalities. A mechanism involving the attack of phenoxide on the aryl halide is incongruent with the findings that the rate of the reaction is not affected by electron-withdrawing or donating substituents, along with the fact that aryl chloride and triflates remained inactive.

In a user's guide for the use of dialkylbiaryl phosphine ligands in Pd catalyzed amination, several key reaction parameters were discussed.³⁶ The ligand's structural qualities have a marked effect on its activity and stability, along with its selectivity for given nucleophiles. Large substituents on phosphine promote reductive elimination, while electron-rich groups enhance rate of oxidative addition. Other features encourage formation of the catalytically active species, or increase catalyst stability by preventing oxidation and cyclometalation. An extra equivalent of ligand relative to Pd stabilizes the catalyst and facilitates its activation. A wide array of solvents can be used for amination reactions, including ethereal

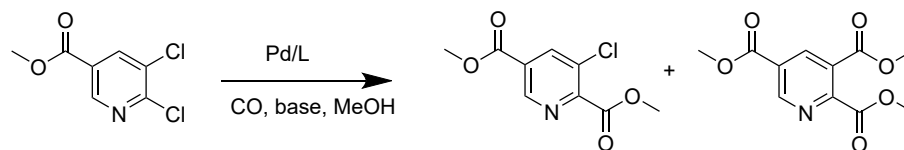


Figure 25: Alkoxy carbonylation of Methyl 5,6-dichloropyridine-3-carboxylate with methanol

solvents, water, tBuOH, and toluene. Choice of base depends on the functional groups that have to be tolerated during the course of the reaction, along with their solubilities (or lack thereof) in the solvent used. The employment of alkoxides often results in highest reaction rates and enables lower catalyst loadings. The use of $LiN(SiMe_3)_2$ allows the amination of aryl halides in presence of protic functional groups. Weak inorganic bases provide a higher degree of functional group tolerance, since these are poorly soluble in non-polar solvents, the acid-base reactions occur at the solid-liquid phase boundary. Addition of celite when using Cs_2CO_3 improves yield, presumably due to its anti-clumping effect. It is suggested that aryl iodides' poor reactivity for amination results from the formation of insoluble Pd dimers bridged by iodide anions. Heteroaryl halides can cause deactivation of the catalyst through phosphine ligand displacement when coordinating.

The ligand's identity significantly influences the course of the amination reaction, as has been demonstrated via the amination of bromobenzene utilizing various ligands.¹² Pincer complexes with wide natural bite angles resulted in greatest conversion and turnover frequencies. It's been suggested that bidentate ligands suppress β -hydride elimination as a consequence of decreased degree of coordinative unsaturation of the central Pd atom. In addition, increased bite angle promotes the reductive elimination step of the catalytic cycle, and is presumed to be responsible for the facile dissociation of the ligand from the central metal atom. The bridging oxygen of xantphos is assumed to interact with Pd upon chelation, as evidenced by the fact that when it's replaced by sulphur - a stronger donor atom - catalysis is halted accompanied by the formation of a stable cationic complex. In the case of xantphos, this donor-metal interaction facilitates halide dissociation from the complex, allowing the cationic active species to form.

2.5 Phenylene-dihalides' homogeneous catalytic reactions

Using methyl 5,6-dichloropyridine-3-carboxylate's palladium catalyzed carbonylation in neat alcohol as a model system, conditions - which were later applied to the alkoxy carbonylation of 2,3-dichloro-5-(methoxy)pyridine - were found to selectively carbonylate the pyridine at position 6, along with mixtures of mono and dicarbonylated products.³⁷ (Figure: 25) Utilizing sodium carbonate facilitated, while sodium acetate inhibited the formation of substituted products. Longer reaction times at high temperatures caused decarboxylation. Utilizing a mixture of tetrahydrofuran and the nucleophile alcohol greatly improved selectivity for the monocarbonylated product. Without water exclusion, reactions involving CO allow for the formation of hydrogen via the water-gas shift reaction, possibly resulting in side product

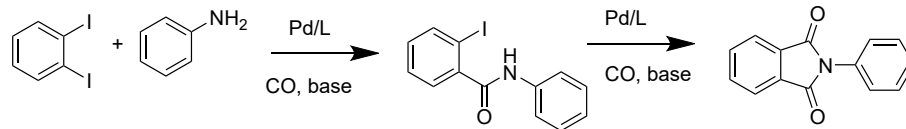


Figure 26: Phthalimide formation

formation. Under these conditions, longer chain alcohols are much less liable to undergo decarboxylation. Rhodium and cobalt salts were not reactive enough to allow for good conversion under these conditions. The use of DPPB allowed for the selective formation of monocarbonylated product, while DPPF was sufficiently active to yield the biscarbonylation product under relatively mild conditions.

With the carbonylative coupling of aniline and *o*-diiodobenzene as a model system, the reaction forming *N*-phenylphthalimide was optimized.³⁸ (Figure: 26) If the catalyst isn't sufficiently activated, the rate of oxidative addition with aryl bromides is slower than CO insertion, resulting in coordinative saturation of the Pd by carbonyl ligands. With aryl iodides, since the rate of oxidative addition is faster than carbonyl insertion, it allows the pressure to be increased without inactivating the catalyst. During the reaction condition screening, increasing temperature to 115° and pressure to 6 bar allowed the reaction to reach completion within 2 hours. The rate of the reaction decreased approximately proportionally to decreased catalyst loading, only the catalysts with phosphine ligands were active. A range of polar aprotic solvents were suitable for the reaction, however dimethylacetamide had the shortest time to completion. DBU, K_2CO_3 and NaOH allowed swift reactions, however the latter two's residual water content allows for side reactions to take place. The system was capable of operating on dibromobenzene, however the reaction took 8 times longer.

While bromiodobenzenes are generally unreactive to biscarbonylation due to the presence of iodide ions inhibiting the carbonylation of aryl bromides, several examples have been reported of their use.^{39,24}

With the use of a palladium catalyst immobilised on a supported dicationic liquid phase, meta and parabromiodobenzene's carbonylation in presence of morpholine produced the biscarbonylated product with varying degrees of success.⁴⁰ When conducting the reaction in DMF the disubstituted products were formed in trace amounts, however utilizing solvent-free conditions in presence of DABCO proved to improve yield greatly. Applying longer reaction times the conversion of *m*-bromiodobenzene and *p*-bromiodobenzene to bisamide was successful, with 73% and 58% isolated yield, respectively. With regards to carbonylation of mixed halides, these results could point toward the importance of solvent-free conditions, or demonstrate the utility of nucleophilic amine bases such as DABCO in facilitating the reaction, perhaps through its ability to break unreactive Pd dimers bridged by halide anions, or by displacing the iodide ion from the Pd's coordination sphere.

