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STUDY OF BIS-IMIDAZOL-2-YLIDINES AS LIGANDS FOR TRANSITION METAL CATALYZED COUPLING REACTIONS

A Dissertation

Submitted to the Graduate Faculty of the
University of New Orleans
in partial fulfillment of the
requirements for the degree of

Doctor of Philosophy
in
The Department of Chemistry

by

Stanhope P. Turnbull Jr.

B.S., Louisiana State University 1989

December 2004

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This work is dedicated to my beloved daughter, Dominique. It is my hope that you learn from both my successes and my failures. May both guide you to achieve far greater accomplishments.

ACKNOWLEDGMENT

I wish to thank Professor Mark Trudell for his assistance and patience in this endeavor. Thanks also to Professor Steven Nolan for useful discussions and access to his equipment and IPr ligand. I would also like to thank Professors Jursic, Wang, and Boyd for their input. Much thanks and appreciation is given to my parents, Anne and Stanhope Turnbull Sr., and my wife Lesley-Ann Turnbull, for their support and encouragement. Also to James E. Snowden Jr., whose toil and struggle in breaking many barriers in chemistry later benefited me; and Dr. Frank Snowden, whose pursuit of his Ph.D. encouraged me to pursue my own. Also, thanks to Dr. William Colucci for his mentorship and lasting friendship. Much thanks to soon-to-be Dr. Florastina Payton for her assistance throughout this pursuit.

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ABSTRACT

Two bis-imidazol-2-ylidene N-heterocyclic carbenes have been employed as ancillary ligands in an attempt to illustrate their utility in the palladium-mediated preparation of aryl ethers from aryl halides. Ullman-type homo-coupling of the aryl halides persistently occurred instead of ether formation. One of the well known N-heterocyclic carbenes, IPr, was employed with the same results. A variety of reaction conditions and reagents were investigated including solvents, N-heterocyclic carbene species, palladium source, alkoxide base, palladium to ligand ratio and reaction time. Reactivity of the individual N-heterocyclic carbenes as ancillary ligands in the palladium-catalyzed amination reaction of aryl halides was investigated to determine functionality of the carbenes.

Alternative procedures to prepare the key intermediates in the synthesis of the bis-imidazol-2-ylidene were developed. In this study the aryl imidazoles were prepared from the corresponding phenol and carbonyldiimidazole. Subsequent N-alkylation then furnished the N-heterocyclic carbenes in high yield.

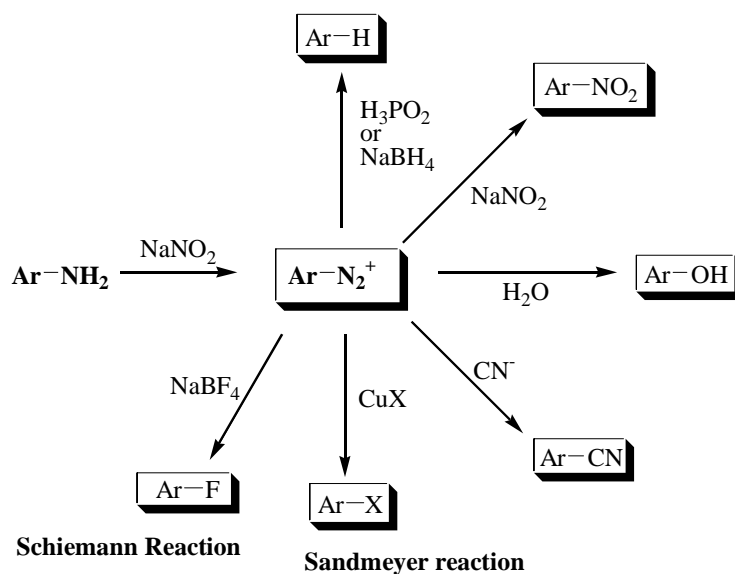
Novel unsymmetrical N-heterocyclic carbenes with aryl and benzylic side groups have been synthesized as models for the subsequent synthesis of unsymmetrical polymer-bound N-heterocyclic carbenes. The unsymmetrical ligands were employed in the palladium-catalyzed amination of aryl halides and in the Suzuki-Miyaura Reaction. Two Merrifield resin polymer-bound N-heterocyclic carbene ligands were then synthesized and employed in the aryl amination and Suzuki-Miyaura Reactions. Both reactions were greatly accelerated by the implementation of microwave heating. The Merrifield resin polymer-bound palladium-ligand complexes have been recycled through several reactions without loss of activity.

INTRODUCTION

Carbon-Carbon Bond Formation with Aryl Diazonium Salts and Aryl Halides

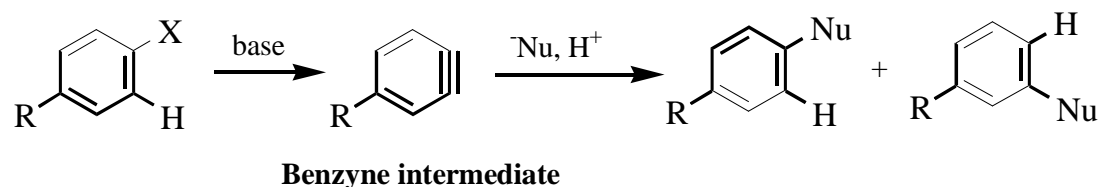
Nucleophilic substitution and carbon-carbon bond formation reactions of aryl substrates are useful transformations in organic synthesis. One typical method requires the formation of aryl diazonium salts from amines followed by reaction with various salts (**Figure 1**).¹

Figure 1. Reactions of Diazonium Salts

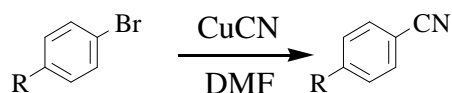


Relatively few examples exist for substitutions of aryl halides. Aryl halides can undergo elimination-addition through a benzyne intermediate, generally initiated with a strong base, followed by nucleophilic substitution (**Scheme 1**).²

Scheme 1



Aryl halides can also react at elevated temperatures with Copper(I) salts in polar aprotic solvents to give nucleophilic substitution products (**Scheme 2**).³

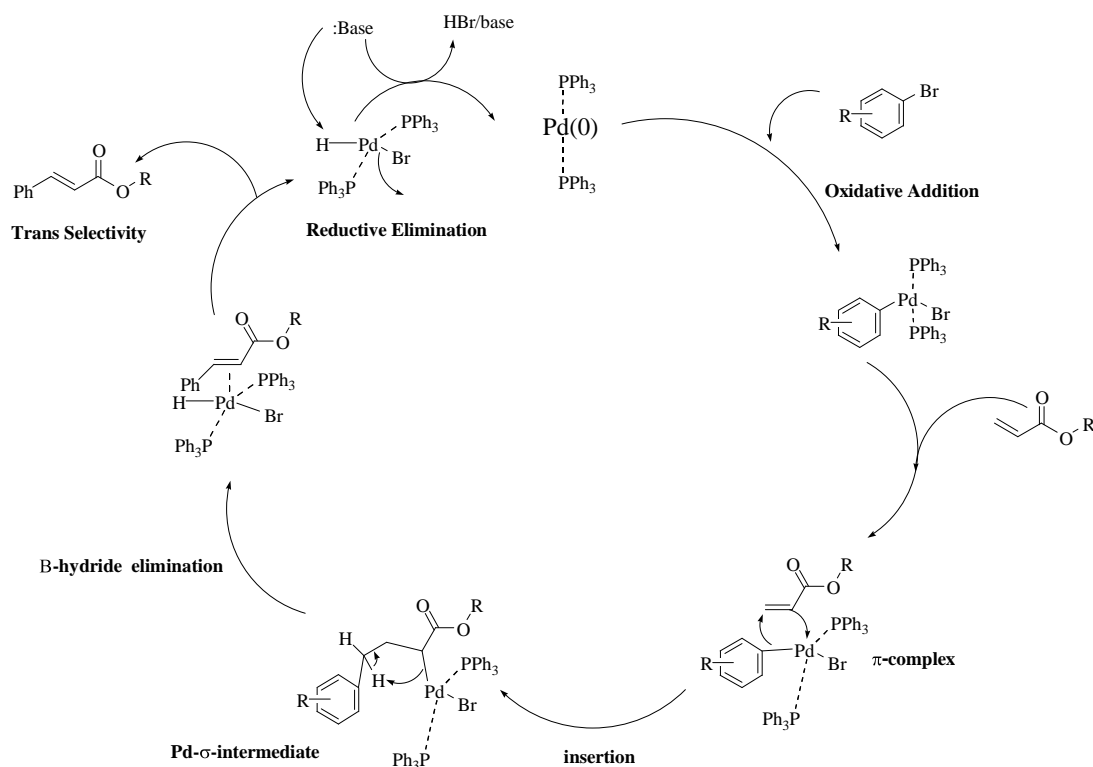
Scheme 2.

Each of these reactions has its own limitations. Reactions of diazonium salts require aryl amine precursors (**Figure 1**). Benzyne requires no *ortho*-substitution and can give isomeric products (**Scheme 1**). Reactions of aryl halides in polar aprotic solvents at elevated temperatures can give biphenyls and other unwanted side products.

Catalyzed Coupling Reactions

Mild, catalytic methods have been sought to transform readily available aryl halides and triflates directly into a plethora of products including amines, ethers, phenols, thiols, nitriles, amides as well as dehalogenated arenes. Palladium has been used catalytically, under mild conditions, to promote carbon-carbon bond formation between aryl halides and alkenes in a reaction named for R.F. Heck.⁴ The Heck Reaction (**Figure 2**) gives a net substitution of the halide by the alkenyl group. The reaction is performed in the presence of a phosphine ligand where the lone pair of electrons on the phosphorus atom coordinates to the palladium atom to form a palladium (0) complex. Further coordination occurs with the introduction of the aryl halide and the alkene. Carbon-carbon bond formation then occurs and elimination of the palladium-phosphine complex gives the arylalkene. The palladium-phosphine complex is then recycled through the process.

Figure 2. The Heck Reaction Mechanism



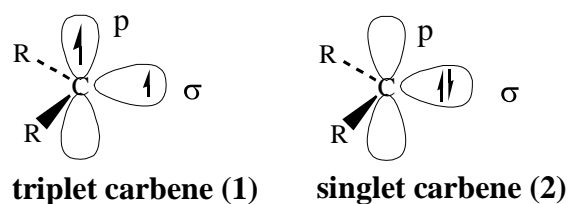
N-Heterocyclic Carbenes

Stable, N-heterocyclic carbenes (NHCs) have been shown to behave as phosphine mimics.⁵ This mimicry of phosphines has prompted the investigation of stable NHCs as replacements or alternates to phosphorus ligands.⁶

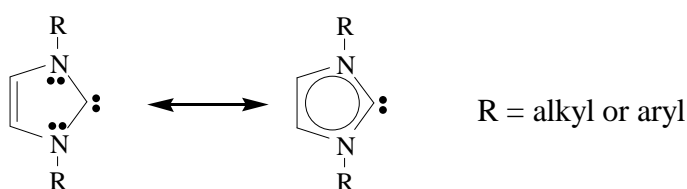
Carbenes are uncharged divalent carbon compounds with two unshared electrons. The electronic configurations of carbenes can be divided into two states. The triplet state **1** exists when one electron is in an sp²-hybridized orbital and the other electron is in an unhybridized p-orbital. The two electrons are thus unpaired in their ground states. The triplet state occurs primarily in linear carbenes but can occur in bent carbenes as well. This configuration allows for maximum separation of the unpaired-spin electrons.

The other state, the singlet state **2**, exists for non-linear carbenes. The bent carbon allows

the p-orbital in the plane of the nucleus to exhibit s-character thereby lowering its energy. Atoms adjacent to the carbene having π -donor orbitals (i.e. N,O,S and halogen) generally increase the p- σ energy gap and increase the thermodynamic stability of the singlet carbene.⁷



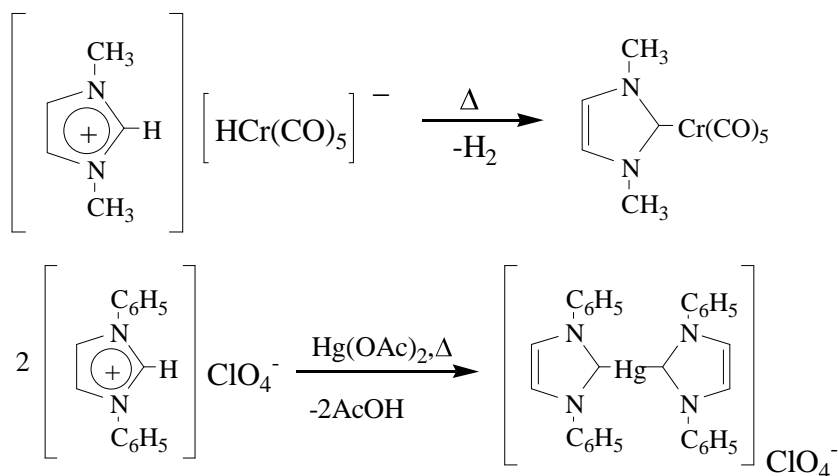
Carbenes with heteroatom donor groups exhibit enhanced nucleophilicity as well as thermodynamic stability.⁸ Singlet carbenes with 2 adjacent nitrogen atoms have been isolated as crystalline compounds. Also 2,3-dihydrothiazol-2-ylidines have been investigated.⁹⁻¹³ Of these isolable compounds, the imidazol-2-ylidines (**3**) have been the subject of the most scrutiny.⁷



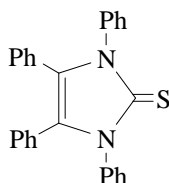
imidazol-2-ylidines (3)

Wanzlick^{14,15} and Ofele¹⁶ first described metal complexes with imidazoline rings. These metal-carbene complexes were obtained from imidazolium salts and basic metal-containing precursors (**Scheme 3**).

Scheme 3



This work led to the synthesis of the stable 1,3-diamantyl-2,3-dihydro-1H-imidazol-2-ylidene (**6**) (Scheme 4) by Arduengo in 1991.¹⁷ Later, synthesis of the imidazol-2-thiones¹³ **4** confirmed earlier findings.

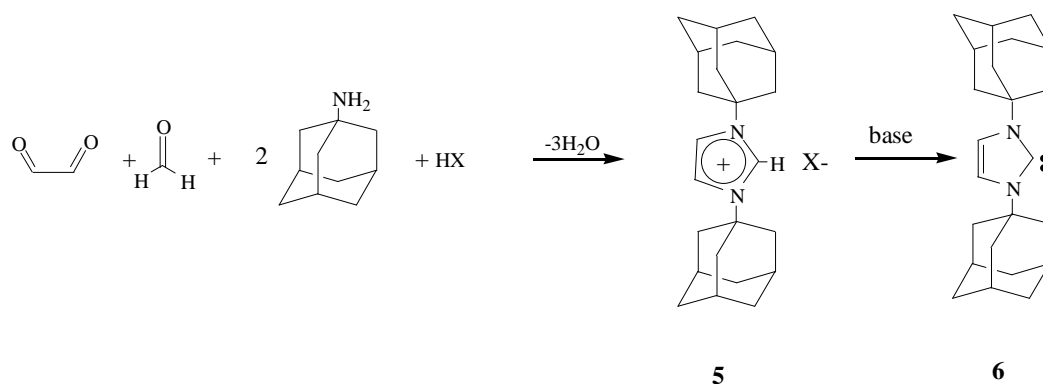


imidazol-2-thiones (4)

The Arduengo synthesis of **6** was achieved by the reaction of one equivalent each of glyoxal and formaldehyde with two equivalents of adamantyl amine in the presence of a mineral acid which provided the counter ion. Removal of water completed the reaction to give the protected carbene. Formation of carbene **6** was achieved by deprotonation with an anhydrous base. Later reports^{18, 19} have indicated that a two-step process to prepare **5** gives higher yields than the one-pot synthesis. The two-step process involves the reaction of glyoxal with two equivalents of the desired amine. The resulting imine is isolated and then reacted with aqueous

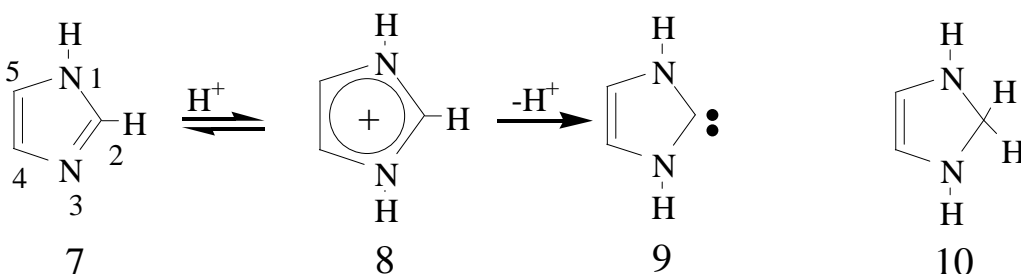
formaldehyde or triethylorthoformate and a mineral acid to give **5**.

Scheme 4.



Imidazol-2-ylidines are tautomers of 1H-imidazole (**7**) (**Scheme 5**). Protonation of **7** at N3 and deprotonation at C2 yields a 1,3-dihydrosubstituted ylidine **9** through intermediate **8**. Ylidine **9** retains aromaticity with 6 π -electrons. The suffix *-ylidine* refers to compounds in which two hydrogen substituents are replaced by two electrons or one pair of electrons. Compound **10** is described as 2,3-dihydro-1H-imidazole. Therefore compound **9** which is derived from **10** is called 2,3-dihydro-1H-imidazole-2-ylidine. When the nitrogen atoms are substituted and R= alkyl or aryl then 1,3-di-substituted-imidazoline-2-ylidine and 1,3-substituted-2,3-dihydro-1H-imidazol-2-ylidine are synonyms due to the substitution pattern of the imidazole-derived carbenes.

Scheme 5



The structural properties of 1,3-bis(adamantyl)imidazol-2-ylidene (**6**) have been studied in detail.^{17,20,21} Compound **6** is the prototype for all imidazol-2-ylidene. The properties of the protected carbene **5** and free carbene **6** are compared in **Table 1**.

Table 1. Comparison of Physical Properties of Protected Carbene (5) and Free Carbene (6).

	Compound 5	Compound 6	CF ₂ :
N1-C2-N3 angle	109°	102°	102
N1-C2 bond length	1.32 Å	1.37 Å	
δ(C2)	136	211	
δ(H4)	7.2	6.9	
Melting point		240-241°C	

Compound **6** and its methyl and *p*-tolyl congeners exhibit N1-C2-N3 angles within $\pm 1^\circ$.^{17,20,21} For the sake of comparison, ¹A' singlet carbenes bearing π -donor fluorine substituents, CF₂:, exhibit an F-C-F angle of 102°. ²² The N1-C2-N3 angle for compound **5** is in good agreement with the values typically found for imidazolium salts, 108.5-109.7°. ²³ The C2 carbon of the ylidene has a chemical shift of $\delta=210-220$ in d₈-THF⁸ and the H4 (H5) protons can be found a $\delta=6.9-7.0$. Aryl substituents on N1 and N3 give rise to H4(H5) chemical shifts of $\delta=7.6-7.8$. ²⁴

In addition, the differences in the $\delta(\text{C}2)$ values and the $\delta(\text{H}4)$ values between **5** and **6** and

the lengthening of the N1-C2 bond distance show strong π -delocalization in protected carbene **5** and weaker π -delocalization in free carbene **6**. Also thermodynamic stabilization is enhanced by an inductive σ effect. The difference in electronegativity between nitrogen and carbon stabilizes the pair of unshared electrons in the in-plane carbene orbital. The nitrogen atoms donate their lone pairs to carbon and the p-orbital yields a π resonance interaction.⁸

The properties of the imidazol-2-ylidene carbene have been summarized by Arudengo:

“The electronic structure of the carbene center of an imidazol-2-ylidene can be simplified to a strongly bent singlet carbene model (1A_1) in which the carbene carbon is approximately sp^2 hybridized. The two substituents and a lone pair of electrons occupy the three sp^2 -hybrid orbitals and a formally vacant p-orbital remains at carbon. The lone pair of electrons on carbon behaves chemically similar to the lone pair of electrons on phosphorus in phosphines. The coordinating lone pair of electrons in an imidazol-2-ylidene is “harder” and more basic than a phosphine lone pair. The formally vacant p-orbital at the carbene center has the potential to function as a weak p-acceptor, but has different directional character than P-X σ^* -bonds (or d-orbitals) on a phosphine. The planar imidazol-2-ylidenes also present a steric profile that is greatly different from that of phosphines.”²⁵

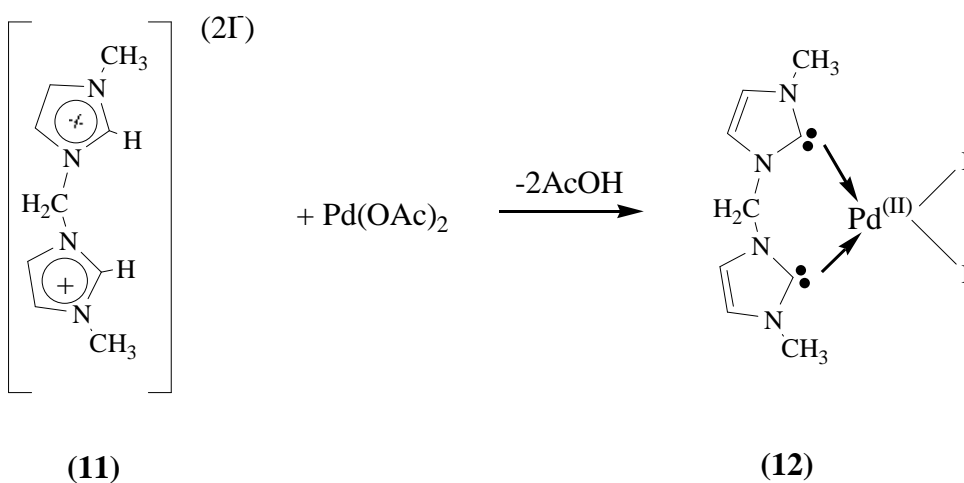
The synthetic utility of the imidazol-2-ylidines as ancillary ligands in palladium-catalyzed coupling reactions has been extensively reported. Stille,²⁶ Heck,²⁷ Suzuki,²⁸ Kumada,²⁹ and amination³⁰ reactions have been investigated with great success.

Multi-dentate NHC Ligands

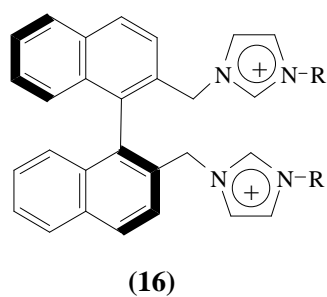
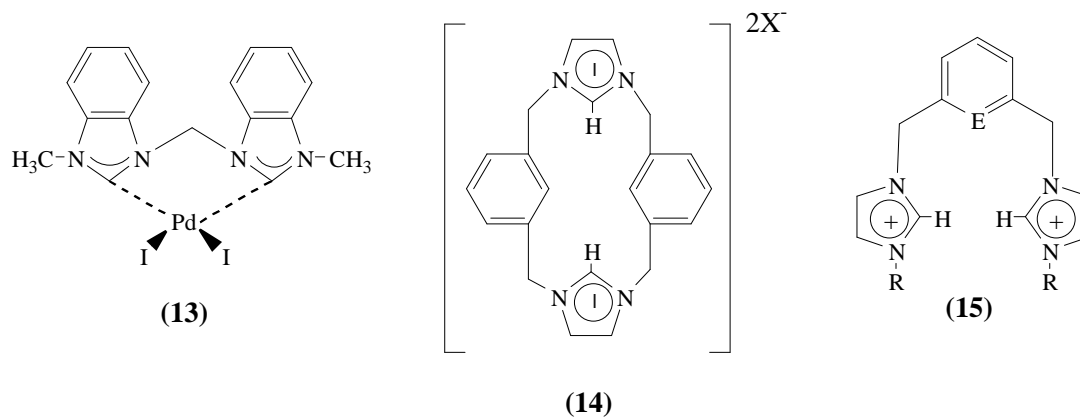
Imidazol-2-ylidines which possess more than one imidazolyl group (multi-dentate) have been of interest due to the multiple coordination sites afforded by the extra imidazolyl rings. Bidentate imidazol-2-ylidines have been investigated as ancillary ligand substitutes for

phosphines in the previously mentioned Heck reaction (**Figure 2**).³¹ The bidentate ligands were believed useful from the stoichiometry of the imidazol-2-ylidene catalyzed Heck reaction where two equivalents of the phosphine ylide were employed. Several reports³¹⁻³³ show the use of a methylene-bridged, bis-imidazol-2-ylidene (**Scheme 6**) to effect the Heck reaction between butyl acrylate and substituted aryl halides.