Under conditions favorable for reductive carbonylation, *p*-bromiodobenzene formed trace amounts of the corresponding diformylated product, with majority of the bromide functionality remaining unreacted.⁴¹ (Figure: 27)

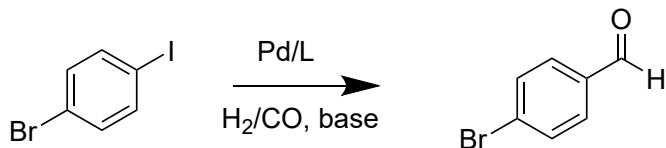


Figure 27: Reductive carbonylation of p-bromoiodobenzene

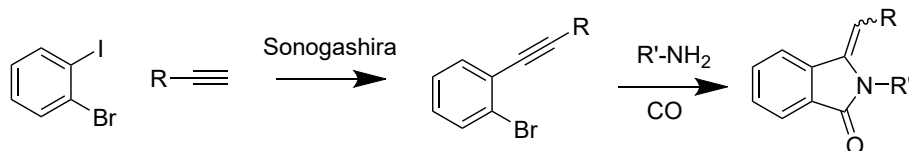


Figure 28: Sonogashira reaction of 2-bromoiodobenzene

A cascade reaction operating on various dihalides successfully resulted in the stereoselective formation of isoindolin-1-one derivatives' Z isomers.⁴² (Figure: 28) The reaction is carried out in a phosphonium salt-based ionic liquid, which facilitates catalyst recycling while also appearing to promote the reaction. During condition screening, the ring forming carbonylation-hydroamination between 1-bromo-2-(phenethynyl)benzene and benzylamine was optimized for, with the final catalytic system being comprised of $PdCl_2(PPh_3)_2/CuI$ and DBU under 1 atm of CO. Applying these conditions o-bromoiodobenzene, phenylacetylene, and benzylamine, the heterocycle was produced in excellent yield. Extending the scope of the reaction, various alkynes and amines were tolerated resulting in good to excellent yield, with the exception of aryl halides containing chlorides, the reactions of which couldn't proceed to completion. The mechanistic pathway beginning with Sonigashira coupling, followed by carbonylation and intramolecular hydroamination is assumed to be prevailing, since the Sonigashara coupling intermediate was isolable from the reaction.

The carbonylative coupling of o-bromoiodobenzene with arylboronic acids under CO successfully produces fluore-9-nones.⁴³ (Figure: 29) In the optimized catalytic system utilizing Pd/PCy_3 with Cs_2CO_3 and pivalic acid in toluene displayed tolerance for both electron-poor and rich arylboronic acids, with formyl functionalities displaying sensitivity. Extension of this method to double annulations using double arylboronic acids or 1,4-dibromo-2,5-diiodobenzene allowed for the preparation of a variety of ladder-type poly-p-phenylenes. The initial step of this reaction is presumed to be the Suzuki coupling, the bond formation of which facilitates C-H activation for the intramolecular carbonylation.

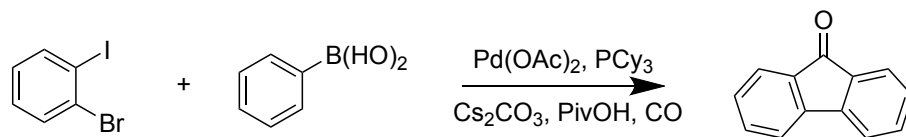


Figure 29: Synthesis of Fluoren-9-ones via Pd-Catalyzed Carbonylative Multiple C–C Bond Formation

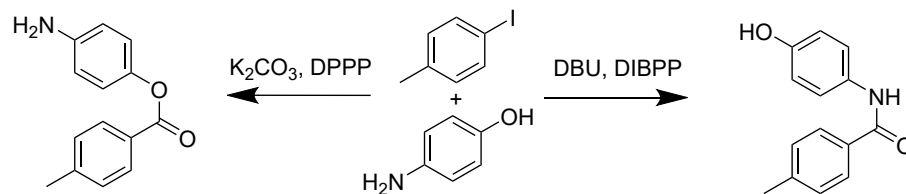


Figure 30: Selective carbonylation of bifunctional nucleophiles.

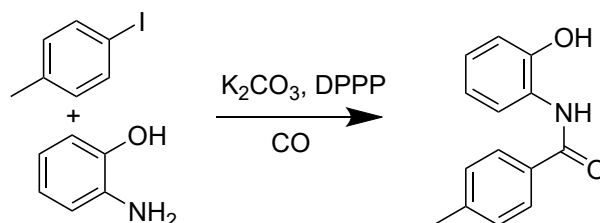


Figure 31: Unexpected selectivity observed during the carbonylation of *o*-aminophenol

2.6 Applications of bifunctional nucleophiles in homogeneous catalytic reactions

Using *p*-aminophenol as a model substrate in the carbonylation of *p*-iodotoluene, several factors' effects on reaction outcome were studied.⁴⁴ (Figure: 30) The use of DBU as a base with DIBPP as a ligand favored ester formation, while the use of K_2CO_3 and DPPP was preferential for alkoxycarbonylation. Steric hindrance appeared to be more detrimental for amide formation, while electron withdrawing groups proved to be beneficial for ester formation due to increased acidity. Electron-rich ligands favor the coordination of the amino group, and possibly those with longer linkers also facilitate the reaction. When *ortho*-aminophenol was carbonylated under the conditions favoring ester formation, only amide was formed. A possible explanation for this phenomenon is the simultaneous coordination of both functional groups to the Pd metal center, and since oxygen has lower binding constants, it is more easily displaced, preventing its migration from occurring. (Figure: 31)

Using *o*-aminophenol and 2-bromofluorobenzene a general method for production of dibenzoxazepinones was developed.¹¹ (Figure: 32) The optimized reaction conditions utilizing DBU and *BuPAd*₂ and moderate CO pressures proved to be tolerant a wide array of substituted *o*-aminophenols and *o*-bromofluorobenzenes.

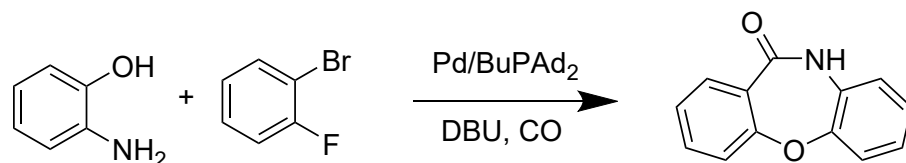


Figure 32: Dibenzoxazepinone formation

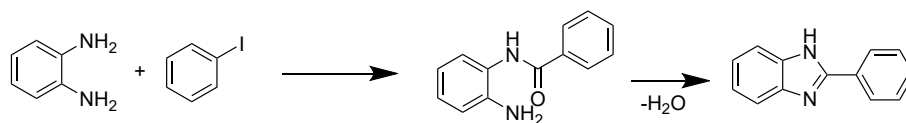


Figure 33: Intramolecular cyclization to yield benzimidazole

Reaction was found to be slowed by steric hindrance caused by 3-methyl substituents on the aminophenol, and the use of 2-(phenylamino)phenol completely halted the reaction, as a consequence of the sterically hindered and acidic amine. During the course of the reaction, initially the bromide carbon is subjected to aminocarbonylation, and in a following step an aromatic nucleophilic substitution is presumed to occur. In an attempt to further understand the mechanism control experiments were conducted, in which a preparation of the presumed intermediate and the initial substrates were separately subjected to the optimized reaction conditions without the presence of the Pd-BuPAd_2 catalyst. In the control experiment using the initial substrates, no reaction occurred, however the intermediate was converted into dibenzoxazepinone in great yield, which shows that DBU facilitates both aminocarbonylation, and the nucleophilic aromatic substitution.

The carbonylation of an aryl-halide with ortho-phenylenediamine, followed by dehydration yields 2-Arylbenzimidazoles.⁴⁵ (Figure: 33) During the screening of bases, a trend between base strength and degree of formation of the doubly carbonylated product was observed. It was noted that steric hindrance of the base wasn't as influential on reaction outcome, since 2,6-dimethylpyridine and 2,4,6-trimethylpyridine have similar steric profiles, but the latter produced bisamide in greater yield. The singly carbonylated intermediate 2-aminobenzilidene was prepared and subjected to various cyclization conditions, demonstrating that stronger bases catalyze the reaction faster. However, acid catalyzed cyclization is 3 orders of magnitude more effective than base catalyzed, and since strong mineral acids are generated during the reaction, using weak bases allows a greater equilibrium concentration of acid to be present. The optimized catalytic system for benzimidazole formation using $\text{PdCl}_2(\text{PPh}_3)_2$ in dimethylacetamide with 2,6-dimethylpyridine at 140-145°C under atmospheric CO pressure tolerated a variety of substrates, with the exception of 2-iodothiophene. In attempt to further decrease bisamide formation, weaker bases were utilized, resulting in palladium assisted solvent decomposition and transacylation.

Previously the carbonylation of aryl halides and o-aminophenol with the subsequent dehydrative cyclization yielding 2-arylbenzoxazoles has been reported by Perry.⁴⁶ Using a catalytic system consisting of $\text{PdCl}_2(\text{PPh}_3)_2$ and DBU in DMAc under 6 bar CO pressure, the intermediate phenol amide was formed, and then reaction conditions were modified to induce condensative cyclization by one of two methods depending on substrate. The first method utilized elevated reaction temperatures (165°C) and addition of HCl, which allowed the transformation of cyano-, chloro-substituted halobenzenes and iodothiophene, however for halides with methoxy-, phenyl-, nitro-substituents the initial carbonylation was performed in toluene, and the cyclization was induced by refluxing in presence of methanesulphonic acid or PTSA.

3 Goal of research

The goal of our experimentation was to examine the carbonylative reactions of bifunctional nucleophiles with aryl dihalides, preferably producing 7 and 8 membered rings in the process. Palladium catalyzed coupling reactions such as the Suzuki coupling and Buchwald-Hartwig amination have become a staple in the repertoire of organic chemists, as shown by numerous applications in the total synthesis of natural products and pharmaceuticals.⁴⁷ There is a great reason for their extensive application, these reactions provide an excellent method of building molecular complexity, due to the notable selectivity, functional tolerance, and efficiency of these reactions.

In literature there are numerous reports on the palladium catalyzed carbonylation reactions of aryl halides with simple nucleophiles, however as more reactive centers are introduced in the substrates, fewer and fewer reports can be found. The extensive body of research available for the former group of reactions ensures that optimal conditions can be chosen with relative ease, in stark contrast to bifunctional nucleophiles and aryl dihalides, where the outcome of the reaction is often difficult to predict. To illustrate, in the case of 2-aminophenol, when conditions preferential for phenoxycarbonylation are supplied, the reaction is extremely selective for aminocarbonylation, presumably as a result of the competitive coordination of the two functional groups to the catalytic center, however since they are in close proximity and binding affinity of amine is much higher, the phenol functionality's coordination is not favored.^{10,44} When the carbonylation of aryl bromides is attempted in the presence of iodide ions, the reaction is slowed to a halt.²⁴ The several reports⁴³⁴¹⁴² of bromiodobenzene's carbonylation show that under certain reaction conditions, the presence of iodide ions results in markedly decreased reactivity of the carbon-bromide bond towards carbonylation.

In attempt to exploit these peculiarities of bifunctional nucleophiles and phenylene dihalides in the process of building molecular complexity, we set our sights on various 7 and 8 membered diaryl scaffolds present in various biologically active compounds.