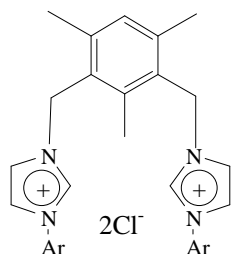
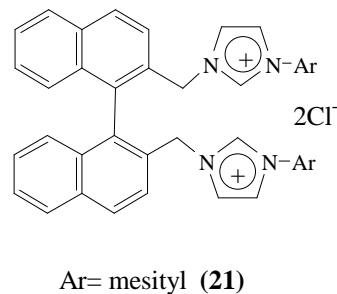
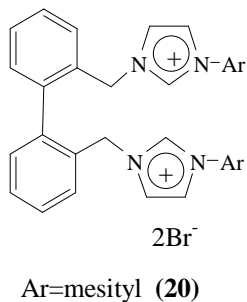
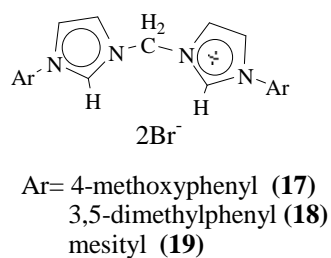
Scheme 6



Prior to Herrmann's work, the syntheses of two tri-dentate ligands were reported however coordination of those ligands to a metal center has not been reported.^{34,35} Herrmann also reported Suzuki, Heck and Sonogashira couplings utilizing **12** as the ancillary ligand with yields ranging from 60-99%.³⁶ Coordination of methylene-bridged bis-imidazol-2-ylidines to nickel^{37,38} and platinum³⁹ have also been reported. Methylene-bridged benzimidazolin-2-ylidene PdI_2 complexes **13**,⁴⁰ Imidazolium-linked ortho-cyclophanes **14**,^{41,42} and tridentate carbene $\text{CCC}^{43,44}$ and $\text{CNC}^{43,44}$ pincer Palladium(II) complexes **15** as well as chiral biscarbenes **16**^{46,47} have been synthesized.

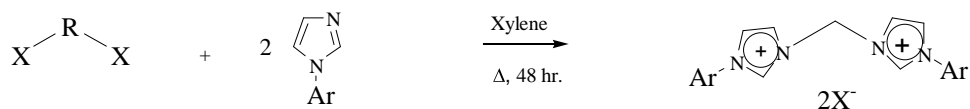


The orthocyclophanes **14**, have shown utility in the Heck Reaction.⁴² Tridentate pincer ligands **15** have been utilized in Sonogashira reactions between aryl halides and terminal acetylenes to produce aryl acetylenes,⁴⁸ and in the Heck Reaction^{43,49} and in coordination with ruthenium.⁴² The Trudell laboratory has reported the synthesis and use^{44,50} of the bidentate ligands **17-24**. These ancillary bidentate ligands have been effective in both palladium-catalyzed Suzuki⁵⁰ and amination⁴⁴ reactions.

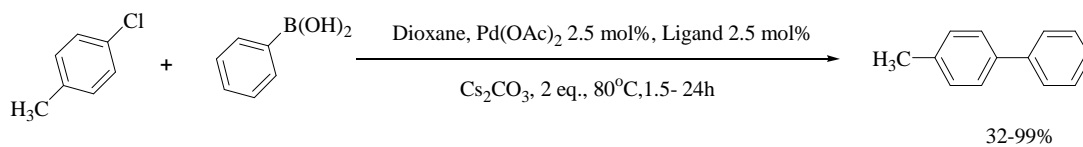


Generally the bisimidazolium salts were prepared from two equivalents of the N-substituted imidazole and the appropriate dihalide in refluxing xylene for 48 hours.

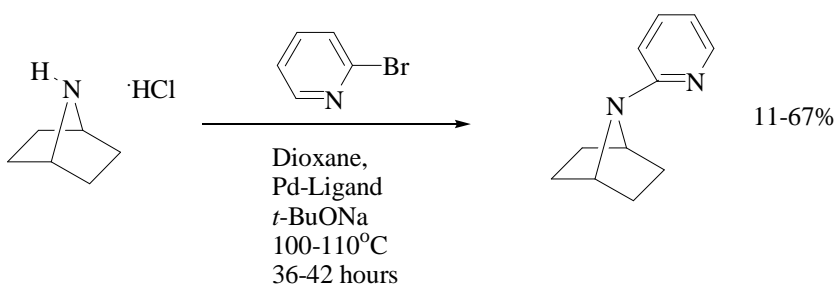
Scheme 7



For the Suzuki reaction of 4-chlorotoluene with phenyl boronic acid, compounds **21** and **22** gave the resultant biphenyl in high yields. Compound **20**, which has less steric bulk, gave lower yields and compounds **17**, **18** and **19** with the least steric bulk, gave poor yields (**Scheme 8**). Decreasing steric bulk around the carbene has a definite deleterious effect on reaction yield. The bisimidazol-2-ylidene ligands showed increased yields with decreased reaction times as the steric bulk increased adjacent to the carbene centers.

Scheme 8.

In the amination reaction of aryl and heteroaryl halides with 7-azabicyclo[2.2.1]heptane⁴⁴ it was found that compound **23** gave higher yields than **22** and all other phosphine ligands investigated. Once again, increased steric hinderance adjacent to the carbene improved the yield of the reaction (**Scheme 9**).

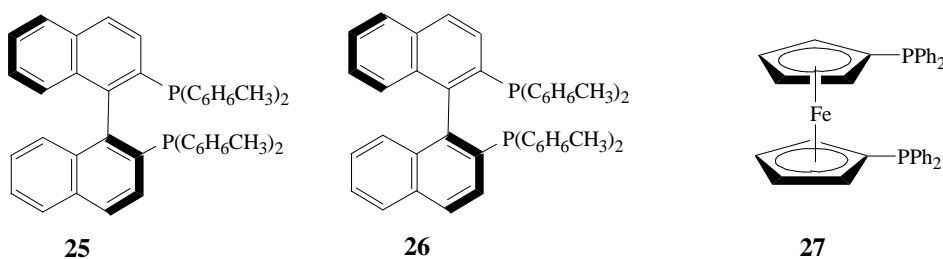
Scheme 9

Thus, the bis-NHCs were shown to have good activity in Suzuki and amination reactions and further investigations employing these ligands would be the subject of future investigations.

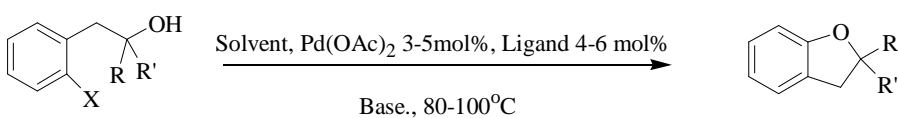
Screening of Oxygen Nucleophiles

One area which has been noticeably absent in the range of synthetic utility of palladium/imidazol-2-ylidene chemistry is the synthesis of aryl-alkyl or aryl-aryl ethers. Aryl ethers are commonly prepared by Ullman coupling or aromatic nucleophilic substitution.⁵¹ Limitations of these methods include high temperatures, excess alcohol, use of copper catalysts and polar aprotic solvents such as DMSO, DMF or HMPA.⁵² Older, less-viable methods include aromatic hydroxylation with hydrogen peroxide-aluminum chloride. Yields are in the 10 to 70% range.^{53,54} A commercial method for the preparation of alkyl aryl ethers involves etherification of a phenol with an olefin in the presence of a cation exchange resin. The yield is approximately 70%.⁵⁵

Buchwald reported the first palladium-catalyzed intramolecular cross coupling reaction of an alkoxide with an aryl halide utilizing an ancillary phosphine ligand.⁵⁶ In this work, the reactions illustrated in Scheme 10 were performed in both toluene and 1,4-dioxane with bis-phosphine ligands. The ligands which were effective include: (S)-(-)-2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl **25** (Tol-BINAP), (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl **26** (BINAP) and 1,1'-bis(diphenylphosphino)-ferrocene, **27** (DPPF).



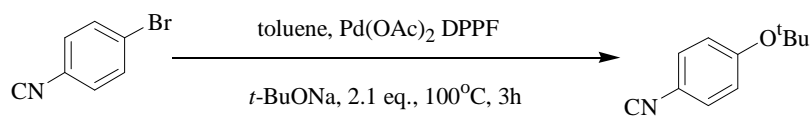
Scheme 10



In the case of cyclization of aryl iodide substrates (X=I), 1,4-dioxane was more expedient than toluene in effecting the cyclizations over 24-36 hours. Yields for all reactions were modest in the 32-89% range.

Concurrent with the Buchwald report, Hartwig⁵⁷ reported the formation of t-butyl ethers from electron deficient aryl bromides in the presence of **27** and toluene. Yields were slightly improved in the 58-69% range(**Scheme 11**).

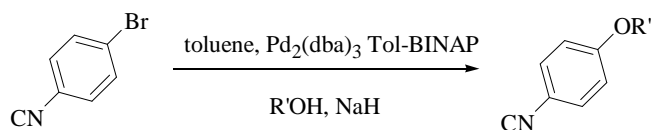
Scheme 11



Hartwig found that the reaction was effective with t-butylalkoxides and electron deficient aryl bromides. However, the reaction was ineffective with primary or secondary alkoxides or with electron-neutral or electron-donating aryl bromides.

Buchwald⁵⁸ revisited aryl ether formation but on an intermolecular level. This time the reaction was effected with electron-withdrawing substrates and primary, secondary and tertiary alcohols. Tol-BINAP(**25**), was employed as the phosphine source and toluene as the solvent. (**Scheme 12**).

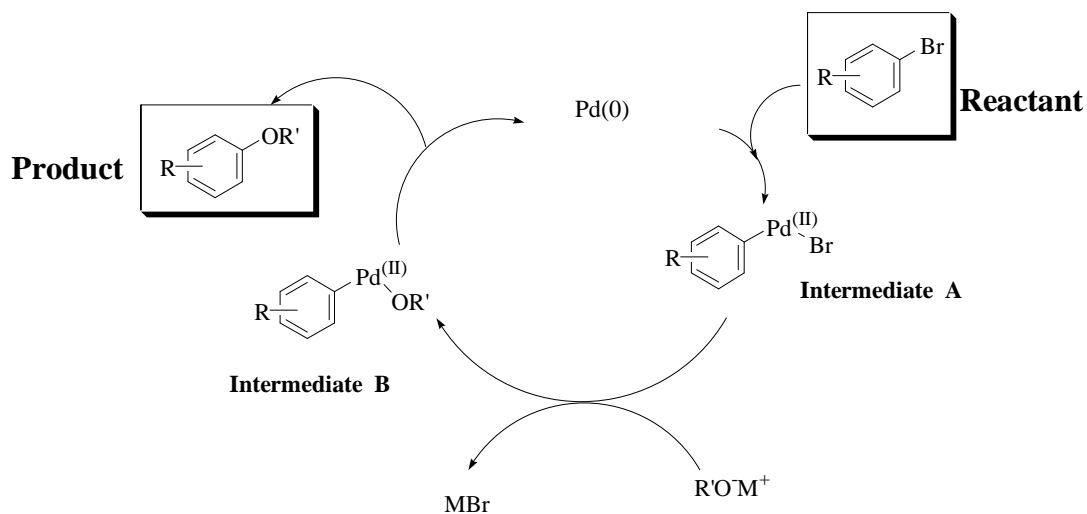
Scheme 12



Yields for substrates with electron-withdrawing groups ranged from 48 to 78%. However, yields for electron-donating groups were less attractive.

The mechanism for ether formation proposed by Buchwald is shown in Scheme 13. The participation of the phosphine ligands was omitted for clarity.

Scheme 13



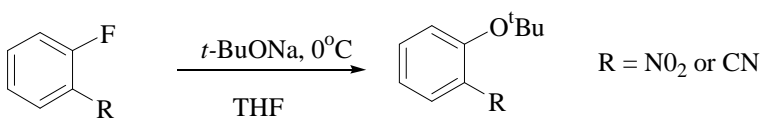
Oxidative addition of the Pd(0)-L complex to the aryl bromide affords Intermediate A. Substitution of the bromide gives Intermediate B. Reductive elimination yields the aryl ether with regeneration of the Pd catalyst. A β -hydride elimination/ reductive elimination sequence which produces a reduced arene side product can be competitive with the reductive elimination. It was also found that employing a polar aprotic solvent, DMF, as a catalyst enhanced the yields of the etherification reaction.

Based on similar work with carbon-nitrogen bond-forming reactions⁵⁹ when bulky triarylphosphine ligands are employed, the key intermediates in the catalytic cycle are mono-phosphine palladium complexes.^{60,61}

Hartwig⁶² then showed that **27** could be used to form diaryl ethers from electron-withdrawing aryl bromides and sodium aryl alkoxides. Reactions were performed in a 9:1 mixture of toluene and THF in the presence of 5-10 mol % Pd(dba)₂ and 6-11 mol% **27**. Yields were in the range of 29 to 92%.

During the course of this study, Wandless⁶³ reported the formation of *t*-butyl ethers from 1-fluoro-2-nitrobenzenes and 1-fluoro-2-cyanobenzenes by direct reaction with sodium *t*-butoxide. The reactions were performed at 0 °C and in a variety of solvents including, THF, 1,4-dioxane and toluene. Reactions were complete within 5 minutes and THF gave the best yields (Scheme 14).

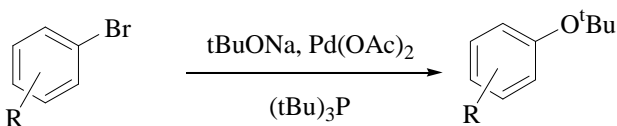
Scheme 14.



In this instance, the 1-fluoro-2-nitrobenzenes (R = NO₂) and 1-fluoro-2-cyanobenzenes (R = CN) are labile toward nucleophilic substitution at the fluorine atom. The reactivity is enhanced by the strongly electron withdrawing 2-nitro and 2-cyano groups thus reducing the activation energy toward reaction with the alkoxide.

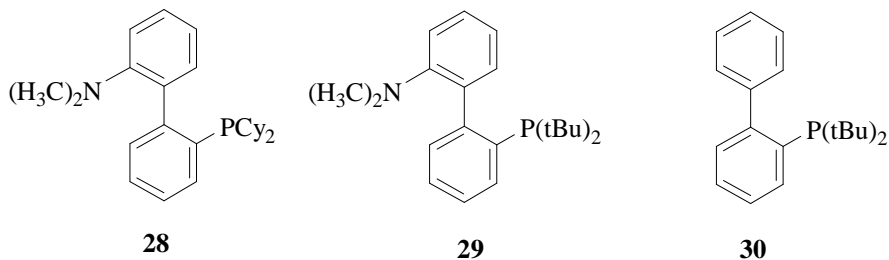
Watanabe⁶⁴ reported the use of palladium acetate (Pd(OAc)₂) with tri-*t*-butylphosphine in xylene to effect the formation of aryl-*t*-butyl ethers in 20-94% yield. Reactions were generally complete within 1-22 hours depending on the substrate.

Scheme 15



The reaction system that is particularly noteworthy is electron neutral bromobenzene (R = H) and electron donating 3-methoxybromobenzene (R₃ = OCH₃) where yields of the corresponding ethers were 89% and 82% respectively.

Buchwald⁶⁰ performed an extensive study on the formation of diaryl ethers utilizing sterically bulky biphenyl phosphines **28**, **29** and **30**.

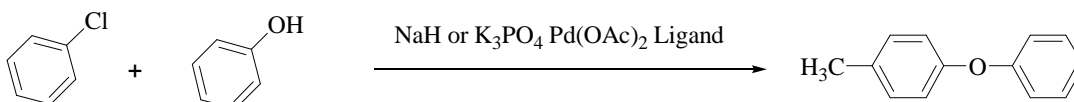


The premise of Buchwald's work was two-fold:

- (1) The rate limiting step "most likely involves the formation of the carbon-oxygen bond via reductive elimination"⁶⁰ and
- (2) "Increasing the steric bulk of ligands can facilitate reductive elimination processes."⁶⁰

Reaction conditions were one equivalent of aryl halide, 1.2 equivalents phenol, NaH or K_3PO_4 as the base, 2.0 mol% $Pd(OAc)_2$ and 3.0 mol% of ligands **28**, **29** or **30** (Scheme 16).

Scheme 16



Yields were in the range of 74-95% for electron-withdrawing substrates and 61-95% for electron-neutral and electron-rich aryl halides. The mechanism illustrated previously in Scheme 13 is the same for the formation of diaryl ethers.

Microwave Assisted Reactions

Microwave-assisted reactions have been popular since their introduction in synthetic organic chemistry in 1986.^{65,66} Reaction rates can be accelerated, yields can be improved, and reaction pathways can be selectively activated or suppressed by the use of microwave irradiation. The microwave portion of the electromagnetic spectrum is characterized by wavelengths between 1 mm and 1 m, and corresponds to frequencies between 100 and 5,000 MHz.⁶⁷

There are two specific mechanisms of interaction between materials and microwaves: (1) dipole interactions and (2) ionic conduction. Both mechanisms require effective coupling between components of the target material and the rapidly oscillating electrical field of the microwaves. Dipole interactions occur with polar molecules. The polar ends of a molecule tend to align themselves and oscillate in step with the oscillating electrical field of the microwaves. Collisions and friction between the moving molecules result in heating. Generally, the more polar a molecule, the more effectively it will couple with, and be influenced by, the microwave field.

Ionic conduction is different from dipole interactions. Ions in solution are charged species that are distributed and can couple with the oscillating electrical field of the microwaves. The effectiveness or rate of microwave heating of an ionic solution is a function of the concentration of ions in solution.

One calculated parameter of a material in a microwave field is the dissipation factor.⁶⁷ The dissipation factor is a ratio of the dielectric loss to the dielectric constant. Simply, the dielectric loss is a measure of how well a material absorbs the electromagnetic energy to which it is exposed, while the dielectric constant is a measure of the polarizability of a material, essentially how strongly it resists the movement of either polar molecules or ionic species in the

material. Both the dielectric loss and the dielectric constant are measurable properties.

Microwave heating occurs somewhat differently from conventional heating. First, the reaction vessel must be substantially transparent to the passage of microwaves. Heating of the reaction mixture does not proceed from the surface of the vessel; the vessel wall is almost always at a lower temperature than the reaction mixture.

Second, for microwave heating to occur, there must be some component of the reaction mixture that absorbs the penetrating microwaves. Microwaves will penetrate the reaction mixture, and if they are absorbed, the energy will be converted into heat. Mixing of the reaction mixture may occur through convection, or mechanical means, stirring can be employed to homogeneously distribute the reactants and temperature throughout the reaction vessel.

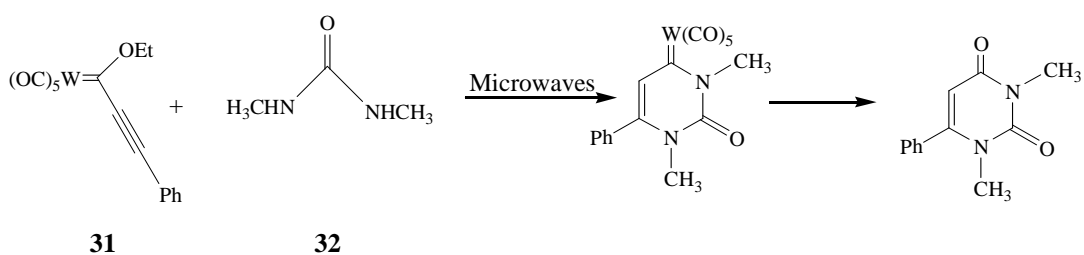
Several procedures exist in the literature for microwave-mediated palladium-catalyzed Suzuki⁶⁸ and amination,^{69, 70, 71} reactions. The microwave-mediated Suzuki reaction with palladium does not require either phosphine or NHC ancillary ligands. Other procedures tout the exclusion of palladium in microwave heated systems for both amination⁷² and Suzuki⁷³ reactions. Interestingly, both types of microwave-mediated Suzuki reactions, with and without palladium, can be performed in heterogeneous conditions with water as the solvent. Reaction times are on the order of 5 minutes and yields are in the 84-100% range. Microwave heating of reactions has found great utility in reducing reaction times and increasing yields.

Microwave-mediated amination reactions performed in DMSO and without ancillary ligands have been shown to proceed via benzyne pathways yielding isomeric products.⁷²

There is one report of utilization a Fisher carbene in the preparation of uracil derivatives (**Scheme 17**)⁷⁴. However, no examples of microwave-mediated, NHC-catalyzed reactions have been reported. In the Fisher carbene synthesis, yields of 92% for the reaction of the tungsten

carbonyl **31** with dimethyl urea **32** were obtained after 5 min at 300W irradiation power. Under solvent-free, microwave mediated conditions yields of 84% were obtained in 10 minutes. Under conventional heating conditions, the uracil compounds were obtained in 50-60% yield.

Scheme 17

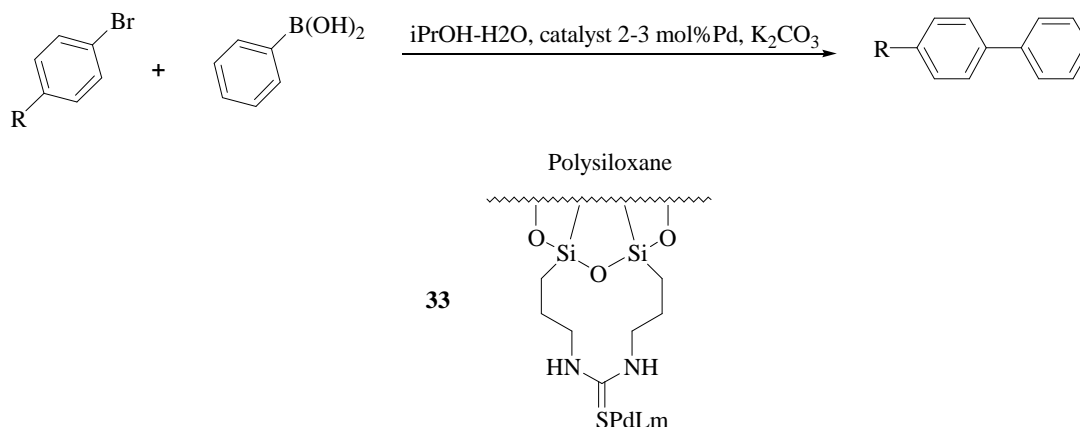


Synthesis and Reaction Screening of Unsymmetrical Polymer-Bound Palladium Imidazol-2-Ylidines

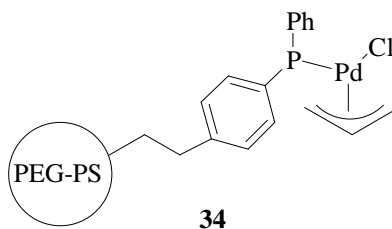
Polymer-bound reactions have enjoyed success in many areas of organic synthesis. Solid-phase peptide synthesis was introduced by Merrifield in 1963.^{75,76} The advantage of polymer bound reactants or catalysts is the ability to recycle those reactants or catalysts many times over. A wide variety of polymers (resins) for combinatorial chemistry are commercially available. The most common resins are polystyrene resins, TantaGelTM, Wang Resins, Merrifield Resins, ArgoGelTM and JandaGelTM resins. Each resin has unique properties in respect to solvent swelling, reactive species and crosslinking.

One of the earliest reports for Suzuki coupling utilizes a commercial Deloxan® resin.⁷⁹ Zheng and Allen showed that the polysiloxane resin could be combined with palladium to give catalyst **33** shown in **Scheme 18**. The solid phase was then used in the Suzuki reaction to give the desired biphenyls. The Deloxan® resin has low solvent swelling and a high degree of crosslinking and the supported palladium species exhibited good stability in air. The Suzuki reaction was performed in a mixture of isopropanol and water with potassium carbonate as the base with 2-3 mol% palladium from the resin. The supported catalyst showed only 3 ppm metal leaching per use. However the catalyst could only be recycled 2 to 3 times before degradation of the catalyst occurred.

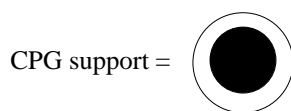
Scheme 18



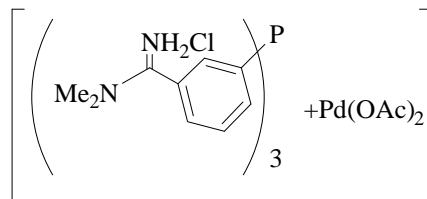
Uozumi⁷⁸ has shown that palladium-phosphine ligands could be bound to polystyrene-based ArgogelTM and TantagelTM resins. The catalysts **34** were then used in Suzuki Reactions, arylation of allyl acetates in water, hydroxycarbonylation of aryl halides in water⁷⁹ and substitution of allyl esters by nucleophiles in water⁸⁰ in high yield.



Controlled-pore glass beads were employed in Heck and Sonogashira Reactions between aryl iodides and substituted alkenes and alkynes.⁸¹ The catalyst is a mixture of the beads, the ligand and a metal complex in a polar solvent giving a supported, non-covalent layer (**35**). Leaching of the catalyst was found to be only 0.1 to 0.2% Pd per reaction.