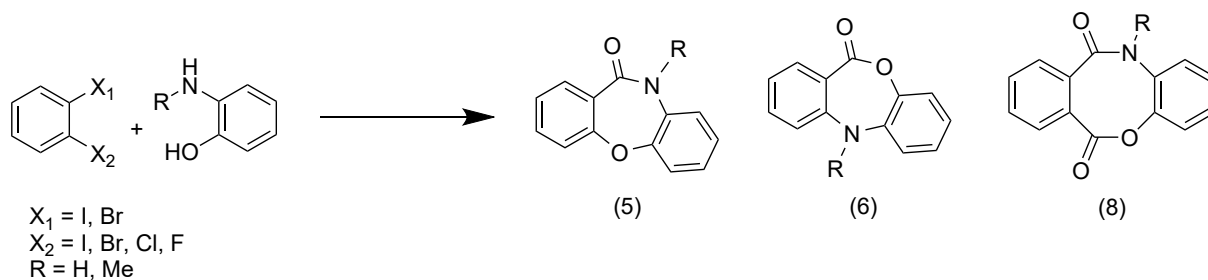


Figure 34: Target reaction

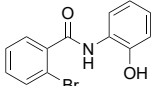
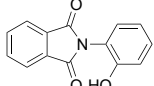
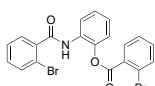
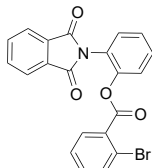
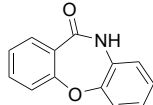
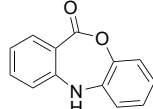
4 Experimental results

4.1 Carbonylation reactions in the presence of 2-aminophenol

During our experimentation, our main goal was the production of 7 and 8 membered ring such as dibenzoxazepinones (**5**, **6**) and dibenzoxazocinone (**8**). (Figure: 34) Formation of (**5**), (**6**), and (**8**) proceed through intermediate (**1**) (Figure: 38, 39), and to produce (**5**) or (**6**) an intramolecular coupling reaction has to occur between the phenol and the sp^2 carbon, while production of (**8**) requires an intramolecular alkoxycarbonylation to take place.

4.1.1 Carbonylation of 1,2-dibromobenzene

For the starting point of our initial experimentation, we chose the carbonylation reaction between 1,2-dibromobenzene and 2-aminophenol.

					
1	3	2	4	5	6

#	ligand (n)	base [mmol] - solvent	T [°C]	conv	(1)	(3)	(2)	(4)	(5)	(6)
1	<i>PPh</i> ₃ (0.02)	<i>Et</i> ₃ <i>N</i> (2) DMF	75	-	-	-	-	-	-	-
2	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	75	35	34	44	-	22	-	-
3	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	100	75	-	87	-	13	-	-
4 ^a	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	100	-	-	-	-	-	-	-
5	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	100	-	-	-	-	-	-	-
6	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	75	-	-	-	-	-	-	-

Primary amines have ability to undergo double carbonylation reaction with phenylene dihalides.

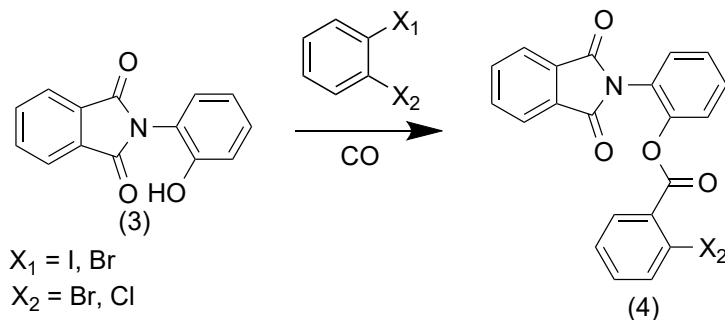


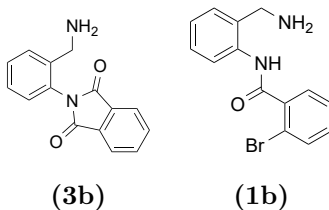
Figure 36: Pathway to phthalimide ester

Since (**2**) wasn't observed in the reaction mixture, the phthalimide ester (**4**) is presumed to form through carbonylation of intermediate phthalimide phenol (**3**). Interestingly, with increased temperatures the formation of (**4**) was suppressed.

During the previous reactions (entries 2 and 4), we observed peaks in the GC-MS spectra alluding to DMF coupling with the aryl halide, to mitigate this phenomenon we attempted the reaction using acetonitrile as a solvent, however the system showed no activity.

4.1.2 Reaction of 2-aminobenzylamine with 1,2-dibromobenzene

To investigate whether the formation of phthalimide can be suppressed by using bifunctional nucleophiles with both aromatic and aliphatic amine functionalities, we decided to employ 2-aminobenzylamine as a nucleophile.



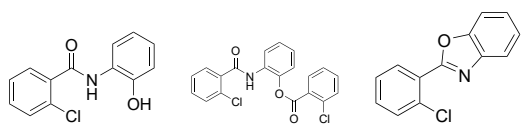
#	ligand (n)	base [mmol] - solvent	T [°C]	conv.	(3b)	(1b)
1	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	100	97	49	32
2 ^a	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	100	-	-	-

Table 2: Condition screening for the carbonylation reaction of 1,2-dibromobenzene and 2-aminobenzylamine. *conv*): Conversion. (**n**): Selectivity for product (**n**). Reactions conducted using 1 bar CO pressures, 0.02% catalyst loading (*Pd*(*OAc*)₂), 5ml solvent, 0.5 mmol of 2-aminobenzylamine and 1,2-dibromobenzene. *a*) Reaction conducted using 2 equivalents of dibromobenzene. Selectivities calculated based on GC measurements

This reaction resulted in further phthalimide formation, accompanied by extensive side reactions with the solvent. Interestingly, the reactivity of the anilinic amine was much greater than the reactivity of the aliphatic amine, with the latter remaining unreacted even in the presence of excess amount of substrate.

4.1.3 Carbonylation of 2-bromochlorobenzene

Aryl chlorides become activated towards carbonylation reactions when electron withdrawing groups are present on the ring, and carbon-chloride bonds are more prone towards undergoing SN_{Ar} reactions than heavier halides. In attempt to investigate these properties, we performed carbonylation of 2-bromochlorobenzene in presence of 2-aminophenol.



(1)
(2)
(7)

#	ligand (<i>n</i>)	base [mmol] - solvent	T [°C]	conv.	(1)	(2)	(7)
1	Xantphos (0.01)	<i>Et</i> ₃ <i>N</i> (2) DMF	100	82	36	22	42

Table 3: Condition screening for the carbonylation reaction of 2-bromochlorobenzene and 2-aminophenol. *conv*): Conversion. (*n*): Selectivity for product (*n*). Reactions conducted using 1 bar CO pressure, 0.02% catalyst loading, 5ml solvent, 0.5 mmol of 2-aminophenol and 2-bromochlorobenzene. Selectivities calculated based on GC measurements.

The intermediate aryl chloride remained inactive under the chosen catalytic conditions, however as a consequence phthalimide formation has been suppressed.

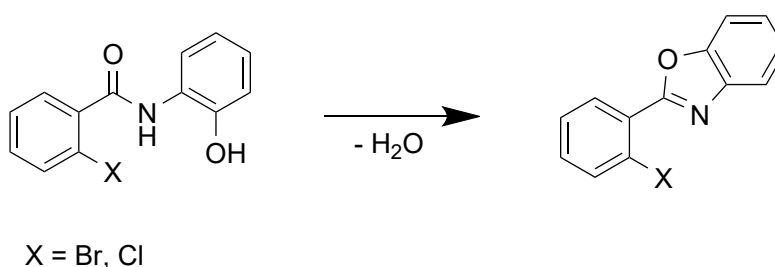
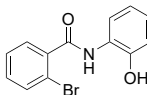
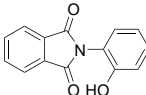
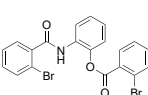
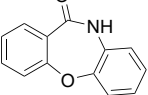
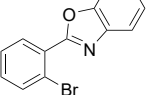


Figure 37: Pathway to benzoxazoles

Following the initial aminocarbonylation, the phenolic functionality of the nucleophile is able to undergo dehydrative cyclization to form benzoxazole (**7**).

4.1.4 Carbonylation of 2-bromoiodobenzene

Since the formation of phthalimides was inevitable when the primary amines are carbonylated with 1,2-dibromobenzene, we decided to use 2-bromoiodobenzene as the substrate - exploiting the decreased reactivity of $sp^2 - Br$ bonds in presence of iodide ions²⁴ - in search of 7 membered rings such as dibenzoxazepinones (**5**). The pathway to (**5**) entails an aminocarbonylation of the aryl-iodide bond to form intermediate (**1**), presumably followed by a C-O coupling reaction. This reaction has been previously reported using 2-bromofluorobenzene,¹¹ with the optimized reaction conditions utilizing a $Pd/BuPAd_2$ in DMSO-DBU at 10bar, 120°C.

				
1	3	2	5	7

#	ligand (n)	base [mmol] - solvent	T [°C]	conv.	(1)	(3)	(2)	(5)	(7)
1 ^{15bar}	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	100	-	-	-	-	-	-
2	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	100	70	22	4	3	38	4
3	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	60	100	-	-	-	-	100
4	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	30	-	-	-	-	-	-
5 ^{40bar}	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	82	-	-	-	-	-	-
6	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	85	-	-	-	-	-	-
7	DPPP (0.01)	<i>K</i> ₂ <i>CO</i> ₃ (2) MeCN	85	-	-	-	-	-	-

Table 4: Condition screening for the carbonylation reaction of 2-bromoiodobenzene and 2-aminophenol. *conv*): Conversion. *(n)*: Selectivity for product (**n**). Reactions conducted under 1 bar of CO pressure in 5ml of solvent, 0.02% catalyst loading ($Pd(OAc)_2$), 0.5 mmol of 2-bromoiodobenzene and 0,5 mmol of 2-aminophenol. *n bar*) reaction conducted using **n** bar of CO pressure. Selectivities calculated based on GC measurements

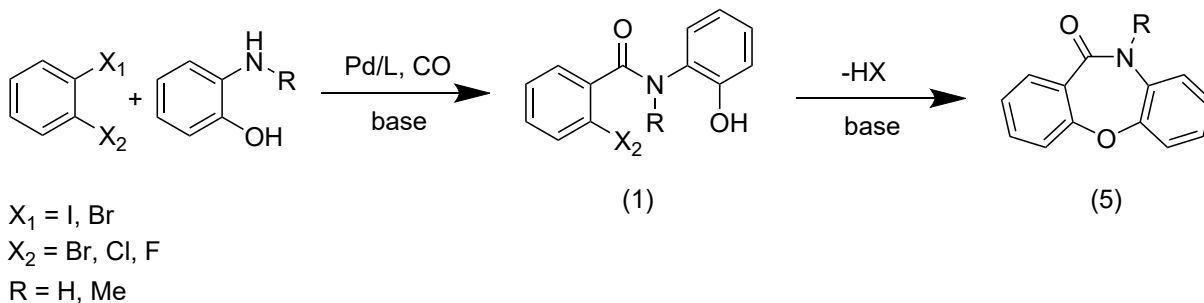
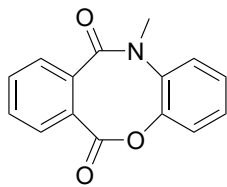


Figure 38: Pathway to dibenzoxazepinone (**5**)

It appeared that phthalimide formation has been suppressed, our initial reactions yielded the target product in acceptable quantities, however during optimization attempts a new side product (**7**) has appeared through dehydrative cyclization, 2-substituted benzoxazoles.

4.1.5 Carbonylation of 1,2-diiodobenzene in presence of 2-(methylamino)phenol



8

n	ligand (n)	base [mmol] - solvent	T [°C]	p [bar]	conv.	(8)
1	Xantphos (0.01)	K_2CO_3 (2) dry DMF	75	1	100	100
2 ^a	Xantphos (0.01)	K_2CO_3 (2) dry DMF	50	40	0	-

Table 5: Condition screening for the carbonylation reaction of 1,2-diiodobenzene and 2-(methylamino)phenol. *conv*): Conversion. (**n**): Selectivity for product (**n**). Reactions conducted using 0.02% catalyst loading ($Pd(OAc)_2$), 0.25mmol diiodobenzene, 0.5mmol 2-aminophenol, P/Pd ratio 4:1 *a*) Reaction time 19 hours. Selectivities calculated based on GC measurements

At this point we were well-acquainted with dibromo-, and bromiodobenzene's reluctance of forming our target compounds, so in response we set our sights even higher, aiming for the 8 membered ring (**8**) utilizing diiodobenzene. Diiodobenzene proved to be vastly superior substrate, allowing for formation of dibenzoxazocinone formation with excellent conversion and selectivity.