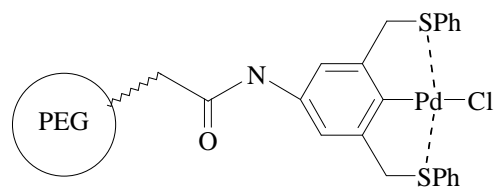


Soluble catalyst on supported layer:



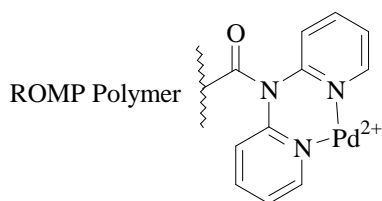
35

A thermally and oxidatively stable PEG polymer with a tridentate SCS ligand, **36**, was shown to be an effective catalyst for the Heck Reaction. This catalyst was reused 3 times without a loss of activity.⁸²



36

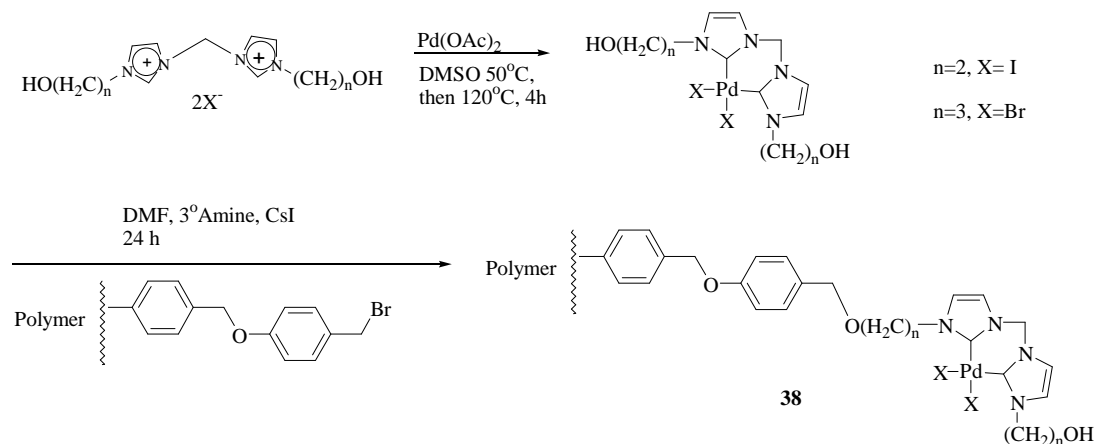
A Ring-Opening Metathesis Polymerization reaction was used to prepare catalyst **37**. This catalyst was then used to catalyze Heck reactions and aminations of aryl bromides. This supported catalyst purportedly gave higher activity than its corresponding non-polymer supported catalyst.⁸³



37

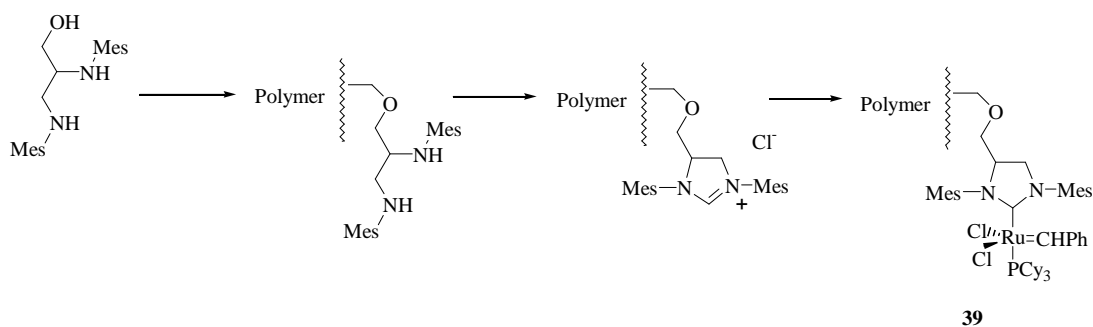
The earliest report of polymer-bound NHCs, was the attachment of a bis-imidazol-2-ylidene to a Wang resin (**Scheme 19**).^{84,85} The bis-imidazol was first complexed with palladium acetate. The subsequent complex **38** was then tethered to a Wang resin and utilized in the Heck Reaction.

Scheme 19



Blechert,⁸⁶ then reported a strategy of attaching a ligand backbone to the polymer, building the ligand and finally treating the catalyst with the metal compound to yield catalyst **39** (**Scheme 20**).

Scheme 20

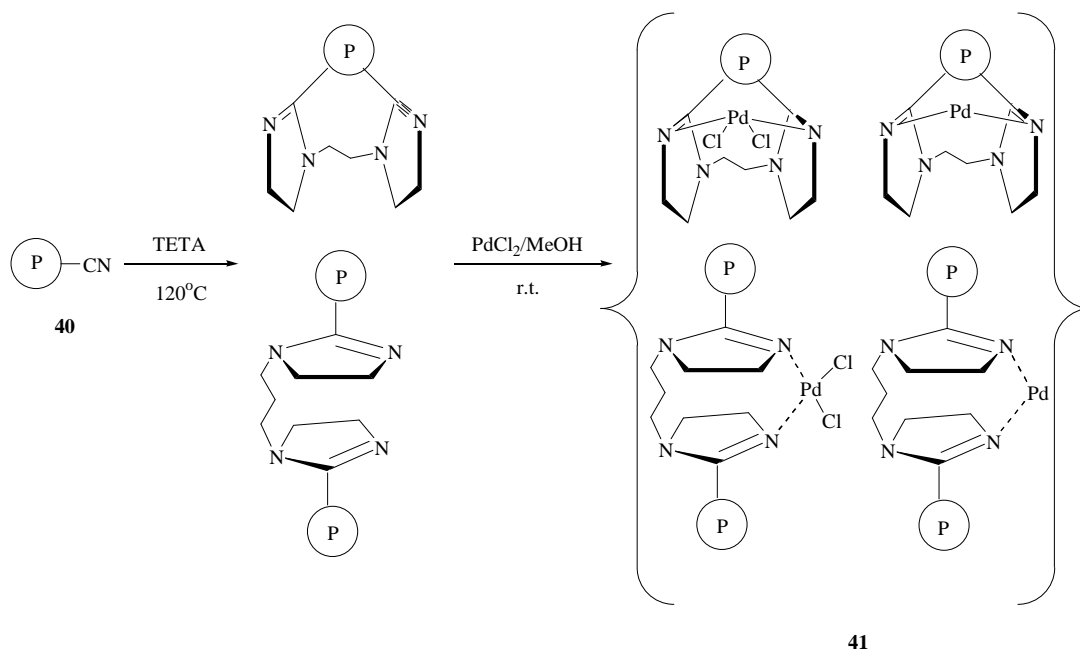


Wu⁸⁷ reported the use of polyacrylonitrile (PAN) fiber to attach imidazoline rings and subsequent coordination of the rings with palladium chloride. The resultant fiber-supported catalysts were then employed in the Heck Reaction. PAN fiber was chosen for its large surface

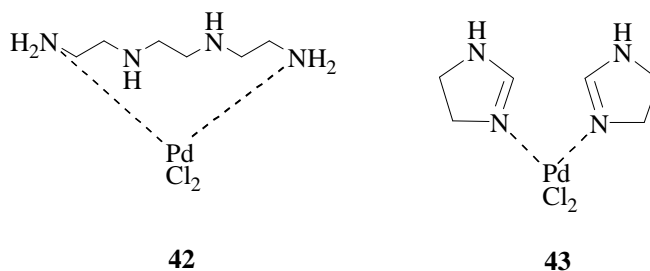
area, ability of the nitrile to be converted into imidazoline and the lower cost of PAN resin compared to other resins.

The PAN fiber **40** was reacted with triethylenetetramine (TETA) to attach the imidazoline rings to the fiber (**Scheme 21**). The fiber was then coordinated with palladium chloride (PdCl_2) to yield the Pd complex **41**.

Scheme 21

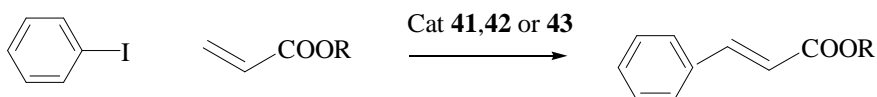


Wu showed further that the original PAN fiber without imidazoline rings would not coordinate with palladium even after refluxing with methanol for 48 hours. Wu then synthesized three complexes, (**41**) is shown in **Scheme 21**. The complex **42** is obtained from TETA and PdCl_2 without PAN fiber while **43** was prepared from the reaction of imidazole with PdCl_2 in the absence of PAN fiber.



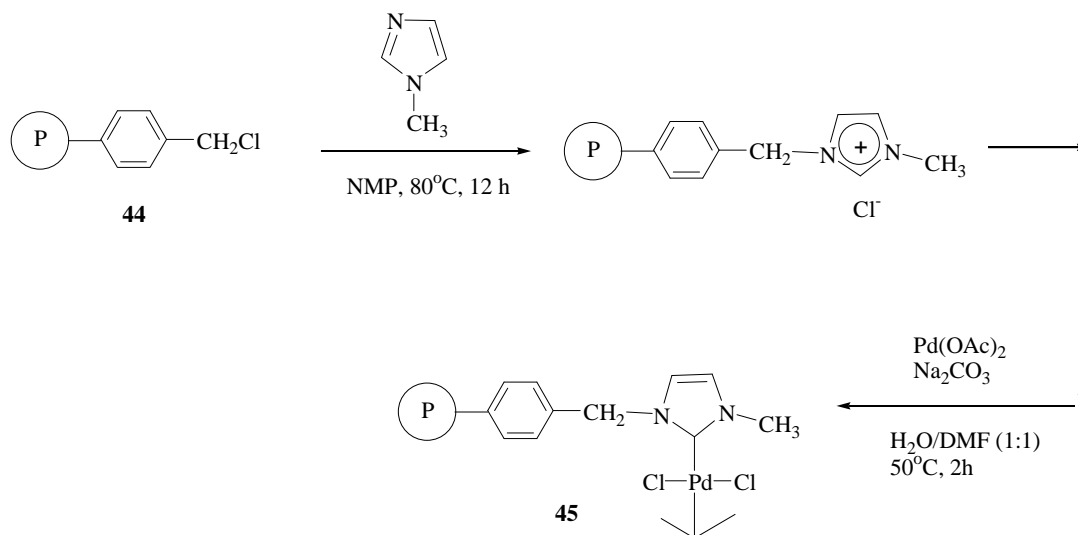
Catalysts **41** and **43** in the Heck Reaction in **Scheme 22** gave isolated yields of 100 and 98% respectively whereas complex **42** gave only 8% yield.⁸⁷ Palladium loadings were 1mmol for **41** and **43** and 2 mmol for **42**. Reaction conditions were 1.0 mmol aryl iodide, 1,4-dioxane as solvent, triethylamine at 100°C for 1 hour. Catalyst **41** was subsequently shown to give turnover numbers (TONs) of 31,500 for a single run and the catalyst was reused 20 times without loss of activity.⁸⁷

Scheme 22

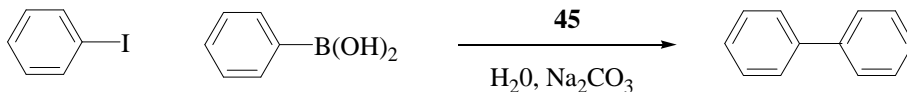


Concurrent with the work in this dissertation, Lee⁸⁸ reported the synthesis of a polymer-supported imidazoline complex with a chloromethylpolystyrene resin, a Merrifield Resin (**44**) (**Scheme 23**).

Scheme 23

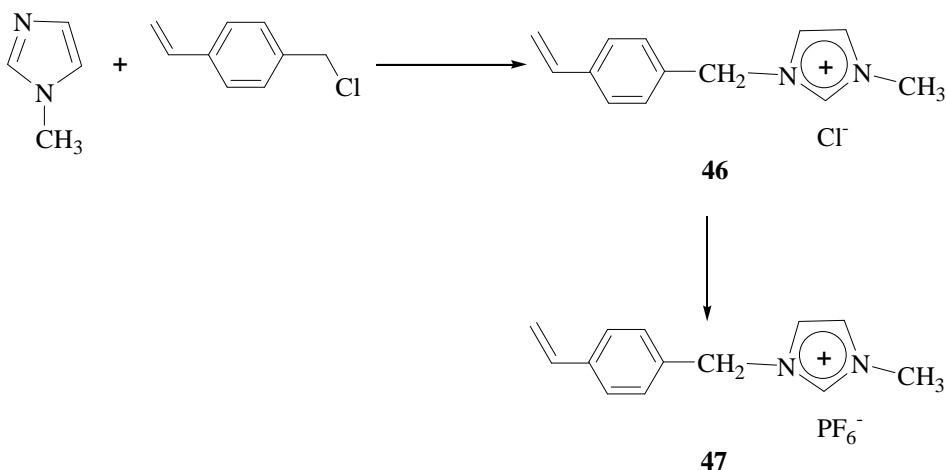


Lee prepared several polymeric supports with different imidazolium loadings and measured the swelling properties in various solvents.⁸⁸ The swelling properties were determined by placing 1 gram of resin in a fritted column. The polymer was then swollen in the desired solvent at room temperature for 30 minutes. The resin was then washed with a 10-fold excess of the solvent. After filtering off the solvent, the new volume of the polymer support was measured. Polar solvents, water, methanol, and DMF gave increased swelling volumes when compared to dichloromethane, THF and toluene. This result was particularly noticeable at the higher imidazolium loading of 1.91 mmol/gram. The polymeric support was then complexed with palladium by reaction with Pd(OAc)_2 in DMF/water 1:1 at 50°C for 2 hours. The palladium loading of **45** was found to be 29% or 0.29 mmol/g by inductively coupled plasma-atomic emission spectroscopy (ICP-AES). Poor diffusion of the imidazolium and palladium through the polymer is cited as the reason for the low yield. The catalytic activity of **45** was then investigated in Suzuki reactions (**Scheme 24**).

Scheme 24

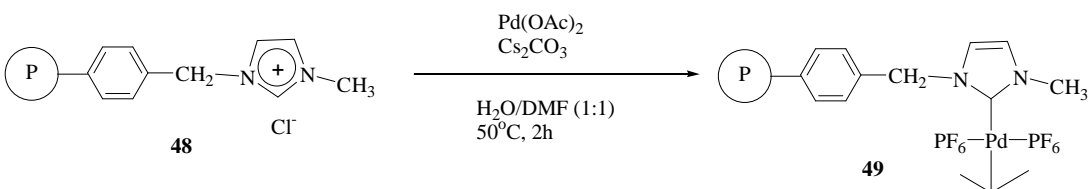
The highest yield of the coupling product was found employing the following conditions: water/DMF, 1:1, 50 °C, 12 h giving 95.6% conversion by GC and 93.3% isolated yield after flash chromatography. The reaction was essentially complete after 3 h with a conversion of 89.6% and 85.1% yield. The reaction in **Scheme 24** was repeated two times with slightly decreased yields due to metal leaching. Several aryl iodides were then combined with phenylboronic acid to give the corresponding biphenyls with conversions from 70.8 to 99.9% and isolated yields from 68.5% to 98%.⁸⁸

A second report by Lee⁸⁹ showed the preparation of a polymer support containing 1-methyl-3-(4-vinylbenzyl)imidazolium hexafluorophosphate **47** and its use in the Suzuki reaction in aqueous solution. Methylimidazole was reacted with chloromethyl styrene yielding 1-methyl-3-(4-vinylbenzyl)imidazolium chloride (**46**). The product was then reacted with NaPF₆. The resulting liquid ionic monomer **47** was insoluble in both the aqueous phase and the styrene phase (**Scheme 25**).

Scheme 25.

The surface grafted (sg) polymer was achieved by suspending **47** in a water-polyvinyl alcohol mixture and polymerizing with styrene and divinyl benzene. The resulting poly(imidazoliummethyl styrene)-sg-PS resin **48** was characterized by Confocal Laser Scanning Microscope (CLSM) and the swelling properties in water, THF, methylcarbonate, DMF and methanol were measured.

The polymer **48** was then metalated with $\text{Pd}(\text{OAc})_2$ in DMF/water for 2 hours at 50°C in the presence of Cs_2CO_3 to give resin **49** (Scheme 25).⁸⁹

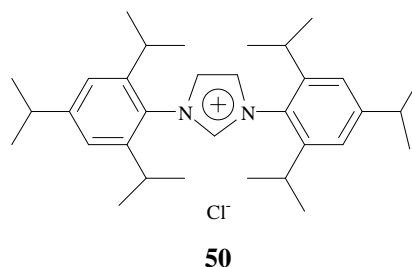
Scheme 25

The quantitative complexation of the imidazolium groups was achieved when a four-fold excess of $\text{Pd}(\text{OAc})_2$ was employed. The resin was then utilized in the Suzuki reaction of aryl iodides with phenylboronic acid. Yields ranged from 20% in water alone to 92-96% in water-DMF.⁸⁹

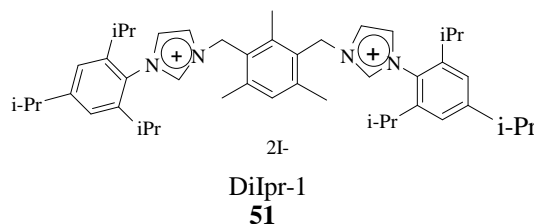
RESULTS AND DISCUSSION

SYNTHESIS OF IMIDAZOYL-2-YLIDINE LIGANDS

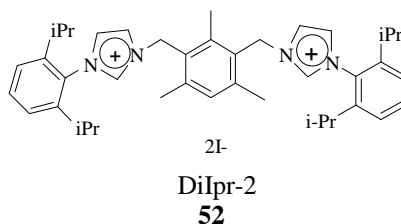
The bidentate ligands synthesized (*vide infra*) and employed in this investigation are dimeric derivatives of 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene hydrochloride (IPr hydrochloride, **50**).



The first bidentate ligand, α,α -1,5-di(N-(2,4,6-triisopropylphenyl)imidazolmethyl)-2,4,6-trimethyl benzene dihydroiodide has three isopropyl groups on the phenyl rings attached to N3 of the imidazoline rings. This version is designated as DiIpr-1 Dihydroiodide, **51**.

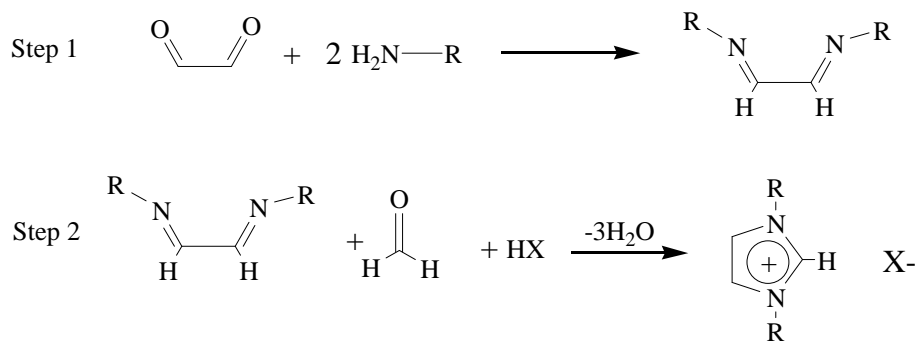


The second bidentate ligand, α,α -1,5-di(N-(2,6-diisopropylphenyl)imidazolmethyl)-2,4,6-trimethyl benzene dihydroiodide has two isopropyl groups on the phenyl rings attached to N3 of the imidazoline rings. This version is designated as DiIpr-2 dihydroiodide **52**.



The synthetic methodology to prepare isolable imidazol-2-ylidines was proposed by Arduengo⁹⁰ and others⁹¹. The basic scheme involves the reaction of two moles of the appropriate primary amine with one mole each of glyoxal, formaldehyde plus an appropriate acid to provide the counter ion. Removal of water completes the reaction and yields the desired protected carbene. Yields are typically reported in the 40-75% range. The Arduengo method was outlined previously in Scheme 5. Later synthetic methods for monodentate imidazol-2-ylidines showed that higher yields can be achieved using a two-step process^{92,93}. In the first step, glyoxal is reacted two equivalents of the appropriate amine. The resulting imine is isolated and subsequently reacted in Step 2 with formaldehyde and the appropriate acid to form the protected carbene. Yields over two steps are in the range of 64-81% (**Scheme 26**).

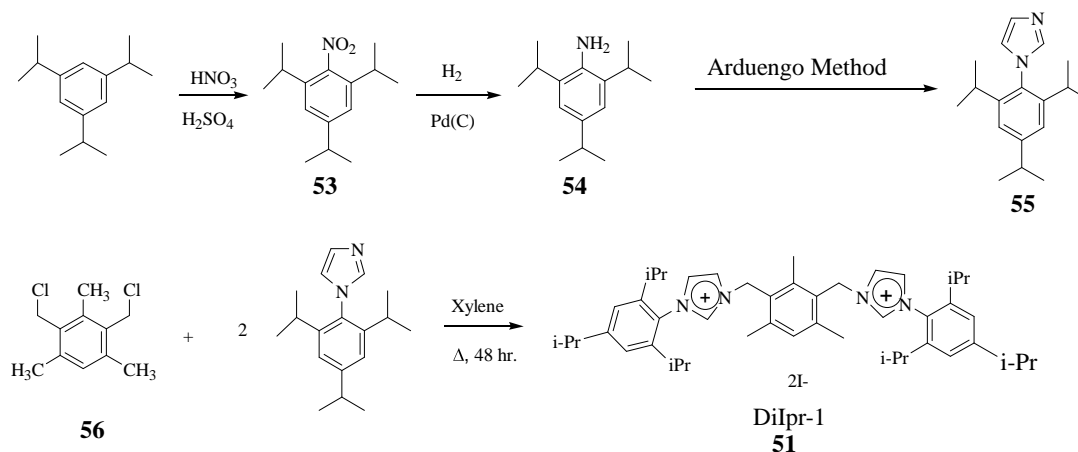
Scheme 26



The bidentate ligands in this study were originally synthesized as the dihydrochlorides starting with Arduengo-type methods to construct the imidazole ring from an aromatic amine (**Scheme 7**).⁵⁰ In this method, commercially available 1,3,5-triisopropylbenzene was nitrated to compound **53** with sulfuric acid and nitric acid. Compound **53** was then hydrogenated over palladium on carbon to give the amine **54**. Using an Arduengo-type imidazole synthesis, the mono-N-substituted imidazole **55** was previously reported⁵⁰ but in subsequent trials could not be repeated. Reaction of two equivalents of **55** with dichloride **56** completed the synthesis of **51**.

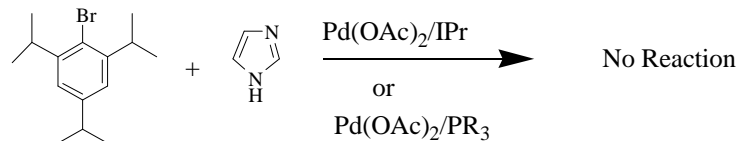
However this step was also difficult to reproduce. This led to an investigation of alternative methods to introduce the imidazole moiety.

Scheme 27



Several methods exist for the N-arylation of imidazoles but none seemed attractive as a viable method to employ here. Methods include nucleophilic aromatic substitution,⁹⁴ Ullmann-type, copper mediated, coupling of imidazoles with aryl halides in polar⁹⁵ and non-polar⁹⁶ solvents, copper catalyzed coupling of aryl boronic acids with imidazoles,⁹⁷ the Goldberg reaction⁹⁸ and copper-diamine mediated N-arylation.⁹⁹ None of these reactions seemed attractive due to the highly toxic copper reagents.

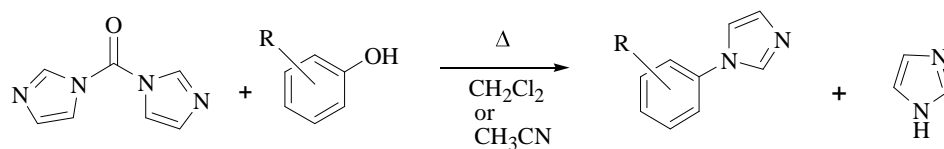
Hartwig¹⁰⁰ reported the one-step synthesis of N-aryl substituted indoles using a palladium-tri-*t*-butylphosphine complex. It was desired to extend this methodology to imidazoles using either **50** or tri-*t*-butylphosphine as the ancillary ligand. Performing the Hartwig method with tri-*t*-butylphosphine/palladium or Ipr/palladium in either dioxane or toluene with imidazole and bromotriisopropylbenzene gave only starting material (**Scheme 28**).

Scheme 28

The lack of reaction here may be due to the rapid tautomerization of imidazole where the potentially reactive secondary amine tautomerizes into a non-reactive tertiary amine.

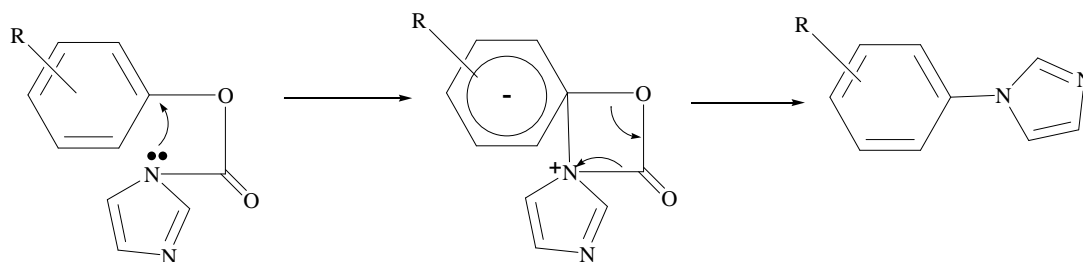
During the course of this study Njar¹⁰¹ reported the synthesis of N-substituted imidazoles directly from N,N-carbonyldiimidazole and the appropriate alcohol or phenol. This reaction was attractive since it obviated the use of a copper catalyst.

A model reaction was investigated by refluxing phenol and carbonyldiimidazole in methylene chloride (**Scheme 29**, R=H).

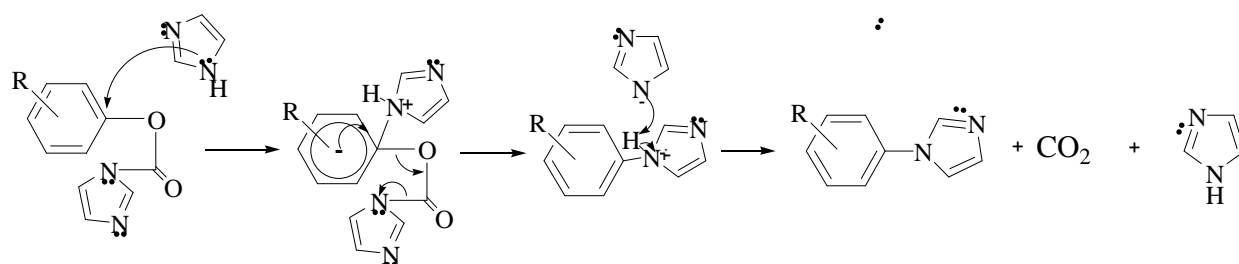
Scheme 29

After 24 hours, the reaction was incomplete by thin layer chromatography. Reflux was continued an additional 24 hours and the reaction was found to be complete by TLC. After work-up and flash chromatography by gradient elution (0-10% ethyl acetate-hexane) the yield was 98%.

The purported mechanism for the reported imidazole addition reaction is shown in **Scheme 29a**.¹⁰¹

Scheme 29a

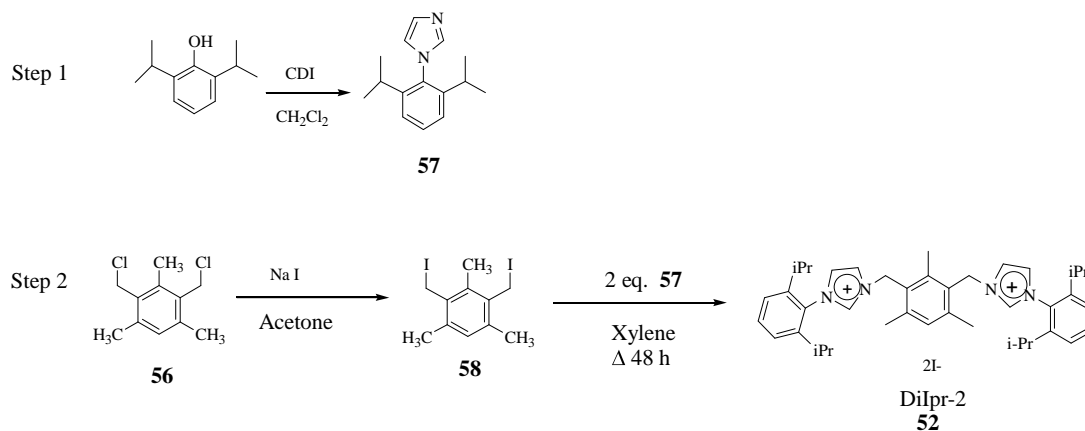
It is doubtful that this is the actual mechanism for two reasons. First: Attack of the lone pair of electrons from the imidazol N-1 nitrogen results in aromaticity being destroyed in the imidazol ring system. This is highly unlikely. Second: The four-member ring system is a high strained ring system which will be highly reactive and transient. It is more likely that the mechanism for the imidazole coupling reaction is bimolecular with participation of the imidazole released in the first step of the reaction adding to the phenyl ring. Re-aromatization results in loss of the imidazole carbamate to give the N-substituted imidazole. Proton transfer completes the process. Addition of a small amount of imidazole to the reaction mixture may enhance the reaction and accelerate the formation of the desired product by providing more imidazole to react with the intermediate carbamate (**Scheme 29b**).

Scheme 29b

With the results of **Scheme 29** in-hand the reaction was extended to employ commercially available 2,6-diisopropylphenol with carbonyldiimidazole in methylene chloride (**Scheme 30**). After refluxing for 48 hours the yield of **57** after chromatography was 95%. The

dichloride compound **56** was converted to the diiodide **58** via a Finkelstein Reaction with sodium iodide in dry acetone.¹⁰² Alkylation of two equivalents of imidazole **57** with **58** in xylene gave **52** in 86% yield overall.

Scheme 30



The alkylation step to give DiIpr-2, **52**, was then optimized. The solvent for this reaction was optimized using the solvents in **Table 2**. The reaction conditions were two equivalents of **57** to one equivalent of **58**. Concentration in solvent was 0.25 Molar. Reaction time was set at 48 hours. Using this methodology, ultra-dry dioxane gave the highest yields as seen in **Table 2**. This afforded **52** in 86% overall yield.

Ultra-dry dioxane was obtained by distilling dioxane over metallic sodium in an inert atmosphere followed by storing over powdered 4-Å molecular sieves. Karl Fischer titration gave 0.05% residual water in the dioxane.

Table 2. Solvent Optimization for Synthesis of DiIpr-2

Run	Solvent	Yield ^a ,%
1	Ether	20
2	THF	38
3	Dioxane	82
4	Toluene	60
5	Ethyl Glyme	42
6	Xylene	24

a= Isolated yield.

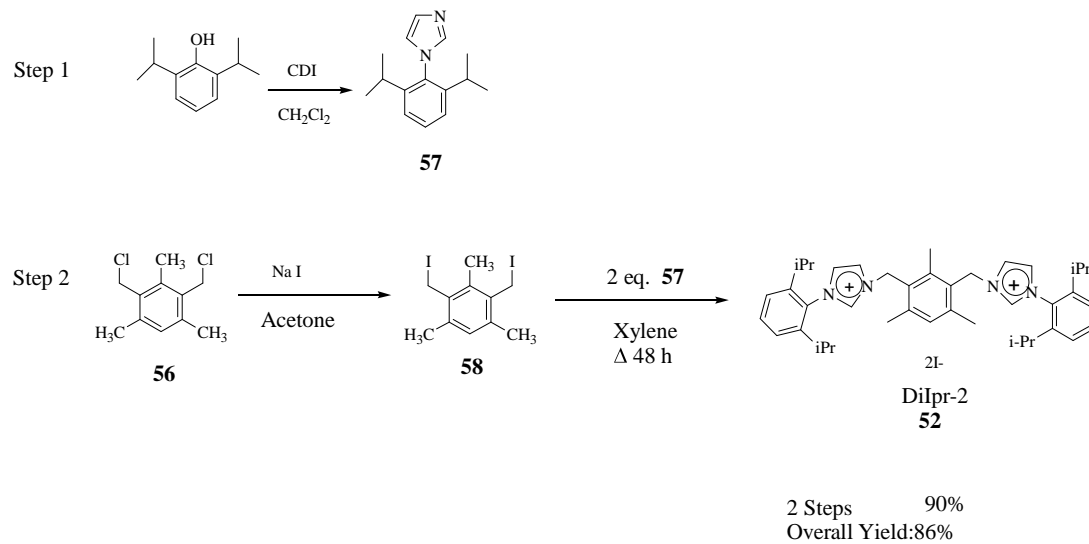
The results for Table 2 are directly related to the ability to obtain dry solvent. The salt **52** should be highly insoluble in each of the solvents employed. Each solvent was distilled from sodium metal under nitrogen. Moisture content was determined by Karl Fischer moisture titration. The high yield in dioxane and the low yield in xylene are a function of the dryness of the solvent employed. For comparison see Table 10 where the unsymmetrical imidazol salts were obtained in high yield from dry xylene.

With the synthetic methodology in-hand, the original ancillary ligand, **51**, DiIpr-1 could now be synthesized. Amine **54** was converted to its diazonium salt analog by first preparing its hydrosulfate salt then treating with sodium nitrite to give the phenol **59**. The diazonium salt was not isolated but was converted directly to **59** in 85% yield by treatment with dilute sulfuric acid.¹⁰³

The phenol **59** was then reacted with carbonyldiimidazole in refluxing methylene chloride to give N-(2,4,6-triisopropylphenyl)imidazole **55** in 95% yield. Two equivalents of **55**

were reacted with **58** in dioxane via the methodology developed for DiIpr-2. Thus DiIpr-1, **51**, was obtained in 65% overall yield (**Scheme 31**).

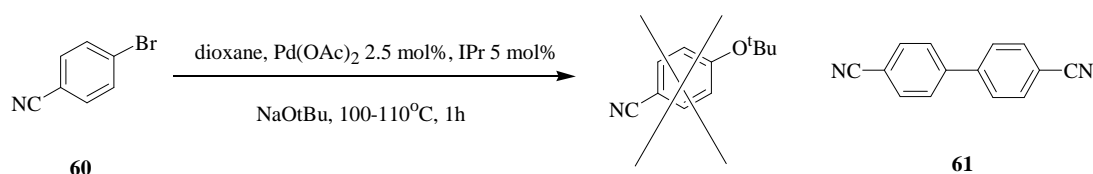
Scheme 31



Screening of Oxygen Nucleophiles.

Based on earlier work in this laboratory,^{44,50} the initial conditions for investigation of ether formation from aryl halides were chosen as: 4-bromobenzonitrile **60**, 0.25 molar in solvent, 2.5 mol% Palladium acetate, 5 mol% **50** and 2.1 equivalents of potassium or sodium *t*-butoxide. Dioxane was chosen as the initial solvent. Standard reaction conditions were 24 hours at reflux (**Scheme 32**).

Scheme 32



Initial results are presented in **Table 3**. All of the aryl substrates containing both electron-donating and electron-withdrawing groups gave homocoupled Ullman-type biphenyls as the products.

Table 3 Attempted Etherification of Aryl Halides.

Entry	Substrate	Product	Yield (%) ^a
1			99 38 ^b 43 ^c
2			95
3			26
4			10 NR ^d
5			82
6			92

a=Isolated yields; b= no NHC catalyst, 100°C, 24h; c= no NHC catalyst, 100°C, 74 days
d= no NHC catalyst, 100°C, 36 days

Entry 1 gave 4,4'-dicyanobiphenyl, **61** as the sole product in quantitative yield in the presence of palladium acetate and **52**. When the reaction was repeated with sodium *t*-butoxide and with palladium but excluding the ancillary ligand NHC, the yield of the biphenyl after 24 hours of reflux was 38%. When the reaction without NHC was repeated for an extended period of 74 days, only a slight increase in yield was obtained over the 24 hour reaction.

Entry 3 of **Table 3** with an electron-donating *t*-butyl group gave the corresponding biphenyl in low yield. Unreacted starting material was recovered to complete the material balance of the reaction to show that no other products were formed.

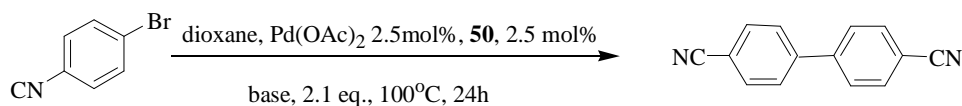
Entry 4 with electron neutral bromobenzene gave only 10% yield as biphenyl with the remainder of the starting material being recovered. Refluxing bromobenzene with potassium *t*-butoxide for 24 hours or 36 days without Pd or NHC gave only unreacted starting material by TLC and GC.

With these results in hand, factors which may have influenced the production of biphenyls were investigated. The reaction of 4-bromobenzonitrile in Scheme 32 was chosen as the subject of this investigation.

Counter Ion Effects With *t*-Butoxide

Table 4 shows the effect of solid lithium-, sodium- and potassium- *t*-butoxide as well as 1.0 M potassium *t*-butoxide solution in THF.

Table 4. Counter ion Effects with *t*-Butoxide



<i>t</i> -Butoxide Counter ion	Product	Isolated yield %
<i>t</i> -BuO ⁻ Li ⁺	-----	-----
<i>t</i> -BuO ⁻ Na ⁺	61	100
<i>t</i> -BuO ⁻ K ⁺	61	100
<i>t</i> -BuO ⁻ K ⁺ /THF	61	100

Lithium *t*-butoxide gave no reaction. Probably due to the increased basicity of the alkoxide due to the harder lithium counter ion. The lithium ion, due to its size and electropositive nature is more tightly bound by the oxygen anion making the *t*-butoxide a slightly stronger base compared to sodium and potassium *t*-butoxide. The relatively harder base in conjunction with the highly nucleophilic carbene may make the reaction mixture too basic to initiate the oxidative-addition step required to start the catalytic cycle to synthesize the homocoupled products. Only 4-bromobenzonitrile starting material was recovered after 24 hours of reflux. Sodium- and potassium *t*-butoxide as dry powders gave 4,4'-dicyanobiphenyl **61** as the sole product in quantitative yield. No difference was observed by employing potassium *t*-butoxide in THF as a 1.0M solution.

Palladium to Ligand Ratio

Table 5 summarizes the results of varying the palladium to ligand ratio. Entries 2 and 5 confirmed the earlier results that electron-donating groups (4-*t*-butyl, **Table 3**, entry 3) give lower yields of the corresponding biphenyl product than electron-withdrawing groups (4-CN, **Table 3**, entry 1). No difference in time of reaction or yield were observed when **50** as used at a 1:2 or 1:1 palladium to ligand ratio. Similar results were observed when **51** and **52** were employed as ligands.

Table 5. Pd to Ligand Ratio.

Pd: Ligand Ratio	R	Ligand	Yield^a
1:2	CN	50	100%
1:2	<i>t</i> -Bu	50	25%
1:1	CN	50	100%
2:1	CN	51	100%
2:1	CN	52	100%
1:1	CN	52	99%
1:1	<i>t</i> -Bu	52	23.8%

^aGC yields.

Results reported in Table 5 are GC yields.

Nolan⁹⁷ has indicated that in the case of the bis-imidazoles **51** and **52** only one of the two available carbenes actually participates in the reaction. Since this seemed to be the case, later studies used one equivalent of **50** to one equivalent of Pd or 0.5 equivalents of **51** or **52** to one equivalent of palladium. Using a 1:1 ratio of carbene to palladium gave the same yields as in **Table 5**.

Reaction Time

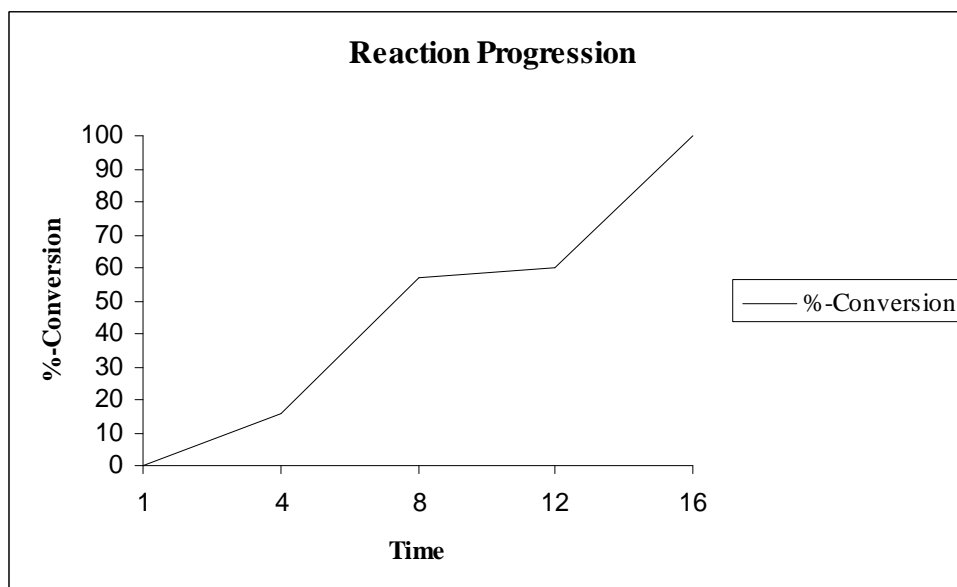
Modifying the initial reaction to use a palladium:ligand ratio of 1:1 with **50** and employing sodium *t*-butoxide as the base, the reaction time was investigated. The reaction was performed monitoring the reaction by GC every 4 hours. This technique showed complete conversion to the biphenyl after 16 hours (**Table 6**). A plot of the reaction yield versus time

clearly shows an equilibrium between 8 and 12 hours with a slow increase in product formation between 12 and 16 hours (**Figure 3**).

Table 6. Reaction Time and Conversion to Product.

Time (hours)	%Conversion
1	0
4	15.65
8	57.2
12	59.9
16	100

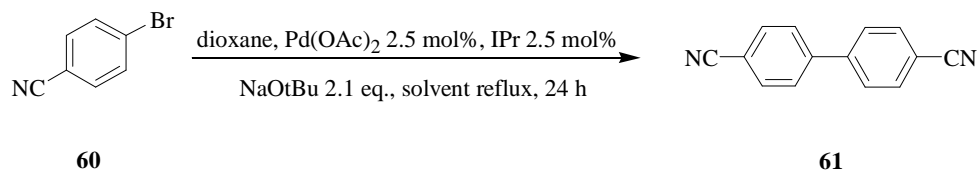
Figure 3. Reaction Progression from Table 3.



Solvent Effects

Table 7 shows the effects of various solvents on biphenyl formation from 4-bromobenzonitrile.

Table 7. Solvent Effect on Biphenyl Formation



Entry	Solvent	Boiling Point (°C)	Yield ^a
1	Dioxane	100	100%
2	THF	65	82%
3	Toluene	110	21%
4	DME	85	100%
5	Ethyl glyme	121	100%
6	DMF	153	100%
7	Heptane	98	No Reaction ^b
8	Diglyme	162	100%
9	DMSO	189	28%
10	Acetonitrile	82	36%
11	Diethyl ether	35	No Reaction ^b

^aGC yields. ^bQuantitative recovery of starting material.

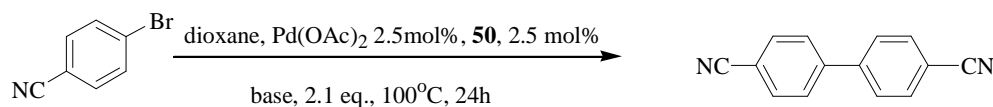
It can clearly be seen that polar aprotic solvents consistently give higher yields of the biphenyl than non-polar solvents (entries 3 and 7). It is interesting to note that the polar solvent acetonitrile gave lower yields of biphenyl with only unreacted starting material recovered.

Reactions in toluene gave low yield of the biphenyl. Further investigation of the reaction in toluene showed only unreacted starting material by GC and NMR.

Base Effects

Several other alkoxides and sodium hydroxide were investigated in the reaction (**Table 8**).

Table 8. Alkoxide Screening in Biphenyl Formation



Entry	Base	Yield ^a
1	<i>t</i> -BuONa	100%
2	NaOH (Cs ₂ CO ₃ /NaOH)	15% (15%)
3	NaOMe	20%
4	NaOEt	15%
5	Sodium pentoxide	3%, 10%
6	Sodium phenoxide	7%, 20%

^aGC yields.

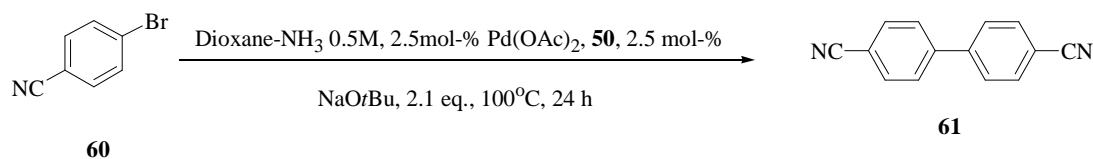
Initially, the alkoxides in entries 5 and 6 of **Table 5** were generated from sodium metal and the appropriate alcohol. When the reactions were found to give low yields, 3% and 7% respectively, the alkoxides were then generated from sodium hydride and the alcohol giving 10% and 20% yield respectively.

The alkoxides in entries 1-4 were commercially available and were used as received. Only the non-nucleophilic base sodium *t*-butoxide gave any appreciable reaction albeit the undesired biphenyl. Use of sodium hydroxide, entry 2, was performed by dissolving moist beads in dioxane under reflux. The catalyst was then added and allowed to react for 30 minutes to

generate the carbene. The substrate was added last in an effort to reduce the side reactions which can occur between hydroxide and nitriles. Only 15% of **61** was produced and no phenol product was observed. Since Cs_2CO_3 is widely used as a non-nucleophilic base in NHC catalyzed Suzuki reactions, the NaOH reaction was repeated by first combining cesium carbonate with palladium acetate and **50** to generate the palladium-ligand complex. Sodium hydroxide was then dissolved once the palladium-ligand complex was observed. Finally the substrate was dissolved and the mixture was heated to reflux. No improvement in yield nor other products were observed by this technique. The bulky *n*-pentyl alkoxide and the aromatic phenoxide, entries 5 and 6 respectively also failed to give high yields of the corresponding biphenyls.

The reaction of **60** was then performed in a 0.5 molar solution of ammonia in dioxane. Ammonia was employed as the base. Initially, no alkoxide was added. The reaction was found to be complete in 12 hours and 4,4'-dicyanobiphenyl was the sole product (**Scheme 33**).

Scheme 33

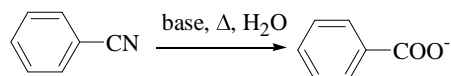


The reaction was repeated with ammonia-dioxane to generate the carbene, then sodium *t*-butoxide was added. Again the reaction was complete in 12 hours and 4,4'-dicyanobiphenyl was the sole product.

Effect of Substrate

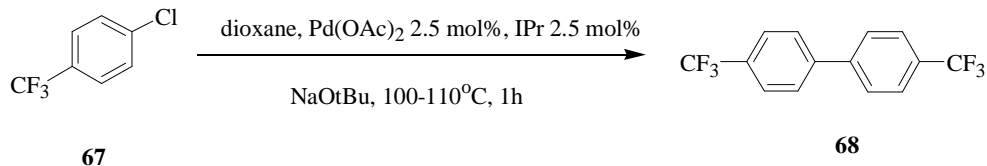
Cyano groups can undergo several reactions under basic conditions however under the conditions employed here the predominant side reaction which can occur is the hydrolysis of the nitrile group to the corresponding carboxylate (**Scheme 34**).

Scheme 34



To determine if the cyano group was either participating in the biphenyl formation or if the cyano group was undergoing an unwanted transformation, two further experiments were performed. First, 4-bromobenzonitrile was refluxed in dioxane in the presence of sodium *t*-butoxide but without palladium acetate or Ipr as catalysts. The mixture was carefully analyzed by GC. Only 4,4'-dicyanobiphenyl was observed as the product after 24 hours at reflux. Results were compared by GC to a solution of 4,4'-biphenyldicarboxylic acid in dioxane. None of the dicarboxylic acid was observed by GC in the reaction mixture. The only other component was found to be starting material. No side reactions of the cyano group were observed.

Second, 4-trifluoromethylchlorobenzene **67** was employed in the reaction as the substrate using the standard conditions of 2.1 equivalents of sodium *t*-butoxide, 2.5 mol% palladium acetate, 2.5 mol% **50** in dioxane (**Scheme 35**). The 4,4'-di(trifluoromethyl)biphenyl **68** was obtained in 96% yield as the sole product.

Scheme 35

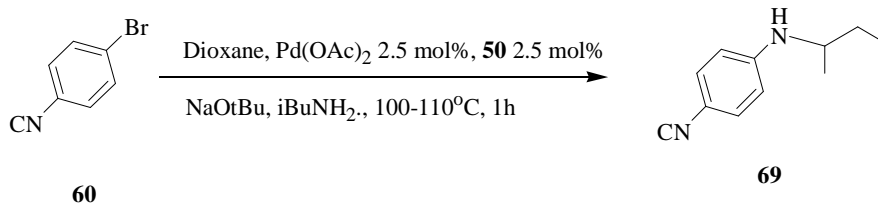
In this instance an aryl halide with a substrate that was unreactive towards base, also gave the homocoupling product in 98% yield.