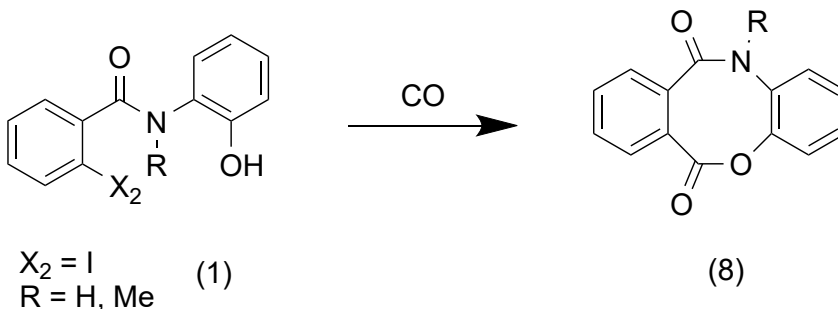
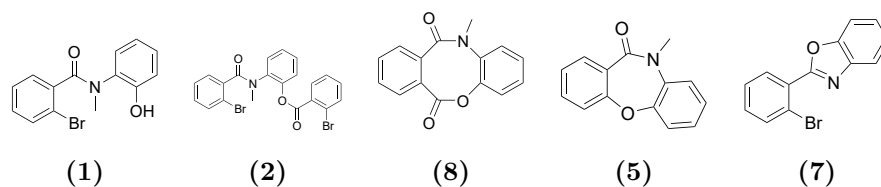


Figure 39: Path to dibenzoxazocinone

4.1.6 Carbonylation of 2-bromiodobenzene in presence of 2-(methylamino)phenol

To inhibit both phthalimide and benzoxazole formation, we employed 2-(methylamino)phenol as our nucleophile, which has the apparent benefit of only being able to participate in carbonylation as a N nucleophile once during the course of the reaction.



n	ligand (n)	base [mmol] - solvent	T [°C]	conv.	(1)	(2)	(8)	(5)	(7)
1	DPPP (0.01)	K_2CO_3 (2) MeCN	60	97	84	7	-	9	-
2 ^c	DPPP (0.01)	K_2CO_3 (2) MeCN	82	27	67	-	-	-	33
3 ^b	DPPP (0.01)	Et_3N (2) DMF	100	-	-	-	-	-	-
4 ^{a,6bar}	DPPP (0.01)	K_2CO_3 (0.8) MeCN	60	-	-	-	-	-	-
6 ^{a,10bar}	DPPP (0.01)	K_2CO_3 (0.8) MeCN	60	28	19	59	-	-	22
5 ^{a,20bar}	DPPP (0.01)	K_2CO_3 (0.8) MeCN	60	22	-	81	-	-	19

Table 6: Condition screening for the carbonylation reaction of 2-bromiodobenzene and 2-(methylamino)-phenol. *conv*): Conversion. **(n)**: Selectivity for product **(n)**. Reactions conducted under 1 bar of CO pressure in 5ml of solvent using 0.5 mmol of 2-bromiodobenzene and 0,5 mmol of 2-(methylamino)phenol. *a*) reactions conducted on a smaller scale using 2/5 the original amount of reagents. *b*) Reaction conducted using 10ml of solvent. *c*) Reaction time 48 hours. *n bar*) reaction conducted using **n** bar of CO pressure. Selectivities calculated based on GC measurements

During the initial trial, traces of dibenzoxazepinones **(5)** were formed, however increased temperatures and CO pressure were both detrimental to conversion.

5 Methodology

5.1 Reagents

The reagents were acquired from sigma aldrich

5.2 Analytical methods

5.2.1 Gas Chromatography - Mass Spectrometry

GC vials are filled up to the mark using DCM, a sample is taken from the reaction mixture or column chromatography fractions using a pasteur pipette, and 3 or 5 drops respectively are added to the vial.

If the contents of the GC vial display Tyndall scattering when placed over a flashlight, alternative solvents are used such as MeOH until a true solution results after the addition of our sample.

5.2.2 Nuclear Magnetic Resonance

The selected column chromatographic fraction(s) are transferred to a round bottom flask, solvent is removed using the rotovap, and then the flask is placed under high vacuum for 30 minutes - 1 hour to remove the residual solvent. An NMR tube is placed inside a 10cm^3 measuring cylinder, and once the compound has dried, it is dissolved in the smallest amount of CDCl_3 possible and transferred to the NMR tube. Addition of small portions of CDCl_3 to the flask and subsequent transfer to the NMR tube is continued until the solvent level reaches the 4cm^3 mark, following which the tube is capped and tagged with the information necessary for its identification.

5.3 Carbonylation reactions

The solid reagents were measured using glass weighing boats, and the liquid reagents were measured using syringes of the smallest possible volume.

For reactions conducted under atmospheric pressure, a three-necked round-bottom flask including a stir bar was equipped with a plug, a vacuum flow-control adapter with a teflon stopcock, and a condenser equipped with a balloon. After a three cycle rinse with argon, the secured reaction setup was charged with the reagents in an argon counter current, followed by replacement of the inert gas by carbon-monoxide.

For reactions conducted under non-atmospheric conditions a pressurized vessel in the form of an autoclave was used to conduct the reaction. The reaction mixture was prepared using a Schlenk-flask in argon counter current, which was transferred to the autoclave using a syringe. Less soluble reagents such as K_2CO_3 were added directly into the autoclave. After changing the atmosphere of the autoclave, it is placed inside an oil bath for the duration of the reaction for heating.

After reaction completion, the CO was removed from the reaction flask using vacuum, and the reaction mixture was cooled down to room temperature the solution was filtered to remove solid impurities, such as

Pd black formed during the reaction. The solvent is removed under reduced pressure, when the reaction was conducted using DMF as a solvent, the solvent was distilled using an oil bath, or using the rotovap with added hexane to form a lower boiling point azeotrope. The remaining material was dissolved in 20cm^3 CHCl_3 and transferred to a separatory funnel, after which it was extracted 3 times with equal volumes of water.

The organic layers are collected, washed using brine, the organic phase is dried over Na_2SO_4 and filtered.

5.4 Product characterisation

To verify the identity and purity of the compounds formed, they were analysed by GC-MS, NMR, and IR spectroscopy.

Once the pure compounds are obtained, they were placed inside a round bottom flask of known weight, dried using the rotovap, and placed under high vacuum while heating to remove excess moisture. When sufficiently dried, the weight of the round bottom flask including the product was measured, and the physical properties of the compound were noted.