Effect of Palladium Source

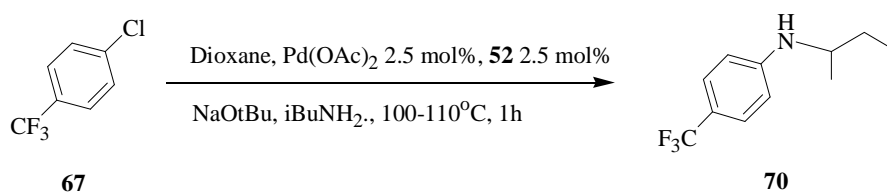
Tris-(dibenzylidene acetone)dipalladium (Pd₂(dba)₃) has been employed as an effective catalyst in other imidazolyl catalyzed transformations.²⁸ It was employed here to determine if a difference could be observed between it and palladium acetate. 4-trifluoromethylbromobenzene was used as the substrate and Pd₂(dba)₃ was used at 2.5 mol% with **50** at 1.25 mol% in the reaction outlined in Scheme 35 above. The 4,4'-di(trifluoromethyl)biphenyl was obtained in 99% yield as the sole product. No difference was observed in reaction time when monitoring by GC.

Reactivity of Carbene Catalysts

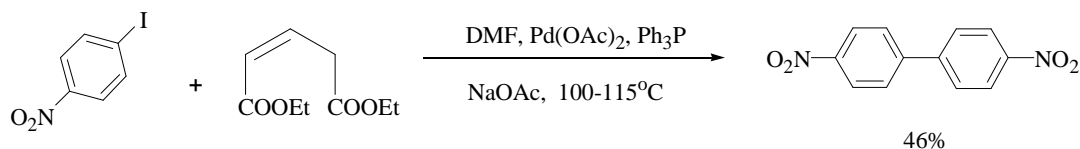
The catalytic action of imidazol-2-ylidines with palladium in the reactions of amines with aryl halides has been well established.¹⁰⁵ To confirm the reactivity of catalysts **50**, **51** and **52**, they were employed in the reaction between isobutyl amine and aryl halides. The 4-bromobenzonitrile was reacted with isobutylamine, 1.2 equivalents in the presence of 2 mol% **50** and 2 mol% palladium acetate in dioxane with 2 eq. sodium *t*-butoxide as the base. The reaction was complete by TLC within 0.5 hours giving 1-(isobutylamino)-4-cyanobenzene(**69**) in 92% yield (**Scheme 36**).

Scheme 36

4-(Trifluoromethyl)chlorobenzene (**67**) was reacted with isobutylamine in the presence of **52** and palladium acetate (**Scheme 37**). The substituted amine **70** was obtained in 98% yield after 7.5 hours at reflux. The reactions in **Scheme 36** and **Scheme 37** confirmed the reactivity of the NHCs employed.

Scheme 37

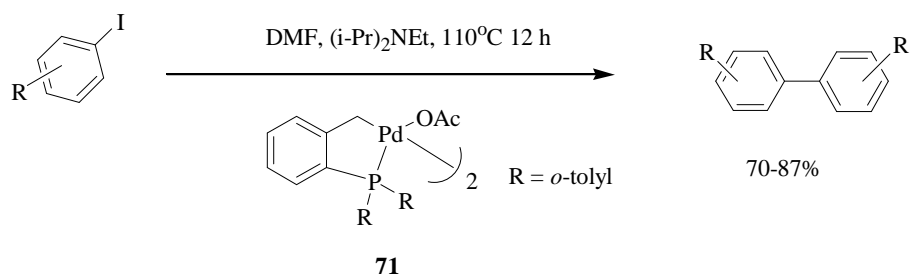
Palladium catalyzed biphenyl formation has been observed in reactions other than the Suzuki Reaction. In early studies of the Heck Reaction, biaryl formation was observed.^{106, 107} The biaryls were unwanted side products but were present in appreciable yields. In this instance the catalyst system was 5 mol% Pd(OAc)₂ and 10 mol% triphenylphosphine.

Scheme 38

Luo¹⁰⁸ showed that monoiodoarenes can be used to synthesize biaryls using less than 0.1 mol% of palladacycle catalyst **71** and N,N-diisopropylethylamine as a base in DMF at 100°C.

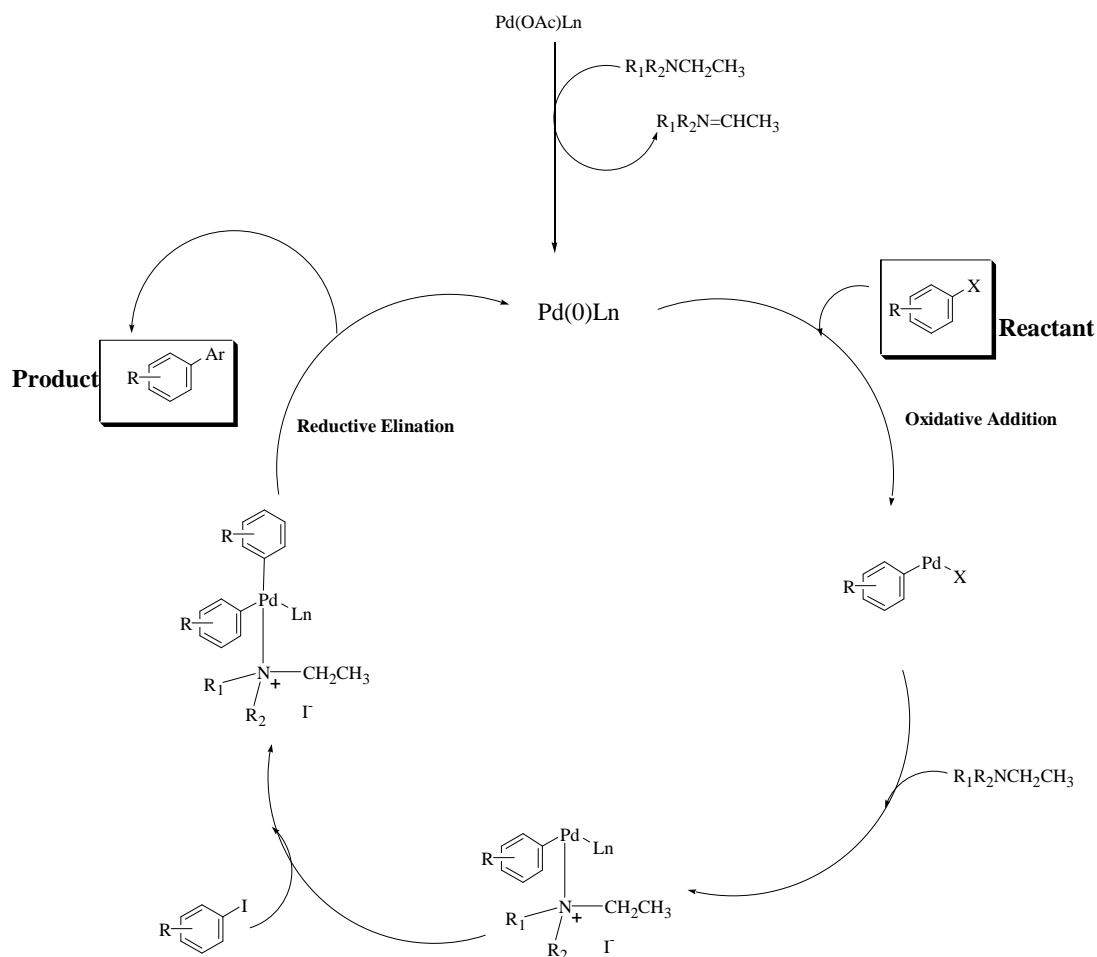
The base effect was studied and the sterically hindered *i*-Pr₂NEt was the most efficient and selective base (**Scheme 39**).

Scheme 39



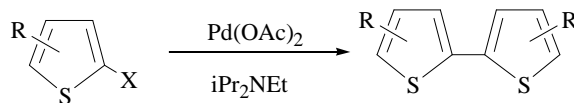
The proposed mechanism is outlined below (**Scheme 40**).

Scheme 40

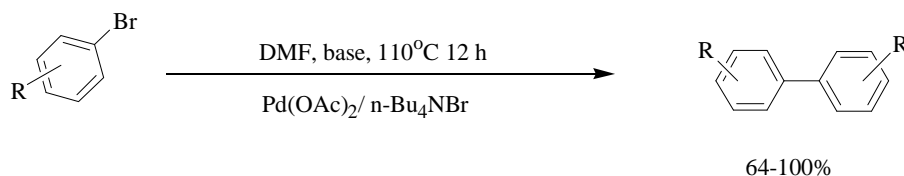


Lu summarized the mechanistic steps: "Oxidation of the tertiary amine by palladacycle may form iminium salt and palladium(0) complexes. The replacement of iodo with amido group followed by another oxidative addition of aryl iodide to form Pd(IV) complexes. The following elimination will form biaryl, hydrogen iodide and iminium salt."¹⁰⁸

Lemaire¹⁰⁹ reported the use of Pd(OAc)_2 in the homocoupling reaction of halothiophene. The reaction is catalyzed by *i*-PrNEt and is accelerated by the addition of tetrabutylammonium bromide. The yields are good to excellent at 62-100% (Scheme 41).

Scheme 41

Lemaire¹¹⁰ then extended this method to the homocoupling of aryl bromides in the presence of Pd(OAc)₂ and tetrabutylammonium bromide. Both electron-donating and electron-withdrawing substrates in the *ortho*-, *meta*- and *para*- positions were coupled in high yields (**Scheme 42**).

Scheme 42

The above examples and others¹¹¹⁻¹¹⁴ provide ample evidence that the homocoupling of halides can occur in the presence of palladium both with and without a phosphine ancillary ligand.

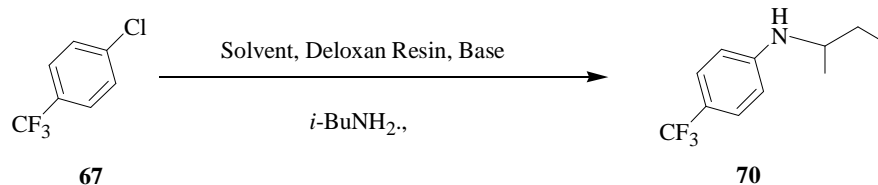
The imidazol-2-ylidines and phosphine ligands have both been shown to effect the Suzuki, Heck and aryl amination reactions. In each of these reactions, the nucleophiles are carbon or nitrogen, which are relatively soft. In the literature reports of etherification reactions with ancillary phosphine ligands those ligands are less nucleophilic than the imidazol-2-ylidines. The combination of highly nucleophilic ligand, imidazol-2-ylidene, and hard nucleophile, alkoxide, appears to inhibit the etherification reaction and the homocoupling reaction with the softer carbon nucleophile occurs. The combination of nucleophilic ligand with softer nucleophiles may be the key to the etherification reaction. If a method can be found to temper the hardness of the alkoxides, it may then be feasible to effect the etherification of aryl halides in the presence of oxygen nucleophiles.

The work presented in this dissertation is consistent with these results. In this work as well as the literature, aryl halides were reacted in polar aprotic solvents with either phosphine or NHC ancillary ligands to give high yields of homocoupled biphenyls. The formation of aryl ethers has been shown to occur in the presence of phosphine ancillary ligands but not in the presence of ancillary NHCs. In this work, the homocoupling product is the sole product in the presence of NHCs.

Synthesis and Reaction Screening of Unsymmetrical and Polymer-Bound Imidazol-2-Ylidines

To prepare novel, polymer-bound imidazol-2-ylidines, a divergent synthetic strategy was employed. The first method was to use an existing, commercially available palladium bound resins either with or without an ancillary NHC to effect the amination or Suzuki reactions. The second method was to prepare unsymmetrical imidazol-2-ylidines bound to a Merrifield or other resin to effect the same reactions.

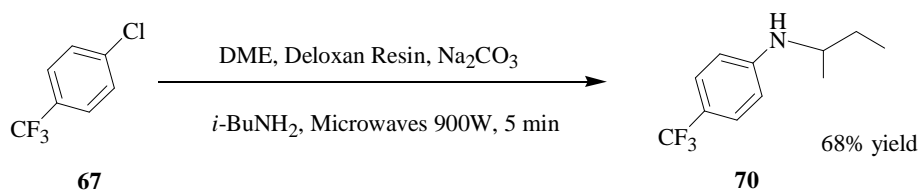
Deloxan[®]-bound palladium **33** is commercially available and was previously shown to effect the Suzuki Reaction in a mixture of isopropanol and water.⁷⁷ (**Scheme 18**). It was not known if the reaction could be enhanced by the presence of an NHC ancillary ligand. To that end, Deloxan was employed in an amination reaction both with and without **50** as the ancillary ligand. The reaction in **Scheme 37** was chosen as the prototype since the conditions and yield were already known.⁷⁷ The reaction with Deloxan[®] but without ancillary ligand was screened to determine a suitable solvent (**Table 9**). The reaction conditions were: **67**, 1 mmol; isobutylamine, 1.2 mmol; sodium carbonate, 2 equivalents; palladium as Deloxan, 5 mol%, solvent: 0.25M solution based on **67**. All yields were monitored by GC.

Table 9. Solvent Screening for Deloxan in Amination Reaction

Solvent	Yield ^a
IPA-Water (1:1)	No reaction ^b
Dioxane	No reaction ^b
DME	12%
DMF	No reaction ^b
DMSO	No reaction ^b

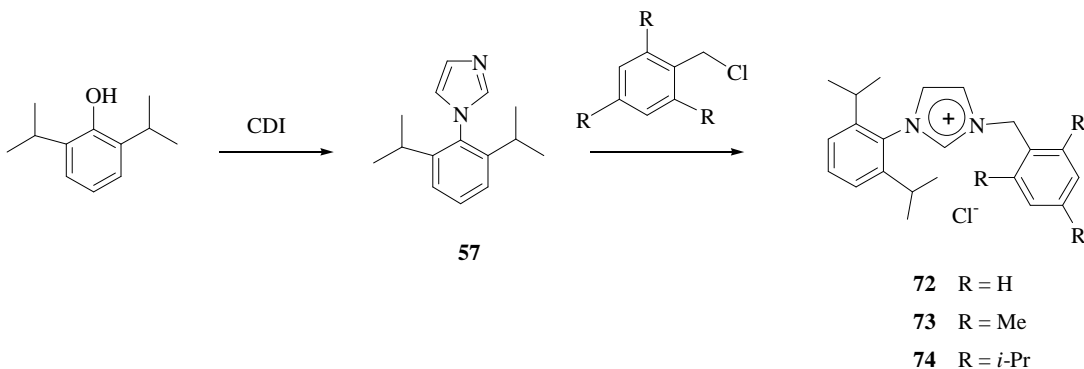
^aGC yield. ^bStarting material recovered.

Only the reaction in DME showed any yield, although poor, at 12%. With these results in hand, it was desired to determine if the incorporation of an NHC would enhance the reaction. Ipr (**50**) was employed as the NHC at 5 mol% in DME keeping all other parameters constant. The yield increased to 29%. The reaction was repeated utilizing a Samsung microwave oven Model MW965WP at its maximum power of 900 watts for 5 minutes. The yield increased to 63%. Heating time was then increased to 10 minutes at 900 watts but no increase in yield was observed (**Scheme 43**).

Scheme 43

Although this chemistry was interesting, conventional heating gave poor yields and only moderate yields were obtained with the assistance of microwave heating. The second approach to polymer-bound NHCs was then investigated. Using the previously defined methodology to prepare N-substituted imidazoles in conjunction with alkylation reactions, unsymmetrical imidazol-2-ylidines could be prepared (**Scheme 44**). 2,6-Diisopropylphenol was chosen as the starting material to impart steric hindrance similar to that of **50** on the target imidazolines. Substituted benzyl halides, with methyl and isopropyl substituents, were also prepared to examine the effect of the benzylic carbon on the reactivity of the unsymmetrical imidazol-2-ylidines.

Scheme 44



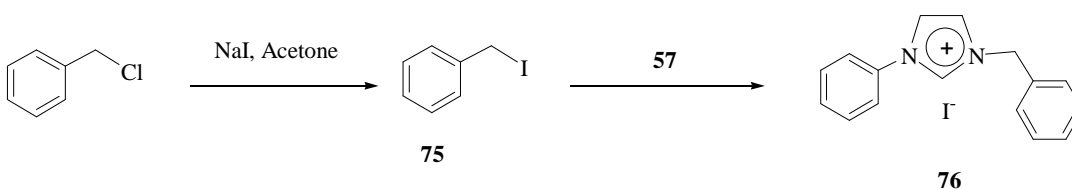
The reaction of **57** with benzyl chloride was investigated extensively as a model reaction for the unsymmetrical imidazol-2-ylidines as well as the coupling reaction between **57** and a Merrifield resin. The solvent system for the reaction of **57** and benzyl chloride was determined (**Table 10**). Ultra-dry xylene was found to be the solvent of choice, giving the highest yield for the alkylation reaction affording **72** in 73% yield. DMF and dimethylacetamide proved difficult to completely remove from the product.

Table 10. Solvent Screening in the Preparation of Unsymmetrical NHCs.

Solvent	Yield ^a
Xylene	73%
Toluene	65%
DME	53%
Dioxane	58%
Dimethylacetamide	71%
DMF	70%

^aIsolated yield

Enhancing the reaction by converting the chloride to an iodide via a Finkelstein reaction was also investigated (**Scheme 45**). Benzyl chloride was reacted with sodium iodide in acetone at room temperature. The resulting benzyl iodide (**75**) was distilled under reduced pressure in 89% yield. Benzyl iodide was then reacted with **57** in ultra-dry xylene under reflux for 48 hours. The yield of the resulting dark-brown solid unsymmetrical product **76** was 78%. The overall yield for the two-step reaction was 69%.

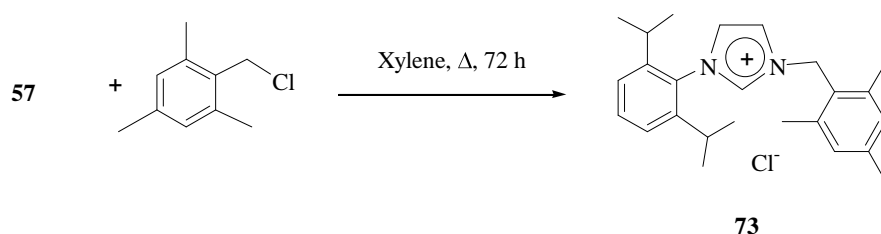
Scheme 45

Since the reaction to prepare **76** was slightly lower in yield than the single-step reaction to prepare **72**, (69% versus 73%) it was decided that the single-step reaction would be suitable as a model reaction for the coupling of **57** with a Merrifield resin and for the synthesis of compounds **73** and **74**.

Since ultra-dry dioxane was the solvent of choice for the final step in the synthesis of DiIpr-1, **51** and DiIpr-2 and **52**, the reaction between benzyl chloride and **57** was repeated in dioxane with microwave heating at 900 Watts. Surprisingly, after a total of 30 minutes of heating, over 5 minute intervals, the yield of the reaction rose modestly from 58% to 64%.

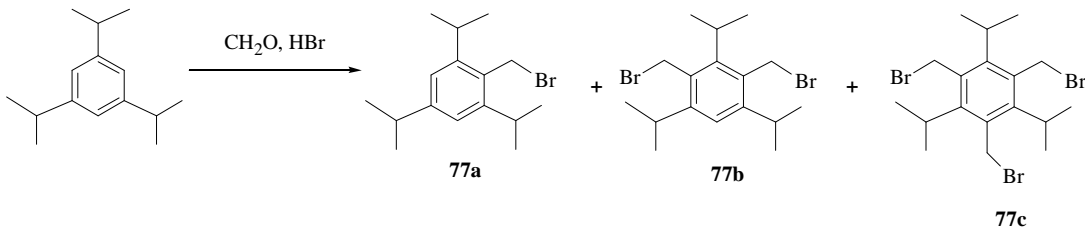
With the above results in-hand the preparation of compound **73** proceeded smoothly from **57** in 62% yield after 72 hours at reflux in ultra-dry xylene (**Scheme 46**).

Scheme 46

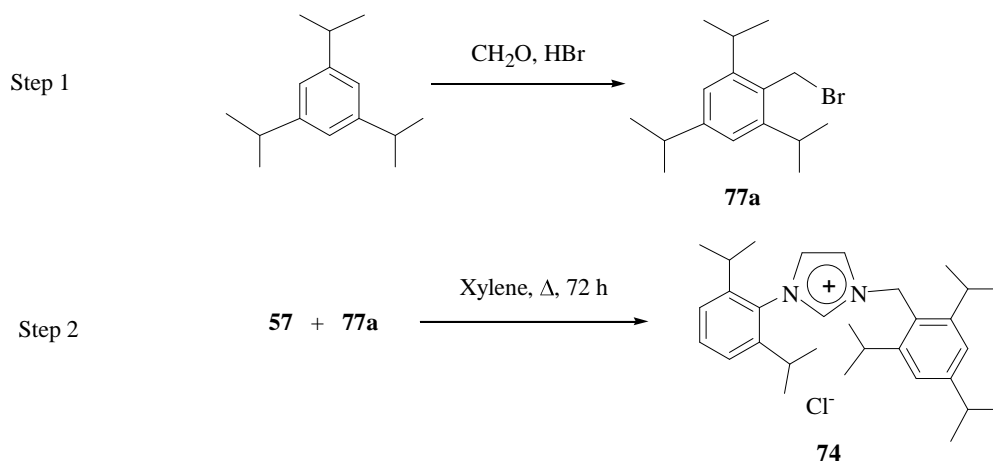


The preparation of compound **74** was achieved by preparing benzyl bromide **77a** from triisopropylbenzene using formaldehyde and 60% hydrobromic acid in acetic acid. The literature procedure¹¹⁵ reported the possibility of addition of up to three benzylic methylenes. Careful control of the temperature by maintaining the temperature at 50°C and careful control of the reflux for 4 hours gave the desired product, **77a**, in 81% yield. At temperatures greater than 70°C, the disubstituted product **77b** was obtained in 59% yield. Longer reaction time, 10-12-hours, at 50°C also gave the trisubstituted product **77c** in 68% yield with the remainder being **77b** (**Scheme 47**). The monobromomethyl compound, (**77a**) was then reacted with **57** in ultra-dry xylene to give **74** in 48% yield (**Scheme 48**).

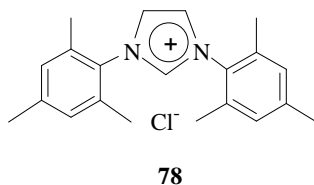
Scheme 47



Scheme 48



The unsymmetrical imidazol-2-ylidines **72**, **73** and **74** were then screened in amination reactions for comparison to the standard IPr (**50**), and IMes (**78**), ligands (Table 11).

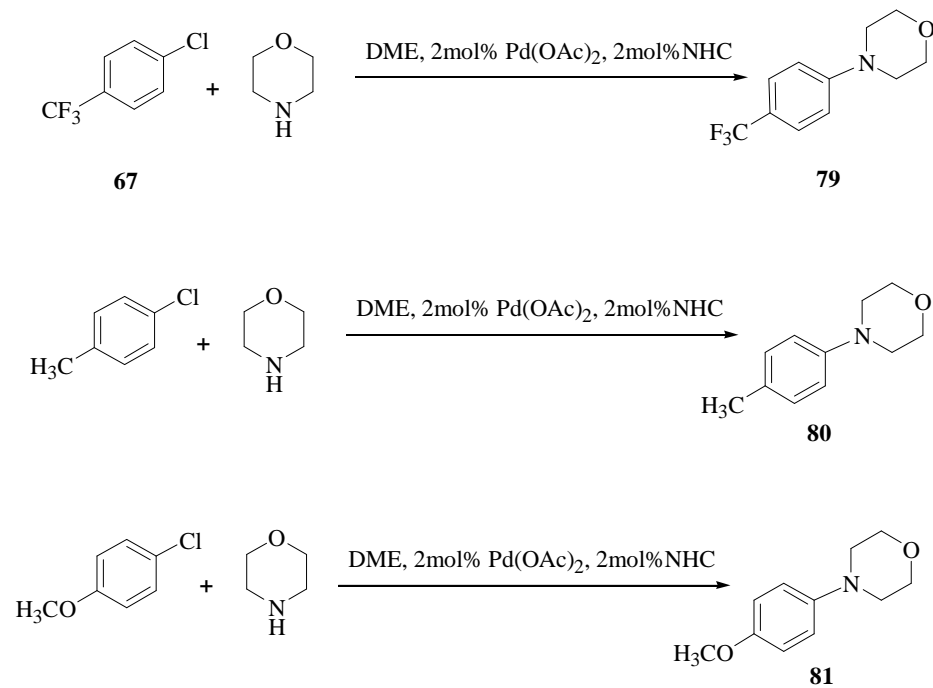


The IMes (**78**) and IPr ligand precursors are commercially available. IMes has generally been found to be less active than IPr in comparable reactions.¹⁰⁵ This is probably due to less steric hindrance of the methyl groups compared to the steric hindrance of the isopropyl groups on IPr.¹⁰⁵

Nolan and coworkers¹¹⁶ have reported the use of 1.0 mmol of aryl halide, 1.2 mmol amine, 1.5 equivalents of *t*-amyl alkoxide, 0.5 mol% **50** and 1 mol % Pd as $\text{Pd}(\text{IPr})\text{Cl}_2$. DME was

employed as the solvent. Improved yields and shorter reaction times were reported using these reaction conditions as compared to the earlier report by Nolan¹⁰⁵ where potassium *t*-butoxide was employed as the base and dioxane as the solvent.

The reaction conditions in this work were chosen as 1.0 mmol aryl chloride, 1.2 mmol morpholine, solvent: DME (0.25 molar in ArCl), 2 eq. sodium *t*-butoxide, 2 mol% Pd(OAc)₂ and 2 mol% NHC ligand. All reactions were performed in Ace Glass pressure tubes with stirring. Conventional heating in an oil bath was used as the heat source. All yields are GC yields. The results are summarized in **Table 11**.

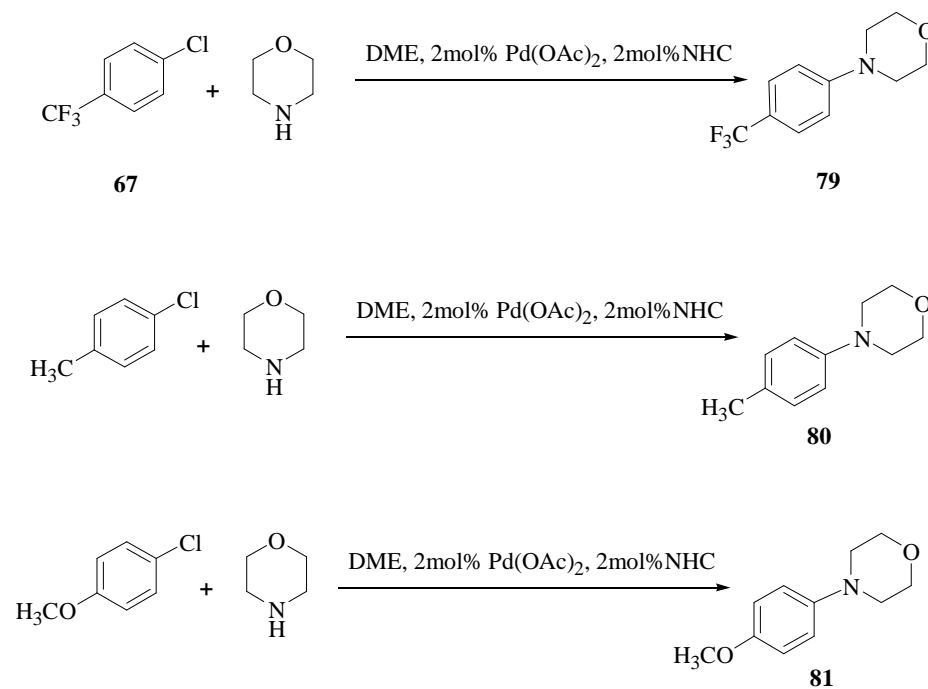
Table 11. Comparison of Symmetrical and Unsymmetrical Ligands.

Product	Ligand	50	78	72	73	74
79	Yield:	100%	98%	97%	97%	98%
	Time:	1 hr.	2.5 hr.	3.5 hr.	2.5 hr	1.5 hr.
80	Yield:	100%	97%	100%	94%	94%
	Time:	2 hr.	4.5 hr.	6 hr	5.5 hr.	5.5 hr.
81	Yield:	100%	97%	100%	94%	94%
	Time:	2.2 hr.	5.2 hr.	6 hr	6 hr.	4 hr.

This survey indicates that the unsymmetrical ligands **73** and **74** are approximately equivalent to their symmetrical congeners, **50** and **80** respectively, in reaction time and yield. In **Table 11**, **72** and **73** which have less steric hindrance than **74** required longer reaction times. This indicates that the benzylic carbon at N-5 of the imidazole ring allows some rotation which

can result in conformations that give lower steric hindrance adjacent to the carbene. The lesser steric hindrance results in lower activity of the carbene center thereby resulting in longer reaction times and lower yields. The reactions in **Table 11** were then repeated with microwave heating at 500 watts power in place of conventional heating. (**Table 12**).

Table 12. Microwave Heating of the Reactions

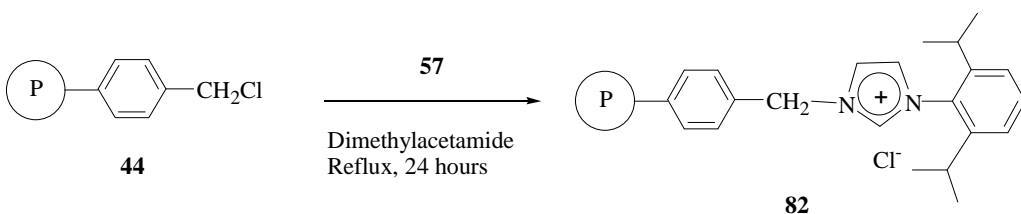


Product	Ligand	50	78	72	73	74
79	Yield:	100%	98%	98%	97%	100%
	Time:	0.33hr.	0.6hr.	0.8hr.	0.8hr	0.5hr.
80	Yield:	100%	97%	95%	96%	99%
	Time:	0.5hr.	0.75 hr.	0.9hr	0.8 hr.	0.5 hr.
81	Yield:	100%	98%	96%	98%	99%
	Time:	0.5hr.	0.5 hr.	0.75 hr	0.9 hr.	0.75 hr.

As expected the reactions were greatly accelerated by microwave heating and less difference in reaction time was observed between the symmetrical and unsymmetrical ligands. All reactions under microwave conditions were performed in less than 1 hour. Among the unsymmetrical ligands, **74** again gave higher yields and shorter reaction times than **72** or **73**.

The reaction scheme illustrated in **Scheme 44** was used as a model for the reactions of Merrifield resins with N-substituted imidazoles. (**Scheme 49**). Concurrently with this work, Lee⁸⁸ reported the attachment of methyl imidazole to a Merrifield resin. With the results of the unsymmetrical ligands above, it was believed that the steric hindrance imparted by **57** bound to a Merrifield resin would enhance the reactivity of the polymer-bound ligand.

Scheme 49



Once the unsymmetrical imidazol-2-ylidines were successfully prepared, the polymer-bound ligand of **Scheme 49** was then prepared.

A Merrifield resin with a reactive chloride content of 1.09 mmol/gram was refluxed with **57** in dimethylacetamide for 24 hours. The imidazole loading on the polymer was determined by quantifying the presence of free **57** by GC as the reaction progressed. A ten-fold excess of **57** was employed. When a nine-fold excess of **57** was found by GC, the reaction was stopped. Following work up, the nitrogen content was determined by micro-Kjeldahl analysis. The analysis showed a yield of 64%. For comparison, the reaction of benzyl chloride with **57** gave 71% yield in dimethylacetamide. (See **Table 10**).

The swelling properties of **82** were then determined by loading 1-gram of the resin into a graduated flash column with a stopcock and fritted glass filter. Polymer **82** was allowed to swell in the desired solvent for 1 hour at room temperature. The resin was washed three times with the solvent and allowed to air dry for 2 hours. The mass, density and volume of the resin was then determined after exposure to the solvent (**Table 13**).

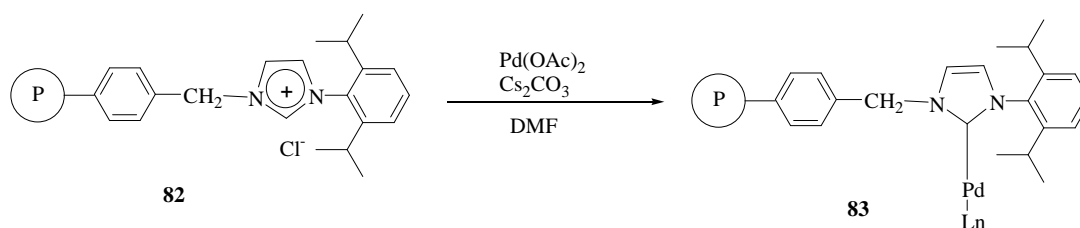
Table 13. Swelling Properties of Polymer 82

Dry Volume (mL/gram)	Swelling volume in:				
	H ₂ O	DMF	Dimethylacetamide	DME	Dioxane
1.8	2.0	4.5	4.3	3.1	2.9

The more polar DMF and dimethylacetamide gave the highest swelling volumes. By contrast, the swelling volume in water was very low.

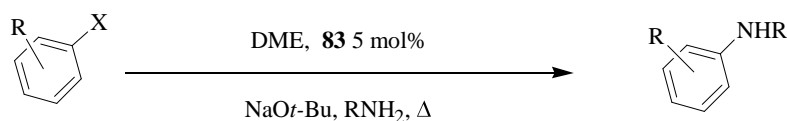
Complex **82** was then reacted with Pd(OAc)₂ in DMF at reflux for 12 hours in the presence of 2 equivalents of Cs₂CO₃ to give the palladium-carbene complex **83** (**Scheme 50**).

Scheme 50



Complex **83** was analyzed by reducing a sample to ash in a porcelain crucible in a furnace at 800°C. The mass of the resulting ash was determined and the presence of Pd was determined by atomic absorption spectroscopy.

Complex **83** was then employed in several amination reactions to prepare substituted aryl amines (**Table 14**). The reaction conditions were chosen as 1.0 mmol aryl chloride, 1.2 mmol amine, solvent: DME (0.25 molar in ArCl), 2 eq. sodium *t*-butoxide, 2 mol% Pd(OAc)₂ and 2 mol% NHC ligand.

Table 14. Amination Reactions Utilizing Complex 83

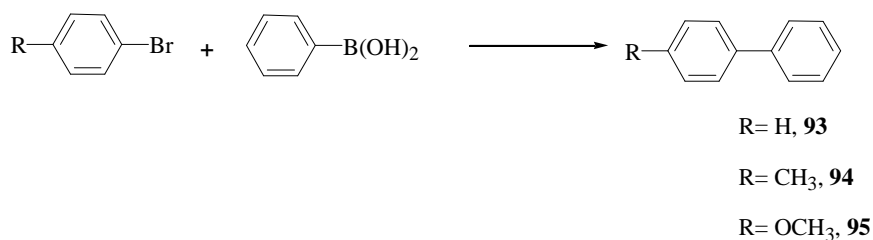
Aryl halide (microwave)	Product	Yield ^a , time (conventional heating)	Yield ^a , time
	 84	95%, 2h	100%, 0.42h
	 85	100%, 4h	100%, 0.25h
	 80	95%, 4h	98%, 0.15h
	 87	94%, 6h	97%, 0.42h
	 88	98%, 3h	98%, 0.42h
	 81	96%, 2h	100%, 0.25h
	 90	98%, 1h	100%, 0.083h
	 79	98%, 1.5h	99%, 0.25h
	 92	73%, 4h	86%, 0.5h

^aGC yields.

All products **84-92** were purified by flash chromatography and compared to their literature values for NMR analysis.¹¹⁷⁻¹²⁴ All yields are GC yields. All reactions show greater or equal yields under microwave conditions when compared to conventional heating. The reaction

to produce compound **90** from **60** was complete in 5 minutes. The reaction was repeated ten times under conventional heating without loss of activity of the catalyst. The reaction was then repeated ten times with a fresh resin sample under microwave heating at 700 watts, again without loss of activity after the tenth cycle. The reactions in **Scheme 51** were performed in DMF with microwave heating and yields were determined by GC. Reaction conditions were 1.0 mmol aryl halide, 1.1 mmol phenylboronic acid, 2.0 equivalents of Na_2CO_3 , 5 mol% Pd as polymer **83** in DMF, microwave 700 watts, 0.75 hours. (**Scheme 51**)

Scheme 51



Comparison of the results of this work for the Suzuki reaction to the results of Lee⁸⁸ are tabulated below (**Table 15**). In this work, the use of a more hindered active site on the polymer, microwave heating and dioxane as the solvent instead of water consistently gave higher yields than the Lee procedure.

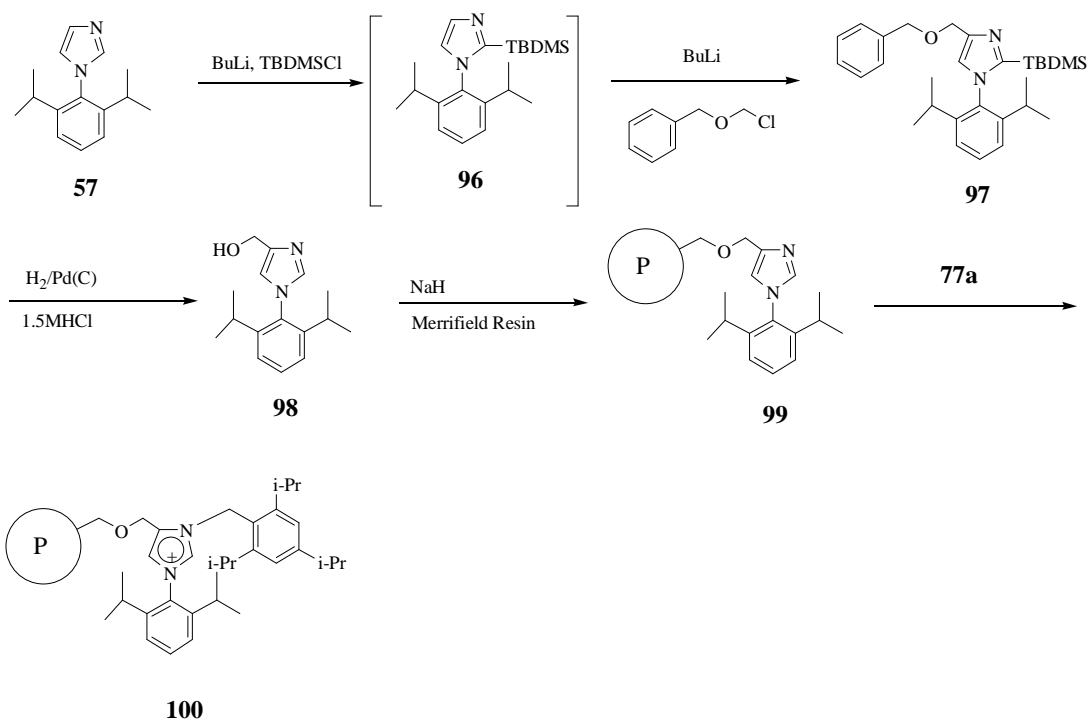
Table 15. Comparison of Suzuki Reaction Yields

	Lee yield ⁸⁸ (conventional heating)	Yield for Compounds 93-95 (microwave heating, GC yield)
93	93%	98%
94	81.9%	96%
95	70.8%	96%

Complex **83** was used in the reaction to form **93** repeating the reaction ten separate times with fresh reagents under microwave conditions with no loss in activity of the complex during the tenth run of the reaction. Longer reaction times were not observed.

Finally, a synthetic strategy was employed to prepare an unsymmetrical version of **74** tethered to a polymer. (**Scheme 52**) In this sequence, **57** was lithiated at C-2 of the imidazole ring with 2.0 molar *n*-butyllithium at -78°C under Argon atmosphere. The resulting anion was trapped by the method of Kudzma¹²⁵ with *t*-butyldimethylsilyl chloride (TBDMS-Cl) giving **96** in 92% yield. The TBDMS-imidazole **96** was lithiated at the C-4(5) position of the imidazole ring. The anion was then trapped by using chloromethylbenzyl ether giving **97** in 57% yield. The benzyl ether **97** was then hydrogenated over Pd on carbon to remove the benzyl group and hydrolyzed with 1.5 M HCl to remove the TBDMS group and gave **98** in 86% yield. Formation of the alkoxide with sodium hydride and attachment to a Merrifield resin gave **99**. Reaction of **99** with **77a** gave the tethered ligand **100** in 75% yield by micro-Kjedahl analysis and 39% overall yield.

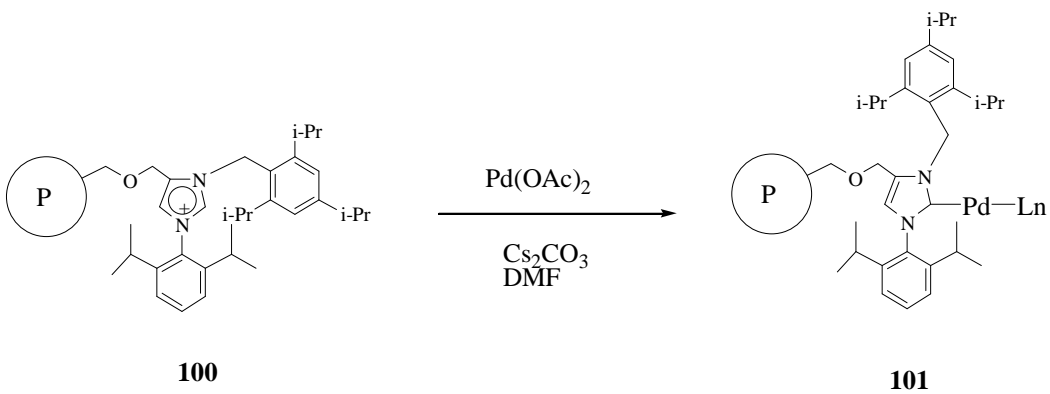
Scheme 52.



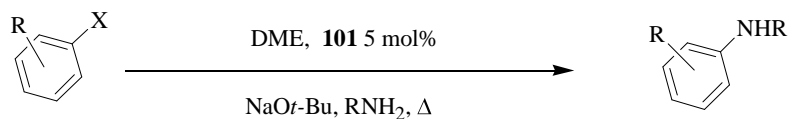
The polymer was then analyzed for its swelling values in DMF and DME giving 4.2 mL/g and 2.9 mL/g respectively. This compares well with the results obtained in Table 13 for polymer **82**. The swelling values seem to be an intrinsic value of the Merrifield resin backbone and less affected by the groups attached to the resin.

Polymer **100** was then complexed with Pd(OAc)_2 in DMF in the presence of Cs_2CO_3 to give palladium complex **101**. (Scheme 53) Again, Pd content was determined by ashing a sample at 800°C to remove all organics leaving only Pd. Palladium content was determined from the residue by atomic absorption. Yield of palladium in polymer **101** was 26%.

Scheme 53



With complex **101** in-hand, the reactions in **Table 14** were repeated with complex **101** and are shown in **Table 16** below.

Table 16. Amination Reactions With Complex 101

Aryl halide	Product	Yield ^a , time (microwave heating)	Table 14 Yield ^a , time (microwave)
	 84	99%, 0.33h	100%, 0.42h
	 85	100%, 0.25h	100%, 0.25h
	 80	97%, 0.10h	98%, 0.15h
	 87	95%, 0.42h	97%, 0.5h
	 88	98%, 0.33h	98%, 0.42h
	 81	98%, 0.15h	100%, 0.25h
	 90	100%, 0.05h	100%, 0.083h
	 79	98%, 0.15h	99%, 0.25h
	 92	89%, 0.33h	86%, 0.5h

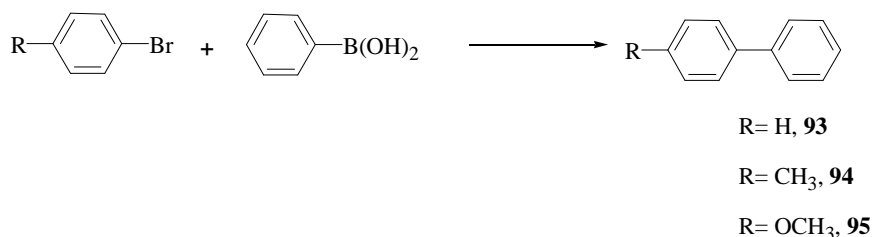
^aGC yields.

Under microwave heating, the reactions using catalyst **101** proceeded in 14-40% less time than the corresponding reactions in **Table 14** where catalyst **83** was employed. This may be due to the greater accessibility of the carbene center in **101** compared to **83**. In **83**, the polymer

may exhibit greater steric hindrance at the carbene center, due to the polymer's proximity to the carbene, preventing participation in the amination reaction whereas in **101** the polymer can be tethered away from the carbene center giving yields and reaction times similar to those of the free, unsymmetrical ligand **74**. Complex **101** was used in the reaction to form **90** repeating the reaction ten separate times with fresh reagents under microwave conditions with no loss in activity of the complex during the tenth run of the reaction. Longer reaction times were not observed.

Complex **101** was then employed in the Suzuki reaction with the results tabulated in Table 17.

Table 17. Suzuki Reaction Yields Using Complex 101.



	Yield, time
93	99%, 0.2 h
94	98%, 0.5 h
95	98%, 0.5 h

The catalyst showed high yields and short reaction times under microwave conditions. The polymer-bound catalysts in conjunction with microwave heating represent a step forward in the utility of NHC systems.

Although the unsymmetrical imidazol-2-ylidines were somewhat lower in reactivity than their symmetrical counterparts for the amination reaction, they are easily prepared in two steps

from hindered phenols in high yields. The yields by this method are generally higher than the Arduengo method. The unsymmetrical ligands were the basis for the formation of polymer-bound ligands. The polymer-bound ligands were somewhat less reactive than the unbound Ipr and Imes ligands with conventional heating however they were comparable using microwave heating. The polymer bound ligands however can be recycled many times, thus reducing overall costs in industrial processes. Use of microwave heating greatly accelerates the amination and Suzuki-Miyaura reactions.

CONCLUSIONS

The reactions of aryl halides in the presence of alkoxides with NHC ancillary ligands were hoped to give aryl ether products as observed with phosphine ligands. Instead, Ullman coupling predominated giving biphenyls in high yields when the aryl halides possessed electron-withdrawing groups. When electron donating groups or nucleophilic alkoxides were employed, yields of the biphenyls were reduced.

The synthesis of unsymmetrical NHCs served as a template for the synthesis of polymer-bound NHCs. The unsymmetrical NHCs were straightforward to prepare by earlier-developed chemistry. Polymer-bound NHCs show slightly reduced yields probably due to lack of reaction on the interior of the polymer. Polymer-bound NHCs, unsymmetrical NHCs and symmetrical NHCs benefited by reduced reaction time and increased yield by microwave heating of the reaction mixtures. The use of polymer-bound NHCs with microwave heating allows the use of NHCs to be more environmentally friendly, more cost effective and can allow the rapid building of combinatorial libraries.

EXPERIMENTAL SECTION

All chemicals were purchased from either Sigma-Aldrich Chemical Co., Milwaukee, WI., or Lancaster Synthesis, Windham, NH unless otherwise noted. Dioxane, dimethoxyethane (DME), diglyme and ethyl glyme were obtained from Ferro Corporation. Dioxane was distilled from sodium under nitrogen atmosphere. Ultra-high purity solvents were obtained by distillation over metallic sodium in an inert atmosphere followed by storing over powdered 4-Angstrom molecular sieves. Solvents were considered ultra-dry when the Karl Fischer titration gave less than 0.05% residual water in the solvent. Ipr ligand was prepared by the group of Dr. Steven Nolan and was used as received. Chromatography refers to flash chromatography on silica gel (Silica Gel 60, 230-400 mesh, E.M. Science). Reported melting points are uncorrected. NMR spectra were recorded on Varian-Gemini 400 MHz and Varian-Gemini 300 MHz multiprobe spectrometers as indicated. Chemical shifts are reported as δ values from chloroform or tetramethylsilane (TMS) as noted. Mass spectra were recorded on a Micromass Autospec Mass Spectrometer fitted with a Fisson 8060 GC. Gas Chromatography was performed on a Hewlett-Packard 5890A gas chromatograph with flame ionization detector with DB-5 30m X 0.25 mm stationary phase or RTX-5 30m X 0.53mm stationary phase. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Micro-Kjeldahl analyses were performed by AgriCure Corporation, Folsom, LA. Atomic Absorption analyses were performed by AgriCure Corporation, Folsom, LA. All reactions were performed under nitrogen atmosphere in oven-dried glassware. All microwave reactions were performed in a Samsung model MW965WP microwave oven at the indicated power and time. All compounds were homogeneous by thin layer chromatography.

2,4,6-Triisopropylnitrobenzene (53). To a stirred solution of 1,3,5-triisopropylbenzene (10.0g, 49.2 mmol) was added a mixture of cold sulfuric acid (10 mL) and nitric acid (5 mL) at 0°C. The mixture was stirred continuously for 3 h during which time a yellow-orange crystalline solid forms. The solid was dissolved in ether (50 mL) and washed with saturated sodium bicarbonate solution until neutral. The organic layer was dried over anhydrous Na₂SO₄ and filtered. Solvent was evaporated under reduced pressure. The resulting solid was recrystallized from refluxing methanol (50 ml) Crystals were filtered and dried *in-vacuo*. Collected 12.0 grams, 48.2 mmol. Yield 98%. mp 94-97°C ¹H NMR (400 MHz, TMS) δ 1.35 (s, 18H), 3.20 (q, *J* = 6 Hz, 3H), 4.2 (s, 2H), 6.60 (s, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 23.7, 24.1, 29.5, 34.0, 122.2, 139.1, 142.2, 148.8, 152.2. MS (CI) *m/z* 249 (MH⁺). *Anal.* Calculated for C₁₅H₂₃NO₂: C, 72.25; H, 9.29; N 5.61. Found: C, 72.36; H, 9.18; N 5.42.