6 Summary

Transition metal catalysis remains a field of research filled with both academic intrigue and industrial utility. From carbonylation's application in various industrial processes to produce acetic acid, aldehydes, to the use of transition metal catalyzed couplings by organic chemists when nothing else can get the job done - is all a result of years of research dissecting the mechanisms, asking why and how, to develop methods that are able to provide the needed transformation.

In a world that's increasingly aware of the consequences of our wasteful lifestyles and methods of production, these reactions can provide us with a glimmer of hope, be a shining beacon of a greener chemistry, showing us the way we should all approach the future - with as little waste as possible.

7 Acknowledgements

Shoutout to my old roommate for coercing me into participating in research. One winter evening he noticed I was famished, and he gave me a deal I couldn't refuse - he would give me his order of fries, but only if I would present at the next TDK.

References

- (1) Beller, M.; Wu, X.-F., *Transition Metal Catalyzed Carbonylation Reactions*; Springer: 2013.

- (2) Chen, X.; Chen, G.; Lian, Z. Recent Advances in Nickel Catalyzed Carbonylative Reactions *via* the Insertion of Carbon Monoxide. *Chinese Journal Of Chemistry* **2024**, *42*, 177–189.
- (3) Giannoccaro, P.; Pannacciulli, E. Nickel-catalyzed amidation of bromo- and iodobenzene. *Journal of Organometallic Chemistry* **1987**, *319*, 119–127.
- (4) Liu, N.; Wu, X.; Wang, C.; Qu, J.; Chen, Y. Nickel-catalyzed alkoxy carbonylation of aryl iodides with 1 atm CO. *Chemical Communications* **2022**, *58*, 4643–4646.
- (5) Amer, I.; Alper, H. Nickel Cyanide And Phase-Transfer-Catalyzed Carbonylation Of Aryl Iodides In The Absence Of Light. *Journal Of Organic Chemistry* **1988**, *53*, 5147–5148.
- (6) Foa, M.; Francalanci, F.; Bencini, E.; Gardano, A. Cobalt-Catalyzed Carbonylation Of Aryl Halides. *Journal Of Organometallic Chemistry* **1985**, *285*, 293–303.
- (7) Miyaura, N.; Yamada, K.; Suzuki, A. New stereospecific cross-coupling by the palladium-catalyzed reaction of 1-alkenylboranes with 1-alkenyl or 1-alkynyl halides. *Tetrahedron Letters* **1979**, *20*, 3437–3440.
- (8) Liu, J.; Yue, C.; Li, F. In *Carbon Monoxide in Organic Synthesis*; John Wiley Sons, Ltd: 2021; Chapter 7, pp 197–234.
- (9) Schoenberg, A.; Heck, R. F. Palladium-catalyzed amidation of aryl, heterocyclic, and vinylic halides. *The Journal of Organic Chemistry* **1974**, *39*, 3327–3331.
- (10) Lin, Y.-S.; Yamamoto, A. Studies Relevant to Palladium-Catalyzed Carbonylation Processes. Mechanisms of Formation of Esters and Amides from Benzylpalladium and (Phenylacetyl)palladium Complexes on Reactions with Alcohols and Amines. *Organometallics* **1998**, *17*, 3466–3478.
- (11) Shen, C.; Neumann, H.; Wu, X.-F. A highly-efficient palladium-catalyzed aminocarbonylation/*S_N* approach to dibenzoxazepinones. *GREEN CHEMISTRY* **2015**, *17*, 2994–2999.
- (12) Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. Wide Bite Angle Diphosphines: Xantphos Ligands in Transition Metal Complexes and Catalysis. *Accounts of Chemical Research* **2001**, *34*, PMID: 11714261, 895–904.
- (13) Ben-David, Y.; Portnoy, M.; Milstein, D. Chelate-assisted, palladium-catalyzed efficient carbonylation of aryl chlorides. *Journal of the American Chemical Society* **1989**, *111*, 8742–8744.
- (14) F., H. J. Carbon-heteroatom bond formation catalysed by organometallic complexes. *Nature* **2008**, *455*, 314–222.
- (15) Wojcik, P.; Trzeciak, A. M. The aminocarbonylation of 1,2-diiodoarenes with primary and secondary amines catalyzed by palladium complexes with imidazole ligands. *Applied Catalysis A-General* **2018**, *560*, 73–83.

- (16) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M.; Barder, T. E.; Buchwald, S. L. Palladium-catalyzed carbonylation reactions of aryl bromides at atmospheric pressure: a general system based on Xantphos. *The Journal of organic chemistry* **2008**, *73*(18), 7102–7107.
- (17) Picard, B.; Fukuyama, T.; Ryu, I. Phosphine-Free Aminocarbonylation Using Pd/DBU Catalyst: Carbonylative Coupling of Aryl Iodides and Amines. *The Journal of Organic Chemistry* **2023**, *88*, PMID: 36525565, 5220–5225.
- (18) Takács, E.; Varga, C.; Skoda-Földes, R.; Kollár, L. Facile synthesis of primary amides and ketoamides via a palladium-catalysed carbonylation–deprotection reaction sequence. *Tetrahedron Letters* **2007**, *48*, 2453–2456.
- (19) Wu, X.-F.; Schranck, J.; Neumann, H.; Beller, M. Convenient palladium-catalyzed aminocarbonylation of anilines to N-arylbenzamides. *Tetrahedron Letters* **2011**, *52*, 3702–3704.
- (20) Perry, R. J.; Wilson, B. D. Palladium-Catalyzed Carbonylation and Coupling Reactions of Aryl Chlorides and Amines. *The Journal of Organic Chemistry* **1996**, *61*, PMID: 11667678, 7482–7485.
- (21) Amatore, C.; Azzabi, M.; Jutand, A. Role and effects of halide ions on the rates and mechanisms of oxidative addition of iodobenzene to low-ligated zerovalent palladium complexes Pd0(PPh3)2. *Journal of the American Chemical Society* **1991**, *113*, 8375–8384.
- (22) Galushko, A. S.; Prima, D. O.; Burykina, J. V.; Ananikov, V. P. Comparative study of aryl halides in Pd-mediated reactions: key factors beyond the oxidative addition step. *Inorg. Chem. Front.* **2021**, *8*, 620–635.
- (23) Wu, X. F.; Neumann, H.; Beller, M. Development of a second generation palladium catalyst system for the aminocarbonylation of aryl halides with CO and ammonia. *Chemistry, an Asian journal* **2010**, *5*, 2168–2172.
- (24) Schoenberg, A.; Bartoletti, I.; Heck, R. F. Palladium-catalyzed carboalkoxylation of aryl, benzyl, and vinylic halides. *The Journal of Organic Chemistry* **1974**, *39*, 3318–3326.
- (25) Mägerlein, W.; Beller, M.; Indolese, A. F. Palladium-catalyzed carbonylation of aryl halides — a detailed investigation of the alkoxycarbonylation of 4-bromoacetophenone. *Journal of Molecular Catalysis A: Chemical* **2000**, *156*, 213–221.
- (26) Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. Palladium-catalyzed phenoxycarbonylation of aryl iodides: electronic effect of the substituents on phenol. *Journal of Molecular Catalysis A: Chemical* **1996**, *111*, 25–31.
- (27) Blaser, H.-U.; Diggelmann, M.; Meier, H.; Naud, F.; Scheppach, E.; Schnyder, A.; Studer, M. No Stirring Necessary: Parallel Carbonylation of Aryl Halides with CO and Various Alcohols under Pressure. *The Journal of Organic Chemistry* **2003**, *68*, PMID: 12713389, 3725–3728.