2,4,6-Triisopropylaniline (54).¹²⁶ A solution of **53** (2.0g, 9.84 mmol) in methanol (100 mL) was hydrogenated on a Parr Hydrogenator in the presence of 10% palladium on carbon at 40 psi and ambient temperature for 16 h. The catalyst was removed by filtration under nitrogen and solvent was removed *in-vacuo*. The resulting oil was purified by column chromatography on silica gel, (5% ethyl acetate-hexane followed by 10% ethyl acetate-hexane). Solvent was removed *in-vacuo* and a crystalline white solid was obtained. Collected 1.92g, 8.7 mmol. Yield 89%. mp 63-67°C. ¹H NMR (400 MHz, TMS) δ 1.19 (d, *J*= 6.2 Hz 6H), 1.26 (d, *J*= 6.2 Hz 6H), 1.36 (d, 6H), 2.7 (q, *J* = 7.2 Hz, 1H), 2.9 (q, *J* = Hz, 2H) 7.01 (s, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 23.2, 24.4, , 33.0, 122.2, 135.0, 138.3, 135.0, 139.9 MS (CI) *m/z* 220 (MH⁺). *Anal.* Calculated for C₁₅H₂₅N: C, 82.13; H, 11.49; N 6.39. Found: C, 81.95; H, 11.28; N 6.51.

2,4,6-Triisopropylphenol (59).¹⁰³ To a stirred solution of H₂SO₄ (8 mL) in water (9 mL) was added a solution of **54** (0.77g, 3.5 mmol) in dioxane (6mL). After stirring 5 min, ice was added and the solution was stirred an additional 5 min. A solution of sodium nitrite (0.245g, 3.55 mmol) in water (5 mL) was added dropwise at 0-5°C. To a separate flask containing 10 mL H₂SO₄ and 5 mL water the above solution was added dropwise over 0.5 h with stirring. The mixture was then refluxed for 5 min. The mixture was neutralized with saturated NaHCO₃ and extracted three times with ethyl acetate (25 mL). Chromatography with gradient elution (hexane followed by 1%-ethyl acetate/hexane followed by 10%-ethylacetate/hexane) afforded the tan crystalline product. Collected 0.66g, 2.9 mmol. Yield 85%. mp 76-78°C ¹H NMR (400 MHz, TMS) δ 1.22 (d, 6H), 1.26 (d, 12H), , 2.84 (q, *J* = 7.2 Hz, 1H), 3.14 (q, *J* = 6.8 Hz, 2H) 4.6 (s, 2H). 6.91 (d, *J* = 6.8 Hz, 2H) ¹³C NMR (400 MHz, CDCl₃) δ 23.2, 24.9, 27.5, 122.2, 133.5, 141.3, 149. MS (CI) *m/z* 221 (MH⁺). . *Anal.* Calculated for C₁₅H₂₄O: C, 81.76; H, 10.98. Found: C, 81.55; H, 10.85.

***N*-(2,4,6-Triisopropylphenyl)imidazole (55). Construction of Imidazole ring. Arduengo Method A.**⁹¹ Phosphoric acid (1.4 mL) was added to 2,4,6-triisopropylaniline (**54**) (0.29g, 1.35 mmol). A tan precipitate formed almost immediately. Water (1.4 mL), dioxane (10 mL), trioxane (0.33g, 1 mmol) and glyoxal(1.5 mL, 40% wt solution) were added and the mixture was heated to 100°C. A 1 mL solution of ammonium chloride (0.52g, 0.97 mmol) was added dropwise over 5 minutes. The mixture was heated for 6 h. The mixture was extracted with methylene chloride (3 X 20 mL each). The methylene chloride phases were dried over magnesium sulfate, filtered and solvent was removed *in-vacuo* to give a dark brown crystalline solid. Collected 0.18g, 0.7 mmol. 51% yield. mp 124-127°C ¹H NMR (400 MHz, TMS) δ 1.25

(d, 6H), 1.28 (d, 12H), 2.95 (q, $J=7.1$ Hz, 1H), 3.18 (q, $J=6.9$ Hz, 2H) 6.95 (d, $J=6.8$ Hz, 2H), 7.37(s,1H),7.5 (s,1H), 8.01 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 23.2, 27.2, 32.5, 119.3, 123.2, 125.1, 131.5, 138.4, 140.5, 148.2 MS (CI) m/z 271 (MH⁺). *Anal.* Calculated for $\text{C}_{18}\text{H}_{26}\text{N}_2$: C, 79.95; H, 9.69; N 10.36. Found: C, 80.07; H, 9.49; N 10.29.

Preparation of *N*-(2,4,6-triisopropylphenyl)imidazole (55). Construction of Imidazole ring.

Arduengo Method B.⁹⁰ To a 3-neck, 25mL flask was added 2 mL glacial acetic acid, trioxane (0.04 g, 0.5 mmol), and 0.21 g of aqueous 40% glyoxal. The flask was heated to reflux and a solution of 3 mL glacial acetic acid, ammonium chloride (0.074g, 1.38 mmol), 1 mL water and 2,4,6-triisopropylaniline (0.3 g, 1.4 mmol) was added dropwise over 0.5 hours. The mixture was refluxed for 16 hours. The mixture was cooled and added dropwise to a 0°C solution of sodium bicarbonate in water. Ether (10 mL) was added and the aqueous phase was extracted three times. The ether phase was dried over magnesium sulfate and was evaporated. The residue was triturated three times with methylene chloride and the methylene chloride evaporated to remove residual acetic acid. A dark brown crystalline solid resulted. Collected 0.21 g, 0.78mmol. 56% yield. The product was compared to the product obtained from Arduengo Method A.

Attempted preparation *N*-(2,4,6-triisopropylphenyl)imidazole (55). Pd catalyzed route, Ipr

ligand.¹⁰⁰ In a pressure tube, to a stirred solution of Pd (OAc)₂, 0.0089g, 4 mol-% and Ipr ligand, 0.017g, 4mol-%, in distilled dioxane under nitrogen is added *t*-BuONa, (0.19 g, 2.0 mmol, 2.0 equivalents). The mixture is refluxed for 0.5 hours to complete formation of the complex. 2,4,6-triisopropylbromobenzene (0.283g 1 mmol), is added. Imidazole, (0.08g, 1.2

mmol), is added and reflux is continued for a total of 48 hours. The reaction is monitored by thin-layer chromatography. No reaction products were obtained.

Attempted preparation of *N*-(2,4,6-triisopropylphenyl)imidazole (55). Lithiation route. To a THF (25 mL) solution of 1-bromo-2,4,6-triisopropylbenzene (0.28g, 1 mmol) at -78°C was added 1.5 mL of 2.0M butyllithium, the reaction was stirred 20 minutes and imidazole (0.075 grams, 1.1 mmol) was added. The mixture was stirred 20 minutes and allowed to warm to room temperature. No reaction products were obtained.

***N*-(2,4,6-triisopropylphenyl)imidazole (55). Reaction of 59 with carbonyldiimidazole.**¹⁰¹ To a dichloromethane (100 mL) solution of 2,4,6-triisopropylphenol, **59** (1.35 grams, 5.0 mol) was added carbonyldiimidazole (1.05 grams, 6.5 mol). The reaction was stirred 24 h at reflux. TLC at that point showed some remaining starting material. The reaction was stirred at reflux an additional 24 h. TLC showed only product at this point. The dichloromethane solution was washed with water (3X 20 mL). The dichloromethane phase was dried over sodium sulfate. The mixture was filtered and solvent was evaporated *in-vacuo*. The crystalline residue was chromatographed (10% ethyl acetate/hexane) to give the product as a tan crystalline solid 1.3g, 4.8 mmol. Yield 95%. mp $124-127^{\circ}\text{C}$ ^1H NMR (400 MHz, CDCl_3) δ 1.25 (d, 6H), 1.28 (d, 12H), 2.95 (q, $J = 7.1$ Hz, 1H), 3.18 (q, $J = 6.9$ Hz, 2H) 6.95 (d, $J = 6.8$ Hz, 2H), 7.37(s,1H),7.5 (s,1H), 8.01 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 23.2, 27.2, 32.5, 119.3, 123.2, 125.1, 131.5, 138.4, 140.5, 148.2 MS (CI) m/z 271 (MH⁺). *Anal.* Calculated for $\text{C}_{18}\text{H}_{26}\text{N}_2$: C, 79.95; H, 9.69; N 10.36. Found: C, 80.07; H, 9.49; N 10.29.

α,α -Di(N-(2,4,6-triisopropylphenyl)imidazolmethyl)-2,4,6-trimethylbenzene

dihydrochloride (DiIpr-1) (51). To a solution of **55** (0.270 g, 1mmol) in ultra-dry xylene (10 mL) was added α,α -dichloromethyl-2,4,6-trimethylbenzene (0.11 g, 0.5 mmol). The mixture was refluxed 72 hours. The resulting solid was filtered and triturated with ether to remove remaining xylene. The solid was dried under vacuum to give **51** 0.045 g, 0.06 mmol. 12% yield. mp 168-171 , ^1H NMR (400 MHz, DMSO) δ 1.24 (d, 12H), 1.28 (d, 6H), 2.55 (d, $J=6.8$ Hz, 9H), 2.95 (d, $J=7.1$ Hz, 9H) 3.14 (q, $J=6.9$ Hz, 4H), 3.96 (d, $J=6.8$ Hz, 4H) 7.3 (d, $J=6.0$ Hz, 4H), 7.4(t,2 H), 8.15 (s, 2H) 10.9 (s, 2H). ^{13}C NMR (400 MHz, DMSO) δ 13.0, 20.6, 25.2, 30.1, 41.5, 110.3, 120.2, 123.9, 129.1, 135.1, 136.3, 136.9, 137.4, 138.4, 140.2, 141.4 MS (CI) m/z 759(MH⁺). *Anal.* Calculated for C₄₇H₆₄N₄·2HCl: C, 74.47; H, 8.78; N 7.39. Found: C, 74.62; H, 9.01; N 7.27.

α,α -Diiodomethyl-2,4,6-trimethylbenzene (58). Formation by Finkelstein Reaction. To a solution of sodium iodide (0.771 g, 5 mmol) in dry acetone (25 mL) was added α,α -dichloromethyl-2,4,6-trimethylbenzene (0.542 g, 2.5 mmol). The mixture was stirred at room temperature for 24 hours during which time a white precipitate formed. The precipitate was filtered and solvent was removed *in-vacuo* resulting in a pale brown solid. Quantitative yield. mp 198-202°C. ^1H NMR (400 MHz, CDCl₃) δ 2.1 (d, 6H), 2.8 (s, 3H), 4.7(s,4H). ^{13}C NMR (400 MHz, CDCl₃) δ 9.7, 17.3, 128.2, 139.2, 140.8, MS (CI) m/z 401(MH⁺). . *Anal.* Calculated for C₁₁H₁₄I₂: C, 33.03; H, 3.53. Found: C, 32.88; H, 3.27.

α,α -Di(N-(2,4,6-triisopropylphenyl)imidazolmethyl)-2,4,6-trimethylbenzene dihydroiodide (DiIpr-1) (51). To a solution of **55** (0.271 g, 0.5mmol) in ultra-dry dioxane (10 mL) was added

α,α -diiodomethyl-2,4,6-trimethylbenzene (**58**) (0.4g, 1 mmol). The mixture was refluxed 72 hours. The resulting solid was filtered and triturated with ether to remove remaining dioxane. The solid was dried under vacuum to give **51** as a solid 0.87g 92% yield. mp 241-243. ^1H NMR (400 MHz, DMSO) δ 1.24 (d, 12H), 1.28 (d, 6H), 2.55 (d, $J=6.8$ Hz, 9H), 2.95 (d, $J=7.1$ Hz, 9H) 3.14 (q, $J=6.9$ Hz, 4H), 3.96 (d, $J=6.8$ Hz, 4H) 7.3 (d, $J=6.0$ Hz, 4H), 7.4(t,2 H), 8.15 (s, 2H) 10.9 (s, 2H). ^{13}C NMR (400 MHz, DMSO) δ 13.0, 20.6, 25.2, 30.1, 41.5, 110.3, 120.2, 123.9, 129.1, 135.1, 136.3, 136.9, 137.4, 138.4, 140.2, 141.4 MS (CI) m/z 929 (MH⁺). *Anal.* Calculated for C₄₇H₆₄N₄·2HI: C, 60.0 H, 7.07; N 5.96. Found: C, 59.84; H, 6.97; N 5.82.

Preparation of *N*-(2,6-diisopropylphenyl)imidazole (57**).** To a dichloromethane solution (100 mL) of 2,6-diisopropylphenol (1.35 grams, 7.69 mol) was added carbonyldiimidazole (1.63g, 10.1 mmol). The reaction was stirred 24 h at reflux. TLC (10% ethyl acetate/ hexane) showed remaining starting material. The reaction was stirred at reflux an additional 24 hours. TLC showed only product at this point. The dichloromethane solution was washed with water (3 X 20 mL). The dichloromethane phase was separated and dried over sodium sulfate. Solvent was evaporated and the crystalline residue was chromatographed (10% ethyl acetate/hexane) to give the product as a white crystalline solid 1.67g, 7.3 mmol. 95% yield. mp 88-90°C. ^1H NMR (400 MHz, CDCl₃) δ 1.26 (d, $J=6.9$ Hz 12H), 2.95 (q, $J=7.1$ Hz, 2H), 6.95 (d, $J=6.8$ Hz, 2H), 7.37(s,1H),7.5 (s,1H), 8.01 (s, 1H). ^{13}C NMR (400 MHz, CDCl₃) δ 23.4, 26.2, 33.5, 119.3, 123.2, 131.5, 138.4, 140.5, 148.2 MS (CI) m/z 229 (MH⁺). *Anal.* Calculated for C₁₅H₂₀N₂: C, 78.90; H, 8.83; N 12.27. Found: C,78.77; H, 8.69; N 12.13.

α,α -Di(N-(2,6-diisopropylphenyl)imidazolymethyl)-2,4,6-trimethylbenzene dihydrochloride (DiIpr-2) (52). *N*-(2,6-diisopropylphenyl)imidazole **57** (0.11g, 0.47 mmol) was dissolved in ultra-dry xylene (10 mL) and α,α -dichloromethyl-2,4,6-trimethylbenzene (0.051g, 0.24 mmol) was added. The mixture was heated to reflux 72 h. The resulting solid was filtered and triturated with ether to remove remaining xylene. The solid was dried under vacuum to give DiIpr-2, 0.14g, 86% yield. ^1H NMR (400 MHz, DMSO) δ 1.24 (d, 24H), 2.55 (d, $J=6.8$ Hz, 4H), 3.14 (q, $J=6.9$ Hz, 4H), 3.96 (d, $J=6.8$ Hz, 4H) 5.25 (d, $J=6.0$ Hz, 4H) 6.8 (m, 3H) 7.1 (d, $J=6.0$ Hz, 4H), 10.9 (s, 2H). ^{13}C NMR (400 MHz, DMSO) δ 13.0, 20.6, 25.2, 30.1, 41.5, 110.3, 120.2, 123.9, 129.1, 135.1, 136.3, 136.9, 137.4, 138.4, 140.2, 141.4 MS (CI) m/z 675 (MH⁺). *Anal.* Calculated for C₄₁H₅₂N₄·2HCl: C, 73.08; H, 8.08; N 8.32. Found: C, 72.87; H, 7.96; N 8.11.

General Procedure A. Homocoupling of Aryl Halides. (Table 3) To a stirred solution of Pd(OAc)₂, 2.5 mol-% and imidazoline ligand, 5 mol-%, in distilled dioxane (4 mL) under nitrogen was added *t*-BuONa (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The aryl halide substrate (1 mmol) was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane).

4,4'-Di(cyano)biphenyl (61). Reaction of 4-bromobenzonitrile (**60**) (0.18g, 1mmol) using General Method A afforded 4,4'-dicyanobiphenyl (**61**) (0.20g, 0.99mmol) 99% yield after

chromatography. mp 234-236°C. ^1H NMR (400 MHz, CDCl_3) δ 7.65 (s, 4H), 7.71 (s, 4H). ^{13}C NMR (400 MHz, CDCl_3) δ 112.3, 119.4, 131.5, 134.4, 140.5, MS (CI) m/z 205 (MH⁺). *Anal.* Calculated for $\text{C}_{14}\text{H}_8\text{N}_2$: C, 82.33; H, 3.95; N 13.71. Found: C, 82.45; H, 4.02; N 13.59.

4,4'- Di(cyano)biphenyl (61) from 60 without NHC ancillary ligand. To a stirred solution of $\text{Pd}(\text{OAc})_2$ (0.0089g, 2.5 mol-%), in distilled dioxane (4 mL) under nitrogen was added sodium *t*-Butoxide (0.20 g, 2.1 mmol) . The mixture was refluxed for 0.5 hours to complete formation of the complex. The aryl halide substrate **60** (0.18g 1.0 mmol) was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids were filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded 4,4'-dicyanobiphenyl, (0.07 g, 0.38 mmol) 38% yield .

4,4'- Di(cyano)biphenyl from 4-Bromobenzonitrile without ligand with heating for extended time. To a stirred solution of $\text{Pd}(\text{OAc})_2$, 2.5 mol-%, in distilled dioxane(4 mL) under nitrogen was added *t*-BuONa (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The aryl halide substrate **60**, 1 mmol, was added and reflux was continued for 74 d. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded 4,4'-dicyanobiphenyl (**61**) (0.09g, 0.43 mmol). 43% yield .

4,4'-Biphenyldicarboxaldehyde (62) from 4-Chlorobenzaldehyde. To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added *t*-BuONa (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-chlorobenzaldehyde (1 mmol) was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded 4,4'-biphenyldicarboxaldehyde (**62**) (0.2g, 0.95 mmol) 95%. mp 56-58°C. ¹H NMR (400 MHz, CDCl₃) δ 7.65 (s, 4H), 7.84 (s, 4H) 9.91 (s, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 128.3, 131.0, 136.5, 144.4, 190.5, MS (CI) *m/z* 211 (MH⁺). *Anal.* Calculated for C₁₄H₁₀O₂: C, 80.0; H, 4.8. Found: C, 80.23; H, 4.89.

4,4'-Di(*t*-butyl)biphenyl (63) from Bromo-4-(*t*-butyl)benzene. To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added *t*-BuONa (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The Bromo-4-(*t*-butyl)benzene (1 mmol) was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded 4,4'-di(*t*-butyl)biphenyl (**63**) as an oil (0.07 g, 0.26 mmol) 26% yield. ¹H NMR (400

MHz, CDCl₃) δ 1.28 (s, 18H) 7.41 (s, 4H), 7.51 (s, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 32.0, 35.2, 126.5, 127.6, 134.4, 147.5, MS (CI) m/z 268 (MH⁺). *Anal.* Calculated for C₂₀H₂₇: C, 89.82; H, 10.18. Found: C, 89.65; H, 10.02.

Biphenyl (64) from Bromobenzene. To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane under nitrogen was added *t*-BuONa (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The bromobenzene, (1 mmol) was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1%-ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded biphenyl (**64**) 0.04g, 0.26 mmol). 26% yield.

Attempted preparation of 64 from Bromobenzene with no ligand and heating for 24 hours.

To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 mmol of *t*-BuONa. The mixture was refluxed for 0.5 hours to complete formation of the complex. The bromobenzene, 1 mmol, was added and reflux was continued for 24 hours. The reaction was monitored by TLC. No reaction products were obtained.

Biphenyl from Bromobenzene with no catalyst and heating for 36 days.

To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 equivalents of *t*-BuONa. The mixture was refluxed for 0.5 hours to complete formation of the complex. The

bromobenzene, 1 equivalent, was added and reflux was continued for 24 h. No reaction products were observed by thin layer chromatography (1% ethyl acetate/hexanes).

4,4'-Dimethoxybiphenyl (65) from 4-Chloroanisole. To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 mmol *t*-BuONa. The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-Chloroanisole, 1 mmol, was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1% ethyl acetate/hexane then 10% ethyl acetate/hexane) which afforded 4,4'-Dimethoxybiphenyl (**63**) in 82% yield. mp 178-180°C. ¹H NMR (400 MHz, CDCl₃) δ 3.8 (s, 6H) 6.99 (4H) 7.48 (s, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 57.0, 115.3, 129.3, 136.9, 162 MS (CI) *m/z* 205 (MH⁺). *Anal.* Calculated for C₁₄H₁₄O₂: C, 78.48; H, 6.59. Found: C, 78.35; H, 6.29.

4,4'-Di(methylcarboxylato)biphenyl (66) from 4-Bromomethylbenzoate. To a stirred solution of Pd(OAc)₂, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 mmol of *t*-BuONa. The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-bromomethylbenzoate, 1 mmol, was added and reflux was continued for 24 hours. The reaction was quenched by addition of 0.5 mL of 5% HCl and stirring for 5 minutes. Magnesium sulfate was added and the solids are filtered. The solids were washed with 5 mL of dioxane and the filtrates were combined. Solvent was removed *in-vacuo* and the resulting crude material was chromatographed (hexane then 1% ethyl acetate/hexane then 10% ethyl acetate/hexane) which

afforded ,4'-Di(methylcarboxylato)biphenyl (**66**) in 92% yield. mp 214-217°C. ¹H NMR (400 MHz, CDCl₃) δ 3.6 (s, 6H), 7.65 (s, 4H), 7.82 (s, 4H). ¹³C NMR (400 MHz, CDCl₃) δ 58.2, 128.5, 136.5, 145.6, 191. MS (CI) *m/z* 271 (MH⁺). *Anal.* Calculated for C₁₆H₁₄O₄: C, 71.1; H, 5.22. Found: C, 71.25; H, 5.38.

General Procedure B. *t*-Butoxide Counter Ion Screening (Table 4). To a stirred solution of Pd(OAc)₂, 2.5 mol-% and Ipr ligand, 5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 mmol of the appropriate *t*-Butyl alkoxide. The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-bromobenzonitrile (**60**) substrate, 1 mmol, was added and reflux was continued for 24 hours. The reaction was monitored by GC for the formation of 4,4'-Di(cyano)biphenyl (**61**).

Preparation of (61) with lithium *t*-butoxide.

The General Procedure B to prepare **61** was performed with lithium *t*-butoxide (FMC Lithium Division) as the alkoxide. No reaction products were observed by GC after 24h at reflux.

Preparation of (61) with potassium *t*-butoxide.

The General Procedure B to prepare **61** was performed with potassium *t*-butoxide as the alkoxide. Quantitative yield of **61** was observed by GC after 24 h at reflux.

Preparation of (61) with 1.0 M potassium *t*-butoxide/THF.

The General Procedure B to prepare **61** was performed with 1.0 M potassium *t*-butoxide/THF as the alkoxide. Quantitative yield of **61** was observed by GC after 24 h at reflux.

General Procedure C. Palladium to Ligand Ratio. Table 5. To a stirred solution of Pd(OAc)₂, 2.5 mol-% and the appropriate ligand, in distilled dioxane under nitrogen was added Sodium *t*-Butoxide (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-bromobenzonitrile (**60**) substrate, (1 mmol), was added and reflux was continued for 24 hours. The reaction was monitored by GC for the formation of 4,4'-Di(cyano)biphenyl (**61**).

Use of Ipr ligand (50) at 1:2 palladium:ligand ratio to prepare 61.

The reaction was performed with 2.5 mol% Pd(OAc)₂ and 5.0 mol% **50**. After 24h at reflux, the yield was quantitative by GC analysis.

Use of Ipr ligand (50) at 1:2 palladium:ligand ratio to prepare 63.

The reaction was performed with 2.5 mol% Pd(OAc)₂ and 5.0 mol% **50**. After 24h at reflux, the yield was 25% by GC analysis.

Use of Ipr ligand (50) at 1:1 palladium:ligand ratio to prepare 61.

The reaction was performed with 2.5 mol% Pd(OAc)₂ and 2.5 mol% **50**. After 24h at reflux, the yield was quantitative by GC analysis.

Use of DiIpr-1 ligand (51) at 2:1 palladium:ligand ratio to prepare 61.

The reaction was performed with 5.0 mol% Pd(OAc)₂ and 2.5 mol% **51**. After 24h at reflux, the yield was quantitative by GC analysis.

Use of DiIpr-2 ligand (52) at 2:1 palladium:ligand ratio to prepare 61.

The reaction was performed with 5.0 mol% Pd(OAc)₂ and 2.5 mol% **52**. After 24h at reflux the yield was quantitative by GC analysis.

Use of DiIpr-2 ligand (52) at 1:1 palladium:ligand ratio to prepare 61.

The reaction was performed with 2.5 mol% Pd(OAc)₂ and 5.0 mol% **52**. After 24h at reflux, the yield was 99% by GC analysis.

Use of DiIpr-1 ligand (52) at 1:1 palladium:ligand ratio to prepare 63.