- (28) Wu, X.-F.; Neumann, H.; Beller, M. Convenient Carbonylation of Aryl Bromides with Phenols to Form Aryl Esters by Applying a Palladium/Di-1-adamantyl-n-butylphosphine Catalyst. *Chem-CatChem* **2010**, *2*, 509–513.
- (29) Watson, D. A.; Fan, X.; Buchwald, S. L. Carbonylation of Aryl Chlorides with Oxygen Nucleophiles at Atmospheric Pressure. Preparation of Phenyl Esters as Acyl Transfer Agents and the Direct Preparation of Alkyl Esters and Carboxylic Acids. *The Journal of Organic Chemistry* **2008**, *73*, PMID: 18720992, 7096–7101.
- (30) Ueda, T.; Konishi, H.; Manabe, K. Palladium-Catalyzed Carbonylation of Aryl, Alkenyl, and Allyl Halides with Phenyl Formate. *Organic Letters* **2012**, *14*, PMID: 22642678, 3100–3103.
- (31) Lindley, J. Tetrahedron report number 163: Copper assisted nucleophilic substitution of aryl halogen. *Tetrahedron* **1984**, *40*, 1433–1456.
- (32) Kosugi, M.; Kameyama, M.; Migita, T. Palladium-Catalyzed Aromatic Amination Of Aryl Bromides With N,N-Di-Ethylamino-Tributyltin. *Chemistry Letters* **2006**, *12*, 927–928.
- (33) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angewandte Chemie International Edition* **1995**, *34*, 1261–1372.
- (34) Louie, J.; Hartwig, J. F. Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. *Tetrahedron Letters* **1995**, *36*, 3609–3612.
- (35) Marcoux, J.-F.; Doye, S.; Buchwald, S. L. A General Copper-Catalyzed Synthesis of Diaryl Ethers. *Journal of the American Chemical Society* **1997**, *119*, 10539–10540.
- (36) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide. *Chemical Science* **2011**, *2*, 27–50.
- (37) Bessard, Y.; Roduit, J. P. Selective alkoxy carbonylation of 2,3-dichloropyridines. *Tetrahedron* **1999**, *55*, 393–404.
- (38) Perry, R.; Turner, S. Preparation of N-Substituted Phthalimides by the Palladium-Catalyzed Carbonylation and Coupling of o-Dihalo Aromatics and Primary Amines. *Journal of Organic Chemistry* **1991**, *56*, 6573–6579.
- (39) Cassar, L.; Foà, M. Nickel-catalyzed carbonylation of aromatic halides at atmospheric pressure of carbon monoxide. *Journal of Organometallic Chemistry* **1973**, *51*, 381–393.
- (40) Papp, M.; Szabo, P.; Sranko, D.; Safran, G.; Kollar, L.; Skoda-Foldes, R. Mono- and double carbonylation of aryl iodides with amine nucleophiles in the presence of recyclable palladium catalysts immobilised on a supported dicationic ionic liquid phase. *Rsc Advances* **2017**, *7*, 44587–44597.
- (41) Ashfield, L.; Barnard, C. F. J. Reductive carbonylation - an efficient and practical catalytic route for the conversion of aryl halides to aldehydes. *Organic Process Research & Development* **2007**, *11*, 39–43.

- (42) Cao, H.; McNamee, L.; Alper, H. Syntheses of Substituted 3-Methyleneisoindolin-1-ones By a Palladium-Catalyzed Sonogashira Coupling-Carbonylation-Hydroamination Sequence in Phosphonium Salt-Based Ionic liquids. *Organic Letters* **2008**, *10*, 5281–5284.
- (43) Song, J.; Wei, F.; Sun, W.; Li, K.; Tian, Y.; Liu, C.; Li, Y.; Xie, L. Synthesis of Fluoren-9-ones and Ladder-Type Oligo-*p*-phenylene Cores via Pd-Catalyzed Carbonylative Multiple C-C Bond Formation. *Organic Letters* **2015**, *17*, 2106–2109.
- (44) Xu, T.; Alper, H. Pd-Catalyzed Chemoselective Carbonylation of Aminophenols with Iodoarenes: Alkoxy carbonylation vs Aminocarbonylation. *Journal Of The American Chemical Society* **2014**, *136*, 16970–16973.
- (45) Perry, R.; Wilson, B. A Novel Palladium-Catalyzed Synthesis Of 2-Arylbenzimidazoles. *Journal Of Organic Chemistry* **1993**, *58*, 7016–7021.
- (46) Perry, R.; Wilson, B.; Miller, R. Synthesis Of 2-Arylbenzoxazoles Via The Palladium-Catalyzed Carbonylation And Condensation Of Aromatic Halides And Ortho-Aminophenols. *Journal Of Organic Chemistry* **1992**, *57*, 2883–2887.
- (47) Tuck, J. R.; Dunlap, L. E.; Olson, D. E. Synthetic Strategies toward Lysergic Acid Diethylamide: Ergoline Synthesis via $\text{C}-\text{Ar}$ Arylation, Borrowing Hydrogen Alkylation, and C-H Insertion. *Journal Of Organic Chemistry* **2023**, *88*, 13712–13719.