The reaction was performed with 5.0 mol% Pd(OAc)₂ and 2.5 mol% **52**. After 24h at reflux, the yield was 23.8% by GC analysis.

General Procedure D. Determination of Reaction Time for the Homocoupling of Aryl Halides to Produce Compound 61 (Table 6). To a stirred solution of Pd(OAc)₂, 2.5 mol-% and Ipr ligand, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added 2.1 equivalents of the appropriate *t*-Butyl alkoxide. The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-bromobenzonitrile (**60**) substrate, (1mmol), was added and heated to reflux. The reaction was monitored every 4 hours by GC for the formation of 4,4'-Di(cyano)biphenyl (**61**) until the yield was quantitative(16 h).

Solvent effects on the homocoupling of bromobenzonitrile to form 61 (Table 7). The reaction of General Procedure D was performed with THF, toluene, DME, ethyl glyme, DMF, heptane, diglyme, DMSO, acetonitrile and diethyl ether as the solvents. Yields were monitored by GC as indicated in **Table 7**.

General Procedure E. Base Effects in the Homocoupling of Aryl Halides (Table 8). To a stirred solution of Pd(OAc)₂, 2.5 mol-% and Ipr ligand, 2.5 mol-%, in distilled dioxane (4 mL) under nitrogen was added the appropriate base (2.1 mmol). The mixture was refluxed for 0.5 hours to complete formation of the complex. The 4-bromobenzonitrile (**60**) substrate, (1 mmol),

was added and heated to reflux. The reaction was monitored by GC for the formation of 4,4'-Di(cyano)biphenyl (**61**) until no increase in yield was observed.

Sodium hydroxide as Base.

The General Procedure E was employed with sodium hydroxide (2.1 mmol) moist beads as the base. The hydroxide was dissolved in dioxane then the other reagents were added. The mixture was heated to reflux for 24 h. The yield of **61** was 15% by GC.

The reaction was repeated by combining 0.5 equivalents of Cs₂CO₃ and Pd(OAc)₂ and **50** in dioxane. After 0.5h moist sodium hydroxide beads were added. Upon dissolution, bromobenzonitrile (1 mmol) was added. The mixture was heated to reflux for 24 h. The yield of **61** was 15% by GC.

Sodium Methoxide as Base.

The General Procedure E was repeated employing sodium methoxide. The mixture was heated to reflux for 24 h. The yield of **61** was 20% by GC.

Sodium Ethoxide as Base.

The General Procedure E was repeated employing sodium ethoxide. The mixture was heated to reflux for 24 h. The yield of **61** was 15% by GC.

Sodium Pentoxide as Base. Generation of Alkoxide from Pentyl Alcohol and Sodium Metal.

Sodium metal pieces were added to a solution of pentyl alcohol (2.1 mmol) in dioxane (4 mL). When the evolution of hydrogen gas ceased and no sodium metal was observed, The General Procedure E was performed. Yield was 3% by GC.

Sodium Pentoxide as Base. Generation of Alkoxide from Pentyl Alcohol and Sodium

Hydride. A 60% Sodium hydride dispersion in mineral oil (2.2mmol) (AgriCure Corporation) was added to a stirred solution of pentyl alcohol (2.1 mmol) in dioxane. The mixture was heated

until the evolution of hydrogen gas ceased. The General procedure E was performed. Yield was 10% by GC.

Sodium Phenoxide as Base. Generation of Alkoxide from Phenol and Sodium Metal.

Sodium metal (2.0 mmol) pieces were added to a solution of phenol (2.0 mmol) in dioxane (4 mL). When the evolution of hydrogen gas ceased and no sodium metal was observed, The General Procedure E was performed. Yield was 7% by GC.

Sodium Phenoxide as Base. Generation of Alkoxide from Phenol and Sodium Hydride.

A 60% Sodium hydride dispersion in mineral oil (2.2mmol) was added to a stirred solution of phenol (2.1 mmol) in dioxane (4mL). The mixture was heated until the evolution of hydrogen gas ceased. The General procedure E was performed. Yield was 20% by GC.

Effect of Substrate in Aryl Halide Homocoupling Reaction.

The reaction mixture from General Procedure D was spiked with a standard of 4,4'-biphenyldicarboxylic acid and the solution was analyzed by GC to determine the retention time of the dicarboxylic acid. The spiked mixture showed two different retention times for the dicarboxylic acid and for **61**. Thus **61** was not undergoing hydrolysis in the presence of sodium t-butoxide.

Synthesis of 4,4'-(trifluoromethyl)biphenyl (68) 4-(trifluoromethyl)chlorobenzene, **67** (1mmol) was employed in General Procedure A. **68** was obtained in 96% yield after 24 hours of reflux. mp 89-93. ^1H NMR (400 MHz, CDCl_3) δ 7.65 (s, 4H), 7.71 (s, 4H). ^{13}C NMR (400 MHz, CDCl_3) δ 112.3, 119.4, 131.5, 134.4, 140.5,. MS (CI) m/z 291 (MH $^+$). *Anal.* Calculated for $\text{C}_{14}\text{H}_8\text{F}_6$: C, 57.94; H, 2.78. Found: C, 57.85; H, 2.66.

Effect of Palladium Source. The General Procedure A was repeated with tris-(dibenzylidene acetone)dipalladium ($\text{Pd}_2(\text{dba})_3$) (0.0071g, 1.25 mol%) with Ipr (**50**) (0.01g, 2.5 mol%) in place of $\text{Pd}(\text{OAc})_2$ in the reaction of 4-trifluoromethylchlorobenzene **67** to prepare 4,4'-(trifluoromethyl)biphenyl **68**. After 24 hours of reflux, **68** was obtained in 99% yield by GC.

Reactivity of Carbene Catalysts.

Synthesis of *N*-isobutyl-4-cyanoaniline (69**).** To a stirred solution of **60** (0.18g 1.0 mmol) in dioxane (4 mL) was added $\text{Pd}(\text{OAc})_2$ 2mol%, **50** 2 mol%, sodium *t*-butoxide (2.1 mmol) and isobutylamine (0.11g, 1.5 mmol). The mixture was monitored by thin-layer chromatography (10%ethylacetate-hexane). Reaction was complete in 1h. The mixture was filtered, dried over MgSO_4 , filtered and solvent evaporated *in-vacuo*. The resulting oil was chromatographed (1% ethyl acetate-hexane followed by 5%ethyl acetate-hexane). Collected 0.16g, 0.92 mmol. Yield 92%. ^1H NMR (400 MHz, CDCl_3) δ 1.02 (s, 3H), 1.28(s, 3H), 1.60 (m, $J= 6.2$ Hz, 2H), 2.92 (q, $J= 6.8$ 1H) 4.5 (s 1H), 6.9 (s, 2H), 7.38 (s, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 9.4, 22.5, 33.2, 57.0, 108.0, 114.4, 118.5 131.5. MS (CI) m/z 175 (MH⁺). *Anal.* Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2$: C, 75.82; H, 8.10; N 16.08. Found: C, 75.66; H, 7.97; N 15.94.

Synthesis of *N*-isobutyl-4-(trifluoromethyl)aniline (70**).** To a stirred solution of **67** (1 mmol) in dioxane was added $\text{Pd}(\text{OAc})_2$ 2mol%, **50** 2mol%, sodium *t*-butoxide (2.0 mmol) and isobutylamine (1.5 mmol). The mixture was monitored by thin-layer chromatography (10%ethylacetate-hexane). Reaction was complete in 1h. The mixture was filtered, dried over MgSO_4 , filtered and solvent evaporated *in-vacuo*. The resulting oil was chromatographed (1% ethyl acetate-hexane followed by 5%ethyl acetate-hexane). Collected 0.21g, 0.98mmol. 98%

yield. ^1H NMR (400 MHz, CDCl_3) δ 1.08 (s, 3H), 1.28(s, 3H), 1.56 (m, $J= 6.4$ Hz, 2H), 2.77 (q, $J= 6.2$ 1H) 4.2 (s 1H), 6.5 (s, 2H), 7.22 (s, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 9.6, 23.5, 31.2, 57.6, 114.4, 119.8, 120.4, 147.2. MS (CI) m/z 218 (MH $^+$). *Anal.* Calculated for $\text{C}_{11}\text{H}_{14}\text{NF}_3$: C, 60.82; H, 6.50; N 6.45. Found: C, 60.55; H, 6.28; N 6.33.

Synthesis and Reaction Screening of Unsymmetrical and Polymer-Bound Palladium Imidazol-2-ylidines.

Preparation of 70 Using Deloxan Resin. Solvent Screening. General Procedure F. To a stirred solution of **67** (1 mmol), in the desired solvent at 0.25M concentration was added isobutylamine (1.2 mmol) sodium carbonate (2 mmol) palladium as Deloxan resin, 0.02g, 5 mol%. All yields were monitored by GC.

Preparation of 70 Using Deloxan Resin using DME as Solvent with Ancillary Ligand 50. The General Procedure F was performed with IPr (**50**) (5 mol%). The reaction was performed in DME and monitored by GC. 29% yield by GC was obtained after 24 h at reflux.

Preparation of 70 Using Deloxan Resin using DME as Solvent with Ancillary Ligand 50 Under Microwave Conditions. In a 10mL borosilicate tube with screw cap was added **67** (1 mmol), and DME at 0.25M concentration solution based on **67**, isobutylamine (1.2 mmol) sodium carbonate (2 mmol) palladium as Deloxan resin, 5 mol% and **50** 5 mol%. The tube was sealed and the mixture was place in the microwave oven at 900 Watts power for 5 minutes. Analysis by GC shows 63% yield. The mixture was heated an additional 5 minutes at 900 watts. No increase in yield was observed by GC.

Preparation of Unsymmetrical Imidazol-2-Ylidines. General Procedure G. To a stirred solution of the appropriate benzyl halide (1.1 mmol) in ultra-dry xylene (4 mL) was added **57** (1.2 mmol). The mixture was refluxed for 72 hours during which time a precipitate formed. The precipitate was triturated with ultra-dry ether and dried under vacuum (0.1mmHg).

***N*-(2,6-Diisopropylphenyl)imidazolmethylbenzene hydrochloride (72).** The General Procedure G was performed with benzyl chloride (0.14g, 1.1 mmol) and **57** (0.27g, 1.2 mmol). The mixture was refluxed for 72 hours during which time an insoluble oil formed. The oil was triturated with ultra-dry ether and dried under vacuum (0.1mmHg). Collected 0.26g, 0.73 mmol. 73% yield. ^1H NMR (400 MHz, CDCl_3) δ 1.28 (d, $J=6.9$ Hz 12H), 2.95 (q, $J=7.1$ Hz, 2H), 4.4 (s, 2H), 6.95 (d, $J=6.8$ Hz, 2H), 7.06 (m, $J=6.2$, 4H) 7.37 (s,1H),7.5 (s,1H), 8.01 (s, 1H) 10.9 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 23.4, 26.2, 53.8, 119.3, 121.2, 125.4, 129.2, 131.5. MS (CI) m/z 356 (MH $^+$). *Anal.* Calculated for $\text{C}_{22}\text{H}_{26}\text{N}_2\cdot\text{HCl}$: C, 74.45; H, 7.67; N 7.89. Found: C, 74.15; H, 7.38; N 7.99.

***N*-(2,6-diisopropylphenyl)imidazolmethyl-2,4,6-trimethylbenzene hydrochloride (73).** The General Procedure G was performed with 2,4,6-trimethylbenzyl chloride (0.19g, 1.1mmol). Collected 0.24 g, 0.62 mmol. Yield 62%. mp 124-126°C. ^1H NMR (400 MHz, CDCl_3) δ 1.26 (d, $J=6.9$ Hz 12H), 2.44(s, 9H), 2.68 (s, 2H) 2.95 (q, $J=7.1$ Hz, 2H), 6.75 (s, 2H), 7.06 (d, $J=6.2$, 2H) 7.37 (s,1H),7.5 (s,2H), 8.01 (s, 1H) 10.9 (s, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 23.4, 26.2, 53.8, 119.3, 121.2, 125.4, 129.2, 131.5. MS (CI) m/z 398 (MH $^+$). *Anal.* Calculated for $\text{C}_{25}\text{H}_{32}\text{N}_2\cdot\text{HCl}$: C, 75.63; H, 8.38; N 7.06. Found: C, 75.44; H, 8.15; N 6.92.

2,4,6-Triisopropylbenzyl bromide (77a).¹¹⁵ To a stirred solution of triisopropylbenzene (5.0g, 24.5 mmol) was added paraformaldehyde (0.75g, 24.5 mmol) and glacial acetic acid (25 mL) was added rapidly 25 mL of 31wt% hydrobromic acid in acetic acid. The mixture was heated to 50°C for 4 hours. The mixture was added to 100 g ice and resulting precipitate was washed with water (3 X 50 mL) and dried under vacuum (0.1mmHg) for 48 hours. Collected 5.9g, 19.8 mmol. 81% yield. mp 91-93°C. ¹H NMR (400 MHz, CDCl₃) δ 1.26 (d, *J* = 6.9 Hz 12H), 1.28 (d, *J* = 6.9 Hz, 6H), 3.1 (q, *J* = 6.4 Hz, 2H), 3.25 (q, *J* = 6.2 Hz, 1H), 4.67 (s, 2H), 6.75 (s, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 23.4, 25.2, 27.9, 33.4, 121.2, 131.5, 149.5. MS (CI) *m/z* 299 (MH⁺). *Anal.* Calculated for C₁₆H₂₅Br: C, 64.64 ; H, 8.48. Found: C, 64.45; H, 8.32.

***N*-(2,6-diisopropylphenyl)imidazolmethyl-2,4,6-triisopropylbenzene hydrobromide (74).**

The General Procedure G was performed with **77a** (0.32g, 1.1mmol). Collected 0.25 g, 0.48 mmol. Yield 48%. mp 138-141°C. ¹H NMR (400 MHz, CDCl₃) δ 1.26 (d, *J* = 6.9 Hz 12H), 1.28 (d, *J* = 6.9 Hz, 6H), 3.1 (q, *J* = 6.4 Hz, 2H), 3.25 (q, *J* = 6.2 Hz, 1H), 4.2 (s, 2H), 6.75 (s, 2H) 7.02 (s, 2H) 7.56 (s, 2H) 10.9 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 23.8, 24.2, 25.2, 27.9, 33.4, 42.8, 117.2, 121.2, 131.5, 133.8, 140.2, 146.1, 149.5. MS (CI) *m/z* 526 (MH⁺). *Anal.* Calculated for C₃₁H₄₃N₂HBr: C, 61.59; H, 7.34; N 4.63. Found: C, 61.68; H, 7.48; N 4.84.

General Procedure H. Solvent Screening for the Synthesis of Unsymmetrical NHCs. (Table 10). To a stirred solution of benzyl chloride (1.1 mmol) in ultra-dry solvent (4 mL) was added **57** (1.2 mmol). The mixture was refluxed for 72 hours during which time a precipitate formed. The precipitate was triturated with ultra-dry ether and dried under vacuum (0.1mmHg).

Preparation of *N*-Phenylmorpholines, 79, 80, 81. General Procedure. Conventional Heating. Table 11. To a stirred 0.25M solution of aryl halide (1mmol) in DME was added morpholine (1.2 mmol), Pd(OAc)₂ (2mol%) and the appropriate NHC ligand (2mol%). The mixture was heated on an oil bath for the time indicated in Table 11. Reaction progress was monitored by GC.

***N*-(4-trifluoromethylphenyl)morpholine (79).** Analytical data has been previously reported.¹¹⁸

***N*-(4-methylphenyl)morpholine (80).** Analytical data has been previously reported.¹²⁰

***N*-(4-methoxyphenyl)morpholine (81).** Analytical data has been previously reported.¹²¹

Preparation of *N*-Phenylmorpholines, 79, 80, 81. General Procedure. Microwave Heating. Table 12. To an unstirred 0.25M solution of aryl halide (1mmol) in DME was added morpholine (1.2 mmol), Pd(OAc)₂ (2mol%) and the appropriate NHC ligand (2mol%). The mixture was heated in the microwave oven at 500 watts for the time indicated in Table 12. Reaction progress was monitored by GC.

Preparation of Merrifield Bound NHC (82). To a solution of **57** (7.5 g, 33 mmol) in dimethylacetamide (20 mL) was added 3 g Merrifield resin (reactive chloride content 1.09 mmol/gram). The mixture was heated to reflux for 24 h at which time a 9-fold excess of **57** remained by GC. 3.58 g of resin was recovered by filtration. Yield 64% by micro-Kjedahl analysis.

Determination of Swelling properties of Polymer 82. General Procedure. Table 13. 1.0 grams of polymer **82** were placed into a graduated flash column with a stopcock and fritted glass filter. Dry volume was 1.8 mL/gram. Polymer **82** was allowed to swell in the desired solvent for

1 hour at room temperature. The resin was washed three times with the solvent and allowed to air dry for 2 hours. The mass, density and volume of the resin was then determined after exposure to the solvent. Results are reported in Table 13.

Preparation of Palladium-NHC Polymer 83. To a stirred solution of polymer **82** (0.25 g) in DMF (10mL) was added Pd(OAc)₂ (0.04g, 0.17 mmol) and Cs₂CO₃ (0.11g, 0.348 mmol). The mixture was refluxed 12 hours to give polymer **83**. The resin was washed with water (3 X 10 mL) and allowed to dry in a desiccator for 48h. A sample of the polymer was placed in a porcelain crucible then reduced to ash in an 800°C oven. The ash was analyzed by atomic absorption. Yield based on palladium 31%.

General Procedure for the Preparation of Aryl Amines from Aryl Halides Using Polymer-Bound NHCs 83 and 101 with Conventional Heating. Table 14. To a stirred 0.25M solution of aryl halide (1mmol) in DME was added morpholine (1.2 mmol), Pd(OAc)₂ (2mol%) and the appropriate NHC ligand (2 mol%). The mixture was heated on an oil bath for the time indicated in **Table 14**. Reaction progress was monitored by GC.

General Procedure for the Preparation of Aryl Amines from Aryl Halides Using Polymer-Bound NHCs 83 and 101 with Microwave Heating. Table 14 and Table 16. To an unstirred 0.25M solution of aryl halide (1mmol) in DME was added morpholine (1.2 mmol), Pd(OAc)₂ (2mol%) and the appropriate NHC ligand (2mol%). The mixture was heated in the microwave oven at 500 watts for the time indicated in Table 12. Reaction progress was monitored by GC.

N-Phenyltolulidine (84). Analytical data was previously reported.¹²²

***N,N*-Di(*n*-butyl)toluidine (85).** Analytical data was previously reported.¹¹⁷

***N*-Phenylanisidine (87).** Analytical data was previously reported.¹²⁴

***N,N*-Di(*n*-butyl)anisidine (88).** Analytical data was previously reported.¹²¹

***N*-(4-cyanophenyl)morpholine (90).** Analytical data was previously reported.¹²³

***N*-Phenyl-2,4,6-trimethylaniline (92).** Analytical data was previously reported.¹¹⁹

General Procedure for the Suzuki reaction Using Polymer Bound NHCs 83 and 101.³⁰

Table 15 and Table 17. To an unstirred 0.25M solution of aryl bromide(1.0 mmol) in dioxane (4 mL) was added phenyl boronic acid (1.1mmol), Na₂CO₃ (2 mmol) and the appropriate resin **83** or **101** (5mol%). The mixture was heated in the microwave oven at the power and time indicated in **Table 15** and **Table 17** respectively.

4-Methylbiphenyl (94). Analytical data was previously reported.³⁰

4-Methoxybiphenyl (95). Analytical data was previously reported.³⁰

Preparation of *N*-(2,6-Diisopropylphenyl)-2-(*t*-butyldimethylsilyl)-4(5)-(methyloxobenzyl)imidazole (97).¹²⁵ A solution of **57** (2.3 g, 10 mmol) in dry THF (100 mL) under nitrogen atmosphere was cooled to -78°C . A solution of 2.0M *n*-butyllithium in cyclohexane (5.5 mL, 11 mmol) was added dropwise. After 0.5 h *t*-butyldimethylsilyl chloride (1.8 g, 12 mmol) was added and the mixture was allowed to warm to r.t.. After 3 h the mixture was cooled to -78°C and *n*-butyllithium (6.5 mL, 13 mmol) was added dropwise over for a second time. After 0.5h benzylchloromethyl ether (90% tech grade 2.6g, 15 mmol) was added and the mixture was allowed to warm to r.t. After 12h, the mixture was quenched with aqueous

saturated Na_2CO_3 (3 mL) and solvent was removed *in-vacuo*. The residue was dissolved in methylene chloride and washed with water (40 mL) and dried over sodium sulfate. Chromatography (hexane followed by 5% ethyl acetate/hexane) gave **97** as a crystalline solid. 2.63g Yield 57% mp 143-146°C. ^1H NMR (400 MHz, CDCl_3) δ 0.04 (s, 6H), 1.06 (s, 9H) 1.27(d, $J=6.2$ Hz,12H), 2.95 (q, $J=6.9$ Hz, 1H), 3.14 (q, $J=6.9$ Hz, 1H), 4.61 (d, $J=6.6$ Hz, 2H), 4.69 (d, $J=6.6$ Hz, 2H), 7.01(d, $J=5.2$ Hz, 2H) 7.22(m,5H) ^{13}C NMR (400 MHz, CDCl_3) δ -4.6, 17.5, 23.6, 25.2, 70.5, 76.1, 123.5, 125.2, 129.4,129.8, 131.5, 136.9, 138.4, 140.5, 148.2 MS (CI) m/z 463 (MH+). . *Anal.* Calculated for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{OSi}$: C, 75.27; H, 9.15; N 6.05. Found: C, 75.03; H, 9.18; N 5.88.

Preparation of *N*-(2,6-Diisopropylphenyl)-4(5)-(hydroxymethyl)imidazole (98). A solution of **96** (2.0g, 4.33 mmol) in methanol (100 mL) was hydrogenated on a Parr Hydrogenator in the presence of 10% palladium on carbon at 40 psi and ambient temperature for 12 h. The catalyst was removed by filtration under nitrogen and solvent was removed *in-vacuo*. The resulting oily solid was dissolved in 1.5N HCl and refluxed for 1.5 h. The solution was cooled by ice bath and 30% ammonium hydroxide was added until the mixture was neutral pH. The mixture was extracted with methylene chloride, the extracts combined and dried over sodium sulfate, filtered and solvent removed *in-vacuo*. The resulting solid was purified by chromatography, (25% ethyl acetate-hexane followed by 50% ethyl acetate-hexane). Solvent was removed *in-vacuo* and a crystalline solid was obtained. 0.96g. Yield 86%. mp 108-113°C. . ^1H NMR (400 MHz, TMS) δ 1.27(d, $J=6.2$ Hz,12H), 2.4(s, 1H) 2.95 (q, $J=6.9$ Hz, 1H), 3.14 (q, $J=6.9$ Hz, 1H), 4.68 (d, $J=6.6$ Hz, 2H), 7.01(s, 1H) 7.18 (s, 1H) 7.22 (s,1H), 7.9(s 1H) ^{13}C NMR (400 MHz, CDCl_3)

δ 23.8, 25.2, 68.5, 123.8, 128.1, 134.2, 140.2, 141.7, 141.9 MS (CI) m/z 260 (MH⁺). *Anal.* Calculated for C₁₆H₂₃N₂O: C, 74.09; H, 8.94; N 10.80. Found: C, 73.88; H, 9.08; N 10.68.

Preparation of Tethered NHC (100). To a solution of **98** (0.519g, 2.0 mmol) in DME (10mL) and dimehtylacetamide (10 mL) was added sodium hydride (60% in mineral oil, 0.84g, 2.1 mmol). The mixture was refluxed 0.5 h. 1 g Merrifield resin (1.0g, reactive chloride content 1.09 mmol/gram) was added to the solution. The mixture was refluxed 24 h. The solution was cooled and 2,4,6-triisopropylbenzyl bromide (**77a**) (0.297g, 1.1mmol) was added. Reflux was continued 72 h to give tethered polymer **100**. Yield by micro-Kjeldahl analysis 75%.

Determination of Swelling properties of Polymer 100. General Procedure. Table 13. 1.0 grams of polymer **100** were placed into a graduated flash column with a stopcock and fritted glass filter. Dry volume was 1.8 mL/gram. Polymer **100** was allowed to swell in the desired solvent for 1 hour at room temperature. The resin was washed three times with the solvent and allowed to air dry for 2 hours. The mass, density and volume of the resin was then determined after exposure to the solvent. Swelling volume in DMF: 4.2 mL/g. Swelling volume in DME: 2.9 mL/g.

Preparation of Tethered Polymer 101 To a stirred solution of polymer **100** (0.25 g) in DMF (10 mL) was added Pd(OAc)₂ (0.07g, 0.3 mmol) and Cs₂CO₃ (0.195g, 0.6 mmol) The mixture was refluxed 12 hours to give polymer **101** The polymer was washed with water (3 X 10 mL). The polymer was placed in a porcelain crucible then reduced to ash in an 800°C oven. The ash was analyzed by atomic absorption. Yield based on palladium was 26%.

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